



República Argentina - Poder Ejecutivo Nacional
Las Malvinas son argentinas

Disposición

Número:

Referencia: EX-2021-113811371-APN-DGA#ANMAT

VISTO el EX-2021-113811371-APN-DGA#ANMAT del Registro de la Administración Nacional de Medicamentos, Alimentos y Tecnología Médica; y

CONSIDERANDO:

Que por las presentes actuaciones la firma BRISTOL MYERS SQUIBB ARGENTINA S.R.L., representante en Argentina de BRISTOL MYERS SQUIBB CO., solicita un nuevo elaborador alternativo y nuevo país de origen alternativo de la Especialidad Medicinal denominada SPRYCEL / DASATINIB, Forma Farmacéutica y Concentración: COMPRIMIDOS RECUBIERTOS, DASATINIB (COMO MONOHIDRATO) 20 mg – 50 mg – 70 mg – 100 mg; aprobado por Certificado N° 53.316.

Que las actividades de importación, comercialización y depósito en jurisdicción nacional o con destino al comercio interprovincial de especialidades medicinales se encuentran referidas por la Ley 16.463 y los Decretos Nros. 9763/64, 150/92 y sus modificaciones 1890/92 y 177/93; y la Disposición N° 262/95.

Que el producto habrá de elaborarse alternativamente en CANADA, siendo dicha Especialidad Medicinal elaborada alternativamente en: PATHEON INC., 2100 Syntex Court, Mississauga Ontario L5N 7K9, Canadá (Elaboración del granel).

Que la empresa solicitante se encuentra habilitada como importadora de especialidades medicinales por esta Administración Nacional.

Que la Dirección de Evaluación y Registro de Medicamentos ha tomado la intervención de su competencia.

Que la Dirección de Asuntos Jurídicos ha tomado la intervención de su competencia.

Que se actúa en virtud de las facultades conferidas por el Decreto N° 1490/92 y sus modificatorios.

Por ello;

EL ADMINISTRADOR NACIONAL DE LA ADMINISTRACIÓN NACIONAL DE
MEDICAMENTOS, ALIMENTOS Y TECNOLOGÍA MÉDICA

DISPONE:

ARTICULO 1°.- Autorízase a la firma BRISTOL MYERS SQUIBB ARGENTINA S.R.L., representante en Argentina de BRISTOL MYERS SQUIBB CO., el nuevo elaborador alternativo para la Especialidad Medicinal denominada SPRYCEL / DASATINIB, Forma Farmacéutica y Concentración: COMPRIMIDOS RECUBIERTOS, DASATINIB (COMO MONOHIDRATO) 20 mg – 50 mg – 70 mg – 100 mg; la que en lo sucesivo se elaborará alternativamente en: PATHEON INC., 2100 Syntex Court, Mississauga Ontario L5N 7K9, Canadá (Elaboración del granel).

ARTICULO 2°.- Autorízase a la firma BRISTOL MYERS SQUIBB ARGENTINA S.R.L., representante en Argentina de BRISTOL MYERS SQUIBB CO., propietaria de la Especialidad Medicinal mencionada en el artículo anterior, el nuevo país de origen alternativo que en lo sucesivo será: CANADA, además de los aprobados anteriormente.

ARTICULO 3°.- Los textos de rótulos y prospectos no se modifican de acuerdo a lo expresado en carácter de Declaración Jurada por el solicitante a fojas 14 del documento IF-2022-07727460-APN-DERM#ANMAT.

ARTICULO 4°.- Practíquese la atestación correspondiente en el Certificado N° 53.316 cuando el mismo se presente acompañado de la copia de la presente disposición.

ARTICULO 5°.- Regístrese, por mesa de entradas notifíquese al interesado, haciéndole entrega de la presente disposición, gírese a la Dirección de Gestión de Información Técnica a los fines de adjuntar al legajo correspondiente, Cumplido, Archívese.

EX-2021-113811371-APN-DGA#ANMAT

Jfs

rl

Buenos Aires, Enero 2022

A la
Administración Nacional de
Medicamentos, Alimentos y
Tecnología Médica
A.N.M.A.T.
Atte.: DERM

Ref.: EX-2021-113811371-APN-DGA#ANMAT
Respuesta a corte de plazo

De nuestra consideración:

En representación de Bristol-Myers Squibb Argentina S.R.L., con domicilio legal en Av. Libertador 101, piso 6°, Vicente López, Prov. de Bs. As., CUIT N° 30-53805805-6, nos dirigimos respetuosamente a las Autoridades de ANMAT para responder al corte de plazo del día 17 de Diciembre de 2021.

A tal efecto, se adjunta

- Formulario NPOA 5.1
- Declaración Jurada respecto al contenido de rótulos y prospectos
- Nuevas copias de los CPPs para las cuatro presentaciones

Se desea aclarar que este trámite corresponde a la inclusión de un sitio elaborador de producto terminado alternativo y que se mantienen los sitios de elaboración aprobados hasta el momento:

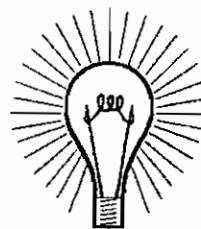
- Laboratorio elaborador y acondicionador de producto terminado
AstraZeneca Pharmaceuticals LP, 4601 Highway 62 East, Mount Vernon, Indiana,
47620, Estados Unidos
- Laboratorio acondicionador (primario y secundario)
AndersonBrecon Inc., 4545 Assembly Drive, Rockford, IL 61109, Estados Unidos

Sin otro particular, saludamos a las Autoridades de la ANMAT con nuestra consideración más distinguida.

**Alejandra
Viceconte**

Digitally signed by Alejandra
Viceconte
DN: cn=Alejandra Viceconte,
o=Bristol Myers Squibb
Argentina S.R.L, ou=Asuntos
Regulatorios- Apoderada,
email=alejandra.viceconte@bms.
com, c=AR
Date: 2022.01.24 17:57:06 -03'00'

Formulario NPOA 5.1



NOMBRE DEL PRODUCTO:

TITULAR:

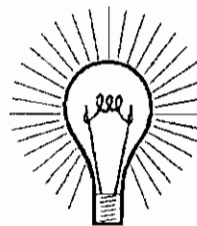
RESERVADO
 A.N.M.A.T.

ÍNDICE DE LA PRESENTACIÓN

TEMA - DOCUMENTO

Página

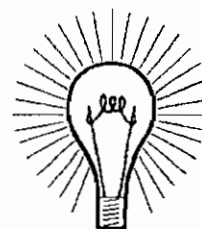
| | | |
|-------|---|--|
| 1. | Datos del solicitante. | |
| 1.1. | Carácter. | |
| 1.2. | Datos del titular. | |
| 2. | Dirección técnica. | |
| 3. | Representante legal. | |
| 4. | Datos del producto. | |
| 4.1. | Datos del titular del certificado. | |
| 4.2. | Nombre. | |
| 4.3. | Clasificación farmacológica. | |
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| 4.8. | Nuevo país de procedencia autorizado. | |
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NOMBRE DEL PRODUCTO:

TITULAR:

| RESERVADO A.N.M.A.T. | | ÍNDICE DE LA PRESENTACIÓN TEMA - DOCUMENTO | | Página |
|-------------------------|--|--|--|--------|
| | | DOCUMENTACIÓN A PRESENTAR SEGÚN DISPOSICIÓN Nº 262/95. (Ver Cuadro explicativo para los distintos casos. Página siguiente) | | |
| A | | Declaración jurada de que el contenido de rótulos y prospectos es idéntico al de los actualmente autorizados. | | |
| B | | Evidencias de comercialización del producto elaborado en el país origen alternativo. (Estuches y prospectos originales) | | |
| C | | Copia autenticada del Certificado de Inscripción al Registro de Especialidades Medicinales. | | |
| D | | Declaración jurada de que los métodos de elaboración y control, y el periodo de vida útil son idénticos a los actualmente autorizados. | | |
| E | | Aprobación de la planta elaboradora en el país de origen alternativo, por la autoridad sanitaria del país de Anexo I o la Secretaría de Salud de la Argentina. | | |
| F | | Copia autenticada del certificado de habilitación como importador. | | |
| G | | Método de elaboración. | | |
| H | | Métodos de control | | |
| I | | Estudio de estabilidad. | | |
| J | | Copia autenticada del certificado de habilitación del Establecimiento. | | |
| K | | Evidencias de comercialización en por lo menos un país del Anexo I del producto elaborado en el país de origen alternativo. | | |
| L | | Copia autenticada y consularizada del certificado de país de origen. | | |



REQUERIMIENTOS DE ORDEN LEGAL EN LA PRESENTACIÓN DE LA DOCUMENTACIÓN

1) CONTRATO.

Contrato o nota suscripta por las partes, con certificación de firmas y autenticadas o con acreditación de la personería de los intervinientes y las copias autenticadas. Debe figurar explícitamente la etapa de la elaboración y/o control de calidad en la que interviene.

2) FORMA EN QUE LOS ADMINISTRADOS DEBERÁN ACREDITAR LA PERSONERÍA.

Sociedad Anónima y Cooperativa:

- a) Estatuto Social, cuyo objeto la faculte para el acto que pretende realizar.
- b) Acta de Designación de Autoridades, que acredite el cargo del firmante de la solicitud.

Sociedad de Responsabilidad Limitada y Sociedad en Comandita por Acciones:

- a) Estatuto Social, cuyo objeto social la faculte para el acto que pretende realizar; y de donde surge la personería del firmante de la solicitud.

Sociedad de Hecho:

- a) La presentación deberá ser suscripta por todos los socios o por apoderado de los mismos, acreditando su identidad.

Personas Individuales:

Deberán suscribir en forma individual la presentación, acreditando su identidad.

Apoderados:

Toda persona física o jurídica puede ser representada por el apoderado, siempre que se cumplan los siguientes requisitos: Poder otorgado ante Escribano Público o de alguna de las formas previstas por los art. 31, 32 y 33 del Decreto 1759/72 (modificado por el 1833/91), reglamentario de la Ley de Procedimientos Administrativos, declarando el apoderado que el mismo se encuentra vigente y donde conste las facultades del poderdante para otorgar el mando.


3) REQUISITOS DE LOS DOCUMENTOS AGREGADOS.

a) Todos los documentos que se presenten, deberán presentarse en idioma castellano o traducidos por Traductor Público Nacional, debidamente legalizados por el Colegio de Traductores.

b) Los documentos de origen extranjero, deberán ser legalizados por el Cónsul argentino y por el Ministerio de Relaciones Exteriores, salvo cuando provienen de países signatarios de la Convención de la Haya, identificados por la correspondiente apostilla (Ley 23.458).

c) Los documentos deberán estar legalizados y acreditarse la personería de todos los contratantes certificadas sus firmas.

4) TODOS LOS DOCUMENTOS MENCIONADOS PRECEDENTEMENTE DEBERÁN SER PRESENTADOS EN ORIGINAL O COPIA DEBIDAMENTE AUTENTICADA.

| | | | |
|--|--|--|---|
| ANMAT ADMINISTRACIÓN NACIONAL DE MEDICAMENTOS, ALIMENTOS Y TECNOLOGÍA MÉDICA | REGISTRO DE ESPECIALIDADES MEDICINALES REM | FORMULARIO N° <div style="border: 1px solid black; padding: 5px; display: inline-block;"> 5.1 </div> |  |
| | NUEVO PAÍS DE ORIGEN ALTERNATIVO NPOA | | |

**CUADRO EXPLICATIVO PARA LOS CASOS POSIBLES
CORRESPONDIENTES AL FORMULARIO 5.1.
(DISPOSICIÓN 262/95)**

| DISP. 262/95 | DE | A | ENCUADRE ACTUAL | ENCUADRE SOLICITADO | DOCUMENTACIÓN A PRESENTAR ITEMS DEL ÍNDICE: |
|-----------------|------------------------------|------------------------------|--------------------|------------------------|---|
| ART. 1° | ANEXO II | ANEXO I | 2.2 | 2.3 | A, C, K |
| | ANEXO I | ANEXO I | 2.3 | 2.3 | |
| | NO ANEXO I NO ANEXO II | ANEXO I | 2.6 | 2.3 | |
| ART. 2° | NO ANEXO I NO ANEXO II | ANEXO II | 2.6 | 2.2 | A, B, C, D, E |
| | ANEXO II | ANEXO II | 2.6 | 2.6 | |
| ART. 4° | ANEXO II (art. 5°) | ANEXO II (art. 5°) | 2.5 | 2.5 | A, C, D, E |
| | NO ANEXO I NO ANEXO II | ANEXO II (art. 5°) | 2.6 | 2.5 | |
| | ANEXO II (art. 3° inc. e) | NO ANEXO I NO ANEXO II | 2.2 | 2.6 | |
| | ANEXO II (art. 5°) | NO ANEXO I NO ANEXO II | 2.5 | 2.6 | |
| | NO ANEXO I NO ANEXO II | NO ANEXO I NO ANEXO II | 2.6 | 2.6 | |
| ART. 5° | ANEXO II (art. 3° inc. e) | ARGENTINA (art. 3°) | 2.2 | 2.1 | A, C, D, J |
| | NO ANEXO I NO ANEXO II | ARGENTINA (art. 3°) | 2.6 | 2.1 | |
| | ANEXO II (art. 5°) | ARGENTINA (art. 5°) | 2.5 | 2.4 | |
| | NO ANEXO I NO ANEXO II | ARGENTINA (art. 5°) | 2.6 | 2.4 | |
| ART. 7° | ARGENTINA (art. 3°) | ANEXO I (art. 4°) | 2.1 | 2.3 | A, C, F, K |
| ART. 8° | ARGENTINA | ANEXO II (art. 3° inc. e) | 2.1 | 2.2 | A, C, D, E, F, L |
| | ARGENTINA (art. 5°) | ANEXO II (art. 5°) | 2.4 | 2.5 | |
| | ARGENTINA (art. 3°) | NO ANEXO I NO ANEXO II | 2.1 | 2.6 | |
| | ARGENTINA (art. 5°) | NO ANEXO I NO ANEXO II | 2.4 | 2.6 | |

**SE PODRÁ SOLICITAR EN EL MISMO FORMULARIO MAS DE UN
NUEVO PAÍS DE ORIGEN (HASTA TRES), DEBIÉNDOSE EN CADA
CASO PAGAR EL ARANCEL Y PRESENTAR LA DOCUMENTACIÓN
CORRESPONDIENTE.**

ANMAT
ADMINISTRACIÓN
NACIONAL DE
MEDICAMENTOS,
ALIMENTOS Y
TECNOLOGÍA MÉDICA

REGISTRO DE ESPECIALIDADES MEDICINALES

REM

NUEVO PAÍS DE ORIGEN ALTERNATIVO

NPOA

FORMULARIO

Nº

5.1



OBJETO: Solicitud de autorización para importar una especialidad medicinal de un país de origen alternativo al que figura inscripto en el Registro.

CORRESPONDE A LA DISPOSICIÓN Nº 262/95

1. DATOS DEL SOLICITANTE.

1.1. Carácter (Laboratorio, farmacia, droguería, Organismo público de salud, Obra Social, representante de empresa extranjera).

Representante de Empresa Extranjera

1.2. Datos del titular:

1.2.1. Nombre: Bristol Myers Squibb Argentina S.R.L representante de Bristol Myers Squibb Co.

1.2.2. Número de legajo: 7206

1.2.3. Número de expediente de habilitación: 1-47-16659-16-1

1.2.4. Domicilio legal:

1.2.4.1. Dirección: Provincia: Buenos Aires

Calle y número: Av. del Libertador 101

Localidad: Vicente Lopez Código Postal: B1638BEA

1.2.4.2. Teléfono: 51988400

Fax:

2. DIRECCIÓN TÉCNICA.

2.1. Datos del profesional farmacéutico a cargo de la Dirección Técnica:

2.1.1. Apellido y nombre: Pugliarello Calvo, Adriana Paula

2.1.2. Documento de Identidad Nº: 21.464.555

2.1.3. Número de matrícula: 12.153

2.1.4. Expediente de autorización Nº: 1-0047-0000-111-06-4

2.2. Datos del profesional farmacéutico a cargo de la Codirección Técnica:

2.2.1. Apellido y nombre: Marquez Adolfo

2.2.2. Documento de Identidad Nº: 17.656.563

2.2.3. Número de matrícula: 12.171

2.2.4. Expediente de autorización Nº: 1-0047-0000-1208-06-7

3. REPRESENTANTE LEGAL (Apoderado).

3.1. Apellido y nombre: Viceconte, Alejandra

3.2. Expediente de autorización Nº:

3.3. Documento de Identidad Nº: 33.203.159



4. DATOS DEL PRODUCTO.

4.1. Datos del titular del certificado:

4.1.1. Nombre:

4.1.2. Domicilio legal:

4.1.3. Dirección: País:

Calle y número:

Localidad: Código Postal:

Teléfono:

Fax:

4.2. Nombre:

4.2.1. Comercial o de marca:

4.2.2. Genérico:

4.3. Clasificación farmacológica:

4.4. Código ATC (aplicación terapéutica):

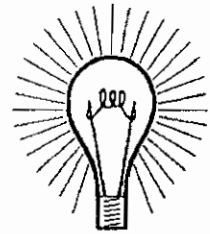
4.5. Principios activos:

4.5.1. Nombre genérico:

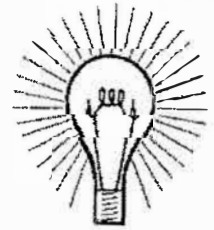
4.5.2. Concentración:

4.5.3. Código OPS:

| | | |
|--|-------------------------------------|----------------------|
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| <input type="text" value="Dasatinib"/> | <input type="text" value="50 mg"/> | <input type="text"/> |
| <input type="text" value="Dasatinib"/> | <input type="text" value="70 mg"/> | <input type="text"/> |
| <input type="text" value="Dasatinib"/> | <input type="text" value="100 mg"/> | <input type="text"/> |
| <input type="text"/> | <input type="text"/> | <input type="text"/> |
| <input type="text"/> | <input type="text"/> | <input type="text"/> |



| | |
|---|-------------------------|
| 4.6. País de procedencia autorizado: | Estados Unidos |
| 4.7. País de origen autorizado: | Estados Unidos |
| 4.8. Nuevo país de procedencia solicitado: | Estados Unidos |
| 4.9. Nuevo país de origen solicitado: | Estados Unidos - Canadá |
| 4.10. Datos del nuevo laboratorio elaborador solicitado: | |
| 4.10.1. País de origen: | Canadá |
| 4.10.2. Dirección: País: | Canadá |
| Calle y número: | 2100 Syntex Court |
| Localidad: | Mississauga, Ontario |
| Código Postal: | L5N 7K9 |
| Teléfono: | |
| Fax: | |
| 4.8'. Nuevo país de procedencia solicitado: | |
| 4.9'. Nuevo país de origen solicitado: | |
| 4.10'. Datos del nuevo laboratorio elaborador solicitado: | |
| 4.10.1'. País de origen: | |
| 4.10.2'. Dirección: País: | |
| Calle y número: | |
| Localidad: | |
| Código Postal: | |
| Teléfono: | |
| Fax: | |
| 4.8''. Nuevo país de procedencia solicitado: | |
| 4.9''. Nuevo país de origen solicitado: | |
| 4.10''. Datos del nuevo laboratorio elaborador solicitado: | |
| 4.10.1''. País de origen: | |
| 4.10.2''. Dirección: País: | |
| Calle y número: | |
| Localidad: | |
| Código Postal: | |
| Teléfono: | |
| Fax: | |



4.11. Participación de terceros.

4.11.1. Empresas participantes en la preparación del medicamento hasta el granel (1):

Etapa A:

Nombre de la Razón Social:

Certificado de habilitación MSAS Nº:

Nombre Director Técnico:

Domicilio:

Teléfono: **Fax:**

Provincia: **Código Postal:**

Etapa B:

Nombre de la Razón Social:

Certificado de habilitación MSAS Nº:

Nombre Director Técnico:

Domicilio:

Teléfono: **Fax:**

Provincia: **Código Postal:**

Etapa C:

Nombre de la Razón Social:

Certificado de habilitación MSAS Nº:

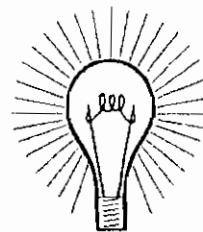
Nombre Director Técnico:

Domicilio:

Teléfono: **Fax:**

Provincia: **Código Postal:**

(1): Indicar separadamente etapas mecánicas y procesos intermedios



4.11.2. Control analítico del granel (2):

Etapa A:

Nombre de la Razón Social:

Certificado de habilitación MSAS N°:

Nombre Director Técnico:

Domicilio:

Teléfono: **Fax:**

Provincia: **Código Postal:**

Etapa B:

Nombre de la Razón Social:

Certificado de habilitación MSAS N°:

Nombre Director Técnico:

Domicilio:

Teléfono: **Fax:**

Provincia: **Código Postal:**

Etapa C:

Nombre de la Razón Social:

Certificado de habilitación MSAS N°:

Nombre Director Técnico:

Domicilio:

Teléfono: **Fax:**

Provincia: **Código Postal:**

(2): Indicar separadamente métodos especializados

4.11.3. Fraccionamiento y envasado:

Etapa A:

Nombre de la Razón Social:

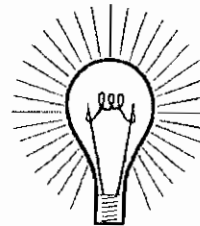
Certificado de habilitación MSAS N°:

Nombre Director Técnico:

Domicilio:

Teléfono: **Fax:**

Provincia: **Código Postal:**



Etapa B:
Nombre de la Razón Social:
Certificado de habilitación MSAS Nº:
Nombre Director Técnico:
Domicilio:
Teléfono: **Fax:**
Provincia: **Código Postal:**

Etapa C:
Nombre de la Razón Social:
Certificado de habilitación MSAS Nº:
Nombre Director Técnico:
Domicilio:
Teléfono: **Fax:**
Provincia: **Código Postal:**

4.11.4. Control del producto terminado (3):

Etapa A:
Nombre de la Razón Social:
Certificado de habilitación MSAS Nº:
Nombre Director Técnico:
Domicilio:
Teléfono: **Fax:**
Provincia: **Código Postal:**

Etapa B:
Nombre de la Razón Social:
Certificado de habilitación MSAS Nº:
Nombre Director Técnico:
Domicilio:
Teléfono: **Fax:**
Provincia: **Código Postal:**

Etapa C:
Nombre de la Razón Social:
Certificado de habilitación MSAS Nº:
Nombre Director Técnico:
Domicilio:
Teléfono: **Fax:**
Provincia: **Código Postal:**

(3): Indicar separadamente métodos especializados

Declaración Jurada

Buenos Aires, Enero de 2022

DECLARACION JURADA

Se informa que el cambio solicitado no impacta en el contenido médico de los rótulos y prospectos.

**Alejandra
Viceconte**

Digitally signed by Alejandra
Viceconte
DN: cn=Alejandra Viceconte,
o=Bristol Myers Squibb
Argentina S.R.L, ou=Asuntos
Regulatorios- Apoderada,
email=alejandra.viceconte@bms.
com, c=AR
Date: 2022.01.24 17:57:58 -03'00'

CPP Sprycel 20 mg

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country: *United States of America*

This public document

2. has been signed by Carole Jones

3. acting in the capacity of Division Director, Exports Compliance Branch

4. bears the seal/stamp of U. S. Department of Health and Human Services

Certified

5. at Washington, D.C.

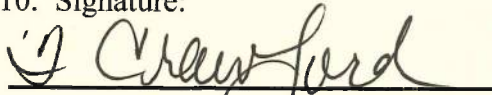
6. the thirtieth of October, 2021

7. by *Assistant Authentication Officer, United States Department of State*

8. No. 22003824-16

9. Seal/Stamp:

10. Signature:



Fernesia T. Crawford

United States Food and Drug Administration
Center for Drug Evaluation and Research

10903 New Hampshire Ave, Silver Spring, MD 20993, United States of America
CDERExportCertificateProgram@fda.hhs.gov - Telephone (301) 796-4950

Certificate of a Pharmaceutical Product - Foreign Manufacturer

Certificate Number: **3BR4-8GY9**

Certificate Issue Date: September 30, 2021

Certificate Expiration Date: September 29, 2023

Importing Country: **ARGENTINA**
Exporting Country: **UNITED STATES OF AMERICA**

1. Drug Trade Name, International or National non-proprietary name (as applicable) & dosage form: **SPRYCEL @, Tablet**

1.1 Active Ingredient(s) and amount(s) per unit dose (complete quantitative composition is preferred): **dasatinib 20 MG**

1.2 Is this product licensed to be placed on the market for use in the exporting country? **Yes**

1.3 Is this product actually on the market in the exporting country? **Yes**

2.A.1 Product license number & date of issue: **021986 06/28/2006**

2.A.2 Product license holder name & address: **Bristol-Myers Squibb Company, PO Box 4000, Princeton, NJ 08543 United States of America**

2.A.3 Status of Product license holder: **Neither**

2.A.3.1 Manufacturer name & address: **Patheon Inc., 2100 Syntex Court, Mississauga, Ontario L5N 7K9 CANADA**

2.A.4 Is a summary basis for approval appended? **No**

2.A.5 Is the attached product information, complete and consonant with the license? **Yes**

2.A.6 Applicant name & address for certificate (if different from the license holder): **Bristol Myers Squibb, 4931 George Road, Tampa, FL 33634 United States of America**

2.B.4 Remarks: **Package: AndersonBrecon Inc., 4545 Assembly Drive, Rockford, IL 61109**
This FDA certification pertains to the product marketed in the United States of America.

3. Does the certifying authority arrange for periodic inspection of the manufacturing plant in which the dosage form is produced? **Yes**

3.1 Periodicity of routine inspections (years): **Pursuant to section 510(b)(3) of the Federal Food, Drug & Cosmetic Act, Inspections will occur in accordance with a risk-based schedule**

3.2 Has the manufacture of this type of dosage form been inspected? **Yes**

3.3 Do the facilities and operations conform to GMPs as recommended by the WHO? (GMPs including 21 Code of Federal Regulations parts 210, 211, or ICH Q7A). **Yes, at time of inspection, site complies with FDA cGMP**

3.4 Does the information submitted by the applicant satisfy the certifying authority on all aspects of the manufacture of the product undertaken by another party? **Yes**

Carole Jones

Carole Jones, Division Director
Exports Compliance Branch
Division of Global Drug Distribution and Policy
FDA, Center for Drug Evaluation and Research



3 9 4 1 9 0 1 X X 1 3 8 6 8 1 A 0

Distributed by:
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

60 Tablets NDC 0003-0527-11

SPRYCEL[®]
(dasatinib)
Tablets

20
mg

Rx only

Do not crush, cut or chew tablets.
Swallow tablets whole.



Bristol-Myers Squibb

Each film-coated tablet contains 20 mg dasatinib.
Usual Dosage: See package insert for dosing instructions,
directions for use, and precautions.
Store at 20°C to 25°C (68°F to 77°F); excursions
permitted between 15°C and 30°C (59°F and 86°F)
(see USP Controlled Room Temperature).

Do not use if inner seal of bottle is broken or missing.



For Position Only

3 0000 0000 00 0




60 Tablets NDC 0003-0527-11

SPRYCEL[®]
(dasatinib)
Tablets

**20
mg**

Rx only

Do not crush, cut or chew tablets.
Swallow tablets whole.

 Bristol-Myers Squibb



Do not use if inner seal of bottle
is broken or missing.

Distributed by:
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

1408223


60 Tablets NDC 0003-0527-11

SPRYCEL[®]
(dasatinib)
Tablets

**20
mg**

Rx only

Do not crush, cut or chew tablets.
Swallow tablets whole.

 Bristol-Myers Squibb

Each film-coated tablet
contains 20 mg dasatinib.
Usual Dosage: See package
insert for dosing instructions,
directions for use, and
precautions.

Store at 20° C to 25° C
(68° F to 77° F); excursions
permitted between
15° C and 30° C
(59° F and 86° F) [see USP
Controlled Room Temperature].

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SPRYCEL[®] safely and effectively. See full prescribing information for SPRYCEL.

SPRYCEL (dasatinib) tablets, for oral use

Initial U.S. Approval: 2006

RECENT MAJOR CHANGES
Warnings and Precautions (5.4) 6/2021
Warnings and Precautions (5.9) 6/2021

INDICATIONS AND USAGE

- newly diagnosed adult with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase, (1, 14)
- adults with chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy including imatinib, (1, 14)
- adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) with resistance or intolerance to prior therapy, (1, 14)
- pediatric patients 1 year of age and older with Ph+ CML in chronic phase, (1, 14)
- pediatric patients 1 year of age and older with newly diagnosed Ph+ ALL in combination with chemotherapy, (1, 14)

DOSE AND ADMINISTRATION

- Chronic phase CML in adults: 100 mg once daily, (2)
- Accelerated phase CML, myeloid or lymphoid blast phase CML, or Ph+ ALL in adults: 140 mg once daily, (2)
- Chronic phase CML and ALL in pediatric patients: starting dose based on body weight, (2)
- Administer orally, with or without a meal. Do not crush, cut, or chew tablets, (2)

DOSE FORMS AND STRENGTHS

Tablets: 20 mg, 50 mg, 70 mg, 80 mg, 100 mg, and 140 mg, (3)

CONTRAINDICATIONS

None, (4)

WARNINGS AND PRECAUTIONS

- Myelosuppression and Bleeding Events:** Severe thrombocytopenia, neutropenia, and anemia may occur. Use caution if used concomitantly with medications that inhibit platelet function or anticoagulants. Monitor complete blood counts regularly. Transfuse and interrupt SPRYCEL when indicated, (2.5, 5.1, 5.3)
- Fluid Retention:** Fluid retention, sometimes severe, including pleural effusion. Manage with supportive care measures and/or dose modification, (2.5, 5.3)

FULL PRESCRIBING INFORMATION: CONTENTS*

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6 ADVERSE REACTIONS

- Cardiovascular Toxicity:** Monitor patients for signs or symptoms and treat appropriately, (5.4)
- Pulmonary Arterial Hypertension (PAH):** SPRYCEL may increase the risk of developing PAH which may be reversible on discontinuation. Consider baseline risk and evaluate patients for signs and symptoms of PAH during treatment. Stop SPRYCEL if PAH is confirmed, (5.5)
- QT Prolongation:** Use SPRYCEL with caution in patients who have or may develop prolongation of the QT interval, (5.6)
- Severe Dermatologic Reactions:** Individual cases of severe mucocutaneous dermatologic reactions have been reported, (5.7)
- Tumor Lysis Syndrome:** Tumor lysis syndrome has been reported. Maintain adequate hydration and correct uric acid levels prior to initiating therapy with SPRYCEL, (5.8)
- Embryo-Fetal Toxicity:** Can cause fetal harm. Advise patients of reproductive potential of potential risk to fetus and to use effective contraception, (5.9, 8.1, 8.3)
- Effects on Growth and Development in Pediatric Patients:** epiphyseal delayed fusion, osteopenia, growth retardation, and gynecomastia have been reported. Monitor bone growth and development in pediatric patients, (5.10)

ADVERSE REACTIONS

Most common adverse reactions (≥15%) in patients receiving SPRYCEL as single-agent therapy included myelosuppression, fluid retention events, diarrhea, headache, skin rash, hemorrhage, dyspnea, fatigue, nausea, and musculoskeletal pain, (6)
Most common adverse reactions (≥10%) in pediatric patients receiving SPRYCEL in combination with chemotherapy included mucositis, febrile neutropenia, pyrexia, diarrhea, nausea, vomiting, musculoskeletal pain, abdominal pain, cough, headache, rash, fatigue, constipation, anemia, hypertension, edema, infections (bacterial, viral and fungal), hypotension, decreased appetite, hypersensitivity, dyspnea, epistaxis, peripheral neuropathy, and altered state of consciousness, (6)

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5972 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Strong CYP3A4 Inhibitors:** Dose reduction may be necessary, (2.3, 7.1)
- Strong CYP3A4 Inducers:** Dose increase may be necessary, (2.3, 7.1)
- Antacids:** Avoid simultaneous administration, (7.1)
- H₂ Antagonists and Proton Pump Inhibitors:** Avoid coadministration, (7.1)

USE IN SPECIFIC POPULATIONS

- Lactation:** Advise women not to breastfeed, (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 6/2021

- 15 REFERENCES
- 16 HOW SUPPLIED/STORAGE AND HANDLING
- 17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

SPRYCEL (dasatinib) is indicated for the treatment of adult patients with

- newly diagnosed Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase,
- chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy including imatinib,
- Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) with resistance or intolerance to prior therapy.

SPRYCEL (dasatinib) is indicated for the treatment of pediatric patients 1 year of age and older with

- Ph+ CML in chronic phase,
- newly diagnosed Ph+ ALL in combination with chemotherapy.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage of SPRYCEL in Adult Patients

The recommended starting dosage of SPRYCEL for chronic phase CML in adults, is 100 mg administered orally once daily. The recommended starting dosage of SPRYCEL for accelerated phase CML, myeloid or lymphoid blast phase CML, or Ph+ ALL in adults is 140 mg administered orally once daily. Tablets should not be crushed, cut, or chewed; they should be swallowed whole. SPRYCEL can be taken with or without a meal, either in the morning or in the evening.

2.2 Dosage of SPRYCEL in Pediatric Patients with CML or Ph+ ALL

The recommended starting dosage for pediatrics is based on body weight as shown in Table 1. The recommended dose should be administered orally once daily with or without food. Recalculate the dose every 3 months based on changes in body weight, or more often if necessary.

Do not crush, cut or chew tablets. Swallow tablets whole. There are additional administration considerations for pediatric patients who have difficulty swallowing tablets whole [see *Use in Specific Populations* (8.4) and *Clinical Pharmacology* (12.3)].

Table 1: Dosage of SPRYCEL for Pediatric Patients^a

| Body Weight (kg) ^b | Daily Dose (mg) |
|-------------------------------|-----------------|
| 10 to less than 20 | 40 mg |
| 20 to less than 30 | 60 mg |
| 30 to less than 45 | 70 mg |
| at least 45 | 100 mg |

^a For pediatric patients with Ph+ ALL, begin SPRYCEL therapy on or before day 15 of induction chemotherapy, when diagnosis is confirmed and continue for 2 years.

^b Tablet dosing is not recommended for patients weighing less than 10 kg.

Refer to Section 2.4 for recommendations on dose escalation in adults with CML and Ph+ ALL, and pediatric patients with CML.

2.3 Dose Modification

Strong CYP3A4 Inducers

Avoid the use of concomitant strong CYP3A4 inducers and St. John's wort. If patients must be coadministered a strong CYP3A4 inducer, consider a SPRYCEL dose increase. If the dose of SPRYCEL is increased, monitor the patient carefully for toxicity [see *Drug Interactions* (7.1)].

Strong CYP3A4 Inhibitors

Avoid the use of concomitant strong CYP3A4 inhibitors and grapefruit juice. Recommend selecting an alternate concomitant medication with no or minimal enzyme inhibition potential, if possible. If SPRYCEL must be administered with a strong CYP3A4 inhibitor, consider a dose decrease to:

- 40 mg daily for patients taking SPRYCEL 140 mg daily,
- 20 mg daily for patients taking SPRYCEL 100 mg daily,
- 20 mg daily for patients taking SPRYCEL 70 mg daily.

For patients taking SPRYCEL 60 mg or 40 mg daily, consider interrupting SPRYCEL until the inhibitor is discontinued. Allow a washout period of approximately 1 week after the inhibitor is stopped before reinitiating SPRYCEL.

These reduced doses of SPRYCEL are predicted to adjust the area under the curve (AUC) to the range observed without CYP3A4 inhibitors; however, clinical data are not available with these dose adjustments in patients receiving strong CYP3A4 inhibitors. If SPRYCEL is not tolerated after dose reduction, either discontinue the strong CYP3A4 inhibitor or interrupt SPRYCEL until the inhibitor is discontinued. Allow a washout period of approximately 1 week after the inhibitor is stopped before the SPRYCEL dose is increased [see *Drug Interactions* (7.1)].

2.4 Dose Escalation in Adults with CML and Ph+ ALL, and Pediatric Patients with CML

For adult patients with CML and Ph+ ALL, consider dose escalation to 140 mg once daily (chronic phase CML) or 180 mg once daily (advanced phase CML and Ph+ ALL) in patients who do not achieve a hematologic or cytogenetic response at the recommended starting dosage. For pediatric patients with CML, consider dose escalation to 120 mg once daily (see Table 2 below) if escalation is not recommended for pediatric patients with Ph+ ALL, where SPRYCEL is administered in combination with chemotherapy.

Escalate the SPRYCEL dose as shown in Table 2 in pediatric patients with chronic phase CML who do not achieve a hematologic or cytogenetic response at the recommended starting dosage.

Table 2: Dose Escalation for Pediatric CML

| Formulation | Dose (maximum dose per day) |
|-------------|-----------------------------|
| | Starting Dose |
| Tablets | 40 mg |
| | 60 mg |
| | 70 mg |
| | 100 mg |

2.5 Dose Adjustment for Adverse Reactions

Myelosuppression

In clinical studies, myelosuppression was managed by dose interruption, dose reduction, or discontinuation of study therapy. Hematopoietic growth factor has been used in patients with resistant myelosuppression. Guidelines for dose modifications for adult and pediatric patients are summarized in Tables 3 and 4, respectively.

Table 3: Dose Adjustments for Neutropenia and Thrombocytopenia in Adults

| Phase | Criteria | Adjustment |
|---|--|--|
| Chronic Phase CML (starting dose 100 mg once daily) | ANC* <0.5 × 10 ⁹ /L or Platelets <50 × 10 ⁹ /L | 1. Stop SPRYCEL until ANC ≥1.0 × 10 ⁹ /L and platelets ≥50 × 10 ⁹ /L. |
| | | 2. Resume treatment with SPRYCEL at the original starting dose if recovery occurs in ≤7 days. |
| | | 3. If platelets <25 × 10 ⁹ /L or recurrence of ANC <0.5 × 10 ⁹ /L for >7 days, repeat Step 1 and resume SPRYCEL at a reduced dose of 80 mg once daily for second episode. For third episode, further reduce dose to 50 mg once daily (for newly diagnosed patients) or discontinue SPRYCEL (for patients resistant or intolerant to prior therapy including imatinib). |
| Accelerated Phase CML, Blast Phase CML, and Ph+ ALL (starting dose 140 mg once daily) | ANC* <0.5 × 10 ⁹ /L or Platelets <10 × 10 ⁹ /L | 1. Check if cytopenia is related to leukemia (marrow aspirate or biopsy). |
| | | 2. If cytopenia is unrelated to leukemia, stop SPRYCEL until ANC ≥1.0 × 10 ⁹ /L and platelets ≥20 × 10 ⁹ /L and resume at the original starting dose. |
| | | 3. If recurrence of cytopenia, repeat Step 1 and resume SPRYCEL at a reduced dose of 100 mg once daily (second episode) or 80 mg once daily (third episode). |
| | | 4. If cytopenia is related to leukemia, consider dose escalation to 180 mg once daily. |

*ANC, absolute neutrophil count

Table 4: Dose Adjustments for Neutropenia and Thrombocytopenia in Pediatric Patients with Ph+ CML

| | Dose (maximum dose per day) | | |
|---|-----------------------------|--------------------------|--------------------------|
| | Original Starting Dose | One-Level Dose Reduction | Two-Level Dose Reduction |
| 1. If cytopenia persists for more than 3 weeks, check if cytopenia is related to leukemia (marrow aspirate or biopsy). | Tablets 40 mg | 20 mg | ** |
| | 60 mg | 40 mg | 20 mg |
| | 70 mg | 60 mg | 50 mg |
| 2. If cytopenia is unrelated to leukemia, stop SPRYCEL until ANC* ≥1.0 × 10 ⁹ /L and platelets ≥75 × 10 ⁹ /L and resume at the original starting dose or at a reduced dose. | 100 mg | 80 mg | 70 mg |
| | | | |
| 3. If cytopenia recurs, repeat marrow aspirate/biopsy and resume SPRYCEL at a reduced dose. | | | |

*ANC, absolute neutrophil count
** lower tablet dose not available

For pediatric patients with chronic phase CML, if Grade ≥3 neutropenia or thrombocytopenia recurs during complete hematologic response (CHR), interrupt SPRYCEL and resume at a reduced dose. Implement temporary dose reductions for intermediate degrees of cytopenia and disease response as needed.

For pediatric patients with Ph+ ALL, if neutropenia and/or thrombocytopenia result in a delay of the next block of treatment by more than 14 days, interrupt SPRYCEL and resume at the same dose level once the next block of treatment is started. If neutropenia and/or thrombocytopenia persist and the next block of treatment is delayed another 7 days, perform a bone marrow assessment to assess cellularity and percentage of blasts. If marrow cellularity is <10%, interrupt treatment with SPRYCEL until ANC >500/μL (0.5 × 10⁹/L), at which time treatment may be resumed at full dose. If marrow cellularity is >10%, resumption of treatment with SPRYCEL may be considered.

Non-Hematologic Adverse Reactions

For adults with Ph+ CML and ALL, and pediatric patients with Ph+ CML, if a severe non-hematologic adverse reaction develops with SPRYCEL use, treatment must be withheld until the

event has resolved or improved. Thereafter, treatment can be resumed as appropriate at a reduced dose depending on the severity and recurrence of the event [see Warnings and Precautions (5.1)].

For pediatric patients with Ph+ ALL, interrupt treatment for cases of grade ≥3 non-hematologic adverse reactions with the exception of liver function test abnormalities, and resume at a reduced dose when resolved to grade ≤1. For elevated direct bilirubin over 5 times the institutional upper limit of normal (ULN), interrupt treatment until improvement to baseline or grade ≤1. For elevated AST/ALT over 15 times the institutional ULN, interrupt treatment until improvement to baseline or grade <1. For recurrent liver function test abnormalities as above, reduce the dose if this adverse reaction recurs after reinitiation of SPRYCEL. Dose reduction recommendations are described in Table 5.

Table 5: Dose Adjustments for Non-Hematologic Toxicities in Pediatric Patients

| | Dose (maximum dose per day) | | |
|---|-----------------------------|--------------------------|--------------------------|
| | Original Starting Dose | One-Level Dose Reduction | Two-Level Dose Reduction |
| 1. If a non-hematologic toxicity grade 2 occurs, consider interrupting SPRYCEL if no recovery despite symptomatic therapy, once recovered to grade ≤1, resume at the original starting dose. Resume SPRYCEL at a reduced dose for recurrent events. | Tablets 40 mg | 20 mg | ** |
| | 60 mg | 40 mg | 20 mg |
| | 70 mg | 60 mg | 50 mg |
| 2. If a non-hematologic toxicity grade 3 occurs, stop SPRYCEL until recovery to grade ≤1 and then resume at a reduced dose. | 100 mg | 80 mg | 70 mg |
| | | | |
| 3. If direct bilirubin is >5 ULN or AST/ALT >15 ULN, interrupt SPRYCEL until recovery to grade ≤1 and then resume SPRYCEL at the original starting dose. Resume SPRYCEL at a reduced dose for recurrent events. | | | |

** lower tablet dose not available

Duration of Treatment

For pediatric patients with chronic phase CML, treatment with SPRYCEL in adults and in pediatric patients with chronic phase CML is continued until disease progression or until no longer tolerated by the patient. The effect of SPRYCEL on long-term disease outcome after the achievement of a cytogenetic complete response (CCR) or major molecular response (MMR) is not yet established.

In pediatric patients with Ph+ ALL, SPRYCEL was administered for up to 2 years [see Dosage and Administration (2.2) and Clinical Studies (7.1)].

Follow applicable special handling and disposal procedures.¹

3 DOSAGE FORMS AND STRENGTHS

SPRYCEL (dasatinib) Tablets are available as 20-mg, 50-mg, 70-mg, 80-mg, 100-mg, and 140-mg white to off-white, biconvex, film-coated tablets.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Myelosuppression

Treatment with SPRYCEL is associated with severe (NCI CTCAE Grade 3 or 4) thrombocytopenia, neutropenia, and anemia, which occur earlier and more frequently in patients with advanced phase CML or Ph+ ALL than in patients with chronic phase CML [see Adverse Reactions (6.1)].

In patients with chronic phase CML, perform complete blood counts (CBCs) every 2 weeks for 12 weeks, then every 3 months thereafter, or as clinically indicated. In patients with advanced phase CML or Ph+ ALL, perform CBCs weekly for the first 2 months and then monthly thereafter, or as clinically indicated.

In pediatric patients with Ph+ ALL treated with SPRYCEL in combination with chemotherapy, perform CBCs prior to the start of each block of chemotherapy and as clinically indicated. During the consolidation blocks of chemotherapy, perform CBCs every 2 days until recovery.

Myelosuppression is generally reversible and usually managed by withholding SPRYCEL temporarily and/or dose reduction [see Dosage and Administration (2.5)].

5.2 Bleeding-Related Events

SPRYCEL can cause serious and fatal bleeding. In all CML or Ph+ ALL clinical studies, Grade ≥3 central nervous system (CNS) hemorrhages, including fatalities, occurred in <1% of patients receiving SPRYCEL. The incidence of Grade 3/4 hemorrhage, occurred in 5.8% of adult patients and generally required treatment interruptions and transfusions. The incidence of Grade 5 hemorrhage occurred in 0.4% of adult patients. The most frequent site of hemorrhage was gastrointestinal [see Adverse Reactions (6.1)]. Most bleeding events in clinical studies were associated with severe thrombocytopenia. In addition to causing thrombocytopenia in human subjects, dasatinib caused platelet dysfunction *in vitro*.

Concomitant medications that inhibit platelet function or anticoagulants may increase the risk of hemorrhage.

5.3 Fluid Retention

SPRYCEL may cause fluid retention [see Adverse Reactions (6.1)]. After 5 years of follow-up in the adult randomized newly diagnosed chronic phase CML study (n=258), Grade 3 or 4 fluid retention was reported in 5% of patients, including 3% of patients with Grade 3 or 4 pleural effusion. In adult patients with newly diagnosed or imatinib-resistant or -intolerant chronic phase CML, Grade 3 or 4 fluid retention occurred in 6% of patients treated with SPRYCEL at the recommended dose (n=548). In adult patients with advanced phase CML or Ph+ ALL treated with SPRYCEL at the recommended dose (n=304), Grade 3 or 4 fluid retention was reported in 8% of patients, including Grade 3 or 4 pleural effusion reported in 7% of patients. In pediatric patients with chronic phase CML, cases of Grade 1 or 2 fluid retention were reported in 10.3% of patients.

Table 7: Adverse Reactions Reported in ≥10% of Adult Patients with Newly Diagnosed Chronic Phase CML in the SPRYCEL-Treated Arm (n=258)

| Adverse Reaction | Minimum of 1 Year Follow-up | | Minimum of 5 Years Follow-up | |
|---|-----------------------------|-----------|------------------------------|-----------|
| | All Grades | Grade 3/4 | All Grades | Grade 3/4 |
| | Percent (%) of Patients | | | |
| Fluid retention | 19 | 1 | 38 | 5 |
| Pleural effusion | 10 | 0 | 28 | 3 |
| Superficial localized edema | 9 | 0 | 14 | 0 |
| Pulmonary hypertension | 1 | 0 | 5 | 1 |
| Generalized edema | 2 | 0 | 4 | 0 |
| Pericardial effusion | 1 | <1 | 4 | 1 |
| Congestive heart failure/cardiac dysfunction ^a | 2 | <1 | 2 | <1 |
| Pulmonary edema | <1 | 0 | 1 | 0 |
| Diarrhea | 17 | <1 | 22 | 1 |
| Musculoskeletal pain | 11 | 0 | 14 | 0 |
| Rash ^b | 11 | 0 | 14 | 0 |
| Headache | 12 | 0 | 14 | 0 |
| Abdominal pain | 7 | 0 | 11 | 0 |
| Fatigue | 8 | <1 | 11 | <1 |
| Nausea | 8 | 0 | 10 | 0 |

^a Includes cardiac failure acute, cardiac failure congestive, cardiomyopathy, diastolic dysfunction, ejection fraction decreased, and left ventricular dysfunction.

^b Includes erythema, erythema multiforme, rash, rash generalized, rash macular, rash papular, rash pustular, skin exfoliation, and rash vesicular.

At 60 months, there were 26 deaths in dasatinib-treated patients (10.1%) and 26 deaths in imatinib-treated patients (10.1%); 1 death in each group was assessed by the investigator as related to study therapy.

Table 8: Adverse Reactions Reported in ≥10% of Adult Patients with Chronic Phase CML Resistant or Intolerant to Prior Imatinib Therapy (minimum of 84 months follow-up)

| Adverse Reaction | 100 mg Once Daily | |
|-----------------------------|-------------------------|-----------|
| | All Grades | Grade 3/4 |
| | Percent (%) of Patients | |
| Fluid retention | 48 | 7 |
| Superficial localized edema | 22 | 0 |
| Pleural effusion | 28 | 5 |
| Generalized edema | 4 | 0 |
| Pericardial effusion | 3 | 1 |
| Pulmonary hypertension | 2 | 1 |
| Headache | 33 | 1 |

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Table 9: Adverse Reactions Reported in ≥10% of Adult Patients with Chronic Phase CML Resistant or Intolerant to Prior Imatinib Therapy (minimum of 84 months follow-up)

| Adverse Reaction | 100 mg Once Daily | |
|---|-------------------------|-----------|
| | All Grades | Grade 3/4 |
| | Percent (%) of Patients | |
| Diarrhea | 28 | 2 |
| Fatigue | 26 | 4 |
| Dyspnea | 24 | 2 |
| Musculoskeletal pain | 22 | 2 |
| Nausea ^a | 18 | 1 |
| Skin rash ^b | 18 | 2 |
| Myalgia | 13 | 0 |
| Arthralgia | 13 | 1 |
| Infection (including bacterial, viral, fungal, and non-specified) | 13 | 1 |
| Abdominal pain | 12 | 1 |
| Hemorrhage | 12 | 1 |
| Gastrointestinal bleeding | 2 | 1 |
| Pruritus | 12 | 1 |
| Pain | 11 | 1 |
| Constipation | 10 | 1 |

^a Includes drug eruption, erythema, erythema multiforme, erythema, exfoliative rash, generalized erythema, genital rash, heat rash, milia, rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, skin exfoliation, skin irritation, urticaria vesiculosa, and rash vesicular.

Cumulative rates of selected adverse reactions that were reported over time in patients treated with the 100 mg once daily recommended starting dose in a randomized dose-optimization trial of imatinib-resistant or -intolerant patients with chronic phase CML are shown in Table 9.

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Table 9: Selected Adverse Reactions Reported in Adult Dose Optimization Trial (Imatinib-Intolerant or -Resistant Chronic Phase CML)^a

| Adverse Reaction | Minimum of 2 Years Follow-up | | Minimum of 5 Years Follow-up | | Minimum of 7 Years Follow-up | |
|---------------------------|------------------------------|-----------|------------------------------|-----------|------------------------------|-----------|
| | All Grades | Grade 3/4 | All Grades | Grade 3/4 | All Grades | Grade 3/4 |
| | Percent (%) of Patients | | | | | |
| Diarrhea | 27 | 2 | 28 | 2 | 28 | 2 |
| Fluid retention | 34 | 4 | 42 | 6 | 48 | 7 |
| Superficial edema | 18 | 0 | 21 | 0 | 22 | 0 |
| Pleural effusion | 18 | 2 | 24 | 4 | 28 | 5 |
| Generalized edema | 3 | 0 | 4 | 0 | 4 | 0 |
| Pericardial effusion | 2 | 1 | 2 | 1 | 3 | 1 |
| Pulmonary hypertension | 0 | 0 | 0 | 0 | 2 | 1 |
| Hemorrhage | 11 | 1 | 11 | 1 | 12 | 1 |
| Gastrointestinal bleeding | 2 | 1 | 2 | 1 | 2 | 1 |

^a Randomized dose-optimization trial results reported in the recommended starting dose of 100 mg once daily (n=165) population.

Table 10: Adverse Reactions Reported in ≥10% of Adult Patients with Advanced Phase CML Resistant or Intolerant to Prior Imatinib Therapy

| Adverse Reaction | 140 mg Once Daily | | | | | |
|---|-------------------------|-----------|----------------------|-----------|-----------------------|-----------|
| | Accelerated (n=157) | | Myeloid Blast (n=74) | | Lymphoid Blast (n=33) | |
| | All Grades | Grade 3/4 | All Grades | Grade 3/4 | All Grades | Grade 3/4 |
| | Percent (%) of Patients | | | | | |
| Infection (including bacterial, viral, fungal, and non-specified) | 10 | 6 | 14 | 7 | 9 | 0 |
| Hemorrhage | 26 | 8 | 19 | 9 | 24 | 9 |
| Gastrointestinal bleeding | 8 | 6 | 9 | 7 | 9 | 3 |
| CNS bleeding | 1 | 1 | 0 | 0 | 3 | 3 |
| Vomiting | 11 | 1 | 12 | 0 | 15 | 0 |
| Pyrexia | 11 | 2 | 18 | 3 | 6 | 0 |
| Febrile neutropenia | 4 | 4 | 12 | 12 | 12 | 12 |

^a Includes ventricular dysfunction, cardiac failure, cardiac failure congestive, cardiomyopathy, congestive cardiomyopathy, diastolic dysfunction, ejection fraction decreased, and ventricular failure.

^b Includes drug eruption, erythema, erythema multiforme, erythema, exfoliative rash, generalized erythema, genital rash, heat rash, milia, rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, skin exfoliation, skin irritation, urticaria vesiculosa, and rash vesicular.

Table 10: Adverse Reactions Reported in ≥10% of Adult Patients with Advanced Phase CML Resistant or Intolerant to Prior Imatinib Therapy

| Adverse Reaction | 140 mg Once Daily | | | | | |
|---|-------------------------|-----------|----------------------|-----------|-----------------------|-----------|
| | Accelerated (n=157) | | Myeloid Blast (n=74) | | Lymphoid Blast (n=33) | |
| | All Grades | Grade 3/4 | All Grades | Grade 3/4 | All Grades | Grade 3/4 |
| | Percent (%) of Patients | | | | | |
| Fluid retention | 35 | 8 | 34 | 7 | 21 | 6 |
| Superficial localized edema | 18 | 1 | 14 | 0 | 3 | 0 |
| Pleural effusion | 21 | 7 | 20 | 7 | 21 | 6 |
| Generalized edema | 1 | 0 | 3 | 0 | 0 | 0 |
| Pericardial effusion | 3 | 1 | 0 | 0 | 0 | 0 |
| Congestive heart failure/cardiac dysfunction ^a | 0 | 0 | 4 | 0 | 0 | 0 |
| Pulmonary edema | 1 | 0 | 4 | 3 | 0 | 0 |
| Diarrhea | 27 | 1 | 18 | 1 | 15 | 3 |
| Fatigue | 31 | 3 | 20 | 5 | 18 | 0 |
| Dyspnea | 19 | 2 | 20 | 1 | 9 | 3 |
| Musculoskeletal pain | 20 | 3 | 15 | 3 | 3 | 3 |
| Nausea ^b | 11 | 0 | 8 | 1 | 0 | 0 |
| Skin rash ^b | 19 | 1 | 23 | 1 | 21 | 3 |
| Myalgia | 15 | 0 | 16 | 1 | 21 | 0 |
| Arthralgia | 10 | 0 | 5 | 1 | 0 | 0 |

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Table 11: Adverse Reactions Reported in ≥10% of Dasatinib-Treated Pediatric Patients with Chronic Phase CML (n=97)

| Adverse Reaction | Grade 3/4 | |
|-------------------|------------|-------------------------|
| | All Grades | Percent (%) of Patients |
| Headache | 28 | 3 |
| Nausea | 20 | 0 |
| Diarrhea | 21 | 0 |
| Skin rash | 19 | 0 |
| Vomiting | 13 | 0 |
| Pain in extremity | 19 | 1 |
| Abdominal pain | 16 | 0 |
| Fatigue | 10 | 0 |
| Arthralgia | 10 | 1 |

Adverse reactions associated with bone growth and development were reported in 5 (5.2%) of pediatric patients with chronic phase CML [see Warnings and Precautions (5.10)].

Laboratory Abnormalities

Myelosuppression was commonly reported in all patient populations. The frequency of Grade 3 or 4 neutropenia, thrombocytopenia, and anemia was higher in patients with advanced phase CML than in chronic phase CML (Tables 12 and 13). Myelosuppression was reported in patients with normal baseline laboratory values as well as in patients with pre-existing laboratory abnormalities.

In patients who experienced severe myelosuppression, recovery generally occurred following dose interruption or reduction, permanent discontinuation of treatment occurred in 2% of adult patients with newly diagnosed chronic phase CML and 3% of adult patients with resistance or intolerance to prior imatinib therapy [see Warnings and Precautions (5.1)].

Grade 3 or 4 elevations of transaminases or bilirubin and Grade 3 or 4 hypocalcemia, hypokalemia, and hypophosphatemia were reported in patients with all phases of CML but were reported with an increased frequency in patients with myeloid or lymphoid blast phase CML. Elevations in transaminases or bilirubin were usually managed with dose reduction or interruption. Patients developing Grade 3 or 4 hypocalcemia during SPRYCEL therapy often had recovery with oral calcium supplementation.

Laboratory abnormalities reported in adult patients with newly diagnosed chronic phase CML are shown in Table 12. There were no discontinuations of SPRYCEL therapy in this patient population due to biochemical laboratory parameters.

Table 12: CTC Grade 3/4 Laboratory Abnormalities in Adult Patients with Newly Diagnosed Chronic Phase CML (minimum of 60 months follow-up)

| Adverse Reaction | Grade 3/4 | |
|--------------------------------|-----------------|------------------|
| | SPRYCEL (n=258) | Imatinib (n=258) |
| Percent (%) of Patients | | |
| Hematology Parameters | | |
| Neutropenia | 29 | 24 |
| Thrombocytopenia | 22 | 14 |
| Anemia | 13 | 9 |
| Biochemistry Parameters | | |
| Hypophosphatemia | 7 | 31 |
| Hypokalemia | 0 | 3 |
| Hypocalcemia | 4 | 3 |
| Elevated SGPT (ALT) | <1 | 2 |
| Elevated SGOT (AST) | <1 | 1 |
| Elevated Bilirubin | 1 | 0 |
| Elevated Creatinine | 1 | 1 |

CTC grades: neutropenia (Grade 3 ≥0.5-1.0 × 10⁹/L, Grade 4 <0.5 × 10⁹/L); thrombocytopenia (Grade 3 ≥25-50 × 10⁹/L, Grade 4 <25 × 10⁹/L); anemia (hemoglobin Grade 3 ≥65-80 g/L, Grade 4 <65 g/L); elevated creatinine (Grade 3 >3-6 × upper limit of normal range (ULN), Grade 4 >6 × ULN); elevated bilirubin (Grade 3 >3-10 × ULN, Grade 4 >10 × ULN); elevated SGOT or SGPT (Grade 3 >5-20 × ULN, Grade 4 >20 × ULN); hypocalcemia (Grade 3 <7.0-6.0 mg/dL, Grade 4 <6.0 mg/dL); hypophosphatemia (Grade 3 <2.0-1.0 mg/dL, Grade 4 <1.0 mg/dL); hypokalemia (Grade 3 <3.0-2.5 mmol/L, Grade 4 <2.5 mmol/L).

Laboratory abnormalities reported in patients with CML resistant or intolerant to imatinib who received the recommended starting doses of SPRYCEL are shown by disease phase in Table 13.

Table 13: CTC Grade 3/4 Laboratory Abnormalities in Clinical Studies of CML in Adults: Resistance or Intolerance to Prior Imatinib Therapy

| Adverse Reaction | Advanced Phase CML | | | |
|--------------------------------|---|---------------------------|----------------------------|-----------------------------|
| | Chronic Phase CML 100 mg Once Daily (n=165) | Accelerated Phase (n=157) | Myeloid Blast Phase (n=74) | Lymphoid Blast Phase (n=33) |
| Percent (%) of Patients | | | | |
| Hematology Parameters* | | | | |
| Neutropenia | 36 | 58 | 77 | 79 |
| Thrombocytopenia | 24 | 63 | 78 | 85 |
| Anemia | 13 | 47 | 74 | 52 |
| Biochemistry Parameters | | | | |
| Hypophosphatemia | 10 | 13 | 12 | 18 |
| Hypokalemia | 2 | 7 | 11 | 15 |
| Hypocalcemia | <1 | 4 | 9 | 12 |
| Elevated SGPT (ALT) | 0 | 2 | 5 | 3 |
| Elevated SGOT (AST) | <1 | 0 | 4 | 3 |
| Elevated Bilirubin | <1 | 1 | 3 | 6 |
| Elevated Creatinine | 6 | 2 | 8 | 0 |

CTC grades: neutropenia (Grade 3 ≥0.5-1.0 × 10⁹/L, Grade 4 <0.5 × 10⁹/L); thrombocytopenia (Grade 3 ≥25-50 × 10⁹/L, Grade 4 <25 × 10⁹/L); anemia (hemoglobin Grade 3 ≥65-80 g/L, Grade 4 <65 g/L); elevated creatinine (Grade 3 >3-6 × upper limit of normal range (ULN), Grade 4 >6 × ULN); elevated bilirubin (Grade 3 >3-10 × ULN, Grade 4 >10 × ULN); elevated SGOT or SGPT (Grade 3 >5-20 × ULN, Grade 4 >20 × ULN); hypocalcemia (Grade 3 <7.0-6.0 mg/dL, Grade 4 <6.0 mg/dL); hypophosphatemia (Grade 3 <2.0-1.0 mg/dL, Grade 4 <1.0 mg/dL); hypokalemia (Grade 3 <3.0-2.5 mmol/L, Grade 4 <2.5 mmol/L).

* Hematology parameters for 100 mg once-daily dosing in chronic phase CML reflects 60-month minimum follow-up.

Among adult patients with chronic phase CML with resistance or intolerance to prior imatinib therapy, cumulative Grade 3 or 4 cytopenias were similar at 2 and 5 years including neutropenia (36% vs 36%), thrombocytopenia (23% vs 24%), and anemia (13% vs 13%).

In the pediatric studies in CML, the rates of laboratory abnormalities were consistent with the known profile for laboratory parameters in adults.

Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ ALL) in Adults

A total of 135 adult patients with Ph+ ALL were treated with SPRYCEL in clinical studies. The median duration of treatment was 3 months (range 0.03-31 months). The safety profile of patients with Ph+ ALL was similar to those with lymphoid blast phase CML. The most frequently reported adverse reactions included fluid retention events, such as pleural effusion (24%) and superficial edema (19%), and gastrointestinal disorders, such as diarrhea (31%), nausea (24%), and vomiting (16%). Hemorrhage (19%), pyrexia (17%), rash (16%), and dyspnea (16%) were also frequently reported. Serious adverse reactions reported in ≥5% of patients included pleural effusion (11%), gastrointestinal bleeding (7%), febrile neutropenia (6%), and infection (5%).

Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ ALL) in Pediatric Patients

The safety of SPRYCEL administered continuously in combination with multiagent chemotherapy was determined in a multicohort study of 81 pediatric patients with newly diagnosed Ph+ ALL. [see Clinical Studies (14.4)]. The median duration of therapy was 24 months (range 2 to 27 months).

Fatal adverse reactions occurred in 3 patients (4%), all of which were due to infections. Eight (10%) patients experienced adverse reactions leading to treatment discontinuation, including fungal sepsis, hepatotoxicity in the setting of graft versus host disease, thrombocytopenia, CMV infection, pneumonia, nausea, enteritis and drug hypersensitivity.

The most common serious adverse reactions (incidence ≥10%) were pyrexia, febrile neutropenia, mucositis, diarrhea, sepsis, hypotension, infections (bacterial, viral and fungal), hypersensitivity, vomiting, renal insufficiency, abdominal pain, and musculoskeletal pain.

The incidence of common adverse reactions (incidence ≥20%) on study are shown in Table 14.

Table 14: Adverse Reactions Reported in ≥20% of Pediatric Patients with Ph+ ALL Treated with SPRYCEL in Combination with Chemotherapy CA180372 (N=81)

| Adverse Reaction | Percent (%) of Patients | |
|----------------------|-------------------------|-----------|
| | All Grades | Grade 3/4 |
| Mucositis | 93 | 60 |
| Febrile neutropenia | 86 | 86 |
| Pyrexia | 85 | 17 |
| Diarrhea | 84 | 31 |
| Nausea | 84 | 11 |
| Vomiting | 83 | 17 |
| Musculoskeletal pain | 83 | 25 |
| Abdominal pain | 78 | 17 |
| Cough | 78 | 7 |
| Headache | 77 | 7 |
| Rash | 68 | 7 |
| Fatigue | 59 | 7 |
| Constipation | 37 | 7 |
| Arrhythmia | 47 | 7 |
| Hypertension | 47 | 7 |



Table 14: Adverse Reactions Reported in ≥10% of Pediatric Patients with Ph+ ALL Treated with SPRYCEL in Combination with Chemotherapy CA180372 (N=81)

| | | |
|--|-----|----|
| Edema | 47 | 6 |
| Viral infection | 40 | 12 |
| Hypotension | 40 | 26 |
| Decreased appetite | 38 | 22 |
| Hypersensitivity | 36 | 20 |
| Upper respiratory tract infection | 36 | 10 |
| Dyspnea | 35 | 10 |
| Epistaxis | 31 | 6 |
| Peripheral neuropathy | 31 | 7 |
| Sepsis (excluding fungal) | n/a | 31 |
| Altered state of consciousness | 30 | 4 |
| Fungal infection | 30 | 11 |
| Pneumonia (excluding fungal) | 28 | 25 |
| Pruritus | 28 | - |
| Clostridial infection (excluding sepsis) | 25 | 14 |
| Urinary Tract Infection | 24 | 14 |
| Bacteremia (excluding fungal) | 22 | 20 |
| Erythema | 22 | 6 |
| Chills | 21 | - |
| Pleural effusion | 21 | 9 |
| Sinusitis | 21 | 10 |
| Dehydration | 20 | 9 |
| Renal insufficiency | 20 | 9 |
| Visual impairment | 20 | - |

The incidence of common adverse reactions attributed by the investigator to SPRYCEL (reported at a frequency of ≥10%, all grades and grade 3/4, respectively) on study (N=81), included febrile

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neutropenia (23%, 23%), nausea (21%, 4%), vomiting (19%, 4%), mucositis (17%, 6%), musculoskeletal pain (17%, 2%), abdominal pain (16%, 5%), diarrhea (16%, 7%), rash (15%, 0%), fatigue (12%, 0%), pyrexia (12%, 6%), and headache (12%, 5%).

CTCAE grade 3/4 laboratory abnormalities in pediatric patients with Ph+ ALL treated with SPRYCEL in combination with chemotherapy are shown in Table 15.

Table 15: CTCAE Grade 3/4 Laboratory Abnormalities in ≥10% of Pediatric Patients with Ph+ ALL Treated with SPRYCEL in Combination with Chemotherapy CA180372 (N=81)

| Percent (%) of Patients | |
|--------------------------------|----|
| Hematology Parameters | |
| Neutropenia | 96 |
| Thrombocytopenia | 88 |
| Anemia | 82 |
| Biochemistry Parameters | |
| Elevated SGPT (ALT) | 47 |
| Hypokalemia | 40 |
| Elevated SGOT (AST) | 26 |
| Hypocalcemia | 19 |
| Hyponatremia | 19 |
| Elevated Bilirubin | 11 |
| Hypophosphatemia | 11 |

Toxicity grading is per CTCAE version 4.

Additional Pooled Data from Clinical Trials

The following additional adverse reactions were reported in adult and pediatric patients (n=2809) in SPRYCEL CML clinical studies and adult patients in Ph+ ALL clinical studies at a frequency of ≥10%, 1%–<10%, 0.1%–<1%, or <0.1%. These adverse reactions are included based on clinical relevance.

Gastrointestinal Disorders: 1%–<10% – mucosal inflammation (including mucositis/stomatitis), dyspepsia, abdominal distension, constipation, gastritis, colitis (including neutropenic colitis), oral soft tissue disorder; 0.1%–<1% – ascites, dysphagia, anal fissure, upper gastrointestinal ulcer, esophagitis, pancreatitis, gastroesophageal reflux disease; <0.1% – protein losing gastroenteropathy, ileus, acute pancreatitis, anal fistula.

General Disorders and Administration-Site Conditions: ≥10% – peripheral edema, face edema; 1%–<10% – asthenia, chest pain, chills; 0.1%–<1% – malaise, other superficial edema, peripheral swelling; <0.1% – gait disturbance.

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Skin and Subcutaneous Tissue Disorders: 1%–<10% – alopecia, acne, dry skin, hyperhidrosis, urticaria, dermatitis (including eczema); 0.1%–<1% – pigmentation disorder, skin ulcer, bullous conditions, photosensitivity, nail disorder, neutrophilic dermatosis, panniculitis, palmar-plantar erythrodysesthesia syndrome, hair disorder; <0.1% – leukocytoclastic vasculitis, skin fibrosis.

Respiratory, Thoracic, and Mediastinal Disorders: 1%–<10% – lung infiltration, pneumonitis, cough; 0.1%–<1% – asthma, bronchospasm, dysphonia, pulmonary arterial hypertension; <0.1% – acute respiratory distress syndrome, pulmonary embolism.

Nervous System Disorders: 1%–<10% – neuropathy (including peripheral neuropathy), dizziness, dysgeusia, somnolence; 0.1%–<1% – amnesia, tremor, syncope, balance disorder; <0.1% – convulsion, cerebrovascular accident, transient ischemic attack, optic neuritis, VIIIth nerve paralysis, dementia, ataxia.

Blood and Lymphatic System Disorders: 0.1%–<1% – lymphadenopathy, lymphopenia; <0.1% – aplasia pure red cell.

Musculoskeletal and Connective Tissue Disorders: 1%–<10% – muscular weakness, musculoskeletal stiffness; 0.1%–<1% – rhabdomyolysis, tendonitis, muscle inflammation, osteonecrosis, arthritis; <0.1% – epiphyses delayed fusion (reported at 1%–<10% in the pediatric studies), growth retardation (reported at 1%–<10% in the pediatric studies).

Investigations: 1%–<10% – weight increased, weight decreased; 0.1%–<1% – blood creatine phosphokinase increased, gamma-glutamyltransferase increased.

Infections and Infestations: 1%–<10% – pneumonia (including bacterial, viral, and fungal), upper respiratory tract infection/inflammation, herpes virus infection, enterocolitis infection, sepsis (including fatal outcomes [0.2%]).

Metabolism and Nutrition Disorders: 1%–<10% – appetite disturbances, hyperuricemia; 0.1%–<1% – hypoalbuminemia, tumor lysis syndrome, dehydration, hypercholesterolemia; <0.1% – diabetes mellitus.

Cardiac Disorders: 1%–<10% – arrhythmia (including tachycardia), palpitations; 0.1%–<1% – angina pectoris, cardiomegaly, pericarditis, ventricular arrhythmia (including ventricular tachycardia), electrocardiogram T-wave abnormal, troponin increased; <0.1% – cor pulmonale, myocarditis, acute coronary syndrome, cardiac arrest, electrocardiogram PR prolongation, coronary artery disease, pleuropericarditis.

Eye Disorders: 1%–<10% – visual disorder (including visual disturbance, vision blurred, and acuity reduced), dry eye; 0.1%–<1% – conjunctivitis, visual impairment, lacrimation; <0.1% – photophobia.

Vascular Disorders: 1%–<10% – flushing, hypertension; 0.1%–<1% – hypotension, thrombosis; <0.1% – livedo reticularis, deep vein thrombosis, embolism.

Psychiatric Disorders: 1%–<10% – insomnia, depression; 0.1%–<1% – anxiety, affect lability, libido decreased.

Reproductive, Maternal, and Perinatal Conditions: <0.1% – abortion.

Breast Disorders: 0.1%–<1% – gynecomastia, menstrual disorder.

Local and Systemic Complications: 1%–<10% – contusion; <0.1% – tinnitus; 0.1%–<1% – vertigo, hearing loss.

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Hepatobiliary Disorders: 0.1%–<1% – cholestasis, cholecystitis, hepatitis.

Renal and Urinary Disorders: 0.1%–<1% – urinary frequency, renal failure, proteinuria; <0.1% – renal impairment.

Immune System Disorders: 0.1%–<1% – hypersensitivity (including erythema nodosum).

Endocrine Disorders: 0.1%–<1% – hypothyroidism, <0.1% – hyperthyroidism, thyroiditis.

6.2 Postmarketing Experience

The following additional adverse reactions have been identified during post approval use of SPRYCEL. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Infections: hepatitis B virus reactivation

Cardiac disorders: atrial fibrillation/atrial flutter

Respiratory, thoracic, and mediastinal disorders: interstitial lung disease

Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome

Renal and urinary disorders: nephrotic syndrome

Blood and lymphatic system disorders: thrombotic microangiopathy

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on Dasatinib

Strong CYP3A4 Inhibitors

The coadministration with strong CYP3A4 inhibitors may increase dasatinib concentrations [see Clinical Pharmacology (12.3)]. Increased dasatinib concentrations may increase the risk of toxicity. Avoid concomitant use of strong CYP3A4 inhibitors. If concomitant administration of a strong CYP3A4 inhibitor cannot be avoided, consider a SPRYCEL dose reduction [see Dosage and Administration (2.5)].

Strong CYP3A4 Inducers

The coadministration of SPRYCEL with strong CYP3A4 inducers may decrease dasatinib concentrations [see Clinical Pharmacology (12.3)]. Decreased dasatinib concentrations may reduce efficacy. Consider alternative drugs with less enzyme induction potential. If concomitant administration of a strong CYP3A4 inducer cannot be avoided, consider a SPRYCEL dose increase.

Gastric Acid Reducing Agents

The coadministration of SPRYCEL with a gastric acid reducing agent may decrease the concentrations of dasatinib. Decreased dasatinib concentrations may reduce efficacy.

Do not administer H₂ antagonists or proton pump inhibitors with SPRYCEL. Consider the use of antacids in place of H₂ antagonists or proton pump inhibitors. Administer the antacid at least 2 hours prior to or 2 hours after the dose of SPRYCEL. Avoid simultaneous administration of SPRYCEL with antacids.

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Dasatinib is a P-20 substrate in vitro with no concentration dependence over the range of 100 ng/mL to 2500 L (C₅₀ 93%). Dasatinib is metabolized in humans, primarily by CYP3A4. CYP3A4 is the major enzyme responsible for the formation of the active metabolite, flavanone, and the inactive metabolite, dihydroflavonol. Dasatinib is metabolized in humans, primarily by CYP3A4. CYP3A4 is the major enzyme responsible for the formation of the active metabolite, flavanone, and the inactive metabolite, dihydroflavonol. Dasatinib is metabolized in humans, primarily by CYP3A4. CYP3A4 is the major enzyme responsible for the formation of the active metabolite, flavanone, and the inactive metabolite, dihydroflavonol.

6 USE IN SPECIFIC POPULATIONS

6.1 Pregnancy

Risk Summary

Based on limited human data, SPRYCEL can cause fetal harm when administered to a pregnant woman. Adverse pharmacologic effects including hydrops fetalis, fetal leukopenia, and fetal thrombocytopenia have been reported with maternal exposure to SPRYCEL. Animal reproduction studies in rats have demonstrated extensive mortality during organogenesis, the fetal period, and in neonates. Skeletal malformations were observed in a limited number of surviving rat and rabbit conceptuses. These findings occurred at dasatinib plasma concentrations below those in humans receiving therapeutic doses of dasatinib [see Data]. Advise a pregnant woman of the potential risk to a fetus.

The estimated background risk in the U.S. general population of major birth defects is 2% to 4% and of miscarriage is 15% to 20% of clinically recognized pregnancies.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Transplacental transfer of dasatinib has been reported. Dasatinib has been measured in fetal plasma and amniotic fluid at concentrations comparable to those in maternal plasma. Hydrops fetalis, fetal leukopenia, and fetal thrombocytopenia have been reported with maternal exposure to dasatinib. These adverse pharmacologic effects on the fetus are similar to adverse reactions observed in adult patients and may result in fetal harm or neonatal death [see Warnings and Precautions (5.1, 5.3)].

Data

Human Data

Based on human experience, dasatinib is suspected to cause congenital malformations, including neural tube defects, and harmful pharmacological effects on the fetus when administered during pregnancy.

Animal Data

In nonclinical studies at plasma concentrations below those observed in humans receiving therapeutic doses of dasatinib, embryo-fetal toxicities were observed in rats and rabbits. Fetal death was observed in rats. In both rats and rabbits, the lowest doses of dasatinib tested (rat: 2.5 mg/kg/day [15 mg/m²/day] and rabbit: 0.5 mg/kg/day [6 mg/m²/day]) resulted in embryo-fetal toxicities. These doses produced maternal AUCs of 105 ng·h/mL and 44 ng·h/mL (0.1-fold the human AUC), in rats and rabbits, respectively. Embryo-fetal toxicities included skeletal malformations at multiple sites (scapula, humerus, femur, radius, ribs, and clavicle), reduced ossification (sternum, thoracic, lumbar, and sacral vertebrae, forepaw phalanges, pelvis, and hyoid body), edema, and microhepatia. In a pre- and postnatal development study in rats, administration of dasatinib from gestation day (GD) 16 through lactation day (LD) 20, GD 21 through LD 20, or LD 4 through LD 20 resulted in extensive pup mortality at maternal exposures that were below the exposures in patients treated with dasatinib at the recommended labeling dose.

6.2 Lactation

Risk Summary

No data are available regarding the presence of dasatinib in human milk, the effects of the drug on the breastfed child, or the effects of the drug on milk production. However, dasatinib is present in

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the milk of lactating rats. Because of the potential for serious adverse reactions in nursing children from SPRYCEL, breastfeeding is not recommended during treatment with SPRYCEL and for 2 weeks after the last dose.

6.3 Females and Males of Reproductive Potential

SPRYCEL can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations (6.1)].

Contraception

Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment with SPRYCEL and for 30 days after the last dose.

Infertility

Based on animal data, dasatinib may result in damage to female and male reproductive tissues [see Nonclinical Toxicology (13.1)].

6.4 Pediatric Use

Ph+ CML in Chronic Phase

The safety and effectiveness of SPRYCEL monotherapy have been demonstrated in pediatric patients with newly diagnosed chronic phase CML [see Clinical Studies (14.3)]. There are no data in children under 1 year of age. Adverse reactions associated with bone growth and development were reported in 5 (5.2%) of patients [see Warnings and Precautions (5.10)].

Ph+ ALL

The safety and effectiveness of SPRYCEL in combination with chemotherapy have been demonstrated in pediatric patients one year and over with newly diagnosed Ph+ ALL. Use of SPRYCEL in pediatric patients is supported by evidence from one pediatric study. There are no data in children under 1 year of age. One case of grade 1 osteopenia was reported.

The safety profile of SPRYCEL in pediatric subjects was comparable to that reported in studies in adult subjects [see Adverse Reactions (6.1) and Clinical Studies (14.3, 14.4)].

Monitor bone growth and development in pediatric patients [see Warnings and Precautions (5.10)].

Pediatric Patients with Difficulty Swallowing Tablets

Five patients with Ph+ ALL 2 to 10 years of age received at least one dose of SPRYCEL tablet dispersed in juice on Study CA180372. The exposure for dispersed tablets was 36% lower as compared to intact tablets in pediatric patients [see Clinical Pharmacology (12.3)]. Due to the limited available clinical data, it is unclear whether dispersing SPRYCEL tablets significantly alters the safety and/or efficacy of SPRYCEL.

6.5 Geriatric Use

Of the 2712 patients in clinical studies of SPRYCEL, 617 (23%) were 65 years of age and older, and 123 (5%) were 75 years of age and older. No differences in confirmed Complete Cytogenetic Response (cCCyR) and MMR were observed between older and younger patients. While the safety profile of SPRYCEL in the geriatric population was similar to that in the younger population, patients aged 65 years and older are more likely to experience the commonly reported adverse reactions of fatigue, pleural effusion, diarrhea, dyspnea, cough, lower gastrointestinal hemorrhage,

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and appetite disturbance, and more likely to experience the less frequently reported adverse reactions of abdominal distention, dizziness, pericardial effusion, congestive heart failure, hypertension, pulmonary edema, and weight decrease, and should be monitored closely.

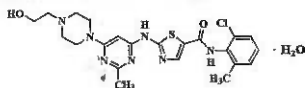
10 OVERDOSAGE

Experience with overdose of SPRYCEL in clinical studies is limited to isolated cases. The highest overdose of 280 mg per day for 1 week was reported in two patients and both developed severe myelosuppression and bleeding. Since SPRYCEL is associated with severe myelosuppression [see Warnings and Precautions (5.1) and Adverse Reactions (6.1)], monitor patients who ingest more than the recommended dosage closely for myelosuppression and give appropriate supportive treatment.

Acute overdose in animals was associated with cardiotoxicity. Evidence of cardiotoxicity included ventricular necrosis and valvular/ventricular/atrial hemorrhage at single doses ≥ 100 mg/kg (600 mg/m²) in rodents. There was a tendency for increased systolic and diastolic blood pressure in monkeys at single doses ≥ 10 mg/kg (120 mg/m²).

11 DESCRIPTION

SPRYCEL (dasatinib) is a kinase inhibitor. The chemical name for dasatinib is N-(2-chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide, monohydrate. The molecular formula is C₂₂H₂₆ClN₆O₂S · H₂O, which corresponds to a formula weight of 506.62 (monohydrate). The anhydrous free base has a molecular weight of 488.01. Dasatinib has the following chemical structure:



Dasatinib is a white to off-white powder. The drug substance is insoluble in water and slightly soluble in ethanol and methanol.

SPRYCEL tablets are white to off-white, biconvex, film-coated tablets containing dasatinib, with the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, and magnesium stearate. The tablet coating consists of hypromellose, titanium dioxide, and polyethylene glycol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Dasatinib, at nanomolar concentrations, inhibits the following kinases: BCR-ABL, SRC family (SRC, LCK, YES, FYN), c-KIT, EphA2, and PDGFR β . Based on modeling studies, dasatinib is predicted to bind to multiple conformations of the ABL kinase.

In vitro, dasatinib was active in leukemic cell lines representing variants of imatinib mesylate-sensitive and resistant disease. Dasatinib inhibited the growth of chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL) cell lines overexpressing BCR-ABL. Under the conditions of the assays, dasatinib could overcome imatinib resistance resulting from BCR-ABL kinase domain mutations, activation of alternate signaling pathways involving the SRC family kinases (LYN, HCK), and multi-drug resistance gene overexpression.

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12.2 Pharmacodynamics

Cardiac Electrophysiology

Of 2440 patients treated with SPRYCEL at all doses tested in clinical trials, 16 patients (<1%) had QTc prolongation reported as an adverse reaction. Twenty-two patients (1%) experienced a QTcF > 500 ms. In 865 patients with leukemia treated with SPRYCEL 70 mg BID in five Phase 2 studies, the maximum mean changes in QTcF (90% upper bound CI) from baseline ranged from 7 ms to 13.4 ms.

An analysis of the data from five Phase 2 studies in patients (70 mg BID) and a Phase 1 study in healthy subjects (100 mg single dose) suggests that there is a maximum increase of 3 to 6 milliseconds in Fridericia corrected QTc interval from baseline for subjects receiving therapeutic doses of dasatinib, with associated upper 95% confidence intervals <10 msec.

12.3 Pharmacokinetics

The pharmacokinetics of dasatinib exhibits dose proportional increases in AUC and linear elimination characteristics over the dose range of 15 mg/day (0.15 times the lowest approved recommended dose) to 240 mg/day (1.7 times the highest approved recommended dose).

At 100 mg QD, the maximum concentration at steady state (C_{max}) is 82.2 ng/mL (CV% 69%), area under the plasma drug concentration time curve (AUC) is 397 ng/mL·hr (CV% 55%). The clearance of dasatinib is found to be time-invariant. When administered to adult healthy subjects as dispersed tablets in juice, the adjusted geometric mean ratio was 0.97 (90% CI: 0.85, 1.10) for C_{max} and 0.84 (90% CI: 0.78, 0.91) for AUC as compared to intact tablets.

Absorption

The maximum plasma concentrations (C_{max}) of dasatinib are observed between 0.5 hours and 6 hours (T_{max}) following oral administration.

Food Effect

A high-fat meal increased the mean AUC of dasatinib following a single dose of 100 mg by 14%. The total calorie content of the high-fat meal was 985 kcal. The calories derived from fat, carbohydrates, and protein were 52%, 34%, and 14% for the high-fat meal.

Distribution

The apparent volume of distribution is 2505 L (CV% 93%).

Binding of dasatinib to human plasma proteins *in vitro* was approximately 96% and metabolite was 93%, with no concentration dependence over the range of 100 ng/mL.

Dasatinib is a P-gp substrate *in vitro*.

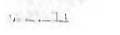
Elimination

The mean terminal half-life of dasatinib is 3 hours to 5 hours. The mean apparent clearance is 363.8 L/hr (CV% 81.3%).

Metabolism

Dasatinib is metabolized in humans, primarily by CYP3A4. CYP3A4 is responsible for the formation of the active metabolite. Flavin-containing monooxygenase 3 and uridine diphosphate-glucuronosyltransferase (UGT) are also involved in the formation of dasatinib metabolites.

SPRYCEL (dasatinib) is a kinase inhibitor. The chemical name for dasatinib is N-(2-chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazolecarboxamide, monohydrate. The molecular formula is C₂₂H₂₆ClN₆O₂S · H₂O, which corresponds to a formula weight of 506.62 (monohydrate). The anhydrous free base has a molecular weight of 488.01. Dasatinib has the following chemical structure:



Dasatinib is a white to off-white powder. The drug substance is insoluble in water and slightly soluble in ethanol and methanol.

SPRYCEL tablets are white to off-white, biconvex, film-coated tablets containing dasatinib, with the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, and magnesium stearate. The tablet coating consists of hypromellose, titanium dioxide, and polyethylene glycol.

Dasatinib, at nanomolar concentrations, inhibits the following kinases: BCR-ABL, SRC family (SRC, LCK, YES, FYN), c-KIT, EphA2, and PDGFR β . Based on modeling studies, dasatinib is predicted to bind to multiple conformations of the ABL kinase.

In vitro, dasatinib was active in leukemic cell lines representing variants of imatinib mesylate-sensitive and resistant disease. Dasatinib inhibited the growth of chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL) cell lines overexpressing BCR-ABL. Under the conditions of the assays, dasatinib could overcome imatinib resistance resulting from BCR-ABL kinase domain mutations, activation of alternate signaling pathways involving the SRC family kinases (LYN, HCK), and multi-drug resistance gene overexpression.

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The exposure of the active metabolite, which is equipotent to dasatinib, represents approximately 5% of the AUC of dasatinib. The active metabolite of dasatinib is unlikely to play a major role in the observed pharmacology of the drug. Dasatinib also has several other inactive oxidation metabolites.

Excretion

Elimination is primarily via the feces. Following a single radiolabeled dose of oral dasatinib, 4% of the administered radioactivity was recovered in the urine and 85% in the feces within 10 days. Unchanged dasatinib accounted for 0.1% of the administered dose in the urine and 19% of the administered dose in the feces with the remainder of the dose being metabolites.

Specific Populations

Age (15 to 86 years old), sex, and renal impairment (creatinine clearance 21.6 mL/min to 342.3 mL/min as estimated by Cockcroft Gault) have no clinically relevant effect on the pharmacokinetics of dasatinib.

Pediatric Patients

The pharmacokinetics of dasatinib were evaluated in 43 pediatric patients with leukemia or solid tumors at oral doses ranging from 60 mg/m² to 120 mg/m² once daily, taken with or without food. The pharmacokinetics showed dose proportionality with a dose-related increase in exposure. The mean T_{max} was observed between 0.5 hours and 6 hours and the mean half-life was 2 hours to 5 hours. The geometric mean (CV%) of body weight normalized clearance in these 43 pediatric patients is 5.98 (41.5%) L/h/kg. In pediatric patients with a dosing regimen of 60 mg/m², the model simulated geometric mean (CV%) steady-state plasma average concentrations of dasatinib were 14.7 (64.6%) ng/mL (for 2 to <6 years old), 16.3 (97.5%) ng/mL (for 6 to <12 years old), and 18.2 (67.7%) ng/mL (for 12 years and older) [see Dosage and Administration (2.2)]. Dasatinib clearance and volume of distribution change with body weight in pediatric patients. Dasatinib has not been studied in patients < 1 year old.

The bioavailability of dispersed tablets in pediatric patients was estimated to be 36% lower than that of intact tablets.

Patients with Hepatic Impairment

Compared to subjects with normal liver function, patients with moderate hepatic impairment (Child Pugh B) had decreases in mean C_{max} by 47% and mean AUC by 8%. Patients with severe hepatic impairment (Child Pugh C) had decreases in mean C_{max} by 43% and in mean AUC by 28% compared to the subjects with normal liver function.

Drug Interaction Studies

Cytochrome P450 Enzymes

The coadministration of ketoconazole (strong CYP3A4 inhibitor) twice daily increased the mean C_{max} of dasatinib by 4-fold and the mean AUC of dasatinib by 5-fold following a single oral dose of 20 mg.

The coadministration of rifampin (strong CYP3A4 inducer) once daily decreased the mean C_{max} of dasatinib by 81% and the mean AUC of dasatinib by 82%.

Dasatinib is a time-dependent inhibitor of CYP3A4. Dasatinib does not inhibit CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, or 2E1. Dasatinib does not induce CYP enzymes.

Gastric Acid Reducing Agents

were Asian. At baseline, the distribution of Hasford scores was similar in the SPRYCEL and imatinib treatment groups (low risk: 33% and 34%; intermediate risk: 48% and 47%; high risk: 19% and 19%, respectively). With a minimum of 12 months follow-up, 85% of patients randomized to SPRYCEL and 81% of patients randomized to imatinib were still on study.

With a minimum of 24 months follow-up, 77% of patients randomized to SPRYCEL and 75% of patients randomized to imatinib were still on study and with a minimum of 60 months follow-up, 61% and 62% of patients, respectively, were still on treatment at the time of study closure.

Efficacy results are summarized in Table 16.

Table 16: Efficacy Results in a Randomized Newly Diagnosed Chronic Phase CML Trial

| | SPRYCEL (n=259) | Imatinib (n=260) |
|---|--------------------|---------------------|
| Confirmed CCyR^a | | |
| Within 12 months (95% CI) | 76.8% (71.2–81.8) | 66.2% (60.1–71.9) |
| P-value | | 0.007* |
| Major Molecular Response^b | | |
| 12 months (95% CI) | 52.1% (45.9–58.3) | 33.8% (28.1–39.9) |
| P-value | | <0.0001 |
| 60 months (95% CI) | 76.4% (70.8–81.5) | 64.2% (58.1–70.1) |

^a Confirmed CCyR is defined as a CCyR noted on two consecutive occasions at least 28 days apart.
^b Major molecular response (at any time) was defined as BCR-ABL ratios ≤0.1% by RQ-PCR in peripheral blood samples standardized on the International scale. These are cumulative rates representing minimum follow-up for the time frame specified.
^c Adjusted for Hasford score and indicated statistical significance at a pre-defined nominal level of significance. CI = confidence interval.

The confirmed CCyR within 24, 36, and 60 months for SPRYCEL versus imatinib arms were 80% versus 74%, 83% versus 77%, and 83% versus 79%, respectively. The MMR at 24 and 36 months for SPRYCEL versus imatinib arms were 65% versus 50% and 69% versus 56%, respectively.

After 60 months follow-up, median time to confirmed CCyR was 3.1 months in 215 SPRYCEL responders and 5.8 months in 204 imatinib responders. Median time to MMR after 60 months follow-up was 9.3 months in 198 SPRYCEL responders and 15.0 months in 167 imatinib responders.

At 60 months follow-up, 8 patients (3%) on the dasatinib arm progressed to either accelerated phase or blast phase and 15 patients (6%) on the imatinib arm progressed to either accelerated phase or blast phase. 60-month survival rates for SPRYCEL- and imatinib-treated patients were 90.9% and 89.6% (CI: 85.2%–92.8%), respectively. Based on data 5 years after the start of treatment, 10% of patients were known to be alive in the SPRYCEL treatment group, 10% were known to have died in both treatment groups, respectively, 10% were known to be alive in both treatment groups, respectively, 7% and 13% had unknown survival status in the dasatinib and imatinib treatment groups, respectively.

In the SPRYCEL arm, the rate of MMR at any time in each risk group was 90% (low risk), 71% (intermediate risk) and 67% (high risk). In

The administration of 30 mL of aluminum hydroxide/magnesium hydroxide 2 hours prior to, a single dose of SPRYCEL was associated with no relevant change in the mean AUC of dasatinib; however, the mean C_{max} of dasatinib was increased by 26%.

The simultaneous administration of 30 mL of aluminum hydroxide/magnesium hydroxide with a single dose of SPRYCEL was associated with a 55% reduction in the mean AUC of dasatinib and a 58% reduction in the mean C_{max} of dasatinib.

The administration of a single dose of SPRYCEL 10 hours following famotidine (H₂ antagonist) reduced the mean AUC of dasatinib by 61% and the mean C_{max} of dasatinib by 63%.

The administration of a single 100 mg dose of SPRYCEL 22 hours following a 40 mg dose of omeprazole (proton pump inhibitor) at steady state reduced the mean AUC of dasatinib by 43% and the mean C_{max} of dasatinib by 42%.

Transporters

Dasatinib is not an inhibitor of P-gp *in vitro*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year carcinogenicity study, rats were administered oral doses of dasatinib at 0.3, 1, and 3 mg/kg/day. The highest dose resulted in a plasma drug exposure (AUC) level approximately 60% of the human exposure at 100 mg once daily. Dasatinib induced a statistically significant increase in the combined incidence of squamous cell carcinomas and papillomas in the uterus and cervix of high-dose females and prostate adenomas in low-dose males.

Dasatinib was clastogenic when tested *in vitro* in Chinese hamster ovary cells, with and without metabolic activation. Dasatinib was not mutagenic when tested in an *in vitro* bacterial cell assay (Ames test) and was not genotoxic in an *in vivo* rat micronucleus study.

Dasatinib did not affect mating or fertility in male and female rats at plasma drug exposure (AUC) similar to the human exposure at 100 mg daily. In repeat dose studies, administration of dasatinib resulted in reduced size and secretion of seminal vesicles, and immature prostate, seminal vesicle, and testis. The administration of dasatinib resulted in uterine inflammation and mineralization in monkeys, and cystic ovaries and ovarian hypertrophy in rodents.

14 CLINICAL STUDIES

14.1 Newly Diagnosed Chronic Phase CML in Adults

DASISION (Dasatinib vs Imatinib Study in Treatment-Naive Chronic Myeloid Leukemia Patients) (NCT00481247) was an open-label, multicenter, international, randomized trial conducted in adult patients with newly diagnosed chronic phase CML. A total of 519 patients were randomized to receive either SPRYCEL 100 mg once daily or imatinib 400 mg once daily. Patients with a history of cardiac disease were included in this trial except those who had a myocardial infarction within 6 months, congestive heart failure within 3 months, significant arrhythmias, or QTc prolongation. The primary endpoint was the rate of confirmed complete cytogenetic response (CCyR) within 12 months. Confirmed CCyR was defined as a CCyR noted on two consecutive occasions (at least 28 days apart).

Median age was 46 years in the SPRYCEL group and 49 years in the imatinib groups, with 10% and 11% of patients ≥65 years of age, respectively. There were slightly more male than female patients in both groups (59% vs 41%). Fifty-three percent of all patients were Caucasian and 39%

the imatinib arm, the rate of MMR at any time in each risk group determined by Hasford score was 69% (low risk), 65% (intermediate risk), and 54% (high risk).

BCR-ABL sequencing was performed on blood samples from patients in the newly diagnosed trial who discontinued dasatinib or imatinib therapy. Among dasatinib-treated patients the mutations detected were T315I, F317I/L, and V299L.

Dasatinib does not appear to be active against the T315I mutation, based on *in vitro* data.

14.2 Imatinib-Resistant or Intolerant CML or Ph+ ALL in Adults

The efficacy and safety of SPRYCEL were investigated in adult patients with CML or Ph+ ALL whose disease was resistant to or who were intolerant to imatinib. 1158 patients had chronic phase CML, 858 patients had accelerated phase, myeloid blast phase, or lymphoid blast phase CML, and 130 patients had Ph+ ALL. In a clinical trial in chronic phase CML, resistance to imatinib was defined as failure to achieve a complete hematologic response (CHR after 3 months), major cytogenetic response (MCyR after 6 months), or complete cytogenetic response (CCyR after 12 months), or loss of a previous molecular response (with concurrent ≥10% increase in Ph+ metaphases), cytogenetic response, or hematologic response. Imatinib intolerance was defined as inability to tolerate 400 mg or more of imatinib per day or discontinuation of imatinib because of toxicity.

Results described below are based on a minimum of 2 years follow-up after the start of SPRYCEL therapy in patients with a median time from initial diagnosis of approximately 5 years. Across all studies, 48% of patients were women, 81% were white, 15% were black or Asian, 25% were 65 years of age or older, and 5% were 75 years of age or older. Most patients had long disease histories with extensive prior treatment, including imatinib, cytotoxic chemotherapy, interferon, and stem cell transplant. Overall, 80% of patients had imatinib-resistant disease and 20% of patients were intolerant to imatinib. The maximum imatinib dose had been 400–600 mg/day in about 60% of the patients and >600 mg/day in 40% of the patients.

The primary efficacy endpoint in chronic phase CML was MCyR, defined as elimination (CCyR) or substantial diminution (by at least 65%, partial cytogenetic response) of Ph+ hematopoietic cells. The primary efficacy endpoint in accelerated phase, myeloid blast phase, lymphoid blast phase CML, and Ph+ ALL was major hematologic response (MaHR), defined as either a CHR or no evidence of leukemia (NEL).

Chronic Phase CML

Dose-Optimization Trial: A randomized, open-label trial (NCT00123474) was conducted in adult patients with chronic phase CML to evaluate the efficacy and safety of SPRYCEL administered once daily compared with SPRYCEL administered twice daily. Patients with significant cardiac diseases, including myocardial infarction within 6 months, congestive heart failure within 3 months, significant arrhythmias, or QTc prolongation were excluded from the trial. The primary efficacy endpoint was MCyR in patients with imatinib-resistant CML. A total of 670 patients, of whom 497 had imatinib-resistant disease, were randomized to the SPRYCEL 100 mg once-daily, 140 mg once-daily, 50 mg twice-daily, or 70 mg twice-daily group. Median duration of treatment was 22 months.

Efficacy was achieved across all SPRYCEL treatment groups with the once-daily schedule demonstrating comparable efficacy (non-inferiority) to the twice-daily schedule on the primary

efficacy endpoint (difference in M_{HR} 1.9%; 95% CI [-6.8% to 10.6%]), however, the 100-mg once-daily regimen demonstrated improved safety and tolerability.

Efficacy results are presented in Tables 17 and 18 for adult patients with chronic phase CML who received the recommended starting dose of 100 mg once daily.

Table 17: Efficacy of SPRYCEL in Adult Patients with Imatinib-Resistant or -Intolerant Chronic Phase CML (minimum of 24 months follow-up)

| | 100 mg Once Daily (n=167) |
|---|---------------------------|
| Hematologic Response Rate % (95% CI) | 92% (86-95) |
| CHR ^a | |
| Cytogenetic Response Rate % (95% CI) | 63% (56-71) |
| MCyR ^b | |
| CCyR | 50% (42-58) |

^a CHR (response confirmed after 4 weeks): WBC ≤ institutional ULN, platelets <450,000/mm³, no blasts or promyelocytes in peripheral blood, <5% myelocytes plus metamyelocytes in peripheral blood, basophils in peripheral blood <20%, and no extramedullary involvement.

^b MCyR combines both complete (0% Ph+ metaphases) and partial (>0%-35%) responses.

Table 18: Long-Term MMR of SPRYCEL in the Dose Optimization Trial: Adult Patients with Imatinib-Resistant or -Intolerant Chronic Phase CML^a

| | Minimum Follow-up Period | | |
|---|--------------------------|--------------|--------------|
| | 2 Years | 5 Years | 7 Years |
| Major Molecular Response^b % (n/N) | | | |
| All Patients Randomized | 34% (57/167) | 43% (71/167) | 44% (73/167) |
| Imatinib-Resistant Patients | 33% (41/124) | 40% (50/124) | 41% (51/124) |
| Imatinib-Intolerant Patients | 37% (16/43) | 49% (21/43) | 51% (22/43) |

^a Results reported in recommended starting dose of 100 mg once daily.

^b Major molecular response criteria: Defined as BCR-ABL/control transcripts ≤ 1% by RQ-PCR in peripheral blood samples.

Based on data 7 years after the last patient was enrolled in the trial, 44% were known to be alive, 31% were known to have died, and 25% had an unknown survival status.

By 7 years, transformation to either accelerated or blast phase occurred in nine patients on treatment in the 100 mg once-daily treatment group.

Advanced Phase CML and Ph+ ALL

Dose-Optimization Trial: One randomized open-label trial (NCT00123487) was conducted in patients with advanced phase CML (accelerated phase CML, myeloid blast phase CML, or lymphoid blast phase CML) to evaluate the efficacy and safety of SPRYCEL administered once daily compared with SPRYCEL administered twice daily. The primary efficacy endpoint was MaHR. A total of 611 patients were randomized to either the SPRYCEL 140 mg once-daily or 70 mg twice-daily group. Median duration of treatment was approximately 6 months for both treatment groups. The once-daily schedule demonstrated comparable efficacy (non-inferiority) to

the twice-daily schedule on the primary efficacy endpoint; however, the 140-mg once-daily regimen demonstrated improved safety and tolerability.

Response rates for patients in the 140 mg once-daily group are presented in Table 19.

Table 19: Efficacy of SPRYCEL in Imatinib-Resistant or -Intolerant Advanced Phase CML and Ph+ ALL (2-Year Results)

| | 140 mg Once Daily | | | Ph+ ALL (n=40) |
|-------------------------|---------------------|----------------------|-----------------------|----------------|
| | Accelerated (n=158) | Myeloid Blast (n=75) | Lymphoid Blast (n=33) | |
| MaHR^a | 66% (59-74) | 28% (18-40) | 42% (26-61) | 38% (23-54) |
| CHR ^a | 47% (40-56) | 17% (10-28) | 21% (9-39) | 33% (19-49) |
| NEL ^a | 19% (13-26) | 11% (5-20) | 21% (9-39) | 5% (1-17) |
| MCyR ^b | 39% (31-47) | 28% (18-40) | 52% (34-69) | 70% (54-83) |
| CCyR | 32% (25-40) | 17% (10-28) | 39% (23-58) | 59% (44-74) |

^a Hematologic response criteria (all responses confirmed after 4 weeks): Major hematologic response: (MaHR) = complete hematologic response (CHR) + no evidence of leukemia (NEL).

CHR: WBC ≤ institutional ULN, ANC ≥1000/mm³, platelets ≥100,000/mm³, no blasts or promyelocytes in peripheral blood, bone marrow blasts <5%, <5% myelocytes plus metamyelocytes in peripheral blood, basophils in peripheral blood <20%, and no extramedullary involvement.

NEL: same criteria as for CHR but ANC ≥500/mm³ and <1000/mm³, or platelets ≥200,000/mm³ and <100,000/mm³.

^b MCyR combines both complete (0% Ph+ metaphases) and partial (>0%-35%) responses.

CI = confidence interval ULN = upper limit of normal range.

In the SPRYCEL 140 mg once-daily group, the median time to MaHR was 1.9 months (min-max: 0.7-14.5) for patients with accelerated phase CML, 1.9 months (min-max: 0.9-6.2) for patients with myeloid blast phase CML, and 1.8 months (min-max: 0.9-2.8) for patients with lymphoid blast phase CML.

In patients with myeloid blast phase CML, the median duration of MaHR was 8.1 months (min-max: 2.7-21.1) and 9.0 (min-max: 1.8-23.1) months for the 140 mg once-daily group and the 70 mg twice-daily group, respectively. In patients with lymphoid blast phase CML, the median duration of MaHR was 4.7 months (min-max: 3.0-9.0) and 7.9 months (min-max: 1.6-22.1) for the 140 mg once-daily group and the 70 mg twice-daily group, respectively. In patients with Ph+ ALL who were treated with SPRYCEL 140 mg once-daily, the median duration of MaHR was 4.6 months (min-max: 1.4-10.2). The medians of progression-free survival for patients with Ph+ ALL treated with SPRYCEL 140 mg once-daily and 70 mg twice-daily were 4.0 months (min-max: 0.4-11.1) and 3.1 months (min-max: 0.3-20.8), respectively.

14.3 CML in Pediatric Patients

The efficacy of SPRYCEL in pediatric patients was evaluated in two pediatric studies of 97 patients with chronic phase CML. Among 97 patients with chronic phase CML treated in two pediatric studies, an open-label, non-randomized dose-ranging trial (NCT00306202) and an open-label, non-randomized, single-arm trial (NCT0077036), 51 patients (exclusively from the single-arm trial) had newly diagnosed chronic phase CML and 46 patients (17 from the dose-ranging trial

and 29 from the single-arm trial) were resistant or intolerant to previous treatment with imatinib. Ninety-one of the 97 pediatric patients were treated with SPRYCEL tablets 60 mg/m² once daily (maximum dose of 100 mg once daily for patients with high BSA). Patients were treated until disease progression or unacceptable toxicity.

Baseline demographic characteristics of the 46 imatinib resistant or intolerant patients were: median age 13.5 years (range 2 to 20 years), 78.3% White, 15.2% Asian, 4.4% Black, 2.2% other, and 52% female. Baseline characteristics of the 51 newly diagnosed patients were: median age 12.8 years (range 1.9 to 17.8 years), 60.8% White, 31.4% Asian, 5.9% Black, 2% Other, and 49% female.

Median duration of follow-up was 5.2 years (range 0.5 to 9.3 years) for the imatinib resistant or intolerant patients and 4.5 years (range 1.3 to 6.4 years) for the newly diagnosed patients, respectively. Efficacy results for the two pediatric studies are summarized in Table 20.

Table 20 shows increasing trend for response for CCyR, MCyR, and MMR across time (3 months to 24 months). The increasing trend in response for all three endpoints is seen in both the newly diagnosed and imatinib resistant or intolerant patients.

Table 20: Efficacy of SPRYCEL in Pediatric Patients with CP-CML: Cumulative Response Over Time by Minimum Follow-Up Period

| | 3 months | 6 months | 12 months | 24 months |
|-------------------------------------|--------------------|--------------------|--------------------|--------------------|
| CCyR | | | | |
| (95% CI) | | | | |
| Newly diagnosed (N=51) ^a | 43.1% (29.3, 57.8) | 66.7% (52.1, 79.2) | 96.1% (86.5, 99.5) | 96.1% (86.5, 99.5) |
| Prior imatinib (N=46) ^b | 45.7% (30.9, 61.0) | 71.7% (56.5, 84.0) | 78.3% (63.6, 89.1) | 82.6% (68.6, 92.2) |
| MCyR | | | | |
| (95% CI) | | | | |
| Newly diagnosed (N=51) ^a | 60.8% (46.1, 74.2) | 90.2% (78.6, 96.7) | 98.0% (89.6, 100) | 98.0% (89.6, 100) |
| Prior imatinib (N=46) ^b | 60.9% (45.4, 74.9) | 82.6% (68.6, 92.2) | 89.1% (76.4, 96.4) | 89.1% (76.4, 96.4) |
| MMR | | | | |
| (95% CI) | | | | |
| Newly diagnosed (N=51) ^a | 7.8% (2.2, 18.9) | 31.4% (19.1, 45.9) | 56.9% (42.2, 70.7) | 74.3% (60.4, 85.7) |
| Prior imatinib (N=46) ^b | 15.2% (6.3, 28.9) | 26.1% (14.3, 41.1) | 39.1% (25.1, 54.6) | 52.2% (36.9, 67.1) |

^a Patients from pediatric study of newly diagnosed CP-CML receiving oral tablet formulation.

^b Patients from pediatric studies of imatinib-resistant or -intolerant CP-CML receiving oral tablet formulation.

the twice-daily schedule on the primary efficacy endpoint; however, the 140-mg once-daily regimen demonstrated improved safety and tolerability.

Response rates for patients in the 140 mg once-daily group are presented in Table 19.

Table 19: Efficacy of SPRYCEL in Imatinib-Resistant or -Intolerant Advanced Phase CML and Ph+ ALL (2-Year Results)

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| CHR ^a | 47% (40-56) | 17% (10-28) | 21% (9-39) | 33% (19-49) |
| NEL ^a | 19% (13-26) | 11% (5-20) | 21% (9-39) | 5% (1-17) |
| MCyR ^b | 39% (31-47) | 28% (18-40) | 52% (34-69) | 70% (54-83) |
| CCyR | 32% (25-40) | 17% (10-28) | 39% (23-58) | 59% (44-74) |

^a Hematologic response criteria (all responses confirmed after 4 weeks): Major hematologic response: (MaHR) = complete hematologic response (CHR) + no evidence of leukemia (NEL).

CHR: WBC ≤ institutional ULN, ANC ≥1000/mm³, platelets ≥100,000/mm³, no blasts or promyelocytes in peripheral blood, bone marrow blasts <5%, <5% myelocytes plus metamyelocytes in peripheral blood, basophils in peripheral blood <20%, and no extramedullary involvement.

NEL: same criteria as for CHR but ANC ≥500/mm³ and <1000/mm³, or platelets ≥200,000/mm³ and <100,000/mm³.

^b MCyR combines both complete (0% Ph+ metaphases) and partial (>0%-35%) responses.

CI = confidence interval ULN = upper limit of normal range.

In the SPRYCEL 140 mg once-daily group, the median time to MaHR was 1.9 months (min-max: 0.7-14.5) for patients with accelerated phase CML, 1.9 months (min-max: 0.9-6.2) for patients with myeloid blast phase CML, and 1.8 months (min-max: 0.9-2.8) for patients with lymphoid blast phase CML.

In patients with myeloid blast phase CML, the median duration of MaHR was 8.1 months (min-max: 2.7-21.1) and 9.0 (min-max: 1.8-23.1) months for the 140 mg once-daily group and the 70 mg twice-daily group, respectively. In patients with lymphoid blast phase CML, the median duration of MaHR was 4.7 months (min-max: 3.0-9.0) and 7.9 months (min-max: 1.6-22.1) for the 140 mg once-daily group and the 70 mg twice-daily group, respectively. In patients with Ph+ ALL who were treated with SPRYCEL 140 mg once-daily, the median duration of MaHR was 4.6 months (min-max: 1.4-10.2). The medians of progression-free survival for patients with Ph+ ALL treated with SPRYCEL 140 mg once-daily and 70 mg twice-daily were 4.0 months (min-max: 0.4-11.1) and 3.1 months (min-max: 0.3-20.8), respectively.

14.3 CML in Pediatric Patients

The efficacy of SPRYCEL in pediatric patients was evaluated in two pediatric studies of 97 patients with chronic phase CML. Among 97 patients with chronic phase CML treated in two pediatric studies, an open-label, non-randomized dose-ranging trial (NCT00306202) and an open-label, non-randomized, single-arm trial (NCT0077036), 51 patients (exclusively from the single-arm trial) had newly diagnosed chronic phase CML and 46 patients (17 from the dose-ranging trial

and 29 from the single-arm trial) were resistant or intolerant to previous treatment with imatinib. Ninety-one of the 97 pediatric patients were treated with SPRYCEL tablets 60 mg/m² once daily (maximum dose of 100 mg once daily for patients with high BSA). Patients were treated until disease progression or unacceptable toxicity.

Baseline demographic characteristics of the 46 imatinib resistant or intolerant patients were: median age 13.5 years (range 2 to 20 years), 78.3% White, 15.2% Asian, 4.4% Black, 2.2% other, and 52% female. Baseline characteristics of the 51 newly diagnosed patients were: median age 12.8 years (range 1.9 to 17.8 years), 60.8% White, 31.4% Asian, 5.9% Black, 2% Other, and 49% female.

Median duration of follow-up was 5.2 years (range 0.5 to 9.3 years) for the imatinib resistant or intolerant patients and 4.5 years (range 1.3 to 6.4 years) for the newly diagnosed patients, respectively. Efficacy results for the two pediatric studies are summarized in Table 20.

Table 20 shows increasing trend for response for CCyR, MCyR, and MMR across time (3 months to 24 months). The increasing trend in response for all three endpoints is seen in both the newly diagnosed and imatinib resistant or intolerant patients.

Table 20: Efficacy of SPRYCEL in Pediatric Patients with CP-CML: Cumulative Response Over Time by Minimum Follow-Up Period

| | 3 months | 6 months | 12 months | 24 months |
|-------------------------------------|--------------------|--------------------|--------------------|--------------------|
| CCyR | | | | |
| (95% CI) | | | | |
| Newly diagnosed (N=51) ^a | 43.1% (29.3, 57.8) | 66.7% (52.1, 79.2) | 96.1% (86.5, 99.5) | 96.1% (86.5, 99.5) |
| Prior imatinib (N=46) ^b | 45.7% (30.9, 61.0) | 71.7% (56.5, 84.0) | 78.3% (63.6, 89.1) | 82.6% (68.6, 92.2) |
| MCyR | | | | |
| (95% CI) | | | | |
| Newly diagnosed (N=51) ^a | 60.8% (46.1, 74.2) | 90.2% (78.6, 96.7) | 98.0% (89.6, 100) | 98.0% (89.6, 100) |
| Prior imatinib (N=46) ^b | 60.9% (45.4, 74.9) | 82.6% (68.6, 92.2) | 89.1% (76.4, 96.4) | 89.1% (76.4, 96.4) |
| MMR | | | | |
| (95% CI) | | | | |
| Newly diagnosed (N=51) ^a | 7.8% (2.2, 18.9) | 31.4% (19.1, 45.9) | 56.9% (42.2, 70.7) | 74.3% (60.4, 85.7) |
| Prior imatinib (N=46) ^b | 15.2% (6.3, 28.9) | 26.1% (14.3, 41.1) | 39.1% (25.1, 54.6) | 52.2% (36.9, 67.1) |

^a Patients from pediatric study of newly diagnosed CP-CML receiving oral tablet formulation.

^b Patients from pediatric studies of imatinib-resistant or -intolerant CP-CML receiving oral tablet formulation.

In the Phase II pediatric study, 1 newly diagnosed patient and 2 imatinib-resistant or -intolerant patients progressed to blast phase CML.

14.4 Ph+ ALL in Pediatric Patients

The efficacy of SPRYCEL in combination with chemotherapy was evaluated in a single cohort (cohort 1) of Study CA180372 (NCT01460160), a multicenter, multiple-cohort study of pediatric patients with newly diagnosed B-cell precursor Ph+ ALL. The 78 patients in cohort 1 received SPRYCEL at a daily dose of 60 mg/m² for up to 24 months, in combination with chemotherapy. The backbone chemotherapy regimen was the AIEOP-BFM ALL 2006 multi-agent chemotherapy protocol.

Patients had a median age of 10.4 years (range 2.6 to 17.9 years) and included 20 patients 2 to 6 years of age, 37 patients (46%) 7 to 12 years of age, and 24 patients (30%) 13 to 17 years of age. Eighty-two percent of patients were white, and 55% were male. Thirty-two patients had a white blood cell count (WBC) of ≥50,000/ml at diagnosis, and 17 patients had extramedullary disease.

Efficacy was established on the basis of 3-year event-free survival (EFS), defined as the start of SPRYCEL to lack of complete response at the end of the third treatment cycle, secondary malignancy, or death from any cause. The 3-year EFS binary endpoint was 64.1% (95% CI: 52.4, 74.7). At the end of induction, 76 patients (97%) achieved therapy.

15 REFERENCES

1. <http://www.osha.gov/SLTC/hazardousdrugs/index.htm>

The confirmed CCyR rates were 77% at 3 months, 89% at 6 months, 96% at 12 months, and 96% at 24 months. The confirmed MCyR rates were 60% at 3 months, 90% at 6 months, 98% at 12 months, and 98% at 24 months. The confirmed MMR rates were 8% at 3 months, 31% at 6 months, 57% at 12 months, and 74% at 24 months.

How Supplied

SPRYCEL® (dasatinib) tablets are available as described in Table 21.

Table 21: SPRYCEL Trade Presentations

| NDC Number | Strength | Description | Tablets per Bottle |
|--------------|----------|---|--------------------|
| 0003-0527-11 | 20 mg | white to off-white, biconvex, round, film-coated tablet with "BMS" debossed on one side and "527" on the other side | 60 |
| 0003-0528-11 | 50 mg | white to off-white, biconvex, oval, film-coated tablet with "BMS" debossed on one side and "528" on the other side | 60 |
| 0003-0524-11 | 70 mg | white to off-white, biconvex, round, film-coated tablet with "BMS" debossed on one side and "524" on the other side | 60 |
| 0003-0855-22 | 80 mg | white to off-white, biconvex, triangle, film-coated tablet with "BMS" and "80" (BMS over 80) debossed on one side and "855" on the other side | 30 |
| 0003-0852-22 | 100 mg | white to off-white, biconvex, oval, film-coated tablet with "BMS 100" debossed on one side and "852" on the other side | 30 |
| 0003-0857-22 | 140 mg | white to off-white, biconvex, round, film-coated tablet with "BMS" and "140" (BMS over 140) debossed on one side and "857" on the other side | 30 |

Storage

SPRYCEL tablets should be stored at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].

Handling and Disposal

SPRYCEL is an antineoplastic product. Follow special handling and disposal procedures.¹

Personnel who are pregnant should avoid exposure to crushed or broken tablets.

SPRYCEL tablets consist of a core tablet, surrounded by a film coating to prevent exposure of healthcare professionals to the active substance. The use of latex or nitrile gloves for appropriate disposal when handling tablets that are inadvertently crushed or broken is recommended, to minimize the risk of dermal exposure.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Myelosuppression

Inform patients of the possibility of developing low blood cell counts. Advise patients to immediately report fever particularly in association with any suggestion of infection [see Warnings and Precautions (5.1)].

Advise patients using antacids to avoid taking SPRYCEL and antacids less than 2 hours apart [see Drug Interactions (7.1)].

Pain

Inform patients that they may experience headache or musculoskeletal pain with SPRYCEL. Advise patients to seek medical attention if these symptoms are bothersome or persistent.

Fatigue

Inform patients that they may experience fatigue with SPRYCEL. Advise patients to seek medical attention if this symptom is bothersome or persistent.

Rash

Inform patients that they may experience skin rash with SPRYCEL. Advise patients to seek medical attention if this symptom is bothersome or persistent.

Lactose

Inform patients that SPRYCEL contains 135 mg of lactose monohydrate in a 100-mg daily dose and 189 mg of lactose monohydrate in a 140-mg daily dose.

Instructions for Taking SPRYCEL

Missed Dose

Advise patients that if they miss a dose of SPRYCEL, they should take the next scheduled dose at its regular time. The patient should not take two doses at the same time.

Grapefruit Juice

Advise patients not to drink grapefruit juice as it may increase the amount of SPRYCEL in their blood and therefore increase their risk of adverse reactions.

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Bleeding

Inform patients of the possibility of serious bleeding and to report immediately any signs or symptoms suggestive of hemorrhage (unusual bleeding or easy bruising) [see Warnings and Precautions (5.2)].

Fluid Retention

Patients should be informed of the possibility of developing fluid retention (swelling, weight gain, dry cough, chest pain on respiration, or shortness of breath) and advised to seek medical attention promptly if those symptoms arise [see Warnings and Precautions (5.3)].

Cardiovascular Toxicity

Inform patients of the possibility of developing cardiovascular toxicity, including cardiac ischemic events, cardiac-related fluid retention, conduction abnormalities, and TIAs. Advise patients to seek immediate medical attention if symptoms suggestive of cardiovascular toxicity occur, such as chest pain, shortness of breath, palpitations, transient vision problems, or slurred speech [see Warnings and Precautions (5.4)].

Pulmonary Arterial Hypertension

Inform patients of the possibility of developing pulmonary arterial hypertension (dyspnea, fatigue, hypoxia, and fluid retention) and advise them to seek medical attention promptly if those symptoms arise [see Warnings and Precautions (5.5)].

Tumor Lysis Syndrome

Inform patients to immediately report and seek medical attention for any symptoms such as nausea, vomiting, weakness, edema, shortness of breath, muscle cramps, and seizures, which may indicate tumor lysis syndrome [see Warnings and Precautions (5.8)].

Growth and Development in Pediatric Patients

Inform pediatric patients and their caregivers of the possibility of developing bone growth abnormalities, bone pain, or gynecomastia and advise them to seek medical attention promptly if those symptoms arise [see Warnings and Precautions (5.10)].

Embryo-Fetal Toxicity

- Advise pregnant women of the potential risk to a fetus [see Warnings and Precautions (5.9) and Use in Specific Populations (8.1)].
- Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment with SPRYCEL and for 30 days after the last dose. Advise females to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, while taking SPRYCEL [see Warnings and Precautions (5.9) and Use in Specific Populations (8.1, 8.3)].

Lactation

- Advise women that breastfeeding is not recommended during treatment with SPRYCEL and for 2 weeks after the final dose [see Use in Specific Populations (8.2)].

Gastrointestinal Complaints

Inform patients that they may experience nausea, vomiting, or diarrhea with SPRYCEL. Advise patients to seek medical attention if these symptoms are bothersome or persistent.

| PATIENT INFORMATION SPRYCEL® (spry-aeil) (dasatinib) tablets |
|---|
| <p>What is SPRYCEL? SPRYCEL is a prescription medicine used to treat:</p> <ul style="list-style-type: none"> adults with newly diagnosed Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase. adults with Ph+ CML who no longer benefit from, or did not tolerate, other treatment, including imatinib. adults with Ph+ acute lymphoblastic leukemia (Ph+ ALL) who no longer benefit from, or did not tolerate, other treatment. children 1 year of age and older with Ph+ CML in chronic phase. children 1 year of age and older with newly diagnosed Ph+ ALL in combination with chemotherapy. <p>It is not known if SPRYCEL is safe and effective in children under 1 year of age.</p> |
| <p>Before taking SPRYCEL, tell your healthcare provider about all of your medical conditions, including if you:</p> <ul style="list-style-type: none"> have problems with your immune system have heart problems, including a condition called congenital long QT syndrome have low potassium or low magnesium levels in your blood are lactose (milk sugar) intolerant are pregnant or plan to become pregnant. SPRYCEL can harm your unborn baby. <p>Females who can become pregnant:</p> <ul style="list-style-type: none"> You should not become pregnant during treatment with SPRYCEL. You should use effective birth control (contraception) during treatment and for 30 days after your last dose of SPRYCEL. <p>Male with female partners who can become pregnant:</p> <ul style="list-style-type: none"> You should use effective birth control (contraception) during treatment and for 30 days after your last dose of SPRYCEL. Your female partner should call her healthcare provider if she becomes pregnant or thinks she is pregnant during your treatment with SPRYCEL. <p>are breastfeeding or plan to breastfeed. It is not known if SPRYCEL passes into your breast milk. You should not breastfeed during treatment and for 2 weeks after your last dose of SPRYCEL.</p> <p>Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, antacids, and herbal supplements. If you take an antacid medicine, take it 2 hours before or 2 hours after your dose of SPRYCEL.</p> |
| <p>How should I take SPRYCEL?</p> <ul style="list-style-type: none"> Take SPRYCEL exactly as your healthcare provider tells you to take it. Your healthcare provider may change your dose of SPRYCEL or temporarily stop treatment with SPRYCEL. Do not change your dose or stop taking SPRYCEL without first talking to your healthcare provider. Take SPRYCEL 1 time a day. Take SPRYCEL with or without food, either in the morning or in the evening. Swallow SPRYCEL tablets whole. Do not crush, cut or chew the tablets. <ul style="list-style-type: none"> If your child cannot swallow tablets whole, talk with your healthcare provider. You should not drink grapefruit juice during treatment with SPRYCEL. <ul style="list-style-type: none"> If you miss a dose of SPRYCEL, take your next scheduled dose at your regular time. Do not take two doses at the same time. If you take too much SPRYCEL, call your healthcare provider or go to the nearest hospital emergency room right away. |
| <p>What are the possible side effects of SPRYCEL? SPRYCEL may cause serious side effects, including:</p> <ul style="list-style-type: none"> Low blood cell counts. Low blood cell counts are common with SPRYCEL and can be severe, including low red blood cell counts (anemia), low white blood cell counts (neutropenia), and low platelet counts (thrombocytopenia). Your healthcare provider will do blood tests to check your blood cell counts regularly during your treatment with |

SPRYCEL. Call your healthcare provider right away if you have a fever or any signs of an infection during treatment with SPRYCEL.

- **Bleeding problems.** Bleeding problems are common with SPRYCEL. Sometimes these bleeding problems can be serious and lead to death. Call your healthcare provider right away if you have:
 - unusual bleeding or bruising of your skin
 - bright red or dark tar-like stools
 - decreased alertness, headache, or change in speech
- **Your body may hold too much fluid (fluid retention).** Fluid retention is common with SPRYCEL and can sometimes be severe. In severe cases, fluid may build up in the lining of your lungs, the sac around your heart, or your stomach cavity. Call your healthcare provider right away if you get any of these symptoms during treatment with SPRYCEL:
 - swelling all over your body
 - weight gain
 - shortness of breath, especially if this happens with low levels of physical activity or at rest
 - dry cough
 - chest pain when taking a deep breath
- **Heart and blood vessel (cardiovascular) problems.** SPRYCEL may cause heart problems, including an abnormal heart rate, a heart attack, or small strokes that last only a few minutes or a few hours, called transient ischemic attacks (TIAs). TIAs are often a warning sign that you are at risk for a more serious stroke. Your healthcare provider will monitor the potassium and magnesium levels in your blood and your heart function. Get medical help right away if you develop any of the following symptoms during treatment with SPRYCEL:
 - chest pain
 - shortness of breath
 - feeling like your heart is beating too fast or you feel abnormal heart beats
 - vision changes that may last for a short time
 - slurred speech
- **Pulmonary Arterial Hypertension (PAH).** SPRYCEL may cause high blood pressure in the vessels of your lungs. PAH may happen at any time during your treatment with SPRYCEL. Your healthcare provider should check your heart and lungs before and during treatment with SPRYCEL. Call your healthcare provider right away if you have shortness of breath, tiredness, or swelling all over your body (fluid retention).
- **Severe skin reactions.** SPRYCEL may cause skin reactions that can sometimes be severe. Get medical help right away if you get a skin reaction with fever, sore mouth or throat, or blistering or peeling of your skin or in the mouth.
- **Tumor Lysis Syndrome (TLS).** TLS is caused by a fast breakdown of cancer cells. TLS can cause you to have kidney failure and the need for dialysis treatment, and an abnormal heartbeat. Your healthcare provider may do blood tests to check you for TLS. Call your healthcare provider or get emergency medical help right away if you develop any of these symptoms during treatment with SPRYCEL:
 - nausea
 - vomiting
 - weakness
 - swelling
 - shortness of breath
 - muscle cramps
 - seizures
- **Slowing of growth and development in children.** Effects on bone growth and development in children have happened with SPRYCEL and can sometimes be severe. Your healthcare provider will monitor your child's bone growth and development during treatment with SPRYCEL. Get medical help right away if your child develops bone pain.

The most common side effects of SPRYCEL in adults and children receiving SPRYCEL alone include:

- diarrhea
- headache
- skin rash
- shortness of breath
- tiredness
- nausea
- muscle pain

The most common side effects of SPRYCEL in children receiving SPRYCEL with chemotherapy include:

- swelling, pain and redness of the lining of your mouth, throat, stomach and bowel (mucositis)
- low white blood cell counts with fever
- fever
- diarrhea
- nausea
- tiredness
- constipation
- abnormal heart rate
- high blood pressure (hypertension)
- swelling
- infections
- low blood pressure

- vomiting
- muscle pain
- stomach-area (abdominal) pain
- cough
- headache
- rash
- decreased appetite
- allergic reactions
- shortness of breath
- nose bleed
- numbness or tingling of your hands and feet
- feeling confused or disoriented

SPRYCEL may cause fertility problems in males and females. Talk to your healthcare provider if this is a concern for you.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all of the possible side effects of SPRYCEL.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store SPRYCEL?

- Store SPRYCEL at room temperature between 68°F to 77°F (20°C to 25°C).
- Ask your healthcare provider or pharmacist about the right way to throw away expired or unused SPRYCEL.
- Wear latex or nitrile gloves when handling tablets that have accidentally been crushed or broken.
- Females who are pregnant should not handle crushed or broken SPRYCEL tablets.

Keep SPRYCEL and all medicines out of the reach of children.

General information about the safe and effective use of SPRYCEL

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use SPRYCEL for a condition for which it is not prescribed. Do not give SPRYCEL to other people even if they have the same symptoms you have. It may harm them. You can ask your healthcare provider or pharmacist for information about SPRYCEL that is written for health professionals.

What are the ingredients in SPRYCEL?

Active ingredient: dasatinib

Inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, and magnesium stearate. The tablet coating consists of hypromellose, titanium dioxide, and polyethylene glycol.

Distributed by: Bristol-Myers Squibb Company, Princeton, NJ 08543 USA
For more information, go to www.sprycel.com or call 1-800-393-2056

This Patient Information has been approved by the U.S. Food and Drug Administration

Revised: June 2011

Advice
their
Distributed by:
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

CERTIFICATE OF A PHARMACEUTICAL PRODUCT

Sprycel® (dasatinib) Tablets NDA 21-986; Approval Date: June 28, 2006

| Ingredient | 20 mg | 50 mg | 70 mg |
|--|-------|-------|-------|
| Dasatinib ^a | 20.0 | 50.0 | 70.0 |
| Lactose Monohydrate ^b | 27.0 | 67.5 | 94.5 |
| Microcrystalline Cellulose | 27.0 | 67.5 | 94.5 |
| Hydroxypropyl Cellulose | 2.4 | 6.0 | 8.4 |
| Croscarmellose Sodium | 3.2 | 8.0 | 11.2 |
| Magnesium Stearate | 0.4 | 1.0 | 1.4 |
| Opadry® White, YS-1-18177-A ^c | 3.2 | 7.0 | 8.4 |
| Purified Water ^d | ---- | ---- | ---- |

^a The amount shown is based on a theoretical Assay of 100% for dasatinib on an anhydrous basis. The exact amount will vary depending on the Assay "as is" of dasatinib.

^b The amount of lactose monohydrate will vary depending upon the amount of dasatinib used.

^c Opadry® White YS-1-18177-A contains hypromellose 6 cP (59.8% w/w), titanium dioxide (31.2% w/w), and polyethylene glycol 400 (9.0% w/w).

^d Removed during processing.

US storage conditions and shelf life: Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature] S h e l f l i f e-36 months

TRADUCCIÓN PÚBLICA

APOSTILLA

(Convención de la Haya del 5 de octubre de 1961)

1. País: **Estados Unidos de Norte América**
2. El presente documento público ha sido firmado por: **Carole Jones**
3. quien actúa en calidad de: **Directora de División, Departamento de Cumplimiento de Exportaciones**
4. y está revestido del sello / timbre del **Ministerio de Salud y Servicios Humanos de los Estados Unidos**

Certificado

5. en: **Washington, DC**
6. el: **30 de octubre de 2021**
7. por el: **Subsecretario de Legalizaciones del Departamento de Estado de los Estados Unidos**
8. con el número: **22003824-16**
9. Sello / timbre: (En blanco)
10. Firma: (Sigue una firma ilegible). **Fernesia T. Crawford.**

RIESGO
PÚBLICA
ES
AP. FEDERAL
QUES
AP. FEDERAL
L. N° 2047

ADMINISTRACIÓN DE MEDICAMENTOS Y ALIMENTOS DE LOS ESTADOS UNIDOS -----

Centro de Evaluación e Investigación de Medicamentos -----

10903 New Hampshire Ave., Silver Spring, MD 20993, Estados Unidos de América. -----

CDERExportCertificateProgram@fda.hhs.gov – Teléfono: (301) 796-4950 -----

Certificado de un Producto Farmacéutico – Fabricante Extranjero -----

Fecha de emisión del certificado: **30 de septiembre de 2021** -----

Certificado Número: **3BR4-8GY9** -----

Fecha de Vencimiento del Certificado: **29 de septiembre de 2023** -----

País Importador: **Argentina** -----

País Exportador: **Estados Unidos de América** -----

1. Nombre Comercial del Medicamento, Denominación común Internacional o Nacional (según corresponda) y forma farmacéutica: **SPRYCEL®, Comprimido**-----

1.1 Principio(s) Activo(s) y cantidad(es) por unidad de dosis (se prefiere la composición cuantitativa completa): **dasatinib 20 MG**-----

1.2. ¿Este producto cuenta con la licencia para colocarlo en el mercado y utilizarlo en el país exportador? **SI** -----

1.3 ¿Este producto está en el mercado en el país exportador? **SI** -----

2.A.1. Número de licencia del producto y fecha de emisión: **021986 28/06/2006** -----

2.A.2. Nombre y dirección del titular de la licencia del producto: **Bristol-Mvers Squibb Company, Casilla de Correo 4000, Princeton, NJ 08543 Estados Unidos de América**-----

2.A.3. Estado del titular de la licencia del producto: **Ninguna.** -----

2.A.3.1. Nombre y dirección del fabricante: **Patheon Inc., 2100 Syntex Court, Mississauga, Ontario L5N 7K9 CANADÁ** -----

2.A.4 ¿Se encuentra adjunto el resumen aprobado? **NO** -----

2.A.5 ¿Está adjunta la información sobre el producto oficialmente completa y de conformidad con la licencia? **SI** -----

2.A.6 Nombre y dirección del solicitante del certificado (si difiere del titular de la licencia): **Bristol Myers Squibb. 4931 George Road, Tampa, FL 33634 Estados Unidos de América**-----

ALTO RIESGO
AGENCIA PÚBLICA
INGLES
- CAP. FEDERAL
PORTUGUES
- CAP. FEDERAL
B.A. Nº 2047

2.B.4 Observaciones: Acondicionador: **AndersonBrecon Inc., 4545 Assembly Drive, Rockford, IL 61109.** -----

Esta certificación de la FDA corresponde al producto comercializados en los Estados Unidos de América. -----

3. ¿La autoridad certificadora organiza inspecciones periódicas de la planta de fabricación en la cual se produce la forma farmacéutica? **SI** -----

3.1. Periodicidad de las inspecciones de rutina (años): **De conformidad con la sección 510(h)(3) de la Ley Federal de Alimentos Fármacos y Cosméticos, las inspecciones tendrán lugar de conformidad a un esquema basado en el riesgo** -----

3.2. ¿Se ha inspeccionado la fabricación de este tipo de forma farmacéutica? **SI** -----

3.3. ¿Las instalaciones y las operaciones cumplen con las normas de Buenas Prácticas de Fabricación tal como recomienda la Organización Mundial de la Salud? (Las Buenas Prácticas de Fabricación incluido el Código de Regulaciones Federales 21 partes 210, 211 o ICH Q7A): **SI, al momento de la inspección, el centro cumple con las cGMP de la FDA.** -----

3.4. ¿La información presentada por el solicitante satisface a la autoridad certificadora con respecto a todos los aspectos de Fabricación del producto a los que se comprometió la otra parte? **SI** -----

Aparece una firma ilegible y debajo se lee: Carole Jones, Directora de División, Departamento de Cumplimiento de Exportaciones -----

El presente certificado es emitido de conformidad al formato recomendado por la Organización Mundial de la Salud revisado el 1° de octubre de 1997. Sitio web: www.who.int. -----

Aparece una estampilla dorada donde se lee: Departamento de Salud y Servicios Humanos - Estados Unidos. -----

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N° 2047

-----CERTIFICADO DE PRODUCTO FARMACÉUTICO-----

-----Sprycel® (dasatinib) Comprimidos -----

-----NDA 21-986; Fecha de Aprobación: 28 de junio de 2006-----

| Principio | 20 mg | 50 mg | 70 mg |
|---|-------|-------|-------|
| Dasatinib ^a | 20,0 | 50,0 | 70,0 |
| Lactosa Monohidrato ^b | 27,0 | 67,5 | 94,5 |
| Celulosa microcristalina | 27,0 | 67,5 | 94,5 |
| Hidroxiopropilcelulosa | 2,4 | 6,0 | 8,4 |
| Croscarmelosa de sodio | 3,2 | 8,0 | 11,2 |
| Estearato de magnesio | 0,4 | 1,0 | 1,4 |
| Opadry® Blanco, YS-1-18177-A ^c | 3,2 | 7,0 | 8,4 |
| Agua Purificada ^d | | | |

a La cantidad indicada se basa en un ensayo teórico del 100% para dasatinib en base anhidra. La cantidad exacta variará según el Ensayo "tal como está" de dasatinib-----

b La cantidad de lactosa monohidrato variará en función de la cantidad de dasatinib utilizada. -----

c Opadry® Blanco YS-1-18177-A contiene hipromelosa 6 cP (59,8% p/p), dióxido de titanio (31,2% p/p) y polietilenglicol 400 (9,0% p/p). -----

d Eliminado durante el procesamiento. -----

Condiciones de conservación y vida útil en los Estados Unidos: Conservar a 20°C a 25°C (68°F a 77°F); se permiten excursiones entre 15°C y 30°C (59°F y 86°F) [ver USP Temperatura ambiente controlada]. -----

Vida útil-36 meses-----

ES TRADUCCIÓN FIEL DEL INGLÉS AL ESPAÑOL (4 PÁGINAS) DE LA PARTE PERTINENTE DEL DOCUMENTO QUE TUVE A LA VISTA Y AL QUE ME REMITO. EN BUENOS AIRES, A LOS 08 DÍAS DEL MES DE NOVIEMBRE DE 2021. -----

Adriana Luis Riesgo
ADRIANA LUIS RIESGO
 TRADUCTORA PÚBLICA

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COLEGIO DE TRADUCTORES PÚBLICOS
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 Corresponde a la Legislación
 N° 70641/21 A
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COLEGIO DE TRADUCTORES PÚBLICOS DE LA CIUDAD DE BUENOS AIRES

República Argentina
Ley 20305

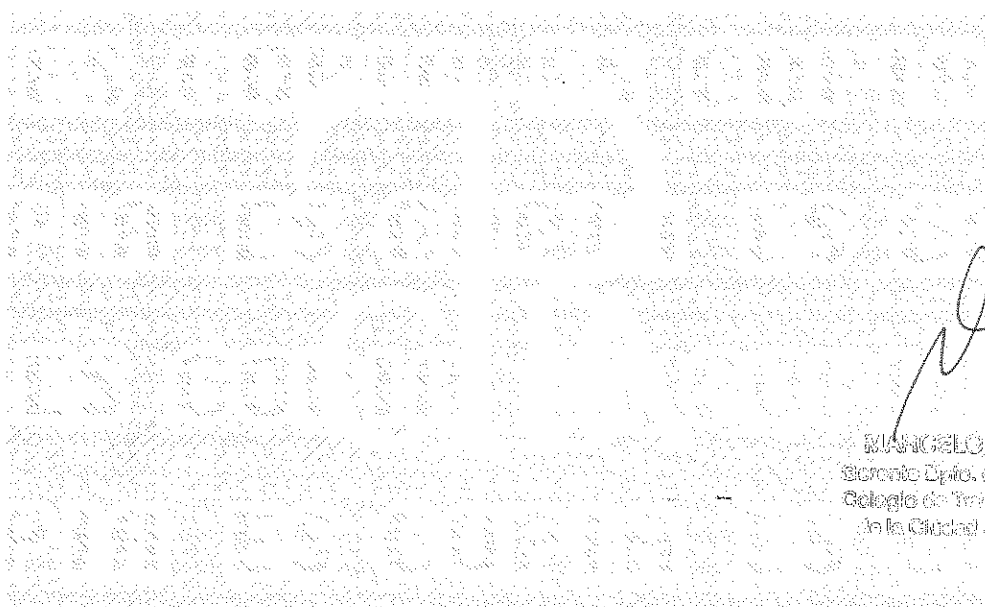
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que obran en los registros de esta institución, en el folio **425** del Tomo **8** en el idioma **INGLÉS**.

Legalización número: **70641**

Buenos Aires, 10/11/2021




WANGELOR SIGALOFF
Secretario Depto. de Legalizaciones
Colegio de Traductores Públicos
de la Ciudad de Buenos Aires

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CPP Sprycel 50 mg

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country: *United States of America*

This public document

2. has been signed by *Carole Jones*

3. acting in the capacity of *Division Director, Exports Compliance Branch*

4. bears the seal/stamp of *U. S. Department of Health and Human Services*

Certified

5. at Washington, D.C.

6. the *thirtieth* of October, 2021

7. by *Assistant Authentication Officer, United States Department of State*

8. No. *22003824-14*

9. Seal/Stamp:

10. Signature:

F. Crawford

Fernesia T. Crawford

United States Food and Drug Administration
Center for Drug Evaluation and Research

9903 New Hampshire Ave, Silver Spring, MD 20993, United States of America
CDERExportCertificateProgram@fda.hhs.gov - Telephone (301) 796-4950

Certificate of a Pharmaceutical Product - Foreign Manufacturer

Certificate Number: 4MK8-3SEE

Certificate Issue Date: September 30, 2021

Certificate Expiration Date: September 29, 2023

Importing Country: ARGENTINA

Exporting Country: UNITED STATES of AMERICA

1. Drug Trade Name, International or National non-proprietary name (as applicable) & dosage form: SPRYCEL®, Tablet

1.1 Active Ingredient(s) and amount(s) per unit dose (complete quantitative composition is preferred): dasatinib 50 MG

1.2 Is this product licensed to be placed on the market for use in the exporting country? Yes

1.3 Is this product actually on the market in the exporting country? Yes

2.A.1 Product license number & date of issue: 021986 06/28/2006

2.A.2 Product license holder name & address: Bristol-Myers Squibb Company, PO Box 4000, Princeton, NJ 08543 United States of America

2.A.3 Status of Product license holder: Neither

2.A.3.1 Manufacturer name & address: Patheon Inc., 2100 Syntex Court, Mississauga, Ontario L5N 7K9 CANADA

2.A.4 Is a summary basis for approval appended? No

2.A.5 Is the attached product information, complete and consonant with the license? Yes

2.A.6 Applicant name & address for certificate (if different from the license holder): Bristol Myers Squibb, 4931 George Road, Tampa, FL 33634 United States of America

2.B.4 Remarks: Package: AndersonBrecon Inc., 4545 Assembly Drive, Rockford, IL 61109

This FDA certification pertains to the product marketed in the United States of America.

3. Does the certifying authority arrange for periodic inspection of the manufacturing plant in which the dosage form is produced? Yes

3.1 Periodicity of routine inspections (years): Pursuant to section 510(b)(3) of the Federal Food, Drug & Cosmetic Act, Inspections will occur in accordance with a risk-based schedule

3.2 Has the manufacture of this type of dosage form been inspected? Yes

3.3 Do the facilities and operations conform to GMPs as recommended by the WHO? (GMPs including 21 Code of Federal Regulations parts 210, 211, or ICH Q7A): Yes, at time of inspection, site complies with FDA cGMP

3.4 Does the information submitted by the applicant satisfy the certifying authority on all aspects of the manufacture of the product undertaken by another party? Yes

Carole Jones

Carole Jones, Division Director
Exports Compliance Branch
Office of Global Drug Distribution



XXXXXXXXXX 1386684A0

Distributed by:
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

60 Tablets NDC 0003-0528-11


SPRYCEL[®]

(dasatinib)
Tablets

50
mg

Rx only

Do not crush, cut or chew tablets.
Swallow tablets whole.

 Bristol-Myers Squibb

Each film-coated tablet contains 50 mg dasatinib.
Usual Dosage: See package insert for dosing instructions,
directions for use, and precautions.
Store at 20°C to 25°C (68°F to 77°F); excursions
permitted between 15°C and 30°C (59°F and 86°F)
(see USP Controlled Room Temperature).
Do not use if inner seal of bottle is broken or missing.



For Position Only

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SPRYCEL[®]
(dasatinib)
Tablets

60 Tablets NDC 0003-0528-11



Each film-coated tablet contains 50 mg dasatinib. Usual Dosage: See package insert for dosing instructions, directions for use, and precautions. Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].

60 Tablets NDC 0003-0528-11

SPRYCEL[®]
(dasatinib)
Tablets



60 Tablets NDC 0003-0528-11

SPRYCEL[®]
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Do not crush, cut or chew tablets. Swallow tablets whole.

Do not crush, cut or chew tablets. Swallow tablets whole.

Bristol-Myers Squibb

Bristol-Myers Squibb

Do not use if inner seal of bottle is broken or missing.

Distributed by:
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA
Product of Switzerland

3041201
1386776A0

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SPRYCEL safely and effectively. See full prescribing information for SPRYCEL.

SPRYCEL (dasatinib) tablets, for oral use
Initial U.S. Approval: 2006

RECENT MAJOR CHANGES

Warnings and Precautions (5.4) 6/2021
Warnings and Precautions (5.5) 6/2021

INDICATIONS AND USAGE

SPRYCEL is a kinase inhibitor indicated for the treatment of:

- newly diagnosed adults with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase. (1, 14)
- adults with chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy including imatinib. (1, 14)
- adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) with resistance or intolerance to prior therapy. (1, 14)
- pediatric patients 1 year of age and older with Ph+ CML in chronic phase. (1, 14)
- pediatric patients 1 year of age and older with newly diagnosed Ph+ ALL in combination with chemotherapy. (1, 14)

DOSE AND ADMINISTRATION

- Chronic phase CML in adults: 100 mg once daily. (2)
- Accelerated phase CML, myeloid or lymphoid blast phase CML, or Ph+ ALL in adults: 140 mg once daily. (2)
- Chronic phase CML and ALL in pediatrics: starting dose based on body weight. (2)
- Administer orally, with or without a meal. Do not crush, cut, or chew tablets. (2)

DOSE FORMS AND STRENGTHS

Tablets: 20 mg, 50 mg, 70 mg, 80 mg, 100 mg, and 140 mg. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Myelosuppression and Bleeding Events:** Severe thrombocytopenia, neutropenia, and anemia may occur. Use caution if used concomitantly with medications that inhibit platelet function or anticoagulants. Monitor complete blood counts regularly. Transfuse and interrupt SPRYCEL when indicated. (2.5, 5.1, 5.2)
- Fluid Retention:** Fluid retention, sometimes severe, including pleural effusions. Manage with supportive care measures and/or dose modification. (2.5, 5.3)

- Cardiovascular Toxicity:** Monitor patients for signs or symptoms and treat appropriately. (5.4)
- Pulmonary Arterial Hypertension (PAH):** SPRYCEL may increase the risk of developing PAH which may be reversible on discontinuation. Consider baseline risk and evaluate patients for signs and symptoms of PAH during treatment. Stop SPRYCEL if PAH is confirmed. (5.5)
- QT Prolongation:** Use SPRYCEL with caution in patients who have or may develop prolongation of the QT interval. (5.6)
- Severe Dermatologic Reactions:** Individual cases of severe mucocutaneous dermatologic reactions have been reported. (5.7)
- Tumor Lysis Syndrome:** Tumor lysis syndrome has been reported. Maintain adequate hydration and correct uric acid levels prior to initiating therapy with SPRYCEL. (5.8)
- Embryo-Fetal Toxicity:** Can cause fetal harm. Advise patients of reproductive potential of potential risk to fetus and to use effective contraception. (5.9, 8.1, 8.3)
- Effects on Growth and Development in Pediatric Patients:** epiphyses delayed fusion, osteopenia, growth retardation, and gynecomastia have been reported. Monitor bone growth and development in pediatric patients. (5.10)

ADVERSE REACTIONS

Most common adverse reactions (≥15%) in patients receiving SPRYCEL as single-agent therapy included myelosuppression, fluid retention events, diarrhea, headache, skin rash, hemorrhage, dyspnea, fatigue, nausea, and musculoskeletal pain. (6)
Most common adverse reactions (≥30%) in pediatric patients receiving SPRYCEL in combination with chemotherapy included mucositis, febrile neutropenia, pyrexia, diarrhea, nausea, vomiting, musculoskeletal pain, abdominal pain, cough, headache, rash, fatigue, constipation, arthralgia, hypertension, edema, infections (bacterial, viral and fungal), hypotension, decreased appetite, hypersensitivity, dyspnea, epistaxis, peripheral neuropathy, and altered state of consciousness. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-888-721-8972 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Strong CYP3A4 Inhibitors:** Dose reduction may be necessary. (2.3, 7.1)
- Strong CYP3A4 Inducers:** Dose increase may be necessary. (2.3, 7.1)
- Antacids:** Avoid simultaneous administration. (7.1)
- H₂ Antagonists and Proton Pump Inhibitors:** Avoid coadministration. (7.1)

USE IN SPECIFIC POPULATIONS

Lactation: Advise women not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 6/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

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| 2.2 | Dosage of SPRYCEL in Pediatric Patients with CML or Ph+ ALL | 7.1 | Effect of Other Drugs on Dasatinib |
| 2.3 | Dose Modification | 8 | USE IN SPECIFIC POPULATIONS |
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| 6 | ADVERSE REACTIONS | 14.3 | CML in Pediatric Patients |
| | | 14.4 | Ph+ ALL in Pediatric Patients |

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

SPRYCEL (dasatinib) is indicated for the treatment of adult patients with

- newly diagnosed Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase.
- chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy including imatinib.
- Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) with resistance or intolerance to prior therapy.

SPRYCEL (dasatinib) is indicated for the treatment of pediatric patients 1 year of age and older with

- Ph+ CML in chronic phase.
- newly diagnosed Ph+ ALL in combination with chemotherapy.

2 DOSAGE AND ADMINISTRATION

2.1 Dosage of SPRYCEL in Adult Patients

The recommended starting dosage of SPRYCEL for chronic phase CML in adults is 100 mg administered orally once daily. The recommended starting dosage of SPRYCEL for accelerated phase CML, myeloid or lymphoid blast phase CML, or Ph+ ALL in adults is 140 mg administered orally once daily. Tablets should not be crushed, cut, or chewed; they should be swallowed whole. SPRYCEL can be taken with or without a meal, either in the morning or in the evening.

2.2 Dosage of SPRYCEL in Pediatric Patients with CML or Ph+ ALL

The recommended starting dosage for pediatrics is based on body weight as shown in Table 1. The recommended dose should be administered orally once daily with or without food. Recalculate the dose every 3 months based on changes in body weight, or more often if necessary.

Do not crush, cut or chew tablets. Swallow tablets whole. There are additional administration considerations for pediatric patients who have difficulty swallowing tablets whole [see Use in Specific Populations (8.4) and Clinical Pharmacology (12.3)].

Table 1: Dosage of SPRYCEL for Pediatric Patients*

| Body Weight (kg) ^b | Daily Dose (mg) |
|-------------------------------|-----------------|
| 10 to less than 20 | 40 mg |
| 20 to less than 30 | 60 mg |
| 30 to less than 45 | 70 mg |
| at least 45 | 100 mg |

* For pediatric patients with Ph+ ALL, begin SPRYCEL therapy on or before day 15 of induction chemotherapy, when diagnosis is confirmed and continue for 2 years.

^b Tablet dosing is not recommended for patients weighing less than 10 kg.

16 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

Refer to Section 2.4 for recommendations on dose escalation in adults with CML and Ph+ ALL, and pediatric patients with CML.

2.3 Dose Modification

Strong CYP3A4 Inducers

Avoid the use of concomitant strong CYP3A4 inducers and St. John's wort. If patients must be coadministered a strong CYP3A4 inducer, consider a SPRYCEL dose increase. If the dose of SPRYCEL is increased, monitor the patient carefully for toxicity [see Drug Interactions (7.1)].

Strong CYP3A4 Inhibitors

Avoid the use of concomitant strong CYP3A4 inhibitors and grapefruit juice. Recommend selecting an alternate concomitant medication with no or minimal enzyme inhibition potential, if possible. If SPRYCEL must be administered with a strong CYP3A4 inhibitor, consider a dose decrease to:

- 40 mg daily for patients taking SPRYCEL 140 mg daily.
- 20 mg daily for patients taking SPRYCEL 100 mg daily.
- 20 mg daily for patients taking SPRYCEL 70 mg daily.

For patients taking SPRYCEL 60 mg or 40 mg daily, consider interrupting SPRYCEL until the inhibitor is discontinued. Allow a washout period of approximately 1 week after the inhibitor is stopped before reinitiating SPRYCEL.

These reduced doses of SPRYCEL are predicted to adjust the area under the curve (AUC) to the range observed without CYP3A4 inhibitors; however, clinical data are not available with these dose adjustments in patients receiving strong CYP3A4 inhibitors. If SPRYCEL is not tolerated after dose reduction, either discontinue the strong CYP3A4 inhibitor or interrupt SPRYCEL until the inhibitor is discontinued. Allow a washout period of approximately 1 week after the inhibitor is stopped before the SPRYCEL dose is increased [see Drug Interactions (7.1)].

2.4 Dose Escalation in Adults with CML and Ph+ ALL, and Pediatric Patients with CML

For adult patients with CML and Ph+ ALL, consider dose escalation to 140 mg once daily (chronic phase CML) or 180 mg once daily (advanced phase CML and Ph+ ALL) in patients who do not achieve a hematologic or cytogenetic response at the recommended starting dosage. For pediatric patients with CML, consider dose escalation to 120 mg once daily (see Table 2 below) if dose escalation is not recommended for pediatric patients with Ph+ ALL, where not recommended in combination with chemotherapy.

Escalate the SPRYCEL dose as shown in Table 2 in pediatric patients with Ph+ ALL who do not achieve a hematologic or cytogenetic response at the recommended starting dosage.

Table 2: Dose Escalation for Pediatric CML

| Formulation | Dose (maximum daily dose) | |
|-------------|---------------------------|----------------|
| | Starting Dose | Escalated Dose |
| Tablets | 40 mg | 60 mg |
| | 60 mg | 70 mg |
| | 70 mg | 100 mg |

2.5 Dose Adjustment for Adverse Reactions

Myelosuppression

In clinical studies, myelosuppression was managed by dose interruption, dose reduction, or discontinuation of study therapy. Hematopoietic growth factor has been used in patients with resistant myelosuppression. Guidelines for dose modifications for adult and pediatric patients are summarized in Tables 3 and 4, respectively.

Table 3: Dose Adjustments for Neutropenia and Thrombocytopenia in Adults

| Chronic Phase CML (starting dose 100 mg once daily) | ANC* <0.5 × 10 ⁹ /L or Platelets <50 × 10 ⁹ /L | 1. Stop SPRYCEL until ANC ≥1.0 × 10 ⁹ /L and platelets ≥50 × 10 ⁹ /L. 2. Resume treatment with SPRYCEL at the original starting dose if recovery occurs in ≤7 days. 3. If platelets <25 × 10 ⁹ /L or recurrence of ANC <0.5 × 10 ⁹ /L for >7 days, repeat Step 1 and resume SPRYCEL at a reduced dose of 80 mg once daily for second episode. For third episode, further reduce dose to 50 mg once daily (for newly diagnosed patients) or discontinue SPRYCEL (for patients resistant or intolerant to prior therapy including imatinib). |
|--|--|--|
| Accelerated Phase CML, Blast Phase CML and Ph+ ALL (starting dose 140 mg once daily) | ANC* <0.5 × 10 ⁹ /L or Platelets <10 × 10 ⁹ /L | 1. Check if cytopenia is related to leukemia (marrow aspirate or biopsy). 2. If cytopenia is unrelated to leukemia, stop SPRYCEL until ANC ≥1.0 × 10 ⁹ /L and platelets ≥20 × 10 ⁹ /L and resume at the original starting dose. 3. If recurrence of cytopenia, repeat Step 1 and resume SPRYCEL at a reduced dose of 100 mg once daily (second episode) or 80 mg once daily (third episode). 4. If cytopenia is related to leukemia, consider dose escalation to 180 mg once daily. |

*ANC: absolute neutrophil count

Table 4: Dose Adjustments for Neutropenia and Thrombocytopenia in Pediatric Patients with Ph+ CML

| | Dose (maximum dose per day) | | |
|--|---|----------------------------------|-------------------------------|
| | Original Starting Dose | One-Level Dose Reduction | Two-Level Dose Reduction |
| 1. If cytopenia persists for more than 3 weeks, check if cytopenia is related to leukemia (marrow aspirate or biopsy) | Tablets 40 mg 60 mg 70 mg 100 mg | 20 mg 40 mg 60 mg 80 mg | ** 20 mg 50 mg 70 mg |
| 2. If cytopenia is unrelated to leukemia, stop SPRYCEL until ANC* ≥1.0 × 10 ⁹ /L and platelets ≥75 × 10 ⁹ /L, and resume at the original starting dose or at a reduced dose. | | | |
| 3. If cytopenia recurs, repeat marrow aspirate/biopsy and resume SPRYCEL at a reduced dose. | | | |

*ANC: absolute neutrophil count
** lower tablet dose not available

For pediatric patients with chronic phase CML, if Grade ≥ 3 neutropenia or thrombocytopenia recurs during complete hematologic response (CHR), interrupt SPRYCEL and resume at a reduced dose. Implement temporary dose reductions for intermediate degrees of cytopenia and disease response as needed.

For pediatric patients with Ph+ ALL, if neutropenia and/or thrombocytopenia result in a delay of the next block of treatment by more than 14 days, interrupt SPRYCEL and resume at the same dose level once the next block of treatment is started. If neutropenia and/or thrombocytopenia persist and the next block of treatment is delayed another 7 days, perform a bone marrow assessment to assess cellularity and percentage of blasts. If marrow cellularity is <10%, interrupt treatment with SPRYCEL until ANC >500/μL (0.5 × 10⁹/L), at which time treatment may be resumed at full dose. If marrow cellularity is >10%, resumption of treatment with SPRYCEL may be considered.

Non-Hematologic Adverse Reactions

For adults with Ph+ CML and ALL, and pediatric patients with Ph+ CML, if a severe non-hematologic adverse reaction develops with SPRYCEL use, treatment must be withheld until the

event has resolved or improved. Thereafter, treatment can be resumed as appropriate at a reduced dose depending on the severity and recurrence of the event [see Warnings and Precautions (5.1)].

For pediatric patients with Ph+ ALL, interrupt treatment for cases of grade ≥ 3 non-hematologic adverse reactions with the exception of liver function test abnormalities, and resume at a reduced dose when resolved to grade ≤1. For elevated direct bilirubin over 5 times the institutional upper limit of normal (ULN), interrupt treatment until improvement to baseline or grade ≤1. For elevated AST/ALT over 15 times the institutional ULN, interrupt treatment until improvement to baseline or grade <1. For recurrent liver function test abnormalities as above, reduce the dose if this adverse reaction recurs after reinitiation of SPRYCEL. Dose reduction recommendations are described in Table 5.

Table 5: Dose Adjustments for Non-Hematologic Toxicities in Pediatric Patients

| | Dose (maximum dose per day) | | |
|---|---|----------------------------------|-------------------------------|
| | Original Starting Dose | One-Level Dose Reduction | Two-Level Dose Reduction |
| 1. If a non-hematologic toxicity grade 2 occurs, consider interrupting SPRYCEL if no recovery despite symptomatic therapy, once recovered to grade ≤1, resume at the original starting dose. Resume SPRYCEL at a reduced dose for recurrent events. | Tablets 40 mg 60 mg 70 mg 100 mg | 20 mg 40 mg 60 mg 80 mg | ** 20 mg 50 mg 70 mg |
| 2. If a non-hematologic toxicity grade 3 occurs, stop SPRYCEL until recovery to grade ≤1 and then resume at a reduced dose. | | | |
| 3. If direct bilirubin is >5 ULN or AST/ALT >15 ULN, interrupt SPRYCEL until recovery to grade ≤1 and then resume SPRYCEL at the original starting dose. Resume SPRYCEL at a reduced dose for recurrent events. | | | |

** lower tablet dose not available

3 DOSAGE FORMS AND STRENGTHS

SPRYCEL (dasatinib) Tablets are available as 20-mg, 50-mg, 70-mg, 80-mg, 100-mg, and 140-mg white to off-white, biconvex, film-coated tablets.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Myelosuppression

Treatment with SPRYCEL is associated with severe (NCI CTCAE Grade 3 or 4) thrombocytopenia, neutropenia, and anemia, which occur earlier and more frequently in patients with advanced phase CML or Ph+ ALL than in patients with chronic phase CML [see Adverse Reactions (6.1)].

In patients with chronic phase CML, perform complete blood counts (CBCs) every 2 weeks for 12 weeks, then every 3 months thereafter, or as clinically indicated. In patients with advanced phase CML or Ph+ ALL, perform CBCs weekly for the first 2 months and then monthly thereafter, or as clinically indicated.

In pediatric patients with Ph+ ALL treated with SPRYCEL in combination with chemotherapy, perform CBCs prior to the start of each block of chemotherapy and as clinically indicated. During the consolidation blocks of chemotherapy, perform CBCs every 2 days until recovery.

Myelosuppression is generally reversible and usually managed by withholding SPRYCEL temporarily and/or dose reduction [see Dosage and Administration (2.5)].

5.2 Bleeding-Related Events

SPRYCEL can cause serious and fatal bleeding. In all CML or Ph+ ALL clinical studies, Grade ≥3 central nervous system (CNS) hemorrhages, including fatalities, occurred in <1% of patients receiving SPRYCEL. The incidence of Grade 3/4 hemorrhage, occurred in 5.8% of adult patients and generally required treatment interruptions and transfusions. The incidence of Grade 5 hemorrhage occurred in 0.4% of adult patients. The most frequent site of hemorrhage was gastrointestinal [see Adverse Reactions (6.1)]. Most bleeding events in clinical studies were associated with severe thrombocytopenia. In addition to causing thrombocytopenia in human subjects, dasatinib caused platelet dysfunction *in vitro*.

Concomitant medications that inhibit platelet function or anticoagulants may increase the risk of hemorrhage.

5.3 Fluid Retention

SPRYCEL may cause fluid retention [see Adverse Reactions (6.1)]. After 5 years of follow-up in the adult randomized newly diagnosed chronic phase CML study (n=258), Grade 3 or 4 fluid retention was reported in 5% of patients, including 3% of patients with Grade 3 or 4 pleural effusion. In adult patients with newly diagnosed or imatinib-resistant or -intolerant chronic phase CML, Grade 3 or 4 fluid retention occurred in 6% of patients treated with SPRYCEL at the recommended dose (n=548). In adult patients with advanced phase CML or Ph+ ALL treated with SPRYCEL at the recommended dose (n=304), Grade 3 or 4 fluid retention was reported in 8% of patients, including Grade 3 or 4 pleural effusion reported in 7% of patients. In pediatric patients with chronic phase CML, cases of Grade 1 or 2 fluid retention were reported in 10.3% of patients.

Duration of Treatment

SPRYCEL in pediatric patients with Ph+ ALL was administered [see Dosage and Administration (2.2) and Clinical Studies (7.1)].

SPRYCEL should be administered according to the following special handling and disposal procedures.¹

1. Do not touch, break, or crush tablets. Do not touch or handle broken tablets. Do not breathe dust from broken tablets. Do not get SPRYCEL on your hands, face, or clothes. Do not get SPRYCEL in your eyes, nose, or mouth. Do not get SPRYCEL on your skin. Do not get SPRYCEL on your hair. Do not get SPRYCEL on your face. Do not get SPRYCEL on your neck. Do not get SPRYCEL on your chest. Do not get SPRYCEL on your stomach. Do not get SPRYCEL on your back. Do not get SPRYCEL on your arms. Do not get SPRYCEL on your legs. Do not get SPRYCEL on your feet. Do not get SPRYCEL on your hands. Do not get SPRYCEL on your fingers. Do not get SPRYCEL on your toes. Do not get SPRYCEL on your nails. Do not get SPRYCEL on your hair. Do not get SPRYCEL on your face. Do not get SPRYCEL on your neck. Do not get SPRYCEL on your chest. Do not get SPRYCEL on your stomach. Do not get SPRYCEL on your back. Do not get SPRYCEL on your arms. Do not get SPRYCEL on your legs. Do not get SPRYCEL on your feet. Do not get SPRYCEL on your hands. Do not get SPRYCEL on your fingers. Do not get SPRYCEL on your toes. Do not get SPRYCEL on your nails.

Table 7: Adverse Reactions Reported in ≥10% of Adult Patients with Newly Diagnosed Chronic Phase CML in the SPRYCEL-Treated Arm (n=258)

| Adverse Reaction | Minimum of 1 Year Follow-up | | Minimum of 5 Years Follow-up | |
|---|-----------------------------|-----------|------------------------------|-----------|
| | All Grades | Grade 3/4 | All Grades | Grade 3/4 |
| | Percent (%) of Patients | | | |
| Fluid retention | 19 | 1 | 38 | 5 |
| Pleural effusion | 10 | 0 | 28 | 3 |
| Superficial localized edema | 9 | 0 | 14 | 0 |
| Pulmonary hypertension | 1 | 0 | 5 | 1 |
| Generalized edema | 2 | 0 | 4 | 0 |
| Pericardial effusion | 1 | <1 | 4 | 1 |
| Congestive heart failure/cardiac dysfunction ^a | 2 | <1 | 2 | <1 |
| Pulmonary edema | <1 | 0 | 1 | 0 |
| Diarrhea | 17 | <1 | 22 | 1 |
| Musculoskeletal pain | 11 | 0 | 14 | 0 |
| Rash ^b | 11 | 0 | 14 | 0 |
| Headache | 12 | 0 | 14 | 0 |
| Abdominal pain | 7 | 0 | 11 | 0 |
| Fatigue | 8 | <1 | 11 | <1 |
| Nausea | 8 | 0 | 10 | 0 |

^a Includes cardiac failure acute, cardiac failure congestive, cardiomyopathy, diastolic dysfunction, ejection fraction decreased, and left ventricular dysfunction.

^b Includes erythema, erythema multiforme, rash, rash generalized, rash macular, rash papular, rash pustular, skin exfoliation, and rash vesicular.

At 60 months, there were 26 deaths in dasatinib-treated patients (10.1%) and 26 deaths in imatinib-treated patients (10.1%); 1 death in each group was assessed by the investigator as related to study therapy.

Table 8: Adverse Reactions Reported in ≥10% of Adult Patients with Chronic Phase CML Resistant or Intolerant to Prior Imatinib Therapy (minimum of 84 months follow-up)

| Adverse Reaction | 100 mg Once Daily Chronic (n=165) | |
|-----------------------------|-----------------------------------|-----------|
| | All Grades | Grade 3/4 |
| | Percent (%) of Patients | |
| Fluid retention | 48 | 7 |
| Superficial localized edema | 22 | 0 |
| Pleural effusion | 28 | 5 |
| Generalized edema | 4 | 0 |
| Pericardial effusion | 3 | 1 |
| Pulmonary hypertension | 2 | 1 |
| Headache | 33 | 1 |

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Table 9: Selected Adverse Reactions Reported in Adult Dose Optimization Trial (Imatinib-Intolerant or -Resistant Chronic Phase CML)^a

| Adverse Reaction | Minimum of 2 Years Follow-up | | Minimum of 5 Years Follow-up | | Minimum of 7 Years Follow-up | |
|---------------------------|------------------------------|-----------|------------------------------|-----------|------------------------------|-----------|
| | All Grades | Grade 3/4 | All Grades | Grade 3/4 | All Grades | Grade 3/4 |
| | Percent (%) of Patients | | | | | |
| Diarrhea | 27 | 2 | 28 | 2 | 28 | 2 |
| Fluid retention | 34 | 4 | 42 | 6 | 48 | 7 |
| Superficial edema | 18 | 0 | 21 | 0 | 22 | 0 |
| Pleural effusion | 18 | 2 | 24 | 4 | 28 | 5 |
| Generalized edema | 3 | 0 | 4 | 0 | 4 | 0 |
| Pericardial effusion | 2 | 1 | 2 | 1 | 3 | 1 |
| Pulmonary hypertension | 0 | 0 | 0 | 0 | 2 | 1 |
| Hemorrhage | 11 | 1 | 11 | 1 | 12 | 1 |
| Gastrointestinal bleeding | 2 | 1 | 2 | 1 | 2 | 1 |

^a Randomized dose-optimization trial results reported in the recommended starting dose of 100 mg once daily (n=165) population.

Table 10: Adverse Reactions Reported in ≥10% of Adult Patients with Advanced Phase CML Resistant or Intolerant to Prior Imatinib Therapy

| Adverse Reaction | 140 mg Once Daily | | | | | |
|--|-------------------------|-----------|----------------------|-----------|-----------------------|-----------|
| | Accelerated (n=157) | | Myeloid Blast (n=74) | | Lymphoid Blast (n=33) | |
| | All Grades | Grade 3/4 | All Grades | Grade 3/4 | All Grades | Grade 3/4 |
| | Percent (%) of Patients | | | | | |
| Fluid retention | 35 | 8 | 34 | 7 | 21 | 6 |
| Superficial localized edema | 18 | 1 | 14 | 0 | 3 | 0 |
| Pleural effusion | 21 | 7 | 20 | 7 | 21 | 6 |
| Generalized edema | 1 | 0 | 3 | 0 | 0 | 0 |
| Pericardial effusion | 3 | 1 | 0 | 0 | 0 | 0 |
| Congestive heart failure/cardiac dysfunction | 0 | 0 | 4 | 0 | 0 | 0 |
| Diarrhea | 1 | 0 | 4 | 3 | 0 | 0 |
| Headache | 27 | 1 | 18 | 1 | 15 | 3 |
| Musculoskeletal pain | 31 | 3 | 20 | 5 | 18 | 0 |
| Abdominal pain | 19 | 2 | 20 | 1 | 9 | 3 |
| Fatigue | 20 | 3 | 15 | 3 | 3 | 3 |
| Nausea | 0 | 0 | 8 | 1 | 0 | 0 |
| Rash | 1 | 0 | 23 | 1 | 21 | 3 |
| Constipation | 0 | 0 | 16 | 1 | 21 | 0 |
| Pruritus | 0 | 0 | 5 | 1 | 0 | 0 |

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Table 8: Adverse Reactions Reported in ≥10% of Adult Patients with Chronic Phase CML Resistant or Intolerant to Prior Imatinib Therapy (minimum of 84 months follow-up)

| Adverse Reaction | 100 mg Once Daily Chronic (n=165) | |
|---|-----------------------------------|-----------|
| | All Grades | Grade 3/4 |
| | Percent (%) of Patients | |
| Diarrhea | 28 | 2 |
| Fatigue | 26 | 4 |
| Dyspnea | 24 | 2 |
| Musculoskeletal pain | 22 | 2 |
| Nausea | 18 | 1 |
| Skin rash ^a | 18 | 2 |
| Myalgia | 13 | 0 |
| Arthralgia | 13 | 1 |
| Infection (including bacterial, viral, fungal, and non-specified) | 13 | 1 |
| Abdominal pain | 12 | 1 |
| Hemorrhage | 12 | 1 |
| Gastrointestinal bleeding | 2 | 1 |
| Pruritus | 12 | 1 |
| Pain | 11 | 1 |
| Constipation | 10 | 1 |

^a Includes drug eruption, erythema, erythema multiforme, erythroderma, exfoliative rash, generalized erythema, genital rash, heat rash, milia, rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, skin exfoliation, skin irritation, urticaria vesiculosa, and rash vesicular.

Cumulative rates of selected adverse reactions that were reported over time in patients treated with the 100 mg once daily recommended starting dose in a randomized dose-optimization trial of imatinib-resistant or -intolerant patients with chronic phase CML are shown in Table 9.

Table 10: Adverse Reactions Reported in ≥10% of Adult Patients with Advanced Phase CML Resistant or Intolerant to Prior Imatinib Therapy

| Adverse Reaction | 140 mg Once Daily | | | | | |
|---|-------------------------|-----------|----------------------|-----------|-----------------------|-----------|
| | Accelerated (n=157) | | Myeloid Blast (n=74) | | Lymphoid Blast (n=33) | |
| | All Grades | Grade 3/4 | All Grades | Grade 3/4 | All Grades | Grade 3/4 |
| | Percent (%) of Patients | | | | | |
| Infection (including bacterial, viral, fungal, and non-specified) | 10 | 6 | 14 | 7 | 9 | 0 |
| Hemorrhage | 26 | 8 | 19 | 9 | 24 | 9 |
| Gastrointestinal bleeding | 8 | 6 | 9 | 7 | 9 | 3 |
| CNS bleeding | 1 | 1 | 0 | 0 | 3 | 3 |
| Vomiting | 11 | 1 | 12 | 0 | 15 | 0 |
| Pyrexia | 11 | 2 | 18 | 3 | 6 | 0 |
| Febrile neutropenia | 4 | 4 | 12 | 12 | 12 | 12 |

^a Includes ventricular dysfunction, cardiac failure, cardiac failure congestive, cardiomyopathy, congestive cardiomyopathy, diastolic dysfunction, ejection fraction decreased, and ventricular failure.

^b Includes drug eruption, erythema, erythema multiforme, erythroderma, exfoliative rash, generalized erythema, genital rash, heat rash, milia, rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, skin exfoliation, skin irritation, urticaria vesiculosa, and rash vesicular.

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Table 11: Adverse Reactions Reported in ≥10% of Dasatinib-Treated Pediatric Patients with Chronic Phase CML (n=97)

| Adverse Reaction | Percent (%) of Patients | |
|-------------------|-------------------------|-----------|
| | All Grades | Grade 3/4 |
| Headache | 28 | 3 |
| Nausea | 20 | 0 |
| Diarrhea | 21 | 0 |
| Skin rash | 19 | 0 |
| Vomiting | 13 | 0 |
| Pain in extremity | 19 | 1 |
| Abdominal pain | 16 | 0 |
| Fatigue | 10 | 0 |
| Arthralgia | 10 | 1 |

Adverse reactions associated with bone growth and development were reported in 5 (5.2%) of pediatric patients with chronic phase CML [see Warnings and Precautions (5.10)].

Laboratory Abnormalities

Myelosuppression was commonly reported in all patient populations. The frequency of Grade 3 or 4 neutropenia, thrombocytopenia, and anemia was higher in patients with advanced phase CML than in chronic phase CML (Tables 12 and 13). Myelosuppression was reported in patients with normal baseline laboratory values as well as in patients with pre-existing laboratory abnormalities.

In patients who experienced severe myelosuppression, recovery generally occurred following dose interruption or reduction; permanent discontinuation of treatment occurred in 2% of adult patients with newly diagnosed chronic phase CML and 5% of adult patients with resistance or intolerance to prior imatinib therapy [see Warnings and Precautions (5.1)].

Grade 3 or 4 elevations of transaminases or bilirubin and Grade 3 or 4 hypocalcemia, hypokalemia, and hypophosphatemia were reported in patients with all phases of CML but were reported with an increased frequency in patients with myeloid or lymphoid blast phase CML. Elevations in transaminases or bilirubin were usually managed with dose reduction or interruption. Patients developing Grade 3 or 4 hypocalcemia during SPRYCEL therapy often had recovery with oral calcium supplementation.

Laboratory abnormalities reported in adult patients with newly diagnosed chronic phase CML are shown in Table 12. There were no discontinuations of SPRYCEL therapy in this patient population due to biochemical laboratory parameters.

Table 12: CTC Grade 3/4 Laboratory Abnormalities in Adult Patients with Newly Diagnosed Chronic Phase CML (minimum of 60 months follow-up)

| | Percent (%) of Patients | |
|--------------------------------|-------------------------|------------------|
| | SPRYCEL (n=258) | Imatinib (n=258) |
| Hematology Parameters | | |
| Neutropenia | 29 | 24 |
| Thrombocytopenia | 22 | 14 |
| Anemia | 13 | 9 |
| Biochemistry Parameters | | |
| Hypophosphatemia | 7 | 31 |
| Hypokalemia | 0 | 3 |
| Hypocalcemia | 4 | 3 |
| Elevated SGPT (ALT) | <1 | 2 |
| Elevated SGOT (AST) | <1 | 1 |
| Elevated Bilirubin | 1 | 0 |
| Elevated Creatinine | 1 | 1 |

CTC grades: neutropenia (Grade 3 ≥0.5–<1.0 × 10⁹/L, Grade 4 <0.5 × 10⁹/L); thrombocytopenia (Grade 3 ≥25–<50 × 10⁹/L, Grade 4 <25 × 10⁹/L); anemia (hemoglobin Grade 3 ≥65–<80 g/L, Grade 4 <65 g/L); elevated creatinine (Grade 3 >3–6 × upper limit of normal range (ULN), Grade 4 >6 × ULN); elevated bilirubin (Grade 3 >3–10 × ULN, Grade 4 >10 × ULN); elevated SGOT or SGPT (Grade 3 >5–20 × ULN, Grade 4 >20 × ULN); hypocalcemia (Grade 3 <7.0–6.0 mg/dL, Grade 4 <6.0 mg/dL); hypophosphatemia (Grade 3 <2.0–1.0 mg/dL, Grade 4 <1.0 mg/dL); hypokalemia (Grade 3 <3.0–2.5 mmol/L, Grade 4 <2.5 mmol/L).

Laboratory abnormalities reported in patients with CML resistant or intolerant to imatinib who received the recommended starting doses of SPRYCEL are shown by disease phase in Table 13.

Table 13: CTC Grade 3/4 Laboratory Abnormalities in Clinical Studies of CML in Adults: Resistance or Intolerance to Prior Imatinib Therapy

| Adverse Reaction | Chronic Phase CML 100 mg Once Daily (n=165) | | Advanced Phase CML 140 mg Once Daily | | |
|--------------------------------|---|----|---|----------------------------------|-----------------------------------|
| | | | Accelerated Phase (n=157) | Myeloid Blast Phase (n=74) | Lymphoid Blast Phase (n=33) |
| Hematology Parameters* | | | | | |
| Neutropenia | 36 | 58 | 77 | 79 | |
| Thrombocytopenia | 24 | 63 | 78 | 85 | |
| Anemia | 13 | 47 | 74 | 52 | |
| Biochemistry Parameters | | | | | |
| Hypophosphatemia | 10 | 13 | 12 | 18 | |
| Hypokalemia | 2 | 7 | 11 | 15 | |
| Hypocalcemia | <1 | 4 | 9 | 12 | |
| Elevated SGPT (ALT) | 0 | 2 | 5 | 3 | |
| Elevated SGOT (AST) | <1 | 0 | 4 | 3 | |
| Elevated Bilirubin | <1 | 1 | 3 | 6 | |
| Elevated Creatinine | 0 | 2 | 8 | 0 | |

CTC grades: neutropenia (Grade 3 ≥0.5–<1.0 × 10⁹/L, Grade 4 <0.5 × 10⁹/L); thrombocytopenia (Grade 3 ≥25–<50 × 10⁹/L, Grade 4 <25 × 10⁹/L); anemia (hemoglobin Grade 3 ≥65–<80 g/L, Grade 4 <65 g/L); elevated creatinine (Grade 3 >3–6 × upper limit of normal range (ULN), Grade 4 >6 × ULN); elevated bilirubin (Grade 3 >3–10 × ULN, Grade 4 >10 × ULN); elevated SGOT or SGPT (Grade 3 >5–20 × ULN, Grade 4 >20 × ULN); hypocalcemia (Grade 3 <7.0–6.0 mg/dL, Grade 4 <6.0 mg/dL); hypophosphatemia (Grade 3 <2.0–1.0 mg/dL, Grade 4 <1.0 mg/dL); hypokalemia (Grade 3 <3.0–2.5 mmol/L, Grade 4 <2.5 mmol/L).

* Hematology parameters for 100 mg once-daily dosing in chronic phase CML reflects 60-month minimum follow-up.

Among adult patients with chronic phase CML with resistance or intolerance to prior imatinib therapy, cumulative Grade 3 or 4 cytopenias were similar at 2 and 5 years including: neutropenia (36% vs 36%), thrombocytopenia (23% vs 24%), and anemia (13% vs 13%).

In the pediatric studies in CML, the rates of laboratory abnormalities were consistent with the known profile for laboratory parameters in adults.

Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ ALL) in Adults

A total of 135 adult patients with Ph+ ALL were treated with SPRYCEL in clinical studies. The median duration of treatment was 3 months (range 0.03–31 months). The safety profile of patients with Ph+ ALL was similar to those with lymphoid blast phase CML. The most frequently reported adverse reactions included fluid retention events, such as pleural effusion (24%) and superficial edema (19%), and gastrointestinal disorders, such as diarrhea (31%), nausea (24%), and vomiting (16%). Hemorrhage (19%), pyrexia (17%), rash (16%), and dyspnea (16%) were also frequently reported. Serious adverse reactions reported in ≥5% of patients included pleural effusion (11%), gastrointestinal bleeding (7%), febrile neutropenia (6%), and infection (5%).

Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ ALL) in Pediatric Patients

The safety of SPRYCEL administered continuously in combination with multiagent chemotherapy was determined in a multicohort study of 81 pediatric patients with newly diagnosed Ph+ ALL [see Clinical Studies (14.4)]. The median duration of therapy was 24 months (range 2 to 27 months).

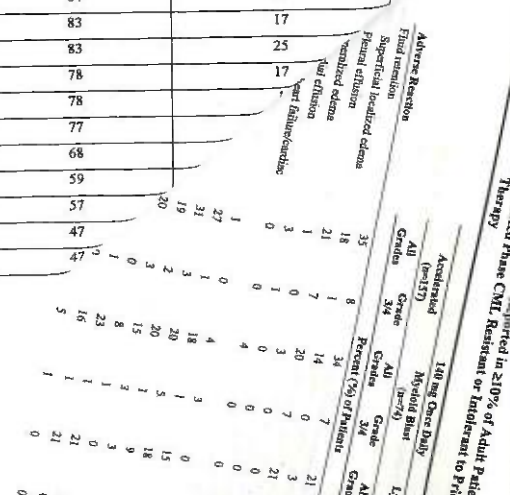
Fatal adverse reactions occurred in 3 patients (4%), all of which were due to infections. Eight (10%) patients experienced adverse reactions leading to treatment discontinuation, including fungal sepsis, hepatotoxicity in the setting of graft versus host disease, thrombocytopenia, CMV infection, pneumonia, nausea, enteritis and drug hypersensitivity.

The most common serious adverse reactions (incidence ≥10%) were pyrexia, febrile neutropenia, mucositis, diarrhea, sepsis, hypotension, infections (bacterial, viral and fungal), hypersensitivity, vomiting, renal insufficiency, abdominal pain, and musculoskeletal pain.

The incidence of common adverse reactions (incidence ≥20%) on study are shown in Table 14:

Table 14: Adverse Reactions Reported in ≥20% of Pediatric Patients with Ph+ ALL Treated with SPRYCEL in Combination with Chemotherapy CA180372 (N=81)

| Adverse Reaction | Percent (%) of Patients | |
|----------------------|-------------------------|-----------|
| | All Grades | Grade 3/4 |
| Mucositis | 93 | 60 |
| Febrile neutropenia | 86 | 86 |
| Pyrexia | 85 | 17 |
| Diarrhea | 84 | 31 |
| Nausea | 84 | 11 |
| Vomiting | 83 | 17 |
| Musculoskeletal pain | 83 | 25 |
| Abdominal pain | 78 | 17 |
| Cough | 78 | 0 |
| Headache | 77 | 0 |
| Rash | 68 | 0 |
| Fatigue | 59 | 0 |
| Constipation | 57 | 0 |
| Arrhythmia | 47 | 0 |
| Hypertension | 47 | 0 |



Adverse Reactions Reported in ≥20% of Adult Patients
 Treated with SPRYCEL in Combination with Chemotherapy
 CA180372 (N=81)

Table 14: Adverse Reactions Reported in ≥20% of Pediatric Patients with Ph+ ALL Treated with SPRYCEL in Combination with Chemotherapy CA180372 (N=81)

| | | |
|--|-----|----|
| Edema | 47 | 6 |
| Viral infection | 40 | 12 |
| Hypotension | 40 | 26 |
| Decreased appetite | 38 | 22 |
| Hypersensitivity | 36 | 20 |
| Upper respiratory tract infection | 36 | 10 |
| Dyspnea | 35 | 10 |
| Epistaxis | 31 | 6 |
| Peripheral neuropathy | 31 | 7 |
| Sepsis (excluding fungal) | n/a | 31 |
| Altered state of consciousness | 30 | 4 |
| Fungal infection | 30 | 11 |
| Pneumonia (excluding fungal) | 28 | 25 |
| Pruritus | 28 | - |
| Clostridial infection (excluding sepsis) | 25 | 14 |
| Urinary Tract Infection | 24 | 14 |
| Bacteremia (excluding fungal) | 22 | 20 |
| Erythema | 22 | 6 |
| Chills | 21 | - |
| Pleural effusion | 21 | 9 |
| Sinusitis | 21 | 10 |
| Dehydration | 20 | 9 |
| Renal insufficiency | 20 | 9 |
| Visual impairment | 20 | - |

The incidence of common adverse reactions attributed by the investigator to SPRYCEL (reported at a frequency of ≥10%, all grades and grade 3/4, respectively) on study (N=81), included febrile

neutropenia (23%, 23%), nausea (21%, 4%), vomiting (19%, 4%), mucositis (17%, 6%), musculoskeletal pain (17%, 2%), abdominal pain (16%, 5%), diarrhea (16%, 7%), rash (15%, 0%), fatigue (12%, 0%), pyrexia (12%, 6%), and headache (12%, 5%).

CTCAE grade 3/4 laboratory abnormalities in pediatric patients with Ph+ ALL treated with SPRYCEL in combination with chemotherapy are shown in Table 15.

Table 15: CTCAE Grade 3/4 Laboratory Abnormalities in ≥10% of Pediatric Patients with Ph+ ALL Treated with SPRYCEL in Combination with Chemotherapy CA180372 (N=81)

| | Percent (%) of Patients |
|--------------------------------|-------------------------|
| Hematology Parameters | |
| Neutropenia | 96 |
| Thrombocytopenia | 88 |
| Anemia | 82 |
| Biochemistry Parameters | |
| Elevated SGPT (ALT) | 47 |
| Hypokalemia | 40 |
| Elevated SGOT (AST) | 26 |
| Hypocalcemia | 19 |
| Hyponatremia | 19 |
| Elevated Bilirubin | 11 |
| Hypophosphatemia | 11 |

Toxicity grading is per CTCAE version 4.

Additional Pooled Data from Clinical Trials

The following additional adverse reactions were reported in adult and pediatric patients (n=2809) in SPRYCEL CML clinical studies and adult patients in Ph+ ALL clinical studies at a frequency of ≥10%, 1%–10%, 0.1%–1%, or <0.1%. These adverse reactions are included based on clinical relevance.

Gastrointestinal Disorders: 1%–10% – mucosal inflammation (including mucositis/stomatitis), dyspepsia, abdominal distension, constipation, gastritis, colitis (including neutropenic colitis), oral soft tissue disorder; 0.1%–1% – ascites, dysphagia, anal fissure, upper gastrointestinal ulcer, esophagitis, pancreatitis, gastroesophageal reflux disease; <0.1% – protein losing gastroenteropathy, ileus, acute pancreatitis, anal fistula.

General Disorders and Administration-Site Conditions: ≥10% – peripheral edema, face edema; 1%–10% – asthenia, chest pain, chills; 0.1%–1% – malaise, other superficial edema, peripheral swelling; <0.1% – gait disturbance.

Hepatobiliary Disorders: 0.1%–1% – cholestasis, cholecystitis, hepatitis.

Renal and Urinary Disorders: 0.1%–1% – urinary frequency, renal failure, proteinuria; <0.1% – renal impairment.

Immune System Disorders: 0.1%–1% – hypersensitivity (including erythema nodosum).

Endocrine Disorders: 0.1%–1% – hypothyroidism; <0.1% – hyperthyroidism, thyroiditis.

6.2 Postmarketing Experience

The following additional adverse reactions have been identified during post approval use of SPRYCEL. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Infections: hepatitis B virus reactivation

Cardiac disorders: atrial fibrillation/atrial flutter

Respiratory, thoracic, and mediastinal disorders: interstitial lung disease

Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome

Renal and urinary disorders: nephrotic syndrome

Blood and lymphatic system disorders: thrombotic microangiopathy

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on Dasatinib

Strong CYP3A4 Inhibitors

The coadministration with strong CYP3A inhibitors may increase dasatinib concentrations [see *Clinical Pharmacology* (12.3)]. Increased dasatinib concentrations may increase the risk of toxicity. Avoid concomitant use of strong CYP3A4 inhibitors. If concomitant administration of a strong CYP3A4 inhibitor cannot be avoided, consider a SPRYCEL dose reduction [see *Dosage and Administration* (2.3)].

Strong CYP3A4 Inducers

The coadministration of SPRYCEL with strong CYP3A inducers may decrease dasatinib concentrations [see *Clinical Pharmacology* (12.3)]. Decreased dasatinib concentrations may reduce efficacy. Consider alternative drugs with less enzyme induction potential. If concomitant administration of a strong CYP3A4 inducer cannot be avoided, consider a SPRYCEL dose increase.

Gastric Acid Reducing Agents

The coadministration of SPRYCEL with a gastric acid reducing agent may decrease the concentrations of dasatinib. Decreased dasatinib concentrations may reduce efficacy.

Do not administer H₂ antagonists or proton pump inhibitors with SPRYCEL. Consider the use of antacids in place of H₂ antagonists or proton pump inhibitors. Administer the antacid at least 2 hours prior to or 2 hours after the dose of SPRYCEL. Avoid simultaneous administration of SPRYCEL with antacids.

Skin and Subcutaneous Tissue Disorders: 1%–10% – alopecia, acne, dry skin, hyperhidrosis, urticaria, dermatitis (including eczema); 0.1%–1% – pigmentation disorder, skin ulcer, bullous conditions, photosensitivity, nail disorder, neutrophilic dermatosis, panniculitis, palmar-plantar erythrodysesthesia syndrome, hair disorder; <0.1% – leukocytoclastic vasculitis, skin fibrosis.

Respiratory, Thoracic, and Mediastinal Disorders: 1%–10% – lung infiltration, pneumonitis, cough; 0.1%–1% – asthma, bronchospasm, dyspnea, pulmonary arterial hypertension; <0.1% – acute respiratory distress syndrome, pulmonary embolism.

Nervous System Disorders: 1%–10% – neuropathy (including peripheral neuropathy), dizziness, dysgeusia, somnolence; 0.1%–1% – amnesia, tremor, syncope, balance disorder; <0.1% – convulsion, cerebrovascular accident, transient ischemic attack, optic neuritis, VIIIth nerve paralysis, dementia, ataxia.

Blood and Lymphatic System Disorders: 0.1%–1% – lymphadenopathy, lymphopenia; <0.1% – aplasia pure red cell.

Musculoskeletal and Connective Tissue Disorders: 1%–10% – muscular weakness, musculoskeletal stiffness; 0.1%–1% – rhabdomyolysis, tendonitis, muscle inflammation, osteonecrosis, arthritis; <0.1% – epiphyses delayed fusion (reported at 1%–10% in the pediatric studies), growth retardation (reported at 1%–10% in the pediatric studies).

Investigations: 1%–10% – weight increased, weight decreased; 0.1%–1% – blood creatine phosphokinase increased, gamma-glutamyltransferase increased.

Infections and Infestations: 1%–10% – pneumonia (including bacterial, viral, and fungal), upper respiratory tract infection/inflammation, herpes virus infection, enterocolitis infection, sepsis (including fatal outcomes [0.2%]).

Metabolism and Nutrition Disorders: 1%–10% – appetite disturbances, hyperuricemia; 0.1%–1% – hypoalbuminemia, tumor lysis syndrome, dehydration, hypercholesterolemia; <0.1% – diabetes mellitus.

Cardiac Disorders: 1%–10% – arrhythmia (including tachycardia), palpitations; 0.1%–1% – angina pectoris, cardiomegaly, pericarditis, ventricular arrhythmia (including ventricular tachycardia), electrocardiogram T-wave abnormal, troponin increased; <0.1% – cor pulmonale, myocarditis, acute coronary syndrome, cardiac arrest, electrocardiogram PR prolongation, coronary artery disease, pleuropericarditis.

Disorders: 1%–10% – visual disorder (including visual disturbance, vision blurred, and acuity reduced), dry eye; 0.1%–1% – conjunctivitis, visual impairment, lacrimation; <0.1% – photophobia.

Disorders: 1%–10% – flushing, hypertension; 0.1%–1% – hypotension, thrombosis; <0.1% – livedo reticularis, deep vein thrombosis, embolism.

Disorders: 1%–10% – insomnia, depression; 0.1%–1% – anxiety, affect lability, dizziness.

Administration Site Conditions: <0.1% – abortion

Disorders: 0.1%–1% – gynecostasia, menstrual disorder.

Disorders: 1%–10% – confusion.

Disorders: 0.1%–1% – vertigo, hearing loss.

am plasma concentration following oral administration. The mean AUC of dasatinib following a single dose of 100 mg was 985 ng·h. The AUCs derived from the high-fat meal were 27%, 34%, and 14% for the high-fat meal.

ect

parent volume of distribution is 2505 L (CV% 93%). The mean terminal half-life of dasatinib is 3 hours to 5 hours. The mean terminal half-life of dasatinib is 3 hours to 5 hours. The mean terminal half-life of dasatinib is 3 hours to 5 hours. Dasatinib is metabolized in humans, primarily by CYP3A4. The major metabolites are the inactive metabolites, which are responsible for the formation of the active metabolites. The formation of dasatinib metabolites is dependent on the activity of CYP3A4 and other enzymes.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on limited human data, SPRYCEL can cause fetal harm when administered to a pregnant woman. Adverse pharmacologic effects including hydrops fetalis, fetal leukopenia, and fetal thrombocytopenia have been reported with maternal exposure to SPRYCEL. Animal reproduction studies in rats have demonstrated extensive mortality during organogenesis, the fetal period, and in neonates. Skeletal malformations were observed in a limited number of surviving rat and rabbit conceptuses. These findings occurred at dasatinib plasma concentrations below those in humans receiving therapeutic doses of dasatinib [see Data]. Advise a pregnant woman of the potential risk to a fetus.

The estimated background risk in the U.S. general population of major birth defects is 2% to 4% and of miscarriage is 15% to 20% of clinically recognized pregnancies.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Transplacental transfer of dasatinib has been reported. Dasatinib has been measured in fetal plasma and amniotic fluid at concentrations comparable to those in maternal plasma. Hydrops fetalis, fetal leukopenia, and fetal thrombocytopenia have been reported with maternal exposure to dasatinib. These adverse pharmacologic effects on the fetus are similar to adverse reactions observed in adult patients and may result in fetal harm or neonatal death [see Warnings and Precautions (5.1, 5.3)].

Data

Human Data

Based on human experience, dasatinib is suspected to cause congenital malformations, including neural tube defects, and harmful pharmacological effects on the fetus when administered during pregnancy.

Animal Data

In nonclinical studies at plasma concentrations below those observed in humans receiving therapeutic doses of dasatinib, embryo-fetal toxicities were observed in rats and rabbits. Fetal death was observed in rats. In both rats and rabbits, the lowest doses of dasatinib tested (rat: 2.5 mg/kg/day [15 mg/m²/day] and rabbit: 0.5 mg/kg/day [6 mg/m²/day]) resulted in embryo-fetal toxicities. These doses produced maternal AUCs of 105 ng·h/mL and 44 ng·h/mL (6.1-fold the human AUC) in rats and rabbits, respectively. Embryo-fetal toxicities included skeletal malformations at multiple sites (scapula, humerus, femur, radius, ribs, and clavicle), reduced ossification (sternum, thoracic, lumbar, and sacral vertebrae; forepaw phalanges; pelvis; and hyoid body), edema, and microhepatia. In a pre- and postnatal development study in rats, administration of dasatinib from gestation day (GD) 16 through lactation day (LD) 20, GD 21 through LD 20, or LD 4 through LD 20 resulted in extensive pup mortality at maternal exposures that were below the exposures in patients treated with dasatinib at the recommended labeling dose.

8.2 Lactation

Risk Summary

No data are available regarding the presence of dasatinib in human milk, the effects of the drug on the breastfed child, or the effects of the drug on milk production. However, dasatinib is present in

the milk of lactating rats. Because of the potential for serious adverse reactions in nursing children from SPRYCEL, breastfeeding is not recommended during treatment with SPRYCEL and for 2 weeks after the last dose.

8.3 Females and Males of Reproductive Potential

SPRYCEL can cause fetal harm when administered to a pregnant woman [see Use in Specific Populations (8.1)].

Contraception

Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment with SPRYCEL and for 30 days after the last dose.

Infertility

Based on animal data, dasatinib may result in damage to female and male reproductive tissues [see Nonclinical Toxicology (13.1)].

8.4 Pediatric Use

Ph+ CML in Chronic Phase

The safety and effectiveness of SPRYCEL monotherapy have been demonstrated in pediatric patients with newly diagnosed chronic phase CML [see Clinical Studies (14.3)]. There are no data in children under 1 year of age. Adverse reactions associated with bone growth and development were reported in 5 (5.2%) of patients [see Warnings and Precautions (5.10)].

Ph+ ALL

The safety and effectiveness of SPRYCEL in combination with chemotherapy have been demonstrated in pediatric patients one year and over with newly diagnosed Ph+ ALL. Use of SPRYCEL in pediatric patients is supported by evidence from one pediatric study. There are no data in children under 1 year of age. One case of grade 1 osteopenia was reported.

The safety profile of SPRYCEL in pediatric subjects was comparable to that reported in studies in adult subjects [see Adverse Reactions (6.1) and Clinical Studies (14.3, 14.4)].

Monitor bone growth and development in pediatric patients [see Warnings and Precautions (5.10)].

Pediatric Patients with Difficulty Swallowing Tablets

Five patients with Ph+ ALL 2 to 10 years of age received at least one dose of SPRYCEL tablet dispersed in juice on Study CA180372. The exposure for dispersed tablets was 36% lower as compared to intact tablets in pediatric patients [see Clinical Pharmacology (12.3)]. Due to the limited available clinical data, it is unclear whether dispersing SPRYCEL tablets significantly alters the safety and/or efficacy of SPRYCEL.

8.5 Geriatric Use

Of the 2712 patients in clinical studies of SPRYCEL, 617 (23%) were 65 years of age and older, and 123 (5%) were 75 years of age and older. No differences in confirmed Complete Cytogenetic Response (cCCyR) and MMR were observed between older and younger patients. While the safety profile of SPRYCEL in the geriatric population was similar to that in the younger population, patients aged 65 years and older are more likely to experience the commonly reported adverse reactions of fatigue, pleural effusion, diarrhea, dyspnea, cough, lower gastrointestinal hemorrhage,

and appetite disturbance, and more likely to experience the less frequently reported adverse reactions of abdominal distention, dizziness, pericardial effusion, congestive heart failure, hypertension, pulmonary edema, and weight decrease, and should be monitored closely.

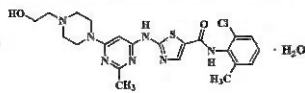
10 OVERDOSAGE

Experience with overdose of SPRYCEL in clinical studies is limited to isolated cases. The highest overdose of 280 mg per day for 1 week was reported in two patients and both developed severe myelosuppression and bleeding. Since SPRYCEL is associated with severe myelosuppression [see Warnings and Precautions (5.1) and Adverse Reactions (6.1)], monitor patients who ingest more than the recommended dosage closely for myelosuppression and give appropriate supportive treatment.

Acute overdose in animals was associated with cardiotoxicity. Evidence of cardiotoxicity included ventricular necrosis and valvular/ventricular/atrial hemorrhage at single doses ≥ 100 mg/kg (600 mg/m²) in rodents. There was a tendency for increased systolic and diastolic blood pressure in monkeys at single doses ≥ 10 mg/kg (120 mg/m²).

11 DESCRIPTION

SPRYCEL (dasatinib) is a kinase inhibitor. The chemical name for dasatinib is N-(2-chloro-6-methylphenyl)-2-[(6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl)amino]-5-thiazolecarboxamide, monohydrate. The molecular formula is C₂₂H₂₆ClN₇O₂S · H₂O, which corresponds to a formula weight of 506.02 (monohydrate). The anhydrous free base has a molecular weight of 488.01. Dasatinib has the following chemical structure:



Dasatinib is a white to off-white powder. The drug substance is insoluble in water and slightly soluble in ethanol and methanol.

SPRYCEL tablets are white to off-white, biconvex, film-coated tablets containing dasatinib, with the following inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, and magnesium stearate. The tablet coating consists of hypromellose, titanium dioxide, and polyethylene glycol.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Dasatinib, at nanomolar concentrations, inhibits the following kinases: BCR-ABL, SRC family (SRC, LCK, YES, FYN), c-KIT, EphA2, and PDGFR β . Based on modeling studies, dasatinib is predicted to bind to multiple conformations of the ABL kinase.

In vitro, dasatinib was active in leukemic cell lines representing variants of imatinib mesylate-sensitive and resistant disease. Dasatinib inhibited the growth of chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL) cell lines overexpressing BCR-ABL. Under the conditions of the assays, dasatinib could overcome imatinib resistance resulting from BCR-ABL kinase domain mutations, activation of alternate signaling pathways involving the SRC family kinases (LYN, HCK), and multi-drug resistance gene overexpression.

12.2 Pharmacodynamics

Cardiac Electrophysiology

Of 2440 patients treated with SPRYCEL at all doses tested in clinical trials, 16 patients (<1%) had QTc prolongation reported as an adverse reaction. Twenty-two patients (1%) experienced a QTcF > 500 ms. In 865 patients with leukemia treated with SPRYCEL 70 mg BID in five Phase 2 studies, the maximum mean changes in QTcF (90% upper bound CI) from baseline ranged from 7 ms to 13.4 ms.

An analysis of the data from five Phase 2 studies in patients (70 mg BID) and a Phase 1 study in healthy subjects (100 mg single dose) suggests that there is a maximum increase of 3 to 6 milliseconds in Fridericia corrected QTc interval from baseline for subjects receiving therapeutic doses of dasatinib, with associated upper 95% confidence intervals <10 msec.

12.3 Pharmacokinetics

The pharmacokinetics of dasatinib exhibits dose proportional increases in AUC and linear elimination characteristics over the dose range of 15 mg/day (0.15 times the lowest approved recommended dose) to 240 mg/day (1.7 times the highest approved recommended dose).

At 100 mg QD, the maximum concentration at steady state (C_{max}) is 82.2 ng/mL (CV% 69%), area under the plasma drug concentration time curve (AUC) is 397 ng/mL·hr (CV% 55%). The clearance of dasatinib is found to be time-invariant. When administered to adult healthy subjects as dispersed tablets in juice, the adjusted geometric mean ratio was 0.97 (90% CI 0.85, 1.10) for C_{max} and 0.84 (90% CI 0.78, 0.91) for AUC as compared to intact tablets.

Absorption

The maximum plasma concentrations (C_{max}) of dasatinib are observed between 0.5 hours and 6 hours (T_{max}) following oral administration.

Food Effect

A high-fat meal increased the mean AUC of dasatinib following a single dose of 100 mg by 14%. The total caloric content of the high-fat meal was 985 kcal. The calories derived from fat, carbohydrates, and protein were 52%, 34%, and 14% for the high-fat meal.

Distribution

The apparent volume of distribution is 2505 L (CV% 93%).

Binding of dasatinib to human plasma proteins *in vitro* was approximately 96% and of metabolite was 93%, with no concentration dependence over the range of 100 ng/mL to 1000 ng/mL.

Dasatinib is a P-gp substrate *in vitro*.

Elimination

The mean terminal half-life of dasatinib is 3 hours to 5 hours. The mean \pm SD is 363.8 L/hr (CV% 81.3%).

Metabolism

Dasatinib is metabolized in humans, primarily by CYP3A4, for the formation of the active metabolite 3) and uridine diphosphate-glucuronosyltransferase. The formation of dasatinib metabolites.

The exposure of the active metabolite, which is equipotent to dasatinib, represents approximately 5% of the AUC of dasatinib. The active metabolite of dasatinib is unlikely to play a major role in the observed pharmacology of the drug. Dasatinib also has several other inactive oxidized metabolites.

Excretion

Elimination is primarily via the feces. Following a single radiolabeled dose of oral dasatinib, 4% of the administered radioactivity was recovered in the urine and 85% in the feces within 10 days. Unchanged dasatinib accounted for 0.1% of the administered dose in the urine and 19% of the administered dose in the feces with the remainder of the dose being metabolites.

Specific Populations

Age (15 to 86 years old), sex, and renal impairment (creatinine clearance 21.6 mL/min to 342.3 mL/min as estimated by Cockcroft Gault) have no clinically relevant effect on the pharmacokinetics of dasatinib.

Pediatric Patients

The pharmacokinetics of dasatinib were evaluated in 43 pediatric patients with leukemia or solid tumors at oral doses ranging from 60 mg/m² to 120 mg/m² once daily, taken with or without food. The pharmacokinetics showed dose proportionality with a dose-related increase in exposure. The mean T_{max} was observed between 0.5 hours and 6 hours and the mean half-life was 2 hours to 5 hours. The geometric mean (CV%) of body weight normalized clearance in these 43 pediatric patients is 5.98 (41.5%) L/h/kg. In pediatric patients with a dosing regimen of 60 mg/m², the model simulated geometric mean (CV%) steady-state plasma average concentrations of dasatinib were 14.7 (64.6%) ng/mL (for 2 to <6 years old), 16.3 (97.5%) ng/mL (for 6 to <12 years old), and 18.2 (67.7%) ng/mL (for 12 years and older) [see Dosage and Administration (2.2)]. Dasatinib clearance and volume of distribution change with body weight in pediatric patients. Dasatinib has not been studied in patients < 1 year old.

The bioavailability of dispersed tablets in pediatric patients was estimated to be 36% lower than that of intact tablets.

Patients with Hepatic Impairment

Compared to subjects with normal liver function, patients with moderate hepatic impairment (Child Pugh B) had decreases in mean C_{max} by 47% and mean AUC by 8%. Patients with severe hepatic impairment (Child Pugh C) had decreases in mean C_{max} by 43% and in mean AUC by 28% compared to the subjects with normal liver function.

Drug Interaction Studies

Cytochrome P450 Enzymes

The coadministration of ketoconazole (strong CYP3A4 inhibitor) twice daily increased the mean C_{max} of dasatinib by 4-fold and the mean AUC of dasatinib by 5-fold following a single oral dose of 20 mg.

The coadministration of rifampin (strong CYP3A4 inducer) once daily decreased the mean C_{max} of dasatinib by 81% and the mean AUC of dasatinib by 82%.

Dasatinib is a time-dependent inhibitor of CYP3A4. Dasatinib does not inhibit CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, or 2E1. Dasatinib does not induce CYP enzymes.

Gastric Acid Reducing Agents

The administration of 30 mL of aluminum hydroxide/magnesium hydroxide 2 hours prior to a single dose of SPRYCEL was associated with no relevant change in the mean AUC of dasatinib; however, the mean C_{max} of dasatinib was increased by 26%.

The simultaneous administration of 30 mL of aluminum hydroxide/magnesium hydroxide with a single dose of SPRYCEL was associated with a 53% reduction in the mean AUC of dasatinib and a 58% reduction in the mean C_{max} of dasatinib.

The administration of a single dose of SPRYCEL 10 hours following famotidine (H₂ antagonist) reduced the mean AUC of dasatinib by 61% and the mean C_{max} of dasatinib by 63%.

The administration of a single 100 mg dose of SPRYCEL 22 hours following a 40 mg dose of omeprazole (proton pump inhibitor) at steady state reduced the mean AUC of dasatinib by 43% and the mean C_{max} of dasatinib by 42%.

Transporters

Dasatinib is not an inhibitor of P-gp *in vitro*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year carcinogenicity study, rats were administered oral doses of dasatinib at 0.3, 1, and 3 mg/kg/day. The highest dose resulted in a plasma drug exposure (AUC) level approximately 60% of the human exposure at 100 mg once daily. Dasatinib induced a statistically significant increase in the combined incidence of squamous cell carcinomas and papillomas in the uterus and cervix of high-dose females and prostate adenoma in low-dose males.

Dasatinib was clastogenic when tested *in vitro* in Chinese hamster ovary cells, with and without metabolic activation. Dasatinib was not mutagenic when tested in an *in vitro* bacterial cell assay (Ames test) and was not genotoxic in an *in vivo* rat micronucleus study.

Dasatinib did not affect mating or fertility in male and female rats at plasma drug exposure (AUC) similar to the human exposure at 100 mg daily. In repeat dose studies, administration of dasatinib resulted in reduced size and secretion of seminal vesicles, and immature prostate, seminal vesicle, and testis. The administration of dasatinib resulted in uterine inflammation and mineralization in monkeys, and cystic ovaries and ovarian hypertrophy in rodents.

14 CLINICAL STUDIES

14.1 Newly Diagnosed Chronic Phase CML in Adults

DASISION (Dasatinib vs Imatinib Study in Treatment-Naïve Chronic Myeloid Leukemia Patients) (NCT00481247) was an open-label, multicenter, international, randomized trial conducted in adult patients with newly diagnosed chronic phase CML. A total of 519 patients were randomized to receive either SPRYCEL 100 mg once daily or imatinib 400 mg once daily. Patients with a history of cardiac disease were included in this trial except those who had a myocardial infarction within 6 months, congestive heart failure within 3 months, significant arrhythmias, or QTc prolongation. The primary endpoint was the rate of confirmed complete cytogenetic response (CCyR) within 12 months. Confirmed CCyR was defined as a CCyR noted on two consecutive occasions (at least 28 days apart).

Median age was 46 years in the SPRYCEL group and 49 years in the imatinib groups, with 10% and 11% of patients ≥65 years of age, respectively. There were slightly more male than female patients in both groups (59% vs 41%). Fifty-three percent of all patients were Caucasian and 39%

were Asian. At baseline, the distribution of Hasford scores was similar in the SPRYCEL and imatinib treatment groups (low risk: 33% and 34%, intermediate risk: 48% and 47%, high risk: 19% and 19%, respectively). With a minimum of 12 months follow-up, 85% of patients randomized to SPRYCEL and 81% of patients randomized to imatinib were still on study.

With a minimum of 24 months follow-up, 77% of patients randomized to SPRYCEL and 75% of patients randomized to imatinib were still on study and with a minimum of 60 months follow-up, 61% and 62% of patients, respectively, were still on treatment at the time of study closure.

Efficacy results are summarized in Table 16.

Table 16: Efficacy Results in a Randomized Newly Diagnosed Chronic Phase CML Trial

| | SPRYCEL (n=259) | Imatinib (n=260) |
|---|--------------------|---------------------|
| Confirmed CCyR^a | | |
| Within 12 months (95% CI) | 76.8% (71.2–81.8) | 66.2% (60.1–71.9) |
| P-value | | 0.007* |
| Major Molecular Response^b | | |
| 12 months (95% CI) | 52.1% (45.9–58.3) | 33.8% (28.1–39.9) |
| P-value | | <0.0001 |
| 60 months (95% CI) | 76.4% (70.8–81.5) | 64.2% (58.1–70.1) |

^a Confirmed CCyR is defined as a CCyR noted on two consecutive occasions at least 28 days apart.
^b Major molecular response (at any time) was defined as BCR-ABL1, mROS ≤0.1% by RQ-PCR in peripheral blood samples standardized on the International scale. These are cumulative rates representing minimum follow up for the time frame specified.
^c Adjusted for Hasford score and indicated statistical significance at a pre-defined nominal level of significance. CI = confidence interval.

The confirmed CCyR within 24, 36, and 60 months for SPRYCEL versus imatinib arms were 80% versus 74%, 83% versus 77%, and 83% versus 79%, respectively. The MMR at 24 and 36 months for SPRYCEL versus imatinib arms were 65% versus 50% and 69% versus 56%, respectively.

After 60 months follow-up, median time to confirmed CCyR was 3.1 months in 215 SPRYCEL responders and 5.8 months in 204 imatinib responders. Median time to MMR after 60 months follow-up was 9.3 months in 198 SPRYCEL responders and 15.0 months in 167 imatinib responders.

At 12 months follow-up, 8 patients (3%) on the dasatinib arm progressed to either accelerated phase or blast phase and 15 patients (6%) on the imatinib arm progressed to either accelerated phase or blast phase. At 24 months follow-up, 8 patients (3%) on the dasatinib arm progressed to either accelerated phase or blast phase and 15 patients (6%) on the imatinib arm progressed to either accelerated phase or blast phase. At 36 months follow-up, 8 patients (3%) on the dasatinib arm progressed to either accelerated phase or blast phase and 15 patients (6%) on the imatinib arm progressed to either accelerated phase or blast phase. At 60 months follow-up, 8 patients (3%) on the dasatinib arm progressed to either accelerated phase or blast phase and 15 patients (6%) on the imatinib arm progressed to either accelerated phase or blast phase.

the imatinib arm, the rate of MMR at any time in each risk group determined by Hasford score was 69% (low risk), 65% (intermediate risk), and 54% (high risk).

BCR-ABL sequencing was performed on blood samples from patients in the newly diagnosed trial who discontinued dasatinib or imatinib therapy. Among dasatinib-treated patients the mutations detected were T315L, F317I/L, and V299L.

Dasatinib does not appear to be active against the T315I mutation, based on *in vitro* data.

14.2 Imatinib-Resistant or -Intolerant CML or Ph+ ALL in Adults

The efficacy and safety of SPRYCEL were investigated in adult patients with CML or Ph+ ALL whose disease was resistant to or who were intolerant to imatinib: 1158 patients had chronic phase CML, 858 patients had accelerated phase, myeloid blast phase, or lymphoid blast phase CML, and 130 patients had Ph+ ALL. In a clinical trial in chronic phase CML, resistance to imatinib was defined as failure to achieve a complete hematologic response (CHR; after 3 months), major cytogenetic response (MCyR; after 6 months), or complete cytogenetic response (CCyR; after 12 months), or loss of a previous molecular response (with concurrent ≥10% increase in Ph+ metaphases), cytogenetic response, or hematologic response. Imatinib intolerance was defined as inability to tolerate 400 mg or more of imatinib per day or discontinuation of imatinib because of toxicity.

Results described below are based on a minimum of 2 years follow-up after the start of SPRYCEL therapy in patients with a median time from initial diagnosis of approximately 5 years. Across all studies, 48% of patients were women, 81% were white, 15% were black or Asian, 25% were 65 years of age or older, and 5% were 75 years of age or older. Most patients had long disease histories with extensive prior treatment, including imatinib, cytotoxic chemotherapy, interferon, and stem cell transplant. Overall, 80% of patients had imatinib-resistant disease and 20% of patients were intolerant to imatinib. The maximum imatinib dose had been 400–600 mg/day in about 60% of the patients and >600 mg/day in 40% of the patients.

The primary efficacy endpoint in chronic phase CML was MCyR, defined as elimination (CCyR) or substantial diminution (by at least 65%, partial cytogenetic response) of Ph+ hematopoietic cells. The primary efficacy endpoint in accelerated phase, myeloid blast phase, lymphoid blast phase CML, and Ph+ ALL was major hematologic response (MaHR), defined as either a CHR or so evidence of leukemia (NEL).

Chronic Phase CML

Dose-Optimization Trial: A randomized, open-label trial (NCT00123474) was conducted in adult patients with chronic phase CML to evaluate the efficacy and safety of SPRYCEL administered once daily compared with SPRYCEL administered twice daily. Patients with significant cardiac disease, including myocardial infarction within 6 months, congestive heart failure within 3 months, significant arrhythmias, or QTc prolongation were excluded from the trial. The primary efficacy endpoint was MCyR in patients with imatinib-resistant CML. A total of 670 patients, of whom 497 had imatinib-resistant disease, were randomized to the SPRYCEL 100 mg once-daily, 140 mg once-daily, 50 mg twice-daily, or 70 mg twice-daily group. Median duration of treatment was 22 months.

Efficacy was achieved across all SPRYCEL treatment groups with the once-daily schedule demonstrating comparable efficacy (non-inferiority) to the twice-daily schedule on the primary

How Supplied

SPRYCEL® (dasatinib) tablets are available as described in Table 21.

Table 21: SPRYCEL Trade Presentations

| NDC Number | Strength | Description | Tablets per Bottle |
|--------------|----------|---|--------------------|
| 0003-0527-11 | 20 mg | white to off-white, biconvex, round, film-coated tablet with "BMS" debossed on one side and "527" on the other side | 60 |
| 0003-0528-11 | 50 mg | white to off-white, biconvex, oval, film-coated tablet with "BMS" debossed on one side and "528" on the other side | 60 |
| 0003-0524-11 | 70 mg | white to off-white, biconvex, round, film-coated tablet with "BMS" debossed on one side and "524" on the other side | 60 |
| 0003-0855-22 | 80 mg | white to off-white, biconvex, triangle, film-coated tablet with "BMS" and "80" (BMS over 80) debossed on one side and "855" on the other side | 30 |
| 0003-0852-22 | 100 mg | white to off-white, biconvex, oval, film-coated tablet with "BMS 100" debossed on one side and "852" on the other side | 30 |
| 0003-0857-22 | 140 mg | white to off-white, biconvex, round, film-coated tablet with "BMS" and "140" (BMS over 140) debossed on one side and "857" on the other side | 30 |

Storage

SPRYCEL tablets should be stored at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].

Handling and Disposal

SPRYCEL is an antineoplastic product. Follow special handling and disposal procedures.¹

Personnel who are pregnant should avoid exposure to crushed or broken tablets.

SPRYCEL tablets consist of a core tablet, surrounded by a film coating to prevent exposure of healthcare professionals to the active substance. The use of latex or nitrile gloves for appropriate disposal when handling tablets that are inadvertently crushed or broken is recommended, to minimize the risk of dermal exposure.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Myelosuppression

Inform patients of the possibility of developing low blood cell counts. Advise patients to immediately report fever particularly in association with any suggestion of infection [see Warnings and Precautions (5.1)].

Bleeding

Inform patients of the possibility of serious bleeding and to report immediately any signs or symptoms suggestive of hemorrhage (unusual bleeding or easy bruising) [see Warnings and Precautions (5.2)].

Fluid Retention

Patients should be informed of the possibility of developing fluid retention (swelling, weight gain, dry cough, chest pain on respiration, or shortness of breath) and advised to seek medical attention promptly if those symptoms arise [see Warnings and Precautions (5.3)].

Cardiovascular Toxicity

Inform patients of the possibility of developing cardiovascular toxicity, including cardiac ischemic events, cardiac-related fluid retention, conduction abnormalities, and TIAs. Advise patients to seek immediate medical attention if symptoms suggestive of cardiovascular toxicity occur, such as chest pain, shortness of breath, palpitations, transient vision problems, or slurred speech [see Warnings and Precautions (5.4)].

Pulmonary Arterial Hypertension

Inform patients of the possibility of developing pulmonary arterial hypertension (dyspnea, fatigue, hypoxia, and fluid retention) and advise them to seek medical attention promptly if those symptoms arise [see Warnings and Precautions (5.5)].

Tumor Lysis Syndrome

Inform patients to immediately report and seek medical attention for any symptoms such as nausea, vomiting, weakness, edema, shortness of breath, muscle cramps, and seizures, which may indicate tumor lysis syndrome [see Warnings and Precautions (5.8)].

Growth and Development in Pediatric Patients

Inform pediatric patients and their caregivers of the possibility of developing bone growth abnormalities, bone pain, or gynecomastia and advise them to seek medical attention promptly if those symptoms arise [see Warnings and Precautions (5.10)].

Embryo-Fetal Toxicity

- Advise pregnant women of the potential risk to a fetus [see Warnings and Precautions (5.9) and Use in Specific Populations (8.1)].
- Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment with SPRYCEL and for 30 days after the last dose. Advise females to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, while taking SPRYCEL [see Warnings and Precautions (5.9) and Use in Specific Populations (8.1, 8.3)].

Lactation

- Advise women that breastfeeding is not recommended during treatment with SPRYCEL and for 2 weeks after the final dose [see Use in Specific Populations (8.2)].

Gastrointestinal Complaints

Inform patients that they may experience nausea, vomiting, or diarrhea with SPRYCEL. Advise patients to seek medical attention if these symptoms are bothersome or persistent.

Advise patients using antacids to avoid taking SPRYCEL and antacids less than 2 hours apart [see Drug Interactions (7.1)].

Pain

Inform patients that they may experience headache or musculoskeletal pain with SPRYCEL. Advise patients to seek medical attention if these symptoms are bothersome or persistent.

Fatigue

Inform patients that they may experience fatigue with SPRYCEL. Advise patients to seek medical attention if this symptom is bothersome or persistent.

Rash

Inform patients that they may experience skin rash with SPRYCEL. Advise patients to seek medical attention if this symptom is bothersome or persistent.

Lactose

Inform patients that SPRYCEL contains 135 mg of lactose monohydrate in a 100-mg daily dose and 189 mg of lactose monohydrate in a 140-mg daily dose.

Instructions for Taking SPRYCEL

Missed Dose

Advise patients that if they miss a dose of SPRYCEL, they should take the next scheduled dose at its regular time. The patient should not take two doses at the same time.

Grapefruit Juice

Advise patients not to drink grapefruit juice as it may increase the amount of SPRYCEL in their blood and therefore increase their risk of adverse reactions.

Distributed by:
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

| PATIENT INFORMATION SPRYCEL® (Spry-asl) (dasatinib) tablets |
|--|
| <p>What is SPRYCEL? SPRYCEL is a prescription medicine used to treat:</p> <ul style="list-style-type: none"> adults with newly diagnosed Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase adults with Ph+ CML who no longer benefit from, or did not tolerate, other treatment, including imatinib. adults with Ph+ acute lymphoblastic leukemia (Ph+ ALL) who no longer benefit from, or did not tolerate, other treatment children 1 year of age and older with Ph+ CML in chronic phase children 1 year of age and older with newly diagnosed Ph+ ALL in combination with chemotherapy. <p>It is not known if SPRYCEL is safe and effective in children under 1 year of age.</p> |
| <p>Before taking SPRYCEL, tell your healthcare provider about all of your medical conditions, including if you:</p> <ul style="list-style-type: none"> have problems with your immune system have heart problems, including a condition called congenital long QT syndrome have low potassium or low magnesium levels in your blood are lactose (milk sugar) intolerant are pregnant or plan to become pregnant. SPRYCEL can harm your unborn baby. <p>Females who can become pregnant:</p> <ul style="list-style-type: none"> You should not become pregnant during treatment with SPRYCEL. You should use effective birth control (contraception) during treatment and for 30 days after your last dose of SPRYCEL. <p>Males with female partners who can become pregnant:</p> <ul style="list-style-type: none"> You should use effective birth control (contraception) during treatment and for 30 days after your last dose of SPRYCEL. Your female partner should call her healthcare provider if she becomes pregnant or thinks she is pregnant during your treatment with SPRYCEL. <ul style="list-style-type: none"> are breastfeeding or plan to breastfeed. It is not known if SPRYCEL passes into your breast milk. You should not breastfeed during treatment and for 2 weeks after your last dose of SPRYCEL. <p>Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, antacids, and herbal supplements. If you take an antacid medicine, take it 2 hours before or 2 hours after your dose of SPRYCEL.</p> |
| <p>How should I take SPRYCEL?</p> <ul style="list-style-type: none"> Take SPRYCEL exactly as your healthcare provider tells you to take it. Your healthcare provider may change your dose of SPRYCEL or temporarily stop treatment with SPRYCEL. Do not change your dose or stop taking SPRYCEL without first talking to your healthcare provider. Take SPRYCEL 1 time a day. Take SPRYCEL with or without food, either in the morning or in the evening. Swallow SPRYCEL tablets whole. Do not crush, cut or chew the tablets. <ul style="list-style-type: none"> If your child cannot swallow tablets whole, talk with your healthcare provider. You should not drink grapefruit juice during treatment with SPRYCEL. If you miss a dose of SPRYCEL, take your next scheduled dose at your regular time. Do not take two doses at the same time. If you take too much SPRYCEL, call your healthcare provider or go to the nearest hospital emergency room right away. |
| <p>What are the possible side effects of SPRYCEL? SPRYCEL may cause serious side effects, including:</p> <ul style="list-style-type: none"> Low blood cell counts. Low blood cell counts are common with SPRYCEL and can be severe, including low red blood cell counts (anemia), low white blood cell counts (neutropenia), and low platelet counts (thrombocytopenia). Your healthcare provider will do blood tests to check your blood cell counts regularly during your treatment with |

SPRYCEL. Call your healthcare provider right away if you have a fever or any signs of an infection during treatment with SPRYCEL.

- **Bleeding problems.** Bleeding problems are common with SPRYCEL. Sometimes these bleeding problems can be serious and lead to death. Call your healthcare provider right away if you have:
 - unusual bleeding or bruising of your skin
 - bright red or dark tar-like stools
 - decreased alertness, headache, or change in speech
- **Your body may hold too much fluid (fluid retention).** Fluid retention is common with SPRYCEL and can sometimes be severe. In severe cases, fluid may build up in the lining of your lungs, the sac around your heart, or your stomach cavity. Call your healthcare provider right away if you get any of these symptoms during treatment with SPRYCEL:
 - swelling all over your body
 - weight gain
 - shortness of breath, especially if this happens with low levels of physical activity or at rest
 - dry cough
 - chest pain when taking a deep breath
- **Heart and blood vessel (cardiovascular) problems.** SPRYCEL may cause heart problems, including an abnormal heart rate, a heart attack, or small strokes that last only a few minutes or a few hours, called transient ischemic attacks (TIAs). TIAs are often a warning sign that you are at risk for a more serious stroke. Your healthcare provider will monitor the potassium and magnesium levels in your blood and your heart function. Get medical help right away if you develop any of the following symptoms during treatment with SPRYCEL:
 - chest pain
 - shortness of breath
 - feeling like your heart is beating too fast or you feel abnormal heart beats
 - vision changes that may last for a short time
 - slurred speech
- **Pulmonary Arterial Hypertension (PAH).** SPRYCEL may cause high blood pressure in the vessels of your lungs. PAH may happen at any time during your treatment with SPRYCEL. Your healthcare provider should check your heart and lungs before and during treatment with SPRYCEL. Call your healthcare provider right away if you have shortness of breath, tiredness, or swelling all over your body (fluid retention).
- **Severe skin reactions.** SPRYCEL may cause skin reactions that can sometimes be severe. Get medical help right away if you get a skin reaction with fever, sore mouth or throat, or blistering or peeling of your skin or in the mouth.
- **Tumor Lysis Syndrome (TLS).** TLS is caused by a fast breakdown of cancer cells. TLS can cause you to have kidney failure and the need for dialysis treatment, and an abnormal heartbeat. Your healthcare provider may do blood tests to check you for TLS. Call your healthcare provider or get emergency medical help right away if you develop any of these symptoms during treatment with SPRYCEL:
 - nausea
 - vomiting
 - weakness
 - swelling
 - shortness of breath
 - muscle cramps
 - seizures
- **Slowing of growth and development in children.** Effects on bone growth and development in children have happened with SPRYCEL and can sometimes be severe. Your healthcare provider will monitor your child's bone growth and development during treatment with SPRYCEL. Get medical help right away if your child develops bone pain.

The most common side effects of SPRYCEL in adults and children receiving SPRYCEL alone include:

- diarrhea
- headache
- skin rash
- shortness of breath
- tiredness
- nausea
- muscle pain

The most common side effects of SPRYCEL in children receiving SPRYCEL with chemotherapy include:

- swelling, pain and redness of the lining of your mouth, throat, stomach and bowel (mucositis)
- low white blood cell counts with fever
- fever
- diarrhea
- nausea
- tiredness
- constipation
- abnormal heart rate
- high blood pressure (hypertension)
- swelling
- infections
- low blood pressure

- vomiting
- muscle pain
- stomach-area (abdominal) pain
- cough
- headache
- rash
- decreased appetite
- allergic reactions
- shortness of breath
- nose bleed
- numbness or tingling of your hands and feet
- feeling confused or disoriented

SPRYCEL may cause fertility problems in males and females. Talk to your healthcare provider if this is a concern for you.
Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all of the possible side effects of SPRYCEL.
Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store SPRYCEL?

- Store SPRYCEL at room temperature between 68°F to 77°F (20°C to 25°C).
- Ask your healthcare provider or pharmacist about the right way to throw away expired or unused SPRYCEL.
- Wear latex or nitrile gloves when handling tablets that have accidentally been crushed or broken.
- Females who are pregnant should not handle crushed or broken SPRYCEL tablets.

Keep SPRYCEL and all medicines out of the reach of children.

General information about the safe and effective use of SPRYCEL.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use SPRYCEL for a condition for which it is not prescribed. Do not give SPRYCEL to other people even if they have the same symptoms you have. It may harm them. You can ask your healthcare provider or pharmacist for information about SPRYCEL that is written for health professionals.

What are the ingredients in SPRYCEL?

Active ingredient: dasatinib

Inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, and magnesium stearate. The tablet coating consists of hypromellose, titanium dioxide, and polyethylene glycol.

Distributed by Bristol-Myers Squibb Company, Princeton, NJ 08543 USA

For more information, go to www.sprycel.com or call 1-800-332-3059

This Patient Information has been approved by the U.S. Food and Drug Administration

Revised: June 2021

Disturbed by:
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

Advise patients not to drink grapefruit juice as it may increase the amount of SPRYCEL in their blood and therefore increase their risk of adverse reactions.

CERTIFICATE OF A PHARMACEUTICAL PRODUCT

Sprycel® (dasatinib) Tablets NDA 21-986; Approval Date: June 28, 2006

| Ingredient | 20 mg | 50 mg | 70 mg |
|--|-------|-------|-------|
| Dasatinib ^a | 20.0 | 50.0 | 70.0 |
| Lactose Monohydrate ^b | 27.0 | 67.5 | 94.5 |
| Microcrystalline Cellulose | 27.0 | 67.5 | 94.5 |
| Hydroxypropyl Cellulose | 2.4 | 6.0 | 8.4 |
| Croscarmellose Sodium | 3.2 | 8.0 | 11.2 |
| Magnesium Stearate | 0.4 | 1.0 | 1.4 |
| Opadry® White, YS-1-18177-A ^c | 3.2 | 7.0 | 8.4 |
| Purified Water ^d | ---- | ---- | ---- |

^a The amount shown is based on a theoretical Assay of 100% for dasatinib on an anhydrous basis. The exact amount will vary depending on the Assay "as is" of dasatinib.

^b The amount of lactose monohydrate will vary depending upon the amount of dasatinib used.

^c Opadry® White YS-1-18177-A contains hypromellose 6 cP (59.8% w/w), titanium dioxide (31.2% w/w), and polyethylene glycol 400 (9.0% w/w).

^d Removed during processing.

US storage conditions and shelf life: Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature] Shelf life-36 months

ADMINISTRACIÓN DE MEDICAMENTOS Y ALIMENTOS DE LOS ESTADOS UNIDOS -----

Centro de Evaluación e Investigación de Medicamentos -----

10903 New Hampshire Ave., Silver Spring, MD 20993, Estados Unidos de América. -----

CDERExportCertificateProgram@fda.hhs.gov – Teléfono: (301) 796-4950 -----

Certificado de un Producto Farmacéutico – Fabricante Extranjero-----

Fecha de emisión del certificado: **30 de septiembre de 2021** -----

Certificado Número: **4MK8-3SEE**-----

Fecha de Vencimiento del Certificado: **29 de septiembre de 2023** -----

País Importador: **Argentina** -----

País Exportador: **Estados Unidos de América** -----

1. Nombre Comercial del Medicamento, Denominación común Internacional o Nacional (según corresponda) y forma farmacéutica: **SPRYCEL®, Comprimido**-----

1.1 Principio(s) Activo(s) y cantidad(es) por unidad de dosis (se prefiere la composición cuantitativa completa): **dasatinib 50 MG**-----

1.2. ¿Este producto cuenta con la licencia para colocarlo en el mercado y utilizarlo en el país exportador? **SI** -----

1.3 ¿Este producto está en el mercado en el país exportador? **SI** -----

2.A.1. Número de licencia del producto y fecha de emisión: **021986 28/06/2006** -----

2.A.2. Nombre y dirección del titular de la licencia del producto: **Bristol-Mvers Squibb Company, Casilla de Correo 4000, Princeton, NJ 08543 Estados Unidos de América**-----

2.A.3. Estado del titular de la licencia del producto: **Ninguna.** -----

2.A.3.1. Nombre y dirección del fabricante: **Patheon Inc., 2100 Syntex Court, Mississauga, Ontario L5N 7K9 CANADÁ** -----

2.A.4 ¿Se encuentra adjunto el resumen aprobado? **No** -----

2.A.5 ¿Está adjunta la información sobre el producto oficialmente completa y de conformidad con la licencia? **SI** -----

2.A.6 Nombre y dirección del solicitante del certificado (si difiere del titular de la licencia): **Bristol Myers Squibb. 4931 George Road, Tampa, FL 33634 Estados Unidos de América**-----

REGISTRO
NACIONAL
DE
MEDICAMENTOS
Y ALIMENTOS
FEDERALES
Nº 2047

2.B.4 Observaciones: Acondicionador: **AndersonBrecon Inc., 4545 Assembly Drive, Rockford, IL 61109.** -----

Esta certificación de la FDA corresponde al producto comercializados en los Estados Unidos de América. -----

3. ¿La autoridad certificadora organiza inspecciones periódicas de la planta de fabricación en la cual se produce la forma farmacéutica? **SI** -----

3.1. Periodicidad de las inspecciones de rutina (años): **De conformidad con la sección 510(h)(3) de la Ley Federal de Alimentos Fármacos y Cosméticos, las inspecciones tendrán lugar de conformidad a un esquema basado en el riesgo** -----

3.2. ¿Se ha inspeccionado la fabricación de este tipo de forma farmacéutica? **SI** -----

3.3. ¿Las instalaciones y las operaciones cumplen con las normas de Buenas Prácticas de Fabricación tal como recomienda la Organización Mundial de la Salud? (Las Buenas Prácticas de Fabricación incluido el Código de Regulaciones Federales 21 partes 210, 211 o ICH Q7A): **SI, al momento de la inspección, el centro cumple con las cGMP de la FDA.** -----

3.4. ¿La información presentada por el solicitante satisface a la autoridad certificadora con respecto a todos los aspectos de Fabricación del producto a los que se comprometió la otra parte? **SI** -----

Aparece una firma ilegible y debajo se lee: Carole Jones, Directora de División,
Departamento de Cumplimiento de Exportaciones -----

El presente certificado es emitido de conformidad al formato recomendado por la Organización Mundial de la Salud revisado el 1º de octubre de 1997. Sitio web: www.who.int. -----

Aparece una estampilla dorada donde se lee: Departamento de Salud y Servicios Humanos - Estados Unidos -----

UNO RIESGO
LA PÚBLICA
INGLES
S. CAP. FEDERAL
PTUGUES
S. CAP. FEDERAL
S.A. Nº 2047

-----CERTIFICADO DE PRODUCTOFARMACÉUTICO-----

-----Sprycel® (dasatinib) Comprimidos -----

-----NDA 21-986; Fecha de Aprobación: 28 de junio de 2006-----

| Principio | 20 mg | 50 mg | 70 mg |
|---|-------|-------|-------|
| Dasatinib ^a | 20,0 | 50,0 | 70,0 |
| Lactosa Monohidrato ^b | 27,0 | 67,5 | 94,5 |
| Celulosa microcristalina | 27,0 | 67,5 | 94,5 |
| Hidroxipropilcelulosa | 2,4 | 6,0 | 8,4 |
| Croscarmelosa de sodio | 3,2 | 8,0 | 11,2 |
| Estearato de magnesio | 0,4 | 1,0 | 1,4 |
| Opadry® Blanco, YS-1-18177-A ^c | 3,2 | 7,0 | 8,4 |
| Agua Purificada ^d | | | |

a La cantidad indicada se basa en un ensayo teórico del 100% para dasatinib en base anhidra. La cantidad exacta variará según el Ensayo "tal como está" de dasatinib -----

b La cantidad de lactosa monohidrato variará en función de la cantidad de dasatinib utilizada. -----


c Opadry® Blanco YS-1-18177-A contiene hipromelosa 6 cP (59,8% p/p), dióxido de titanio (31,2% p/p) y polietilenglicol 400 (9,0% p/p).-----

d Eliminado durante el procesamiento. -----

Condiciones de almacenamiento y vida útil en los Estados Unidos: Almacenar a 20°C a 25°C (68°F a 77°F); se permiten excursiones entre 15°C y 30°C (59°F y 86°F) [ver USP Temperatura ambiente controlada].-----

Vida útil-36 meses -----

ES TRADUCCIÓN FIEL DEL INGLÉS AL ESPAÑOL (4 PÁGINAS) DE LA PARTE PERTINENTE DEL DOCUMENTO QUE TUVE A LA VISTA Y AL QUE ME REMITO. EN BUENOS AIRES, A LOS 08 DÍAS DEL MES DE NOVIEMBRE DE 2021. -----


ADRIANA LUIS RIECCO
 TRADUCTORA PÚBLICA
 IDIOMA INGLÉS
 MAT. T° VIII - F° 425 - CAP. FEDERAL
 IDIOMA PORTUGUES
 MAT. T° XVIII F° 008 - CAP. FEDERAL
 INSCRIP. C.T.P.C.B.A. N° 2047

COLEGIO DE TRADUCTORES PUBLICOS
 DE LA CIUDAD DE BUENOS AIRES
 Corresponde a la Legalización
 N° 70638/21 A
 JACQUELINE...

RIECCO
 PÚBLICA
 LES
 AP. FEDERAL
 GUES
 AP. FEDERAL
 N° 2047



COLEGIO DE TRADUCTORES PÚBLICOS DE LA CIUDAD DE BUENOS AIRES

República Argentina
Ley 20305

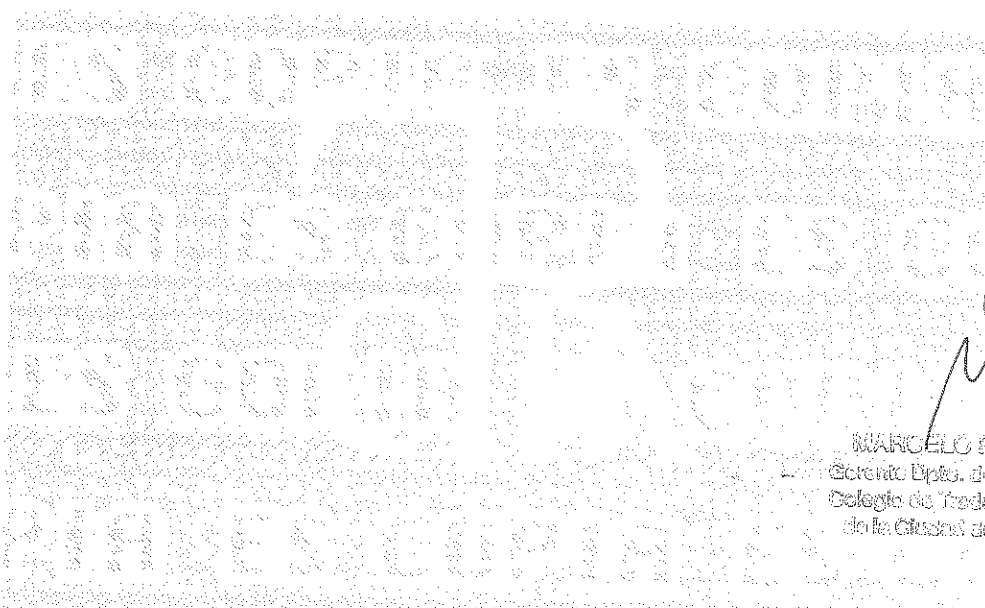
LEGALIZACIÓN

Por la presente, el COLEGIO DE TRADUCTORES PÚBLICOS DE LA CIUDAD DE BUENOS AIRES, en virtud de la facultad que le confiere el artículo 10 inc. d) de la ley 20305, certifica únicamente que la firma y el sello que aparecen en la traducción adjunta concuerdan con los correspondientes al/a la Traductor/a Público/a **LUIS RIESGO, ADRIANA**

que obran en los registros de esta institución, en el folio **425** del Tomo **8** en el idioma **INGLÉS**.

Legalización número: **70639**

Buenos Aires, 10/11/2021



MARCELO E. SIGALOFF
Gerente Depto. de Legalizaciones
Colegio de Traductores Públicos
de la Ciudad de Buenos Aires

ESTA LEGALIZACIÓN NO SE CONSIDERARÁ VÁLIDA SIN EL CORRESPONDIENTE
TIMBRADO DE CONTROL EN LA ÚLTIMA HOJA DE LA TRADUCCIÓN ADJUNTA

51039370639

Control interno:



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By virtue of the authority vested in the COLEGIO DE TRADUCTORES PÚBLICOS DE LA CIUDAD DE BUENOS AIRES (Buenos Aires Sworn Translators Association) by Argentine law No. 20 305 section 10(d), I hereby CERTIFY that the seal and signature affixed on the attached translation are consistent with the seal and signature on file in our records.

The Colegio de Traductores Públicos de la Ciudad de Buenos Aires only certifies that the signature and seal on the translation are genuine; it will not attest to the contents of the document.

THIS CERTIFICATION WILL BE VALID ONLY IF IT BEARS THE PERTINENT CHECK STAMP ON THE LAST PAGE OF THE ATTACHED TRANSLATION.

Vu par le COLEGIO DE TRADUCTORES PÚBLICOS DE LA CIUDAD DE BUENOS AIRES (Ordre des Traducteurs Officiels de la ville de Buenos Aires), en vertu des attributions qui lui ont été accordées par l'article 10, alinéa d) de la Loi n° 20.305, pour la seule légalisation matérielle de la signature et du sceau du Traductor Público (Traducteur Officiel) apposés sur la traduction du document ci-joint, qui sont conformes à ceux déposés aux archives de cette Institution.

LE TIMBRE APOSÉ SUR LA DERNIÈRE PAGE DE LA TRADUCTION FERA PREUVE DE LA VALIDITÉ DE LA LÉGALISATION.

II COLEGIO DE TRADUCTORES PÚBLICOS DE LA CIUDAD DE BUENOS AIRES (Ordine dei Traduttori abilitati della Città di Buenos Aires) CERTIFICA ai sensi dell'articolo 10, lettera d) della legge 20.305 che la firma e il timbro apposti sulla qui unita traduzione sono conformi alla firma e al timbro del Traduttore abilitato depositati presso questo Ente. Non certifica il contenuto della traduzione sulla quale la certificazione è apposta.

LA VALIDITÀ DELLA PRESENTE CERTIFICAZIONE È SUBORDINATA ALL'APPOSIZIONE DEL TIMBRO DI CONTROLLO DEL CTPCBA SULL'ULTIMA PAGINA DELL'ALLEGATA TRADUZIONE.

Por meio desta legalização, o COLEGIO DE TRADUCTORES PÚBLICOS DE LA CIUDAD DE BUENOS AIRES (Colégio dos Tradutores Públicos da Cidade de Buenos Aires), no uso de suas atribuições e em conformidade com o artigo 10, alínea "d", da Lei 20.305, somente reconhece a assinatura e o carimbo do Tradutor Público que subscreve a tradução em anexo por semelhança com a assinatura e o carimbo arquivados nos registros desta instituição.

A PRESENTE LEGALIZAÇÃO SÓ TERÁ VALIDADE COM A CORRESPONDENTE CHANCELA MECÂNICA APOSTA NA ÚLTIMA FOLHA DA TRADUÇÃO.

COLEGIO DE TRADUCTORES PÚBLICOS DE LA CIUDAD DE BUENOS AIRES (Kammer der vereidigten Übersetzer der Stadt Buenos Aires). Kraft der Befugnisse, die ihr nach Art. 10 Abs. d) von Gesetz 20.305 zustehen, bescheinigt die Kammer hiermit lediglich die Übereinstimmung der Unterschrift und des Siegelabdruckes auf der beigefügten Übersetzung mit der entsprechenden Unterschrift und dem Siegelabdruck des vereidigten Übersetzers (Traductor Público) in unseren Registern.

DIE VORLIEGENDE ÜBERSETZUNG IST OHNE DEN ENTSPRECHENDEN GEBÜHRENSTEMPEL AUF DEM LETZTEN BLATT DER BEIGEFÜGTEN ÜBERSETZUNG NICHT GÜLTIG.

CPP Sprycel 70 mg

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country: *United States of America*

This public document

2. has been signed by Carole Jones

3. acting in the capacity of Division Director, Exports Compliance Branch

4. bears the seal/stamp of U. S. Department of Health and Human Services

Certified

5. at Washington, D.C.

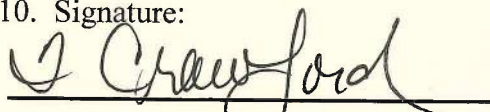
6. the thirtieth of October, 2021

7. by *Assistant Authentication Officer, United States Department of State*

8. No. 22003824-15

9. Seal/Stamp:

10. Signature:



Fernesia T. Crawford

United States Food and Drug Administration

Center for Drug Evaluation and Research

10903 New Hampshire Ave, Silver Spring, MD 20993, United States of America
CDER.exportCertificateProgram@fda.hhs.gov - Telephone (301) 796-4950

Certificate of a Pharmaceutical Product - Foreign Manufacturer

Certificate Number: P2G6-7MQN

Certificate Issue Date: September 30, 2021

Certificate Expiration Date: September 29, 2023

Exporting Country: UNITED STATES OF AMERICA

| | |
|---------|--|
| 1. | Drug Trade Name, International or National non-proprietary name (as applicable) & dosage form: SPRYCEL ®, Tablet |
| 1.1 | Active Ingredient(s) and amount(s) per unit dose (complete quantitative composition is preferred): dasatinib 70 MG |
| 1.2 | Is this product licensed to be placed on the market for use in the exporting country? Yes |
| 1.3 | Is this product actually on the market in the exporting country? Yes |
| 2.A.1 | Product license number & date of issue: 021986 06/28/2006 |
| 2.A.2 | Product license holder name & address: Bristol-Myers Squibb Company, PO Box 4000, Princeton, NJ 08543 United States of America |
| 2.A.3 | Status of Product license holder: Neither |
| 2.A.3.1 | Manufacturer name & address: Pathcon Inc., 2100 Syntex Court, Mississauga, Mississauga, Ontario L5N 7K9 CANADA |
| 2.A.4 | Is a summary basis for approval appended? No |
| 2.A.5 | Is the attached product information, complete and consonant with the license? Yes |
| 2.A.6 | Applicant name & address for certificate (if different from the license holder): Bristol Myers Squibb, 4931 George Road, Tampa, FL 33634 United States of America |
| 2.B.4 | Remarks: Packager: AndersonBrecon Inc., 4545 Assembly Drive, Rockford, IL 61109 This FDA certification pertains to the product marketed in the United States of America. |
| 3. | Does the certifying authority arrange for periodic inspection of the manufacturing plant in which the dosage form is produced? Yes |
| 3.1 | Periodicity of routine inspections (years): Pursuant to section 510(h)(3) of the Federal Food, Drug & Cosmetic Act, inspections will occur in accordance with a risk-based schedule |
| 3.2 | Has the manufacture of this type of dosage form been inspected? Yes |
| 3.3 | Do the facilities and operations conform to GMPs as recommended by the WHO? (GMPs including 21 Code of Federal Regulations parts 210, 211, or ICH Q7A): Yes, at time of inspection, site complies with FDA cGMP |
| 3.4 | Does the information submitted by the applicant satisfy the certifying authority on all aspects of the manufacture of the product undertaken by another party? Yes |

Carole Jones

Carole Jones, Division Director
Exports Compliance Branch
of Global Drug Distribution



XXXXXXXXXX 1386686A0

Distributed by:
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA


60 Tablets NDC 0003-0524-11

SPRYCEL[®]
(dasatinib)
Tablets

70 mg

Rx only

**Do not crush, cut or chew tablets.
Swallow tablets whole.**

 Bristol-Myers Squibb

Each film-coated tablet contains 70 mg dasatinib.
Usual Dosage: See package insert for dosing instructions,
directions for use, and precautions.
Store at 20°C to 25°C (68°F to 77°F), excursions
permitted between 15°C and 30°C (59°F and 86°F)
(see USP Controlled Room Temperature).
Do not use if inner seal of bottle is broken or missing.



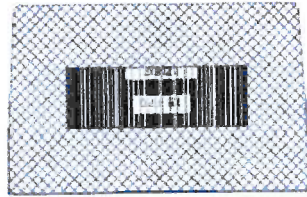
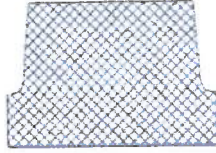
GSN 00000000000000
SN 00000000000000
Lot 00000000
Exp. 00/00/00



60 Tablets NDC 0003-0524-11

SPRYCEL®
(dasatinib)
Tablets

70 mg



Each film-coated tablet contains 70 mg dasatinib.
Usual Dosage: See package insert for dosing instructions, directions for use, and precautions.
Store at 20°C to 25°C (68°F to 77°F), excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].

60 Tablets NDC 0003-0524-11

SPRYCEL®
(dasatinib)
Tablets

70 mg

Rx only

Do not crush, cut or chew tablets.
Swallow tablets whole.

Bristol-Myers Squibb

For Posters Only
0000 0000 00

Do not use if inner seal of bottle is broken or missing.

Distributed by:
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA
Product of Switzerland

3241301
138681440

60 Tablets NDC 0003-0524-11

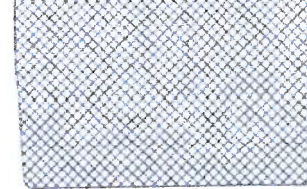
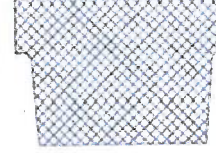
SPRYCEL®
(dasatinib)
Tablets

70 mg

Rx only

Do not crush, cut or chew tablets.
Swallow tablets whole.

Bristol-Myers Squibb



HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use SPRYCEL[®] safely and effectively. See full prescribing information for SPRYCEL.

SPRYCEL (dasatinib) tablets, for oral use
Initial U.S. Approval: 2009

RECENT MAJOR CHANGES

| | |
|--------------------------------|--------|
| Warnings and Precautions (5.4) | 6/2021 |
| Warnings and Precautions (5.9) | 6/2021 |

INDICATIONS AND USAGE

- SPRYCEL is a kinase inhibitor indicated for the treatment of
- newly diagnosed adults with Philadelphia chromosome-positive (Ph⁺) chronic myeloid leukemia (CML) in chronic phase (1, 14)
 - adults with chronic, accelerated, or myeloid or lymphoid blast phase Ph⁺ CML with resistance or intolerance to prior therapy including imatinib (1, 14)
 - adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph⁺ ALL) with resistance or intolerance to prior therapy (1, 14)
 - pediatric patients 1 year of age and older with Ph⁺ CML in chronic phase (1, 14)
 - pediatric patients 1 year of age and older with newly diagnosed Ph⁺ ALL in combination with chemotherapy (1, 14)

DOSE AND ADMINISTRATION

- Chronic phase CML in adults: 100 mg once daily (2)
- Accelerated phase CML, myeloid or lymphoid blast phase CML, or Ph⁺ ALL in adults: 140 mg once daily (2)
- Chronic phase CML and ALL in pediatric patients: starting dose based on body weight (2)
- Administer orally, with or without a meal. Do not crush, cut, or chew tablets (2)

DOSE FORMS AND STRENGTHS

Tablets: 20 mg, 50 mg, 70 mg, 80 mg, 100 mg, and 140 mg (3)

CONTRAINDICATIONS

None (4)

WARNINGS AND PRECAUTIONS

- Myelosuppression and Bleeding Events:** Severe thrombocytopenia, neutropenia, and anemia may occur. Use caution if used concomitantly with medications that inhibit platelet function or anticoagulants. Monitor complete blood counts regularly. Transfuse and interrupt SPRYCEL when indicated (2.5, 5.1, 5.2)
- Fluid Retention:** Fluid retention, sometimes severe, including pleural effusions. Manage with supportive care measures and/or dose modification (2.5, 5.3)

FULL PRESCRIBING INFORMATION: CONTENTS*

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| 6 | ADVERSE REACTIONS | 14.3 | CML in Pediatric Patients |
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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

SPRYCEL (dasatinib) is indicated for the treatment of adult patients with

- newly diagnosed Philadelphia chromosome-positive (Ph⁺) chronic myeloid leukemia (CML) in chronic phase.
- chronic, accelerated, or myeloid or lymphoid blast phase Ph⁺ CML with resistance or intolerance to prior therapy including imatinib
- Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph⁺ ALL) with resistance or intolerance to prior therapy.

SPRYCEL (dasatinib) is indicated for the treatment of pediatric patients 1 year of age and older with

- Ph⁺ CML in chronic phase.
- newly diagnosed Ph⁺ ALL in combination with chemotherapy.

2 DOSE AND ADMINISTRATION

2.1 Dosage of SPRYCEL in Adult Patients

The recommended starting dosage of SPRYCEL for chronic phase CML in adults is 100 mg administered orally once daily. The recommended starting dosage of SPRYCEL for accelerated phase CML, myeloid or lymphoid blast phase CML, or Ph⁺ ALL in adults is 140 mg administered orally once daily. Tablets should not be crushed, cut, or chewed; they should be swallowed whole. SPRYCEL can be taken with or without a meal, either in the morning or in the evening.

2.2 Dosage of SPRYCEL in Pediatric Patients with CML or Ph⁺ ALL

The recommended starting dosage for pediatric patients is based on body weight as shown in Table 1. The recommended dose should be administered orally once daily with or without food. Recalculate the dose every 3 months based on changes in body weight, or more often if necessary.

Do not crush, cut or chew tablets. Swallow tablets whole. There are additional administration considerations for pediatric patients who have difficulty swallowing tablets whole [see *Use in Specific Populations (8.4) and Clinical Pharmacology (12.3)*].

| Body Weight (kg) ^b | Daily Dose (mg) |
|-------------------------------|-----------------|
| 10 to less than 20 | 40 mg |
| 20 to less than 30 | 60 mg |
| 30 to less than 45 | 70 mg |
| at least 45 | 100 mg |

* For pediatric patients with Ph⁺ ALL, begin SPRYCEL therapy on or before day 15 of induction chemotherapy, when diagnosis is confirmed and continue for 2 years.
^b Tablet dosing is not recommended for patients weighing less than 10 kg.

15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

Refer to Section 2.4 for recommendations on dose escalation in adults with CML and Ph⁺ ALL, and pediatric patients with CML.

2.3 Dose Modification

Strong CYP3A4 Inducers

Avoid the use of concomitant strong CYP3A4 inducers and St. John's wort. If patients must be coadministered a strong CYP3A4 inducer, consider a SPRYCEL dose increase. If the dose of SPRYCEL is increased, monitor the patient carefully for toxicity [see *Drug Interactions (7.1)*].

Strong CYP3A4 Inhibitors

Avoid the use of concomitant strong CYP3A4 inhibitors and grapefruit juice. Recommend selecting an alternate concomitant medication with no or minimal enzyme inhibition potential, if possible. If SPRYCEL must be administered with a strong CYP3A4 inhibitor, consider a dose decrease to:

- 40 mg daily for patients taking SPRYCEL 140 mg daily.
- 20 mg daily for patients taking SPRYCEL 100 mg daily.
- 20 mg daily for patients taking SPRYCEL 70 mg daily.

For patients taking SPRYCEL 60 mg or 40 mg daily, consider interrupting SPRYCEL until the inhibitor is discontinued. Allow a washout period of approximately 1 week after the inhibitor is stopped before reinitiating SPRYCEL.

These reduced doses of SPRYCEL are predicted to adjust the area under the curve (AUC) to the range observed without CYP3A4 inhibitors; however, clinical data are not available with these dose adjustments in patients receiving strong CYP3A4 inhibitors. If SPRYCEL is not tolerated after dose reduction, either discontinue the strong CYP3A4 inhibitor or interrupt SPRYCEL until the inhibitor is discontinued. Allow a washout period of approximately 1 week after the inhibitor is stopped before the SPRYCEL dose is increased [see *Drug Interactions (7.1)*].

2.4 Dose Escalation in Adults with CML and Ph⁺ ALL, and Pediatric Patients with CML

For adult patients with CML and Ph⁺ ALL, consider dose escalation to 140 mg once daily (chronic phase CML) or 180 mg once daily (advanced phase CML and Ph⁺ ALL) in patients who do not achieve a hematologic or cytogenetic response at the recommended starting dosage. For pediatric patients with CML, consider dose escalation to 120 mg once daily (see Table 2) if escalation is not recommended for pediatric patients with Ph⁺ ALL, who are administered in combination with chemotherapy.

Escalate the SPRYCEL dose as shown in Table 2 in pediatric patients who do not achieve a hematologic or cytogenetic response at the recommended starting dosage.

| Formulation | Dose (maximum dose per Starting Dose) |
|-------------|---------------------------------------|
| Tablets | 40 mg |
| | 60 mg |
| | 70 mg |
| | 100 mg |

2.5 Dose Adjustment for Adverse Reactions
Myelosuppression

In clinical studies, myelosuppression was managed by dose interruption, dose reduction, or discontinuation of study therapy. Hematopoietic growth factor has been used in patients with resistant myelosuppression. Guidelines for dose modifications for adult and pediatric patients are summarized in Tables 3 and 4, respectively.

Table 3: Dose Adjustments for Neutropenia and Thrombocytopenia in Adults

| | | Dose (maximum dose per day) | | |
|--|--|--|--------------------------|--------------------------|
| | | Original Starting Dose | One-Level Dose Reduction | Two-Level Dose Reduction |
| Chronic Phase CML (starting dose 100 mg once daily) | ANC* <0.5 × 10 ⁹ /L or Platelets <50 × 10 ⁹ /L | 1. Stop SPRYCEL until ANC ≥1.0 × 10 ⁹ /L and platelets ≥50 × 10 ⁹ /L. | | |
| | | 2. Resume treatment with SPRYCEL at the original starting dose if recovery occurs in ≤7 days. | | |
| | | 3. If platelets <25 × 10 ⁹ /L or recurrence of ANC <0.5 × 10 ⁹ /L for >7 days, repeat Step 1 and resume SPRYCEL at a reduced dose of 80 mg once daily for second episode. For third episode, further reduce dose to 50 mg once daily (for newly diagnosed patients) or discontinue SPRYCEL (for patients resistant or intolerant to prior therapy including imatinib). | | |
| Accelerated Phase CML, Blast Phase CML and Ph+ ALL (starting dose 140 mg once daily) | ANC* <0.5 × 10 ⁹ /L or Platelets <10 × 10 ⁹ /L | 1. Check if cytopenia is related to leukemia (marrow aspirate or biopsy). | | |
| | | 2. If cytopenia is unrelated to leukemia, stop SPRYCEL until ANC ≥1.0 × 10 ⁹ /L and platelets ≥20 × 10 ⁹ /L and resume at the original starting dose. | | |
| | | 3. If recurrence of cytopenia, repeat Step 1 and resume SPRYCEL at a reduced dose of 100 mg once daily (second episode) or 80 mg once daily (third episode). | | |
| | | 4. If cytopenia is related to leukemia, consider dose escalation to 180 mg once daily. | | |

*ANC: absolute neutrophil count

Table 4: Dose Adjustments for Neutropenia and Thrombocytopenia in Pediatric Patients with Ph+ CML

| | Dose (maximum dose per day) | | |
|--|-----------------------------|--------------------------|--------------------------|
| | Original Starting Dose | One-Level Dose Reduction | Two-Level Dose Reduction |
| 1. If cytopenia persists for more than 3 weeks, check if cytopenia is related to leukemia (marrow aspirate or biopsy). | 40 mg | 20 mg | ** |
| | 60 mg | 40 mg | 20 mg |
| | 70 mg | 60 mg | 50 mg |
| 2. If cytopenia is unrelated to leukemia, stop SPRYCEL until ANC ≥1.0 × 10 ⁹ /L and platelets ≥75 × 10 ⁹ /L and resume at the original starting dose or at a reduced dose. | 100 mg | 80 mg | 70 mg |
| | | | |
| | | | |
| 3. If cytopenia recurs, repeat marrow aspirate/biopsy and resume SPRYCEL at a reduced dose. | | | |

*ANC: absolute neutrophil count
 ** lower tablet dose not available

For pediatric patients with chronic phase CML, if Grade ≥3 neutropenia or thrombocytopenia recurs during complete hematologic response (CHR), interrupt SPRYCEL and resume at a reduced dose. Implement temporary dose reductions for intermediate degrees of cytopenia and disease response as needed.

For pediatric patients with Ph+ ALL, if neutropenia and/or thrombocytopenia result in a delay of the next block of treatment by more than 14 days, interrupt SPRYCEL and resume at the same dose level once the next block of treatment is started. If neutropenia and/or thrombocytopenia persist and the next block of treatment is delayed another 7 days, perform a bone marrow assessment to assess cellularity and percentage of blasts. If marrow cellularity is <10%, interrupt treatment with SPRYCEL until ANC >500/μL (0.5 × 10⁹/L), at which time treatment may be resumed at full dose. If marrow cellularity is >10%, resumption of treatment with SPRYCEL may be considered.

Non-Hematologic Adverse Reactions

For adults with Ph+ CML and ALL, and pediatric patients with Ph+ CML, if a severe non-hematologic adverse reaction develops with SPRYCEL use, treatment must be withheld until the

event has resolved or improved. Thereafter, treatment can be resumed as appropriate at a reduced dose depending on the severity and recurrence of the event [see Warnings and Precautions (5.1)].

For pediatric patients with Ph+ ALL, interrupt treatment for cases of grade ≥3 non-hematologic adverse reactions with the exception of liver function test abnormalities, and resume at a reduced dose when resolved to grade ≤1. For elevated direct bilirubin over 5 times the institutional upper limit of normal (ULN), interrupt treatment until improvement to baseline or grade ≤1. For elevated AST/ALT over 15 times the institutional ULN, interrupt treatment until improvement to baseline or grade <1. For recurrent liver function test abnormalities as above, reduce the dose if this adverse reaction recurs after reinitiation of SPRYCEL. Dose reduction recommendations are described in Table 5.

Table 5: Dose Adjustments for Non-Hematologic Toxicities in Pediatric Patients

| | Dose (maximum dose per day) | | |
|---|-----------------------------|--------------------------|--------------------------|
| | Original Starting Dose | One-Level Dose Reduction | Two-Level Dose Reduction |
| 1. If a non-hematologic toxicity grade 2 occurs, consider interrupting SPRYCEL if no recovery despite symptomatic therapy; once recovered to grade ≤1, resume in the original starting dose. Resume SPRYCEL at a reduced dose for recurrent events. | 40 mg | 20 mg | ** |
| | 60 mg | 40 mg | 20 mg |
| | 70 mg | 60 mg | 50 mg |
| 2. If a non-hematologic toxicity grade 3 occurs, stop SPRYCEL until recovery to grade ≤1 and then resume at a reduced dose. | 100 mg | 80 mg | 70 mg |
| | | | |
| 3. If direct bilirubin is >5 ULN or AST/ALT >15 ULN, interrupt SPRYCEL until recovery to grade ≤1 and then resume SPRYCEL at the original starting dose. Resume SPRYCEL at a reduced dose for recurrent events. | | | |

** lower tablet dose not available

3 DOSAGE FORMS AND STRENGTHS

SPRYCEL (dasatinib) Tablets are available as 20-mg, 50-mg, 70-mg, 80-mg, 100-mg, and 140-mg white to off-white, biconvex, film-coated tablets.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Myelosuppression

Treatment with SPRYCEL is associated with severe (NCI CTCAE Grade 3 or 4) thrombocytopenia, neutropenia, and anemia, which occur earlier and more frequently in patients with advanced phase CML or Ph+ ALL than in patients with chronic phase CML [see Adverse Reactions (6.1)].

In patients with chronic phase CML, perform complete blood counts (CBCs) every 2 weeks for 12 weeks, then every 3 months thereafter, or as clinically indicated. In patients with advanced phase CML or Ph+ ALL, perform CBCs weekly for the first 2 months and then monthly thereafter, or as clinically indicated.

In pediatric patients with Ph+ ALL treated with SPRYCEL in combination with chemotherapy, perform CBCs prior to the start of each block of chemotherapy and as clinically indicated. During the consolidation blocks of chemotherapy, perform CBCs every 2 days until recovery.

Myelosuppression is generally reversible and usually managed by withholding SPRYCEL temporarily and/or dose reduction [see Dosage and Administration (2.5)].

5.2 Bleeding-Related Events

SPRYCEL can cause serious and fatal bleeding. In all CML or Ph+ ALL clinical studies, Grade ≥3 central nervous system (CNS) hemorrhages, including fatalities, occurred in <1% of patients receiving SPRYCEL. The incidence of Grade 3/4 hemorrhage, occurred in 5.8% of adult patients and generally required treatment interruptions and transfusions. The incidence of Grade 5 hemorrhage occurred in 0.4% of adult patients. The most frequent site of hemorrhage was gastrointestinal [see Adverse Reactions (6.1)]. Most bleeding events in clinical studies were associated with severe thrombocytopenia. In addition to causing thrombocytopenia in human subjects, dasatinib caused platelet dysfunction *in vitro*.

Concomitant medications that inhibit platelet function or anticoagulants may increase the risk of hemorrhage.

5.3 Fluid Retention

SPRYCEL may cause fluid retention [see Adverse Reactions (6.1)]. After 5 years of follow-up in the adult randomized newly diagnosed chronic phase CML study (n=258), Grade 3 or 4 fluid retention was reported in 5% of patients, including 3% of patients with Grade 3 or 4 pleural effusion. In adult patients with newly diagnosed or imatinib-resistant or -intolerant chronic phase CML, Grade 3 or 4 fluid retention occurred in 6% of patients treated with SPRYCEL at the recommended dose (n=548). In adult patients with advanced phase CML or Ph+ ALL treated with SPRYCEL at the recommended dose (n=304), Grade 3 or 4 fluid retention was reported in 8% of patients, including Grade 3 or 4 pleural effusion reported in 7% of patients. In pediatric patients with chronic phase CML, cases of Grade 1 or 2 fluid retention were reported in 10.3% of patients.

CNS bleeding
 Vomiting
 Muscle spasms
 Includes cardiac failure acute, cardiac failure congestive, cardiomyopathy, diastolic dysfunction, decreased and left ventricular dysfunction.
 Includes erythema, erythema multiforme, rash, rash generalized, rash macular, rash papular, exfoliation, and rash vesicular.
 Adverse reaction of special interest with <10% frequency
 Includes conjunctival hemorrhage, ear hemorrhage, epistaxis, eye hemorrhage, hematuria, hemoptysis, intra-abdominal hemorrhage, petechiae, scleral hemorrhage, and vaginal hemorrhage.
 A comparison of cumulative rates of adverse reactions reported in 2 years of follow-up of 1 and 5 years in a randomized trial of newly diagnosed Ph+ ALL treated with SPRYCEL are shown in Table 7.
 Applicable special handling and disposal procedures.¹

Evaluate patients who develop symptoms of pleural effusion or other fluid retention, such as new or worsened dyspnea on exertion or at rest, pleuritic chest pain, or dry cough, promptly with a chest x-ray or additional diagnostic imaging as appropriate. Fluid retention events were typically managed by supportive care measures that may include diuretics or short courses of steroids. Severe pleural effusion may require thoracentesis and oxygen therapy. Consider dose reduction or treatment interruption [see Dosage and Administration (2.5)].

5.4 Cardiovascular Toxicity

SPRYCEL can cause cardiac dysfunction [see Adverse Reactions (6.1)]. After 5 years of follow-up in the randomized newly diagnosed chronic phase CML trial in adults (n=258), the following cardiac adverse reactions occurred: cardiac ischemic events (3.9% dasatinib vs 1.6% imatinib), cardiac-related fluid retention (8.5% dasatinib vs 3.9% imatinib), and conduction system abnormalities, most commonly arrhythmia and palpitations (7.0% dasatinib vs 5.0% imatinib). Two cases (0.8%) of peripheral arterial occlusive disease occurred with imatinib and 2 (0.8%) transient ischemic attacks occurred with dasatinib. Monitor patients for signs or symptoms consistent with cardiac dysfunction and treat appropriately.

5.5 Pulmonary Arterial Hypertension

SPRYCEL may increase the risk of developing pulmonary arterial hypertension (PAH) in adult and pediatric patients which may occur any time after initiation, including after more than 1 year of treatment. Manifestations include dyspnea, fatigue, hypoxia, and fluid retention [see Adverse Reactions (6.1)]. PAH may be reversible on discontinuation of SPRYCEL. Evaluate patients for signs and symptoms of underlying cardiopulmonary disease prior to initiating SPRYCEL and during treatment. If PAH is confirmed, SPRYCEL should be permanently discontinued.

5.6 QT Prolongation

SPRYCEL may increase the risk of prolongation of QTc in patients including those with hypokalemia or hypomagnesemia, patients with congenital long QT syndrome, patients taking antiarrhythmic medicines or other medicinal products that lead to QT prolongation, and cumulative high-dose anthracycline therapy [see Adverse Reactions (6.1)]. Correct hypokalemia or hypomagnesemia prior to and during SPRYCEL administration.

5.7 Severe Dermatologic Reactions

Cases of severe mucocutaneous dermatologic reactions, including Stevens-Johnson syndrome [see Adverse Reactions (6.2)] and erythema multiforme, have been reported in patients treated with SPRYCEL. Discontinue permanently in patients who experience a severe mucocutaneous reaction during treatment if no other etiology can be identified.

5.8 Tumor Lysis Syndrome

Tumor lysis syndrome has been reported in patients with resistance to prior imatinib therapy, primarily in advanced phase disease. Due to potential for tumor lysis syndrome, maintain adequate hydration, correct uric acid levels prior to initiating therapy with SPRYCEL, and monitor electrolyte levels. Patients with advanced stage disease and/or high tumor burden may be at increased risk and should be monitored more frequently [see Adverse Reactions (6.1)].

5.9 Embryo-Fetal Toxicity

Based on limited human data, SPRYCEL can cause fetal harm when administered to a pregnant woman. Adverse pharmacologic effects of SPRYCEL including hydrops fetalis, fetal leukopenia, and fetal thrombocytopenia have been reported with maternal exposure to SPRYCEL. Advise

females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment with SPRYCEL and for 30 days after the last dose [see Use in Specific Populations (8.1, 8.3)].

5.10 Effects on Growth and Development in Pediatric Patients

In pediatric trials of SPRYCEL in chronic phase CML after at least 2 years of treatment, adverse reactions associated with bone growth and development were reported in 5 (5.2%) patients, one of which was severe in intensity (Growth Retardation Grade 3). These 5 cases included cases of epiphyses delayed fusion, osteopenia, growth retardation, and gynecomastia [see Adverse Reactions (6.1) and Use in Specific Populations (8.4)]. Of these 5 cases, 1 case of osteopenia and 1 case of gynecomastia resolved during treatment.

Monitor bone growth and development in pediatric patients.

6 ADVERSE REACTIONS

The following clinically significant adverse reactions are discussed in greater detail in other sections of the labeling:

- Myelosuppression [see Dosage and Administration (2.5) and Warnings and Precautions (5.1)].
- Bleeding-related events [see Warnings and Precautions (5.2)].
- Fluid retention [see Warnings and Precautions (5.3)].
- Cardiovascular toxicity [see Warnings and Precautions (5.4)].
- Pulmonary arterial hypertension [see Warnings and Precautions (5.5)].
- QT prolongation [see Warnings and Precautions (5.6)].
- Severe dermatologic reactions [see Warnings and Precautions (5.7)].
- Tumor lysis syndrome [see Warnings and Precautions (5.8)].
- Effects on growth and development in pediatric patients [see Warnings and Precautions (5.10)].

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The data described below reflect exposure to SPRYCEL administered as single-agent therapy at all doses tested in clinical studies (n=2809), including 324 adult patients with newly diagnosed chronic phase CML, 2388 adult patients with imatinib-resistant or -intolerant chronic or advanced phase CML or Ph+ ALL, and 97 pediatric patients with chronic phase CML. The median duration of therapy in a total of 2712 adult patients was 19.2 months (range 0 to 93.2 months). In a randomized trial in patients with newly diagnosed chronic phase CML, the median duration of therapy was approximately 60 months. The median duration of therapy in 1618 adult patients with chronic phase CML was 29 months (range 0 to 92.9 months).

The median duration of therapy in 1094 adult patients with advanced phase CML or Ph+ ALL was 6.2 months (range 0 to 93.2 months).

In two non-randomized trials in 97 pediatric patients with chronic phase CML (51 patients newly diagnosed and 46 patients resistant or intolerant to previous treatment with imatinib), the median duration of therapy was 51.1 months (range 1.9 to 99.6 months).

In the overall population of 2712 adult patients, 88% of patients experienced adverse reactions at some time and 19% experienced adverse reactions leading to treatment discontinuation.

In the randomized trial in adult patients with newly diagnosed chronic phase CML, drug was discontinued for adverse reactions in 16% of patients with a minimum of 60 months of follow-up. After a minimum of 60 months of follow-up, the cumulative discontinuation rate was 39%. Among the 1618 patients with chronic phase CML, drug-related adverse reactions leading to discontinuation were reported in 329 (20.3%) patients; among the 1094 patients with advanced phase CML or Ph+ ALL, drug-related adverse reactions leading to discontinuation were reported in 191 (17.5%) patients.

Among the 97 pediatric subjects, drug-related adverse reactions leading to discontinuation were reported in 1 patient (1%).

Adverse reactions reported in ≥10% of adult patients, and other adverse reactions of interest, in a randomized trial in patients with newly diagnosed chronic phase CML at a median follow-up of approximately 60 months are presented in Table 6.

Adverse reactions reported in ≥10% of adult patients treated at the recommended dose of 100 mg once daily (n=165), and other adverse reactions of interest, in a randomized dose-optimization trial of patients with chronic phase CML resistant or intolerant to prior imatinib therapy at a median follow-up of approximately 84 months are presented in Table 8.

Adverse reactions reported in ≥10% of pediatric patients at a median follow-up of approximately 51.1 months are presented in Table 11.

Drug-related serious adverse reactions (SARs) were reported for 16.7% of adult patients in the randomized trial of patients with newly diagnosed chronic phase CML. Serious adverse reactions reported in ≥5% of patients included pleural effusion (5%).

Drug-related SARs were reported for 26.1% of patients treated at the recommended dose of 100 mg once daily in the randomized dose-optimization trial of adult patients with chronic phase CML resistant or intolerant to prior imatinib therapy. Serious adverse reactions reported in ≥5% of patients included pleural effusion (10%).

Drug-related SARs were reported for 14.4% of pediatric patients.

Chronic Myeloid Leukemia (CML)

Adverse reactions (excluding laboratory abnormalities) that were reported in at least 10% of adult patients are shown in Table 6 for newly diagnosed patients with chronic phase CML and Tables 8 and 10 for CML patients with resistance or intolerance to prior imatinib therapy.

Table 6: Adverse Reactions Reported in ≥10% of Adult Patients with Newly Diagnosed Chronic Phase CML (minimum of 60 months follow-up)

| Adverse Reaction | All Grades | | Grade 3/4 | |
|---|-------------------------|------------------|-----------------|------------------|
| | SPRYCEL (n=258) | Imatinib (n=258) | SPRYCEL (n=258) | Imatinib (n=258) |
| | Percent (%) of Patients | | | |
| Fluid retention | 38 | 45 | 5 | 1 |
| Pleural effusion | 28 | 1 | 3 | 0 |
| Superficial localized edema | 14 | 38 | 0 | <1 |
| Pulmonary hypertension | 5 | <1 | 1 | 0 |
| Generalized edema | 4 | 7 | 0 | 0 |
| Pericardial effusion | 4 | 1 | 1 | 0 |
| Congestive heart failure/ cardiac dysfunction ^a | 2 | 1 | <1 | <1 |
| Pulmonary edema | 1 | 0 | 0 | 0 |
| Diarrhea | 22 | 23 | 1 | 1 |
| Musculoskeletal pain | 14 | 17 | 0 | <1 |
| Rash ^b | 14 | 18 | 0 | 2 |
| Headache | 14 | 11 | 0 | 0 |
| Abdominal pain | 11 | 8 | 0 | 1 |
| Fatigue | 11 | 12 | <1 | 0 |
| Nausea | 10 | 25 | 0 | 0 |
| Myalgia | 7 | 12 | 0 | 0 |
| Arthralgia | 7 | 10 | 0 | <1 |
| Hemorrhage ^c | 8 | 8 | 1 | 1 |
| Gastrointestinal bleeding | 2 | 2 | 1 | 0 |
| Other bleeding ^d | 6 | 6 | 0 | 0 |
| CNS bleeding | <1 | <1 | 0 | 0 |
| Vomiting | 5 | 12 | 0 | 0 |
| Muscle spasms | 5 | 21 | 0 | 0 |

^a Includes cardiac failure-acute, cardiac failure congestive, cardiomyopathy, diastolic dysfunction, decreased, and left ventricular dysfunction.

^b Includes erythema, erythema multiforme, rash, rash generalized, rash macular, rash papular, exfoliation, and rash vesicular.

^c Adverse reaction of special interest with <10% frequency.

^d Includes conjunctival hemorrhage, or hemorrhage, ecchymosis, epistaxis, eye hemorrhage, hematuria, hematuria, hemoptysis, intra-abdominal hemorrhage, petechiae, scleral hemorrhage, and vaginal hemorrhage.

A comparison of cumulative rates of adverse reactions reported in follow-up of 1 and 5 years in a randomized trial of newly diagnosed CML treated with SPRYCEL are shown in Table 7.

SPRYCEL in pediatric patients with Ph+ ALL was evaluated in a phase 1/2 trial. The primary objective of this study was to evaluate the safety and efficacy of SPRYCEL in pediatric patients with Ph+ ALL. The study is ongoing and results will be reported in the future. For more information, please contact the medical information department at 1-800-393-9878.

1. If you are pregnant, please inform your doctor. You should avoid becoming pregnant while taking SPRYCEL and for 30 days after the last dose. 2. If you are breastfeeding, please inform your doctor. You should avoid breastfeeding while taking SPRYCEL and for 30 days after the last dose. 3. If you have any other medical conditions, please inform your doctor. 4. If you are taking any other medications, please inform your doctor. 5. If you experience any side effects, please inform your doctor. 6. If you experience any allergic reactions, please inform your doctor. 7. If you experience any bleeding, please inform your doctor. 8. If you experience any fluid retention, please inform your doctor. 9. If you experience any cardiovascular symptoms, please inform your doctor. 10. If you experience any pulmonary symptoms, please inform your doctor. 11. If you experience any QT prolongation, please inform your doctor. 12. If you experience any severe dermatologic reactions, please inform your doctor. 13. If you experience any tumor lysis syndrome, please inform your doctor. 14. If you experience any effects on growth and development, please inform your doctor.

Table 7: Adverse Reactions Reported in ≥10% of Adult Patients with Newly Diagnosed Chronic Phase CML in the SPRYCEL-Treated Arm (n=258)

| Adverse Reaction | Minimum of 1 Year Follow-up | | Minimum of 5 Years Follow-up | |
|---|-----------------------------|-----------|------------------------------|-----------|
| | All Grades | Grade 3/4 | All Grades | Grade 3/4 |
| Fluid retention | 19 | 1 | 38 | 5 |
| Pleural effusion | 10 | 0 | 28 | 3 |
| Superficial localized edema | 9 | 0 | 14 | 0 |
| Pulmonary hypertension | 1 | 0 | 5 | 1 |
| Generalized edema | 2 | 0 | 4 | 0 |
| Pericardial effusion | 1 | <1 | 4 | 1 |
| Congestive heart failure/cardiac dysfunction ^a | 2 | <1 | 2 | <1 |
| Pulmonary edema | <1 | 0 | 1 | 0 |
| Diarrhea | 17 | <1 | 22 | 1 |
| Musculoskeletal pain | 11 | 0 | 14 | 0 |
| Rash ^b | 11 | 0 | 14 | 0 |
| Headache | 12 | 0 | 14 | 0 |
| Abdominal pain | 7 | 0 | 11 | 0 |
| Fatigue | 8 | <1 | 11 | <1 |
| Nausea | 8 | 0 | 10 | 0 |

^a Includes cardiac failure acute, cardiac failure congestive, cardiomyopathy, diastolic dysfunction, ejection fraction decreased, and left ventricular dysfunction.

^b Includes erythema, erythema multiforme, rash, rash generalized, rash macular, rash papular, rash pustular, skin exfoliation, and rash vesicular.

At 60 months, there were 26 deaths in dasatinib-treated patients (10.1%) and 26 deaths in imatinib-treated patients (10.1%). 1 death in each group was assessed by the investigator as related to study therapy.

Table 8: Adverse Reactions Reported in ≥10% of Adult Patients with Chronic Phase CML Resistant or Intolerant to Prior Imatinib Therapy (minimum of 84 months follow-up)

| Adverse Reaction | 100 mg Once Daily Chronic (n=165) | |
|-----------------------------|-----------------------------------|-----------|
| | All Grades | Grade 3/4 |
| Fluid retention | 48 | 7 |
| Superficial localized edema | 22 | 0 |
| Pleural effusion | 28 | 5 |
| Generalized edema | 4 | 0 |
| Pericardial effusion | 3 | 1 |
| Pulmonary hypertension | 2 | 1 |
| Headache | 33 | 1 |

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Table 8: Adverse Reactions Reported in ≥10% of Adult Patients with Chronic Phase CML Resistant or Intolerant to Prior Imatinib Therapy (minimum of 84 months follow-up)

| Adverse Reaction | 100 mg Once Daily Chronic (n=165) | |
|---|-----------------------------------|-----------|
| | All Grades | Grade 3/4 |
| Diarrhea | 28 | 2 |
| Fatigue | 26 | 4 |
| Dyspnea | 24 | 2 |
| Musculoskeletal pain | 22 | 2 |
| Nausea | 18 | 1 |
| Skin rash ^a | 18 | 2 |
| Myalgia | 13 | 0 |
| Arthralgia | 13 | 1 |
| Infection (including bacterial, viral, fungal, and non-specified) | 13 | 1 |
| Abdominal pain | 12 | 1 |
| Hemorrhage | 12 | 1 |
| Gastrointestinal bleeding | 2 | 1 |
| Pruritus | 12 | 1 |
| Pain | 11 | 1 |
| Constipation ^b | 10 | 1 |

^a Includes drug eruption, erythema, erythema multiforme, erythrodermia, exfoliative rash, generalized erythema, genital rash, heat rash, milia, rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, skin exfoliation, skin irritation, urticaria vesiculosa, and rash vesicular.

Cumulative rates of selected adverse reactions that were reported over time in patients treated with the 100 mg once daily recommended starting dose in a randomized dose-optimization trial of imatinib-resistant or -intolerant patients with chronic phase CML are shown in Table 9.

Table 9: Selected Adverse Reactions Reported in Adult Dose Optimization Trial (Imatinib-Intolerant or -Resistant Chronic Phase CML)^a

| Adverse Reaction | Minimum of 2 Years Follow-up | | Minimum of 5 Years Follow-up | | Minimum of 7 Years Follow-up | |
|---------------------------|------------------------------|-----------|------------------------------|-----------|------------------------------|-----------|
| | All Grades | Grade 3/4 | All Grades | Grade 3/4 | All Grades | Grade 3/4 |
| Diarrhea | 27 | 2 | 28 | 2 | 28 | 2 |
| Fluid retention | 34 | 4 | 42 | 6 | 48 | 7 |
| Superficial edema | 18 | 0 | 21 | 0 | 22 | 0 |
| Pleural effusion | 18 | 2 | 24 | 4 | 28 | 5 |
| Generalized edema | 3 | 0 | 4 | 0 | 4 | 0 |
| Pericardial effusion | 2 | 1 | 2 | 1 | 3 | 1 |
| Pulmonary hypertension | 0 | 0 | 0 | 0 | 2 | 1 |
| Hemorrhage | 11 | 1 | 11 | 1 | 12 | 1 |
| Gastrointestinal bleeding | 2 | 1 | 2 | 1 | 2 | 1 |

^a Randomized dose-optimization trial results reported in the recommended starting dose of 100 mg once daily (n=165) population.

Table 10: Adverse Reactions Reported in ≥10% of Adult Patients with Advanced Phase CML Resistant or Intolerant to Prior Imatinib Therapy

| Adverse Reaction | 140 mg Once Daily | | | | | |
|--|---------------------|-----------|----------------------|-----------|-----------------------|-----------|
| | Accelerated (n=157) | | Myeloid Blast (n=74) | | Lymphoid Blast (n=33) | |
| | All Grades | Grade 3/4 | All Grades | Grade 3/4 | All Grades | Grade 3/4 |
| Fluid retention | 35 | 8 | 34 | 7 | 21 | 6 |
| Superficial localized edema | 18 | 1 | 14 | 0 | 3 | 0 |
| Pleural effusion | 21 | 7 | 20 | 7 | 21 | 6 |
| Generalized edema | 1 | 0 | 3 | 0 | 0 | 0 |
| Pericardial effusion | 3 | 1 | 0 | 0 | 0 | 0 |
| Congestive heart failure/cardiac dysfunction | 0 | 0 | 4 | 0 | 0 | 0 |
| Diarrhea | 1 | 0 | 4 | 3 | 0 | 0 |
| Nausea | 27 | 1 | 18 | 1 | 15 | 3 |
| Vomiting | 31 | 3 | 20 | 5 | 18 | 0 |
| Musculoskeletal pain | 19 | 2 | 20 | 1 | 9 | 3 |
| Abdominal pain | 20 | 3 | 15 | 3 | 3 | 3 |
| Cough | 11 | 0 | 8 | 1 | 0 | 0 |
| Headache | 1 | 1 | 23 | 1 | 21 | 3 |
| Rash | 0 | 0 | 16 | 1 | 21 | 0 |
| Fatigue | 0 | 0 | 5 | 1 | 0 | 0 |
| Constipation | | | | | | |
| Arrhythmia | | | | | | |
| Hypertension | | | | | | |

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Table 10: Adverse Reactions Reported in ≥10% of Adult Patients with Advanced Phase CML Resistant or Intolerant to Prior Imatinib Therapy

| Adverse Reaction | 140 mg Once Daily | | | | | |
|---|---------------------|-----------|----------------------|-----------|-----------------------|-----------|
| | Accelerated (n=157) | | Myeloid Blast (n=74) | | Lymphoid Blast (n=33) | |
| | All Grades | Grade 3/4 | All Grades | Grade 3/4 | All Grades | Grade 3/4 |
| Infection (including bacterial, viral, fungal, and non-specified) | 10 | 6 | 14 | 7 | 9 | 0 |
| Hemorrhage | 26 | 8 | 19 | 9 | 24 | 9 |
| Gastrointestinal bleeding | 8 | 6 | 9 | 7 | 9 | 3 |
| CNS bleeding | 1 | 1 | 0 | 0 | 3 | 3 |
| Vomiting | 11 | 1 | 12 | 0 | 15 | 0 |
| Pyrexia | 11 | 2 | 18 | 3 | 6 | 0 |
| Febile neutropenia | 4 | 4 | 12 | 12 | 12 | 12 |

^a Includes ventricular dysfunction, cardiac failure, cardiac failure congestive, cardiomyopathy, congestive cardiomyopathy, diastolic dysfunction, ejection fraction decreased, and ventricular failure.

^b Includes drug eruption, erythema, erythema multiforme, erythrodermia, exfoliative rash, generalized erythema, genital rash, heat rash, milia, rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, skin exfoliation, skin irritation, urticaria vesiculosa, and rash vesicular.

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Table 11: Adverse Reactions Reported in ≥10% of Dasatinib-Treated Pediatric Patients with Chronic Phase CML (n=97)

| Adverse Reaction | All Grades | Grade 3/4 |
|-------------------|-------------------------|-----------|
| | Percent (%) of Patients | |
| Headache | 28 | 3 |
| Nausea | 20 | 0 |
| Diarrhea | 21 | 0 |
| Skin rash | 19 | 0 |
| Vomiting | 13 | 0 |
| Pain in extremity | 19 | 1 |
| Abdominal pain | 16 | 0 |
| Fatigue | 10 | 0 |
| Arthralgia | 10 | 1 |

Adverse reactions associated with bone growth and development were reported in 5 (5.2%) of pediatric patients with chronic phase CML [see Warnings and Precautions (5.10)].

Laboratory Abnormalities

Myelosuppression was commonly reported in all patient populations. The frequency of Grade 3 or 4 neutropenia, thrombocytopenia, and anemia was higher in patients with advanced phase CML than in chronic phase CML (Tables 12 and 13). Myelosuppression was reported in patients with normal baseline laboratory values as well as in patients with pre-existing laboratory abnormalities.

In patients who experienced severe myelosuppression, recovery generally occurred following dose interruption or reduction; permanent discontinuation of treatment occurred in 2% of adult patients with newly diagnosed chronic phase CML and 5% of adult patients with resistance or intolerance to prior imatinib therapy [see Warnings and Precautions (5.1)].

Grade 3 or 4 elevations of transaminases or bilirubin and Grade 3 or 4 hypocalcemia, hypokalemia, and hypophosphatemia were reported in patients with all phases of CML, but were reported with an increased frequency in patients with myeloid or lymphoid blast phase CML. Elevations in transaminases or bilirubin were usually managed with dose reduction or interruption. Patients developing Grade 3 or 4 hypocalcemia during SPRYCEL therapy often had recovery with oral calcium supplementation.

Laboratory abnormalities reported in adult patients with newly diagnosed chronic phase CML are shown in Table 12. There were no discontinuations of SPRYCEL therapy in this patient population due to biochemical laboratory parameters.

Table 12: CTC Grade 3/4 Laboratory Abnormalities in Adult Patients with Newly Diagnosed Chronic Phase CML (minimum of 60 months follow-up)

| Hematology Parameters | SPRYCEL (n=258) | Imatinib (n=288) | |
|-------------------------|-------------------------|------------------|----|
| | Percent (%) of Patients | | |
| Neutropenia | 29 | 24 | |
| Thrombocytopenia | 22 | 14 | |
| Anemia | 13 | 9 | |
| Biochemistry Parameters | Percent (%) of Patients | | |
| | Hypophosphatemia | 7 | 31 |
| | Hypokalemia | 0 | 3 |
| | Hypocalcemia | 4 | 3 |
| | Elevated SGPT (ALT) | <1 | 2 |
| | Elevated SGOT (AST) | <1 | 1 |
| | Elevated Bilirubin | 1 | 0 |
| Elevated Creatinine | 1 | 1 | |

CTC grades: neutropenia (Grade 3 ≥0.5-1.0 × 10⁹/L, Grade 4 <0.5 × 10⁹/L); thrombocytopenia (Grade 3 ≥25-50 × 10⁹/L, Grade 4 <25 × 10⁹/L); anemia (hemoglobin Grade 3 ≥65-80 g/L, Grade 4 <65 g/L); elevated creatinine (Grade 3 >3-6 × upper limit of normal range (ULN), Grade 4 >6 × ULN); elevated bilirubin (Grade 3 >3-10 × ULN, Grade 4 >10 × ULN); elevated SGOT or SGPT (Grade 3 >5-20 × ULN, Grade 4 >20 × ULN); hypocalcemia (Grade 3 <7.0-6.0 mg/dL, Grade 4 <6.0 mg/dL); hypophosphatemia (Grade 3 <2.0-1.0 mg/dL, Grade 4 <1.0 mg/dL); hypokalemia (Grade 3 <3.0-2.5 mmol/L, Grade 4 <2.5 mmol/L).

Laboratory abnormalities reported in patients with CML resistant or intolerant to imatinib who received the recommended starting doses of SPRYCEL are shown by disease phase in Table 13.

Table 13: CTC Grade 3/4 Laboratory Abnormalities in Clinical Studies of CML in Adults: Resistance or Intolerance to Prior Imatinib Therapy

| Hematology Parameters* | Chronic Phase CML 100 mg Once Daily (n=165) | Advanced Phase CML 140 mg Once Daily | | | |
|-------------------------|---|--------------------------------------|----------------------------|-----------------------------|----|
| | | Accelerated Phase (n=157) | Myeloid Blast Phase (n=74) | Lymphoid Blast Phase (n=33) | |
| Percent (%) of Patients | | | | | |
| Neutropenia | 36 | 58 | 77 | 79 | |
| Thrombocytopenia | 24 | 63 | 78 | 85 | |
| Anemia | 13 | 47 | 74 | 52 | |
| Biochemistry Parameters | Percent (%) of Patients | | | | |
| | Hypophosphatemia | 10 | 13 | 12 | 18 |
| | Hypokalemia | 2 | 7 | 11 | 15 |
| | Hypocalcemia | <1 | 4 | 9 | 12 |
| | Elevated SGPT (ALT) | 0 | 2 | 5 | 3 |
| | Elevated SGOT (AST) | <1 | 0 | 4 | 3 |
| | Elevated Bilirubin | <1 | 1 | 3 | 6 |
| Elevated Creatinine | 0 | 2 | 8 | 0 | |

CTC grades: neutropenia (Grade 3 ≥0.5-1.0 × 10⁹/L, Grade 4 <0.5 × 10⁹/L); thrombocytopenia (Grade 3 ≥25-50 × 10⁹/L, Grade 4 <25 × 10⁹/L); anemia (hemoglobin Grade 3 ≥65-80 g/L, Grade 4 <65 g/L); elevated creatinine (Grade 3 >3-6 × upper limit of normal range (ULN), Grade 4 >6 × ULN); elevated bilirubin (Grade 3 >3-10 × ULN, Grade 4 >10 × ULN); elevated SGOT or SGPT (Grade 3 >5-20 × ULN, Grade 4 >20 × ULN); hypocalcemia (Grade 3 <7.0-6.0 mg/dL, Grade 4 <6.0 mg/dL); hypophosphatemia (Grade 3 <2.0-1.0 mg/dL, Grade 4 <1.0 mg/dL); hypokalemia (Grade 3 <3.0-2.5 mmol/L, Grade 4 <2.5 mmol/L).

* Hematology parameters for 100 mg once-daily dosing in chronic phase CML reflects 60-month minimum follow-up.

Among adult patients with chronic phase CML with resistance or intolerance to prior imatinib therapy, cumulative Grade 3 or 4 cytopenias were similar at 2 and 5 years including: neutropenia (36% vs 36%), thrombocytopenia (23% vs 24%), and anemia (13% vs 13%).

In the pediatric studies in CML, the rates of laboratory abnormalities were consistent with the known profile for laboratory parameters in adults.

Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ ALL) in Adults

A total of 135 adult patients with Ph+ ALL were treated with SPRYCEL in clinical studies. The median duration of treatment was 3 months (range 0.03-31 months). The safety profile of patients with Ph+ ALL was similar to those with lymphoid blast phase CML. The most frequently reported adverse reactions included fluid retention events, such as pleural effusion (24%) and superficial edema (19%), and gastrointestinal disorders, such as diarrhea (31%), nausea (24%), and vomiting (16%). Hemorrhage (19%), pyrexia (17%), rash (16%), and dyspnea (16%) were also frequently reported. Serious adverse reactions reported in ≥5% of patients included pleural effusion (11%), gastrointestinal bleeding (7%), febrile neutropenia (6%), and infection (5%).

Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ ALL) in Pediatric Patients

The safety of SPRYCEL administered continuously in combination with multiagent chemotherapy was determined in a multicohort study of 81 pediatric patients with newly diagnosed Ph+ ALL [see Clinical Studies (14.4)]. The median duration of therapy was 24 months (range 2 to 27 months).

Fatal adverse reactions occurred in 3 patients (4%), all of which were due to infections. Eight (10%) patients experienced adverse reactions leading to treatment discontinuation, including fungal sepsis, hepatotoxicity in the setting of graft versus host disease, thrombocytopenia, CMV infection, pneumonia, nausea, enteritis and drug hypersensitivity.

The most common serious adverse reactions (incidence ≥10%) were pyrexia, febrile neutropenia, mucositis, diarrhea, sepsis, hypotension, infections (bacterial, viral and fungal), hypersensitivity, vomiting, renal insufficiency, abdominal pain, and musculoskeletal pain.

The incidence of common adverse reactions (incidence ≥20%) on study are shown in Table 14:

Table 14: Adverse Reactions Reported in ≥20% of Pediatric Patients with Ph+ ALL Treated with SPRYCEL in Combination with Chemotherapy CA180372 (N=81)

| Adverse Reaction | Percent (%) of Patients | |
|----------------------|-------------------------|-----------|
| | All Grades | Grade 3/4 |
| Mucositis | 93 | 60 |
| Febrile neutropenia | 86 | 86 |
| Pyrexia | 85 | 17 |
| Diarrhea | 84 | 31 |
| Nausea | 84 | 11 |
| Vomiting | 83 | 17 |
| Musculoskeletal pain | 83 | 25 |
| Abdominal pain | 78 | 18 |
| Cough | 78 | 18 |
| Headache | 77 | 18 |
| Rash | 68 | 18 |
| Fatigue | 59 | 18 |
| Constipation | 57 | 18 |
| Arrhythmia | 47 | 18 |
| Hypertension | 47 | 18 |

Table 14: Adverse Reactions Reported in ≥10% of Pediatric Patients with Ph+ ALL Treated with SPRYCEL in Combination with Chemotherapy CA180372 (N=81)

| | | |
|--|-----|----|
| Edema | 47 | 6 |
| Viral infection | 40 | 12 |
| Hypotension | 40 | 26 |
| Decreased appetite | 38 | 22 |
| Hypersensitivity | 36 | 20 |
| Upper respiratory tract infection | 36 | 10 |
| Dyspnea | 35 | 10 |
| Epistaxis | 31 | 6 |
| Peripheral neuropathy | 31 | 7 |
| Sepsis (excluding fungal) | n/a | 31 |
| Altered state of consciousness | 30 | 4 |
| Fungal infection | 30 | 11 |
| Pneumonia (excluding fungal) | 28 | 25 |
| Pruritus | 28 | - |
| Clostridial infection (excluding sepsis) | 25 | 14 |
| Urinary Tract Infection | 24 | 14 |
| Bacteremia (excluding fungal) | 22 | 20 |
| Erythema | 22 | 6 |
| Chills | 21 | - |
| Pleural effusion | 21 | 9 |
| Sinusitis | 21 | 10 |
| Dehydration | 20 | 9 |
| Renal insufficiency | 20 | 9 |
| Visual impairment | 20 | - |

The incidence of common adverse reactions attributed by the investigator to SPRYCEL (reported at a frequency of ≥10%, all grades and grade 3/4, respectively) on study (N=81), included febrile

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neutropenia (23%, 23%), nausea (21%, 4%), vomiting (19%, 4%), mucositis (17%, 6%), musculoskeletal pain (17%, 2%), abdominal pain (16%, 5%), diarrhea (16%, 7%), rash (15%, 0%), fatigue (12%, 0%), pyrexia (12%, 6%), and headache (12%, 3%).

CTCAE grade 3/4 laboratory abnormalities in pediatric patients with Ph+ ALL treated with SPRYCEL in combination with chemotherapy are shown in Table 15.

Table 15: CTCAE Grade 3/4 Laboratory Abnormalities in ≥10% of Pediatric Patients with Ph+ ALL Treated with SPRYCEL in Combination with Chemotherapy CA180372 (N=81)

| Percent (%) of Patients | |
|--------------------------------|----|
| Hematology Parameters | |
| Neutropenia | 96 |
| Thrombocytopenia | 88 |
| Anemia | 82 |
| Biochemistry Parameters | |
| Elevated SGPT (ALT) | 47 |
| Hypokalemia | 40 |
| Elevated SGOT (AST) | 26 |
| Hypoalbuminemia | 19 |
| Hyponatremia | 19 |
| Elevated Bilirubin | 11 |
| Hypophosphatemia | 11 |

Toxicity grading is per CTCAE version 4.

Additional Pooled Data from Clinical Trials

The following additional adverse reactions were reported in adult and pediatric patients (n=2809) in SPRYCEL CML clinical studies and adult patients in Ph+ ALL clinical studies at a frequency of ≥10%, 1%–10%, 0.1%–1%, or <0.1%. These adverse reactions are included based on clinical relevance.

Gastrointestinal Disorders: 1%–10% – mucosal inflammation (including mucositis/stomatitis), dyspepsia, abdominal distension, constipation, gastritis, colitis (including neutropenic colitis), oral soft tissue disorder; 0.1%–1% – ascites, dysphagia, anal fissure, upper gastrointestinal ulcer, esophagitis, pancreatitis, gastroesophageal reflux disease; <0.1% – protein losing gastroenteropathy, ileus, acute pancreatitis, anal fistula.

General Disorders and Administration-Site Conditions: ≥10% – peripheral edema, face edema; 1%–10% – asthenia, chest pain, chills, 0.1%–1% – malaise, other superficial edema, peripheral swelling, <0.1% – gait disturbance.

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Skin and Subcutaneous Tissue Disorders: 1%–10% – alopecia, acne, dry skin, hyperhidrosis, urticaria, dermatitis (including eczema), 0.1%–1% – pigmentation disorder, skin ulcer, bullous conditions, photosensitivity, nail disorder, neutrophilic dermatosis, panniculitis, palmar-plantar erythrodysesthesia syndrome, hair disorder; <0.1% – leukocytoclastic vasculitis, skin fibrosis.

Respiratory, Thoracic, and Mediastinal Disorders: 1%–10% – lung infiltration, pneumonitis, cough; 0.1%–1% – asthma, bronchospasm, dysphonia, pulmonary arterial hypertension; <0.1% – acute respiratory distress syndrome, pulmonary embolism.

Nervous System Disorders: 1%–10% – neuropathy (including peripheral neuropathy), dizziness, dysgeusia, somnolence, 0.1%–1% – anorexia, tremor, syncope, balance disorder; <0.1% – convulsion, cerebrovascular accident, transient ischemic attack, optic neuritis, VIIIth nerve paralysis, dementia, ataxia.

Blood and Lymphatic System Disorders: 0.1%–1% – lymphadenopathy, lymphopenia; <0.1% – aplasia pure red cell.

Musculoskeletal and Connective Tissue Disorders: 1%–10% – muscular weakness, musculoskeletal stiffness, 0.1%–1% – rhabdomyolysis, tendonitis, muscle inflammation, osteonecrosis, arthritis; <0.1% – epiphyseal delayed fusion (reported at 1%–10% in the pediatric studies), growth retardation (reported at 1%–10% in the pediatric studies).

Investigations: 1%–10% – weight increased, weight decreased; 0.1%–1% – blood creatine phosphokinase increased, gamma-glutamyltransferase increased.

Infections and Infestations: 1%–10% – pneumonia (including bacterial, viral, and fungal), upper respiratory tract infection/inflammation, herpes virus infection, enterocolitis infection, sepsis (including fatal outcomes [0.2%]).

Metabolism and Nutrition Disorders: 1%–10% – appetite disturbances, hyperuricemia; 0.1%–1% – hyposalbuminemia, tumor lysis syndrome, dehydration, hypercholesterolemia; <0.1% – diabetes mellitus.

Cardiac Disorders: 1%–10% – arrhythmia (including tachycardia), palpitations; 0.1%–1% – angina pectoris, cardiomegaly, pericarditis, ventricular arrhythmia (including ventricular tachycardia), electrocardiogram T-wave abnormal, troponin increased; <0.1% – cor pulmonale, myocarditis, acute coronary syndrome, cardiac arrest, electrocardiogram PR prolongation, coronary artery disease, pleuropericarditis.

Eye Disorders: 1%–10% – visual disorder (including visual disturbance, vision blurred, and reduced), dry eye; 0.1%–1% – conjunctivitis, visual impairment, lacrimation; <0.1% – photophobia.

Other Disorders: 1%–10% – flushing, hypertension; 0.1%–1% – hypotension, thrombocytopenia; <0.1% – livedo reticularis, deep vein thrombosis, embolism.

Other Disorders: <0.1% – insomnia, depression; 0.1%–1% – anxiety, affect lability, decreased libido.

Reproductive System Disorders: <0.1% – abortion.

Other Disorders: 0.1%–1% – gynecomastia, menstrual disorder.

Other Disorders: 1%–10% – contusion.

Other Disorders: 0.1%–1% – vertigo, hearing loss.

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Hepatobiliary Disorders: 0.1%–1% – cholestasis, cholecystitis, hepatitis.

Renal and Urinary Disorders: 0.1%–1% – urinary frequency, renal failure, proteinuria; <0.1% – renal impairment.

Immune System Disorders: 0.1%–1% – hypersensitivity (including erythema nodosum).

Endocrine Disorders: 0.1%–1% – hypothyroidism; <0.1% – hyperthyroidism, thyroiditis.

6.2 Postmarketing Experience

The following additional adverse reactions have been identified during post approval use of SPRYCEL. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Infections: hepatitis B virus reactivation

Cardiac disorders: atrial fibrillation/atrial flutter

Respiratory, thoracic, and mediastinal disorders: interstitial lung disease

Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome

Renal and urinary disorders: nephrotic syndrome

Blood and lymphatic system disorders: thrombotic microangiopathy

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on Dasatinib

Strong CYP3A4 Inhibitors

The coadministration with strong CYP3A inhibitors may increase dasatinib concentrations [see *Clinical Pharmacology* (12.3)]. Increased dasatinib concentrations may increase the risk of toxicity. Avoid concomitant use of strong CYP3A4 inhibitors. If concomitant administration of a strong CYP3A4 inhibitor cannot be avoided, consider a SPRYCEL dose reduction [see *Dosage and Administration* (2.5)].

Strong CYP3A4 Inducers

The coadministration of SPRYCEL with strong CYP3A inducers may decrease dasatinib concentrations [see *Clinical Pharmacology* (12.3)]. Decreased dasatinib concentrations may reduce efficacy. Consider alternative drugs with less enzyme induction potential. If concomitant administration of a strong CYP3A4 inducer cannot be avoided, consider a SPRYCEL dose increase.

Gastric Acid Reducing Agents

The coadministration of SPRYCEL with a gastric acid reducing agent may decrease the concentrations of dasatinib. Decreased dasatinib concentrations may reduce efficacy.

Do not administer H₂ antagonists or proton pump inhibitors with SPRYCEL. Consider the use of antacids in place of H₂ antagonists or proton pump inhibitors. Administer the antacid at least 2 hours prior to or 2 hours after the dose of SPRYCEL. Avoid simultaneous administration of SPRYCEL with antacids.

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...the mean AUC of dasatinib following a single dose of 100 mg by 14%...
 ...carbohydrates, and protein were 52%, 34%, and 14% for the high-fat meal.
Distribution
 The apparent volume of distribution is 2305 L (CV% 93%).
 Binding of dasatinib to human plasma proteins *in vitro* was approximately 96% and...
 ...was 25%, with no concentration dependence over the range of 100 ng/mL to 10 μg/mL.
 Dasatinib is a P-gp substrate *in vitro*.
Elimination
 The mean terminal half-life of dasatinib is 3 hours to 5 hours. The...
 ...is 363.8 L/hr (CV% 81.3%).
Metabolism
 Dasatinib is metabolized in humans, primarily by CYP3A4 and...
 ...and uridine diphosphate-glucuronosyltransferase...
 ...metabolites.

The exposure of the active metabolite, which is equipotent to dasatinib, represents approximately 5% of the AUC of dasatinib. The active metabolite of dasatinib is unlikely to play a major role in the observed pharmacology of the drug. Dasatinib also has several other inactive oxidative metabolites.

Excretion

Elimination is primarily via the feces. Following a single radiolabeled dose of oral dasatinib, 4% of the administered radioactivity was recovered in the urine and 85% in the feces within 10 days. Unchanged dasatinib accounted for 0.1% of the administered dose in the urine and 19% of the administered dose in the feces with the remainder of the dose being metabolites.

Specific Populations

Age (15 to 86 years old), sex, and renal impairment (creatinine clearance 21.6 mL/min to 342.3 mL/min as estimated by Cockcroft Gault) have no clinically relevant effect on the pharmacokinetics of dasatinib.

Pediatric Patients

The pharmacokinetics of dasatinib were evaluated in 43 pediatric patients with leukemia or solid tumors at oral doses ranging from 60 mg/m² to 120 mg/m² once daily, taken with or without food. The pharmacokinetics showed dose proportionality with a dose-related increase in exposure. The mean T_{max} was observed between 0.5 hours and 6 hours and the mean half-life was 2 hours to 5 hours. The geometric mean (CV%) of body weight normalized clearance in these 43 pediatric patients is 5.98 (41.5%) L/h/kg. In pediatric patients with a dosing regimen of 60 mg/m², the model simulated geometric mean (CV%) steady-state plasma average concentrations of dasatinib were 14.7 (64.6%) ng/mL (for 2 to <6 years old), 16.3 (97.5%) ng/mL (for 6 to <12 years old), and 18.2 (67.7%) ng/mL (for 12 years and older) [see Dosage and Administration (2.2)]. Dasatinib clearance and volume of distribution change with body weight in pediatric patients. Dasatinib has not been studied in patients < 1 year old.

The bioavailability of dispersed tablets in pediatric patients was estimated to be 36% lower than that of intact tablets.

Patients with Hepatic Impairment

Compared to subjects with normal liver function, patients with moderate hepatic impairment (Child Pugh B) had decreases in mean C_{max} by 47% and mean AUC by 8%. Patients with severe hepatic impairment (Child Pugh C) had decreases in mean C_{max} by 43% and in mean AUC by 28% compared to the subjects with normal liver function.

Drug Interaction Studies

Cytochrome P450 Enzymes

The coadministration of ketoconazole (strong CYP3A4 inhibitor) twice daily increased the mean C_{max} of dasatinib by 4-fold and the mean AUC of dasatinib by 5-fold following a single oral dose of 20 mg.

The coadministration of rifampin (strong CYP3A4 inducer) once daily decreased the mean C_{max} of dasatinib by 81% and the mean AUC of dasatinib by 82%.

Dasatinib is a time-dependent inhibitor of CYP3A4. Dasatinib does not inhibit CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, or 2E1. Dasatinib does not induce CYP enzymes.

Gastric Acid Reducing Agents

The administration of 30 mL of aluminum hydroxide/magnesium hydroxide 2 hours prior to a single dose of SPRYCEL was associated with no relevant change in the mean AUC of dasatinib; however, the mean C_{max} of dasatinib was increased by 26%.

The simultaneous administration of 30 mL of aluminum hydroxide/magnesium hydroxide with a single dose of SPRYCEL was associated with a 55% reduction in the mean AUC of dasatinib and a 58% reduction in the mean C_{max} of dasatinib.

The administration of a single dose of SPRYCEL 10 hours following famotidine (H₂ antagonist) reduced the mean AUC of dasatinib by 61% and the mean C_{max} of dasatinib by 63%.

The administration of a single 100 mg dose of SPRYCEL 22 hours following a 40 mg dose of omeprazole (proton pump inhibitor) at steady state reduced the mean AUC of dasatinib by 43% and the mean C_{max} of dasatinib by 42%.

Transporters

Dasatinib is not an inhibitor of P-gp *in vitro*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year carcinogenicity study, rats were administered oral doses of dasatinib at 0.3, 1, and 3 mg/kg/day. The highest dose resulted in a plasma drug exposure (AUC) level approximately 60% of the human exposure at 100 mg once daily. Dasatinib induced a statistically significant increase in the combined incidence of squamous cell carcinomas and papillomas in the uterus and cervix of high-dose females and prostate adenoma in low-dose males.

Dasatinib was clastogenic when tested *in vitro* in Chinese hamster ovary cells, with and without metabolic activation. Dasatinib was not mutagenic when tested in an *in vitro* bacterial cell assay (Ames test) and was not genotoxic in an *in vivo* rat micronucleus study.

Dasatinib did not affect mating or fertility in male and female rats at plasma drug exposure (AUC) similar to the human exposure at 100 mg daily. In repeat dose studies, administration of dasatinib resulted in reduced size and secretion of seminal vesicles, and immature prostate, seminal vesicle, and testis. The administration of dasatinib resulted in uterine inflammation and mineralization in monkeys, and cystic ovaries and ovarian hypertrophy in rodents.

14 CLINICAL STUDIES

14.1 Newly Diagnosed Chronic Phase CML in Adults

DASISION (Dasatinib vs Imatinib Study in Treatment-Naive Chronic Myeloid Leukemia Patients) (NCT00481247) was an open-label, multicenter, international, randomized trial conducted in adult patients with newly diagnosed chronic phase CML. A total of 519 patients were randomized to receive either SPRYCEL 100 mg once daily or imatinib 400 mg once daily. Patients with a history of cardiac disease were included in this trial except those who had a myocardial infarction within 6 months, congestive heart failure within 3 months, significant arrhythmias, or QTc prolongation. The primary endpoint was the rate of confirmed complete cytogenetic response (CCyR) within 12 months. Confirmed CCyR was defined as a CCyR noted on two consecutive occasions (at least 28 days apart).

Median age was 46 years in the SPRYCEL group and 49 years in the imatinib groups, with 10% and 11% of patients ≥65 years of age, respectively. There were slightly more male than female patients in both groups (59% vs 41%). Fifty-three percent of all patients were Caucasian and 39%

were Asian. At baseline, the distribution of Hasford scores was similar in the SPRYCEL and imatinib treatment groups (low risk: 33% and 34%, intermediate risk: 48% and 47%; high risk: 19% and 19%, respectively). With a minimum of 12 months follow-up, 85% of patients randomized to SPRYCEL and 81% of patients randomized to imatinib were still on study.

With a minimum of 24 months follow-up, 77% of patients randomized to SPRYCEL and 75% of patients randomized to imatinib were still on study and with a minimum of 60 months follow-up, 61% and 62% of patients, respectively, were still on treatment at the time of study closure.

Efficacy results are summarized in Table 16.

Table 16: Efficacy Results in a Randomized Newly Diagnosed Chronic Phase CML Trial

| | SPRYCEL (n=259) | Imatinib (n=260) |
|---|--------------------|---------------------|
| Confirmed CCyR^a | | |
| Within 12 months (95% CI) | 76.8% (71.2–81.8) | 66.2% (60.1–71.9) |
| P-value | | 0.007* |
| Major Molecular Response^b | | |
| 12 months (95% CI) | 52.1% (45.9–58.3) | 33.8% (28.1–39.9) |
| P-value | | <0.0001 |
| 60 months (95% CI) | 76.4% (70.8–81.5) | 64.2% (58.1–70.1) |

^a Confirmed CCyR is defined as a CCyR noted on two consecutive occasions at least 28 days apart.
^b Major molecular response (at any time) was defined as BCR-ABL ratios ≤0.1% by RQ-PCR in peripheral blood samples standardized on the International scale. These are cumulative rates representing minimum follow up for the time frame specified.
^c Adjusted for Hasford score and indicated statistical significance at a pre-defined nominal level of significance. CI = confidence interval.

The confirmed CCyR within 24, 36, and 60 months for SPRYCEL versus imatinib arms were 80% versus 74%, 83% versus 77%, and 83% versus 79%, respectively. The MMR at 24 and 36 months for SPRYCEL versus imatinib arms were 65% versus 50% and 69% versus 56%, respectively.

After 60 months follow-up, median time to confirmed CCyR was 3.1 months in 215 SPRYCEL responders and 5.8 months in 204 imatinib responders. Median time to MMR after 60 months follow-up was 9.3 months in 198 SPRYCEL responders and 15.0 months in 167 imatinib responders.

At the end of the study, 30% of patients (3%) on the dasatinib arm progressed to either accelerated phase or blast phase (30%) and 6% on the imatinib arm progressed to either accelerated phase or blast phase (30%). At the end of the study, 10% of patients (10%) had unknown survival status in the dasatinib and imatinib arms, the rate of MMR at any time in each risk group was 69% (low risk), 65% (intermediate risk), and 54% (high risk).

the imatinib arm, the rate of MMR at any time in each risk group determined by Hasford score was 69% (low risk), 65% (intermediate risk), and 54% (high risk).

BCR-ABL sequencing was performed on blood samples from patients in the newly diagnosed trial who discontinued dasatinib or imatinib therapy. Among dasatinib-treated patients the mutations detected were T315I, F317L/L, and V299L.

Dasatinib does not appear to be active against the T315I mutation, based on *in vitro* data.

14.2 Imatinib-Resistant or -Intolerant CML or Ph+ ALL in Adults

The efficacy and safety of SPRYCEL were investigated in adult patients with CML or Ph+ ALL whose disease was resistant to or who were intolerant to imatinib. 1158 patients had chronic phase CML, 858 patients had accelerated phase, myeloid blast phase, or lymphoid blast phase CML, and 130 patients had Ph+ ALL. In a clinical trial in chronic phase CML, resistance to imatinib was defined as failure to achieve a complete hematologic response (CHR; after 3 months), major cytogenetic response (MCyR; after 6 months), or complete cytogenetic response (CCyR; after 12 months), or loss of a previous molecular response (with concurrent ≥10% increase in Ph+ metaphases), cytogenetic response, or hematologic response. Imatinib intolerance was defined as inability to tolerate 400 mg or more of imatinib per day or discontinuation of imatinib because of toxicity.

Results described below are based on a minimum of 2 years follow-up after the start of SPRYCEL therapy in patients with a median time from initial diagnosis of approximately 5 years. Across all studies, 48% of patients were women, 81% were white, 15% were black or Asian, 25% were 65 years of age or older, and 5% were 75 years of age or older. Most patients had long disease histories with extensive prior treatment, including imatinib, cytotoxic chemotherapy, interferon, and stem cell transplant. Overall, 80% of patients had imatinib-resistant disease and 20% of patients were intolerant to imatinib. The maximum imatinib dose had been 400–600 mg/day in about 60% of the patients and >600 mg/day in 40% of the patients.

The primary efficacy endpoint in chronic phase CML was MCyR, defined as elimination (CCyR) or substantial diminution (by at least 65%, partial cytogenetic response) of Ph+ hematopoietic cells. The primary efficacy endpoint in accelerated phase, myeloid blast phase, lymphoid blast phase CML, and Ph+ ALL was major hematologic response (MaHR), defined as either a CHR or no evidence of leukemia (NEL).

Chronic Phase CML

Dose-Optimization Trial: A randomized, open-label trial (NCT00123474) was conducted in adult patients with chronic phase CML to evaluate the efficacy and safety of SPRYCEL administered once daily compared with SPRYCEL administered twice daily. Patients with significant cardiac diseases, including myocardial infarction within 6 months, congestive heart failure within 3 months, significant arrhythmias, or QTc prolongation were excluded from the trial. The primary efficacy endpoint was MCyR in patients with imatinib-resistant CML. A total of 670 patients, of whom 497 had imatinib-resistant disease, were randomized to the SPRYCEL 100 mg once-daily, 140 mg once-daily, 50 mg twice-daily, or 70 mg twice-daily group. Median duration of treatment was 22 months.

Efficacy was achieved across all SPRYCEL treatment groups with the once-daily schedule demonstrating comparable efficacy (non-inferiority) to the twice-daily schedule on the primary

... combination with chemotherapy was evaluated in a single cohort of Study CA180372 (NCT01460160), a multicenter, multiple-cohort study of pediatric patients with newly diagnosed B-cell precursor Ph+ ALL. The backbone chemotherapy regimen was the AEOB-BFM ALL 2000 multi-agent...
 ... patients had a median age of 10.4 years (range 2.6 to 17.9 years) and included 20 patients (3%) on the dasatinib arm progressed to either accelerated phase or blast phase (30%) and 6% on the imatinib arm progressed to either accelerated phase or blast phase (30%). At the end of the study, 10% of patients (10%) had unknown survival status in the dasatinib and imatinib arms, the rate of MMR at any time in each risk group was 69% (low risk), 65% (intermediate risk), and 54% (high risk). In

REFERENCES

1. <http://www.cda.gov/STC/hazardousdrugs>

How Supplied

SPRYCEL® (dasatinib) tablets are available as described in Table 21.

Table 21: SPRYCEL Trade Presentations

| NDC Number | Strength | Description | Tablets per Bottle |
|--------------|----------|---|--------------------|
| 0003-0527-11 | 20 mg | white to off-white, biconvex, round, film-coated tablet with "BMS" debossed on one side and "527" on the other side | 60 |
| 0003-0528-11 | 50 mg | white to off-white, biconvex, oval, film-coated tablet with "BMS" debossed on one side and "528" on the other side | 60 |
| 0003-0524-11 | 70 mg | white to off-white, biconvex, round, film-coated tablet with "BMS" debossed on one side and "524" on the other side | 60 |
| 0003-0855-22 | 80 mg | white to off-white, biconvex, triangle, film-coated tablet with "BMS" and "80" (BMS over 80) debossed on one side and "855" on the other side | 30 |
| 0003-0852-22 | 100 mg | white to off-white, biconvex, oval, film-coated tablet with "BMS 100" debossed on one side and "852" on the other side | 30 |
| 0003-0857-22 | 140 mg | white to off-white, biconvex, round, film-coated tablet with "BMS" and "140" (BMS over 140) debossed on one side and "857" on the other side | 30 |

Storage

SPRYCEL tablets should be stored at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].

Handling and Disposal

SPRYCEL is an antineoplastic product. Follow special handling and disposal procedures.¹

Personnel who are pregnant should avoid exposure to crushed or broken tablets.

SPRYCEL tablets consist of a core tablet, surrounded by a film coating to prevent exposure of healthcare professionals to the active substance. The use of latex or nitrile gloves for appropriate disposal when handling tablets that are inadvertently crushed or broken is recommended, to minimize the risk of dermal exposure.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Myelosuppression

Inform patients of the possibility of developing low blood cell counts. Advise patients to immediately report fever particularly in association with any suggestion of infection [see Warnings and Precautions (5.1)].

Advise patients using antacids to avoid taking SPRYCEL and antacids less than 2 hours apart [see Drug Interactions (7.1)].

Pain

Inform patients that they may experience headache or musculoskeletal pain with SPRYCEL. Advise patients to seek medical attention if these symptoms are bothersome or persistent.

Fatigue

Inform patients that they may experience fatigue with SPRYCEL. Advise patients to seek medical attention if this symptom is bothersome or persistent.

Rash

Inform patients that they may experience skin rash with SPRYCEL. Advise patients to seek medical attention if this symptom is bothersome or persistent.

Lactose

Inform patients that SPRYCEL contains 135 mg of lactose monohydrate in a 100-mg daily dose and 189 mg of lactose monohydrate in a 140-mg daily dose.

Instructions for Taking SPRYCEL**Missed Dose**

Advise patients that if they miss a dose of SPRYCEL, they should take the next scheduled dose at its regular time. The patient should not take two doses at the same time.

Grapefruit Juice

Advise patients not to drink grapefruit juice as it may increase the amount of SPRYCEL in their blood and therefore increase their risk of adverse reactions.

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Bleeding

Inform patients of the possibility of serious bleeding and to report immediately any signs or symptoms suggestive of hemorrhage (unusual bleeding or easy bruising) [see Warnings and Precautions (5.2)].

Fluid Retention

Patients should be informed of the possibility of developing fluid retention (swelling, weight gain, dry cough, chest pain on respiration, or shortness of breath) and advised to seek medical attention promptly if those symptoms arise [see Warnings and Precautions (5.3)].

Cardiovascular Toxicity

Inform patients of the possibility of developing cardiovascular toxicity, including cardiac ischemic events, cardiac-related fluid retention, conduction abnormalities, and TIAs. Advise patients to seek immediate medical attention if symptoms suggestive of cardiovascular toxicity occur, such as chest pain, shortness of breath, palpitations, transient vision problems, or slurred speech [see Warnings and Precautions (5.4)].

Pulmonary Arterial Hypertension

Inform patients of the possibility of developing pulmonary arterial hypertension (dyspnea, fatigue, hypoxia, and fluid retention) and advise them to seek medical attention promptly if those symptoms arise [see Warnings and Precautions (5.5)].

Tumor Lysis Syndrome

Inform patients to immediately report and seek medical attention for any symptoms such as nausea, vomiting, weakness, edema, shortness of breath, muscle cramps, and seizures, which may indicate tumor lysis syndrome [see Warnings and Precautions (5.8)].

Growth and Development in Pediatric Patients

Inform pediatric patients and their caregivers of the possibility of developing bone growth abnormalities, bone pain, or gynecomastia and advise them to seek medical attention promptly if those symptoms arise [see Warnings and Precautions (5.10)].

Embryo-Fetal Toxicity

- Advise pregnant women of the potential risk to a fetus [see Warnings and Precautions (5.9) and Use in Specific Populations (8.1)].
- Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment with SPRYCEL and for 30 days after the last dose. Advise females to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, while taking SPRYCEL [see Warnings and Precautions (5.9) and Use in Specific Populations (8.1, 8.3)].

Lactation

- Advise women that breastfeeding is not recommended during treatment with SPRYCEL and for 2 weeks after the final dose [see Use in Specific Populations (8.2)].

Gastrointestinal Complaints

Inform patients that they may experience nausea, vomiting, or diarrhea with SPRYCEL. Advise patients to seek medical attention if these symptoms are bothersome or persistent.

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| PATIENT INFORMATION SPRYCEL® (Spry-sell) (dasatinib) tablets |
|---|
| <p>What is SPRYCEL?</p> <p>SPRYCEL is a prescription medicine used to treat:</p> <ul style="list-style-type: none"> adults with newly diagnosed Philadelphia chromosome-positive (Ph⁺) chronic myeloid leukemia (CML) in chronic phase. adults with Ph⁺ CML who no longer benefit from, or did not tolerate, other treatment, including imatinib. adults with Ph⁺ acute lymphoblastic leukemia (Ph⁺ ALL) who no longer benefit from, or did not tolerate, other treatment. children 1 year of age and older with Ph⁺ CML in chronic phase. children 1 year of age and older with newly diagnosed Ph⁺ ALL in combination with chemotherapy. <p>It is not known if SPRYCEL is safe and effective in children under 1 year of age.</p> |
| <p>Before taking SPRYCEL, tell your healthcare provider about all of your medical conditions, including if you:</p> <ul style="list-style-type: none"> have problems with your immune system have heart problems, including a condition called congenital long QT syndrome have low potassium or low magnesium levels in your blood are lactose (milk sugar) intolerant are pregnant or plan to become pregnant. SPRYCEL can harm your unborn baby. <p>Females who can become pregnant:</p> <ul style="list-style-type: none"> You should not become pregnant during treatment with SPRYCEL. You should use effective birth control (contraception) during treatment and for 30 days after your last dose of SPRYCEL. <p>Talk to your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with SPRYCEL.</p> <p>Males with female partners who can become pregnant:</p> <ul style="list-style-type: none"> You should use effective birth control (contraception) during treatment and for 30 days after your last dose of SPRYCEL. Your female partner should call her healthcare provider if she becomes pregnant or thinks she is pregnant during your treatment with SPRYCEL. <p>are breastfeeding or plan to breastfeed. It is not known if SPRYCEL passes into your breast milk. You should not breastfeed during treatment and for 2 weeks after your last dose of SPRYCEL.</p> <p>Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, antacids, and herbal supplements. If you take an antacid medicine, take it 2 hours before or 2 hours after your dose of SPRYCEL.</p> |
| <p>How should I take SPRYCEL?</p> <ul style="list-style-type: none"> Take SPRYCEL exactly as your healthcare provider tells you to take it. Your healthcare provider may change your dose of SPRYCEL or temporarily stop treatment with SPRYCEL. Do not change your dose or stop taking SPRYCEL without first talking to your healthcare provider. Take SPRYCEL 1 time a day. Take SPRYCEL with or without food, either in the morning or in the evening. Swallow SPRYCEL tablets whole. Do not crush, cut or chew the tablets. <ul style="list-style-type: none"> If your child cannot swallow tablets whole, talk with your healthcare provider. You should not drink grapefruit juice during treatment with SPRYCEL. If you miss a dose of SPRYCEL, take your next scheduled dose at your regular time. Do not take two doses at the same time. If you take too much SPRYCEL, call your healthcare provider or go to the nearest hospital emergency room right away. |
| <p>What are the possible side effects of SPRYCEL?</p> <p>SPRYCEL may cause serious side effects, including:</p> <ul style="list-style-type: none"> Low blood cell counts. Low blood cell counts are common with SPRYCEL and can be severe, including low red blood cell counts (anemia), low white blood cell counts (neutropenia), and low platelet counts (thrombocytopenia). Your healthcare provider will do blood tests to check your blood cell counts regularly during your treatment with |

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SPRYCEL. Call your healthcare provider right away if you have a fever or any signs of an infection during treatment with SPRYCEL.

- **Bleeding problems.** Bleeding problems are common with SPRYCEL. Sometimes these bleeding problems can be serious and lead to death. Call your healthcare provider right away if you have:
 - unusual bleeding or bruising of your skin
 - bright red or dark tar-like stools
 - decreased alertness, headache, or change in speech
- **Your body may hold too much fluid (fluid retention).** Fluid retention is common with SPRYCEL and can sometimes be severe. In severe cases, fluid may build up in the lining of your lungs, the sac around your heart, or your stomach cavity. Call your healthcare provider right away if you get any of these symptoms during treatment with SPRYCEL:
 - swelling all over your body
 - weight gain
 - shortness of breath, especially if this happens with low levels of physical activity or at rest
 - dry cough
 - chest pain when taking a deep breath
- **Heart and blood vessel (cardiovascular) problems.** SPRYCEL may cause heart problems, including an abnormal heart rate, a heart attack, or small strokes that last only a few minutes or a few hours, called transient ischemic attacks (TIAs). TIAs are often a warning sign that you are at risk for a more serious stroke. Your healthcare provider will monitor the potassium and magnesium levels in your blood and your heart function. Get medical help right away if you develop any of the following symptoms during treatment with SPRYCEL:
 - chest pain
 - shortness of breath
 - feeling like your heart is beating too fast or you feel abnormal heart beats
 - vision changes that may last for a short time
- **Pulmonary Arterial Hypertension (PAH).** SPRYCEL may cause high blood pressure in the vessels of your lungs. PAH may happen at any time during your treatment with SPRYCEL. Your healthcare provider should check your heart and lungs before and during treatment with SPRYCEL. Call your healthcare provider right away if you have shortness of breath, tiredness, or swelling all over your body (fluid retention).
- **Severe skin reactions.** SPRYCEL may cause skin reactions that can sometimes be severe. Get medical help right away if you get a skin reaction with fever, sore mouth or throat, or blistering or peeling of your skin or in the mouth.
- **Tumor Lysis Syndrome (TLS).** TLS is caused by a fast breakdown of cancer cells. TLS can cause you to have kidney failure and the need for dialysis treatment, and an abnormal heartbeat. Your healthcare provider may do blood tests to check you for TLS. Call your healthcare provider or get emergency medical help right away if you develop any of these symptoms during treatment with SPRYCEL:
 - nausea
 - vomiting
 - weakness
 - swelling
 - shortness of breath
 - muscle cramps
 - seizures
- **Slowing of growth and development in children.** Effects on bone growth and development in children have happened with SPRYCEL, and can sometimes be severe. Your healthcare provider will monitor your child's bone growth and development during treatment with SPRYCEL. Get medical help right away if your child develops bone pain.

The most common side effects of SPRYCEL in adults and children receiving SPRYCEL alone include:

- diarrhea
- headache
- skin rash
- shortness of breath
- tiredness
- nausea
- muscle pain

The most common side effects of SPRYCEL in children receiving SPRYCEL with chemotherapy include:

- swelling, pain and redness of the lining of your mouth, throat, stomach and bowels (mucositis)
- low white blood cell counts with fever
- fever
- diarrhea
- nausea
- tiredness
- constipation
- abnormal heart rate
- high blood pressure (hypertension)
- swelling
- infections
- low blood pressure

- vomiting
- muscle pain
- stomach-ache (abdominal) pain
- cough
- headache
- rash
- decreased appetite
- allergic reactions
- shortness of breath
- nose bleed
- numbness or tingling of your hands and feet
- feeling confused or disoriented

SPRYCEL may cause fertility problems in males and females. Talk to your healthcare provider if this is a concern for you.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all of the possible side effects of SPRYCEL.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store SPRYCEL?

- Store SPRYCEL at room temperature between 68°F to 77°F (20°C to 25°C).
- Ask your healthcare provider or pharmacist about the right way to throw away expired or unused SPRYCEL.
- Wear latex or nitrile gloves when handling tablets that have accidentally been crushed or broken.
- Females who are pregnant should not handle crushed or broken SPRYCEL tablets.

Keep SPRYCEL and all medicines out of the reach of children.

General information about the safe and effective use of SPRYCEL.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use SPRYCEL for a condition for which it is not prescribed. Do not give SPRYCEL to other people even if they have the same symptoms you have. It may harm them. You can ask your healthcare provider or pharmacist for information about SPRYCEL that is written for health professionals.

What are the ingredients in SPRYCEL?

Active ingredient: dasatinib

Inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, and magnesium stearate. The tablet coating consists of hypromellose, titanium dioxide, and polyethylene glycol.

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For more information, go to www.sprycel.com or call 1-800-332-2055.

This Patient Information has been approved by the U.S. Food and Drug Administration.

Revised: June 2021

Distributed by:
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

• Grapefruit juice
Advise patients not to drink grapefruit juice as it may increase their blood and therefore increase their risk of adverse reactions.

CERTIFICATE OF A PHARMACEUTICAL PRODUCT

Sprycel® (dasatinib) Tablets NDA 21-986; Approval Date: June 28, 2006

| Ingredient | 20 mg | 50 mg | 70 mg |
|--|-------|-------|-------|
| Dasatinib ^a | 20.0 | 50.0 | 70.0 |
| Lactose Monohydrate ^b | 27.0 | 67.5 | 94.5 |
| Microcrystalline Cellulose | 27.0 | 67.5 | 94.5 |
| Hydroxypropyl Cellulose | 2.4 | 6.0 | 8.4 |
| Croscarmellose Sodium | 3.2 | 8.0 | 11.2 |
| Magnesium Stearate | 0.4 | 1.0 | 1.4 |
| Opadry® White, YS-1-18177-A ^c | 3.2 | 7.0 | 8.4 |
| Purified Water ^d | ---- | ---- | ---- |

^a The amount shown is based on a theoretical Assay of 100% for dasatinib on an anhydrous basis. The exact amount will vary depending on the Assay "as is" of dasatinib.

^b The amount of lactose monohydrate will vary depending upon the amount of dasatinib used.

^c Opadry® White YS-1-18177-A contains hypromellose 6 cP (59.8% w/w), titanium dioxide (31.2% w/w), and polyethylene glycol 400 (9.0% w/w).

^d Removed during processing.

US storage conditions and shelf life: Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature] Shelf life-36 months

TRADUCCIÓN PÚBLICA

APOSTILLA

(Convención de la Haya del 5 de octubre de 1961)

1. País: **Estados Unidos de Norte América**
2. El presente documento público ha sido firmado por: **Carole Jones**
3. quien actúa en calidad de: **Directora de División, Departamento de Cumplimiento de Exportaciones**
4. y está revestido del sello / timbre del **Ministerio de Salud y Servicios Humanos de los Estados Unidos**
- Certificado-----
5. en: **Washington, DC**
6. el: **30 de octubre de 2021**
7. por el: **Subsecretario de Legalizaciones del Departamento de Estado de los Estados Unidos**
8. con el número: **22003824-15**
9. Sello / timbre: (En blanco)
10. Firma: (Sigue una firma ilegible). **Fernesia T. Crawford.**

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Nº 2047

ADMINISTRACIÓN DE MEDICAMENTOS Y ALIMENTOS DE LOS ESTADOS UNIDOS

Centro de Evaluación e Investigación de Medicamentos -----

10903 New Hampshire Ave., Silver Spring, MD 20993, Estados Unidos de América. -----

CDERExportCertificateProgram@fda.hhs.gov – Teléfono: (301) 796-4950 -----

Certificado de un Producto Farmacéutico – Fabricante Extranjero-----

Fecha de emisión del certificado: **30 de septiembre de 2021** -----

Certificado Número: **P2G6-7MQN**-----

Fecha de Vencimiento del Certificado: **29 de septiembre de 2023** -----

País Importador: **Argentina** -----

País Exportador: **Estados Unidos de América** -----

1. Nombre Comercial del Medicamento, Denominación común Internacional o Nacional (según corresponda) y forma farmacéutica: **SPRYCEL®, Comprimido**-----

1.1 Principio(s) Activo(s) y cantidad(es) por unidad de dosis (se prefiere la composición cuantitativa completa): **dasatinib 70 MG**-----

1.2. ¿Este producto cuenta con la licencia para colocarlo en el mercado y utilizarlo en el país exportador? **SI** -----

1.3 ¿Este producto está en el mercado en el país exportador? **SI** -----

2.A.1. Número de licencia del producto y fecha de emisión: **021986 28/06/2006** -----

2.A.2. Nombre y dirección del titular de la licencia del producto: **Bristol-Myers Squibb Company, Casilla de Correo 4000, Princeton, NJ 08543 Estados Unidos de América**-----

2.A.3. Estado del titular de la licencia del producto: **Ninguna.** -----

2.A.3.1. Nombre y dirección del fabricante: **Patheon Inc., 2100 Syntex Court, Mississauga, Ontario L5N 7K9 CANADÁ** -----

2.A.4 ¿Se encuentra adjunto el resumen aprobado? **No** -----

2.A.5 ¿Está adjunta la información sobre el producto oficialmente completa y de conformidad con la licencia? **SI** -----

2.A.6 Nombre y dirección del solicitante del certificado (si difiere del titular de la licencia): **Bristol Myers Squibb. 4931 George Road, Tampa, FL 33634 Estados Unidos de América**-----

RIESGO
PÚBLICA
GLES
CAP. FEDERAL
TUGUES
CAP. FEDERAL
A. N° 2047

2.B.4 Observaciones: Acondicionador: **AndersonBrecon Inc., 4545 Assembly Drive, Rockford, IL 61109.** -----

Esta certificación de la FDA corresponde al producto comercializados en los Estados Unidos de América. -----

3. ¿La autoridad certificadora organiza inspecciones periódicas de la planta de fabricación en la cual se produce la forma farmacéutica? **SI** -----

3.1. Periodicidad de las inspecciones de rutina (años): **De conformidad con la sección 510(h)(3) de la Ley Federal de Alimentos Fármacos y Cosméticos, las inspecciones tendrán lugar de conformidad a un esquema basado en el riesgo** -----

3.2. ¿Se ha inspeccionado la fabricación de este tipo de forma farmacéutica? **SI** -----

3.3. ¿Las instalaciones y las operaciones cumplen con las normas de Buenas Prácticas de Fabricación tal como recomienda la Organización Mundial de la Salud? (Las Buenas Prácticas de Fabricación incluido el Código de Regulaciones Federales 21 partes 210, 211 o ICH Q7A): **SI, al momento de la inspección, el centro cumple con las cGMP de la FDA.**

3.4. ¿La información presentada por el solicitante satisface a la autoridad certificadora con respecto a todos los aspectos de Fabricación del producto a los que se comprometió la otra parte? **SI** -----

Aparece una firma ilegible y debajo se lee: Carole Jones, Directora de División, Departamento de Cumplimiento de Exportaciones -----

El presente certificado es emitido de conformidad al formato recomendado por la Organización Mundial de la Salud revisado el 1º de octubre de 1997. Sitio web: www.who.int. -----

Aparece una estampilla dorada donde se lee: Departamento de Salud y Servicios Humanos - Estados Unidos. -----

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RTUGUES
IS - CAP. FEDERAL
C.B.A. Nº 2047

-----CERTIFICADO DE PRODUCTO FARMACÉUTICO-----

-----Sprycel® (dasatinib) Comprimidos -----

-----NDA 21-986; Fecha de Aprobación: 28 de junio de 2006-----

| Principio | 20 mg | 50 mg | 70 mg |
|---|-------|-------|-------|
| Dasatinib ^a | 20,0 | 50,0 | 70,0 |
| Lactosa Monohidrato ^b | 27,0 | 67,5 | 94,5 |
| Celulosa microcristalina | 27,0 | 67,5 | 94,5 |
| Hidroxiopropilcelulosa | 2,4 | 6,0 | 8,4 |
| Croscarmelosa de sodio | 3,2 | 8,0 | 11,2 |
| Estearato de magnesio | 0,4 | 1,0 | 1,4 |
| Opadry® Blanco, YS-1-18177-A ^c | 3,2 | 7,0 | 8,4 |
| Agua Purificada ^d | - | - | - |

a La cantidad indicada se basa en un ensayo teórico del 100% para dasatinib en base anhidra. La cantidad exacta variará según el Ensayo "tal como está" de dasatinib-----

b La cantidad de lactosa monohidrato variará en función de la cantidad de dasatinib utilizada. -----

c Opadry® Blanco YS-1-18177-A contiene hipromelosa 6 cP (59,8% p/p), dióxido de titanio (31,2% p/p) y polietilenglicol 400 (9,0% p/p). -----

d Eliminado durante el procesamiento. -----

Condiciones de conservación y vida útil en los Estados Unidos: Conservar a 20°C a 25°C (68°F a 77°F); se permiten excursiones entre 15°C y 30°C (59°F y 86°F) [ver USP Temperatura ambiente controlada]. -----

Vida útil-36 meses-----

ES TRADUCCIÓN FIEL DEL INGLÉS AL ESPAÑOL (4 PÁGINAS) DE LA PARTE PERTINENTE DEL DOCUMENTO QUE TUVE A LA VISTA Y AL QUE ME REMITO. EN BUENOS AIRES, A LOS 08 DÍAS DEL MES DE NOVIEMBRE DE 2021. -----

Adriana Luis Riesgo
ADRIANA LUIS RIESGO
 TRADUCTORA PÚBLICA

IDIOMA INGLÉS
 MAT. Tº VIII - Fº 425 - CAP. FEDERAL
 IDIOMA PORTUGUES
 MAT. Tº XVIII Fº 008 - CAP. FEDERAL
 INSCRIP. C.T.P.C.B.A. Nº 2047

COLEGIO DE TRADUCTORES PUBLICOS
 DE LA CIUDAD DE BUENOS AIRES
 Corresponde a la Legalización
 Nº 70640/21 9
 JACOBO A. GORRINIHOVSIK MICHELL

RIESGO
 PÚBLICA
 LES
 CAP. FEDERAL
 UGUES
 CAP. FEDERAL
 A. Nº 2047



COLEGIO DE TRADUCTORES PÚBLICOS DE LA CIUDAD DE BUENOS AIRES


República Argentina
Ley 20305

LEGALIZACIÓN

Por la presente, el COLEGIO DE TRADUCTORES PÚBLICOS DE LA CIUDAD DE BUENOS AIRES, en virtud de la facultad que le confiere el artículo 10 inc. d) de la ley 20305, certifica únicamente que la firma y el sello que aparecen en la traducción adjunta concuerdan con los correspondientes al/a Traductor/a Público/a **LUIS RIESGO, ADRIANA** que obran en los registros de esta institución, en el folio **425** del Tomo **8** en el idioma **INGLÉS**

Legalización número: **70640**

Buenos Aires, 10/11/2021


MARCELO R. SIGALOFF
Gerente Dpto. de Legalización
Colegio de Traductores Públicos
de la Ciudad de Buenos Aires

ESTA LEGALIZACIÓN NO SE CONSIDERARÁ VÁLIDA SIN EL CORRESPONDIENTE
TIMBRADO DE CONTROL EN LA ÚLTIMA HOJA DE LA TRADUCCIÓN ADJUNTA

51039370640

Control interno:



5 1 0 3 9 3 7 0 6 4 0

By virtue of the authority vested in the COLEGIO DE TRADUCTORES PÚBLICOS DE LA CIUDAD DE BUENOS AIRES (Buenos Aires Sworn Translators Association) by Argentine law No. 20 305 section 10(d), I hereby CERTIFY that the seal and signature affixed on the attached translation are consistent with the seal and signature on file in our records.

The Colegio de Traductores Públicos de la Ciudad de Buenos Aires only certifies that the signature and seal on the translation are genuine; it will not attest to the contents of the document.

THIS CERTIFICATION WILL BE VALID ONLY IF IT BEARS THE PERTINENT CHECK STAMP ON THE LAST PAGE OF THE ATTACHED TRANSLATION.

Vu par le COLEGIO DE TRADUCTORES PÚBLICOS DE LA CIUDAD DE BUENOS AIRES (Ordre des Traducteurs Officiels de la ville de Buenos Aires), en vertu des attributions qui lui ont été accordées par l'article 10, alinéa d) de la Loi n° 20.305, pour la seule légalisation matérielle de la signature et du sceau du Traductor Público (Traducteur Officiel) apposés sur la traduction du document ci-joint, qui sont conformes à ceux déposés aux archives de cette Institution.

LE TIMBRE APPOSÉ SUR LA DERNIÈRE PAGE DE LA TRADUCTION FERA PREUVE DE LA VALIDITÉ DE LA LÉGALISATION.

Il COLEGIO DE TRADUCTORES PÚBLICOS DE LA CIUDAD DE BUENOS AIRES (Ordine dei Traduttori abilitati della Città di Buenos Aires) CERTIFICA ai sensi dell'articolo 10, lettera d) della legge 20.305 che la firma e il timbro apposti sulla qui unita traduzione sono conformi alla firma e al timbro del Traduttore abilitato depositati presso questo Ente. Non certifica il contenuto della traduzione sulla quale la certificazione è apposta.

LA VALIDITÀ DELLA PRESENTE CERTIFICAZIONE È SUBORDINATA ALL'APPOSIZIONE DEL TIMBRO DI CONTROLLO DEL CTPCBA SULL'ULTIMA PAGINA DELL'ALLEGATA TRADUZIONE.

Por meio desta legalização, o COLEGIO DE TRADUCTORES PÚBLICOS DE LA CIUDAD DE BUENOS AIRES (Colégio dos Tradutores Públicos da Cidade de Buenos Aires), no uso de suas atribuições e em conformidade com o artigo 10, alínea "d", da Lei 20.305, somente reconhece a assinatura e o carimbo do Tradutor Público que subscreve a tradução em anexo por semelhança com a assinatura e o carimbo arquivados nos registros desta instituição.

A PRESENTE LEGALIZAÇÃO SÓ TERÁ VALIDADE COM A CORRESPONDENTE CHANCELA MECÂNICA APOSTA NA ÚLTIMA FOLHA DA TRADUÇÃO.

COLEGIO DE TRADUCTORES PÚBLICOS DE LA CIUDAD DE BUENOS AIRES (Kammer der vereidigten Übersetzer der Stadt Buenos Aires). Kraft der Befugnisse, die ihr nach Art. 10 Abs. d) von Gesetz 20.305 zustehen, bescheinigt die Kammer hiermit lediglich die Übereinstimmung der Unterschrift und des Siegelabdruckes auf der beigelegten Übersetzung mit der entsprechenden Unterschrift und dem Siegelabdruck des vereidigten Übersetzers (Traductor Público) in unseren Registern.

DIE VORLIEGENDE ÜBERSETZUNG IST OHNE DEN ENTSPRECHENDEN GEBÜHRENSTEMPEL AUF DEM LETZTEN BLATT DER BEIGEFÜGTEN ÜBERSETZUNG NICHT GÜLTIG.

CPP Sprycel 100 mg

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country: *United States of America*

This public document

2. has been signed by Carole Jones

3. acting in the capacity of Division Director, Exports Compliance Branch

4. bears the seal/stamp of U. S. Department of Health and Human Services

Certified

5. at Washington, D.C.

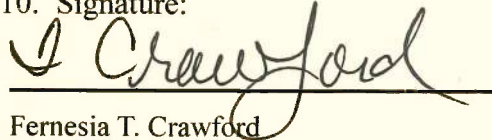
6. the thirtieth of October, 2021

7. by *Assistant Authentication Officer, United States Department of State*

8. No. 22003824-17

9. Seal/Stamp:

10. Signature:



Fernesia T. Crawford

United States Food and Drug Administration

Center for Drug Evaluation and Research

10903 New Hampshire Ave, Silver Spring, MD 20993, United States of America

CDERExportCertificateProgram@fda.hhs.gov - Telephone (301) 796-4950

Certificate of a Pharmaceutical Product - Foreign Manufacturer

Certificate Number: VXR-ETMY

Certificate Issue Date: September 29, 2021

Certificate Expiration Date: September 28, 2023

Exporting Country: UNITED STATES of AMERICA

| | |
|---------|--|
| 1. | Drug Trade Name, International or National non-proprietary name (as applicable) & dosage form: SPRYCEL®, Tablet |
| 1.1 | Active Ingredient(s) and amount(s) per unit dose (complete quantitative composition is preferred): dasatinib 100 MG |
| 1.2 | Is this product licensed to be placed on the market for use in the exporting country? Yes |
| 1.3 | Is this product actually on the market in the exporting country? Yes |
| 2.A.1 | Product license number & date of issue: 021986 06/28/2006 |
| 2.A.2 | Product license holder name & address: Bristol-Myers Squibb Company, PO Box 4000, Princeton, NJ 08543 United States of America |
| 2.A.3 | Status of Product license holder: Neither |
| 2.A.3.1 | Manufacturer name & address: Patheon Inc., 2100 Syntex Court, Mississauga, Ontario L5N 7K9 CANADA |
| 2.A.4 | Is a summary basis for approval appended? No |
| 2.A.5 | Is the attached product information, complete and consonant with the license? Yes |
| 2.A.6 | Applicant name & address for certificate (if different from the license holder): Bristol Myers Squibb, 4931 George Road, Tampa, FL 33634 United States of America |
| 2.B.4 | Remarks: Packager: AndersonBrecon Inc., 4545 Assembly Drive, Rockford, IL 61109 This FDA certification pertains to the product marketed in the United States of America. |
| 3. | Does the certifying authority arrange for periodic inspection of the manufacturing plant in which the dosage form is produced? Yes |
| 3.1 | Periodicity of routine inspections (years): Pursuant to section 510(b)(3) of the Federal Food, Drug & Cosmetic Act, inspections will occur in accordance with a risk-based schedule |
| 3.2 | Has the manufacture of this type of dosage form been inspected? Yes |
| 3.3 | Do the facilities and operations conform to GMPs as recommended by the WHO? (GMPs including 21 Code of Federal Regulations parts 210, 211, or ICH Q7A): Yes, at time of inspection, site complies with FDA cGMP |
| 3.4 | Does the information submitted by the applicant satisfy the certifying authority on all aspects of the manufacture of the product undertaken by another party? Yes |

Carole Jones

Carole Jones, Division Director
Exports Compliance Branch
Division of Global Drug Distribution and Policy



3 9 4 2 3 0 1 X X 1 3 8 6 8 7 A 0

Distributed by:
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

30 Tablets NDC 0003-0852-22

SPRYCEL[®]
(dasatinib)
Tablets

100
mg

Rx only

Do not crush, cut or chew tablets.
Swallow tablets whole.



Bristol-Myers Squibb

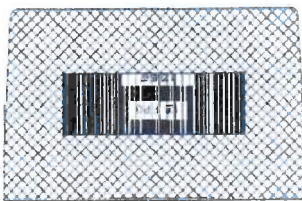
Each film-coated tablet contains 100 mg dasatinib.
Usual Dosage: See package insert for dosing instructions,
directions for use, and precautions.
Store at 20°C to 25°C (68°F to 77°F); excursions
permitted between 15°C and 30°C (59°F and 86°F)
[see USP Controlled Room Temperature].
Do not use if inner seal of bottle is broken or missing.



For Position Only

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GTIN: 00000000000000
S/N: 00000000000000
Lot: 000000
Exp: MM/YYYY



Each film-coated tablet contains 100 mg dasatinib.
Usual Dosage: See package insert for dosing instructions, directions for use, and precautions.
Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].

30 Tablets NDC 0003-0852-22

SPRYCEL®
(dasatinib)
Tablets

100 mg

Rx only

Do not crush, cut or chew tablets.
Swallow tablets whole.

Bristol-Myers Squibb

For Positron Only
0000 0000 00

Do not use if inner seal of bottle is broken or missing.

Distributed by
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA
Product of Switzerland

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30 Tablets NDC 0003-0852-22

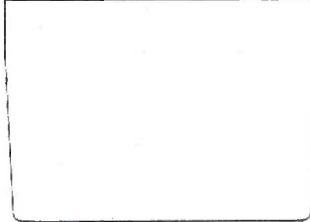
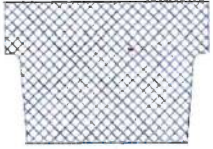
SPRYCEL®
(dasatinib)
Tablets

100 mg

Rx only

Do not crush, cut or chew tablets.
Swallow tablets whole.

Bristol-Myers Squibb



HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use SPRYCEL® safely and effectively. See full prescribing information for SPRYCEL.

SPRYCEL (dasatinib) tablets, for oral use
Initial U.S. Approval: 2006

RECENT MAJOR CHANGES

Warnings and Precautions (5.4) 6/2021
Warnings and Precautions (5.9) 6/2021

INDICATIONS AND USAGE

- SPRYCEL is a tyrosine kinase inhibitor indicated for the treatment of
- newly diagnosed adults with Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase. (1, 1.4)
 - adults with chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy including imatinib. (1, 1.4)
 - adults with Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) with resistance or intolerance to prior therapy. (1, 1.4)
 - pediatric patients 1 year of age and older with Ph+ CML in chronic phase. (1, 1.4)
 - pediatric patients 1 year of age and older with newly diagnosed Ph+ ALL in combination with chemotherapy. (1, 1.4)

DOSE AND ADMINISTRATION

- Chronic phase CML in adults: 100 mg once daily. (2)
- Accelerated phase CML, myeloid or lymphoid blast phase CML, or Ph+ ALL in adults: 140 mg once daily. (2)
- Chronic phase CML and ALL in pediatric: starting dose based on body weight. (2)
- Administer orally, with or without a meal. Do not crush, cut, or chew tablets. (2)

DOSE FORMS AND STRENGTHS

Tablets: 20 mg, 50 mg, 70 mg, 80 mg, 100 mg, and 140 mg. (3)

CONTRAINDICATIONS

None. (4)

WARNINGS AND PRECAUTIONS

- Myelosuppression and Bleeding Events:** Severe thrombocytopenia, neutropenia, and anemia may occur. Use caution if used concomitantly with medications that inhibit platelet function or anticoagulants. Monitor complete blood counts regularly. Transfuse and interrupt SPRYCEL when indicated. (2.5, 5.1, 5.2)
- Fluid Retention:** Fluid retention, sometimes severe, including pleural effusions. Manage with supportive care measures and/or dose modification. (2.5, 5.3)

- Cardiovascular Toxicity:** Monitor patients for signs or symptoms and treat appropriately. (5.4)
- Pulmonary Arterial Hypertension (PAH):** SPRYCEL may increase the risk of developing PAH which may be reversible or life-threatening. Consider baseline risk and evaluate patients for signs and symptoms of PAH during treatment. Stop SPRYCEL if PAH is confirmed. (5.5)
- QT Prolongation:** Use SPRYCEL with caution in patients who have or may develop prolongation of the QT interval. (5.6)
- Severe Dermatologic Reactions:** Individual cases of severe mucocutaneous dermatologic reactions have been reported. (5.7)
- Tumor Lysis Syndrome:** Tumor lysis syndrome has been reported. Maintain adequate hydration and correct uric acid levels prior to initiating therapy with SPRYCEL. (5.8)
- Embryo-Fetal Toxicity:** Can cause fetal harm. Advise patients of reproductive potential of potential risk to fetus and to use effective contraception. (5.9, 8.1, 8.2)
- Effects on Growth and Development in Pediatric Patients:** Epiphyseal delayed fusion, osteopenia, growth retardation, and gynecomastia have been reported. Monitor bone growth and development in pediatric patients. (5.10)

ADVERSE REACTIONS

Most common adverse reactions (≥15%) in patients receiving SPRYCEL as single-agent therapy included myelosuppression, fluid retention, events, diarrhea, headache, skin rash, hemorrhage, dyspnea, fatigue, nausea, and musculoskeletal pain. (6)

Most common adverse reactions (≥30%) in pediatric patients receiving SPRYCEL in combination with chemotherapy included mucositis, febrile neutropenia, pyrexia, diarrhea, nausea, vomiting, musculoskeletal pain, abdominal pain, cough, headache, rash, fatigue, constipation, arthralgia, hyperkalemia, edema, infections (bacterial, viral and fungal), hypotension, decreased appetite, hypercatabolism, dyspnea, epistaxis, peripheral neuropathy, and altered state of consciousness. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Bristol-Myers Squibb at 1-800-721-5072 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- Strong CYP3A4 Inhibitors:** Dose reduction may be necessary. (2.3, 7.1)
- Strong CYP3A4 Inducers:** Dose increase may be necessary. (2.3, 7.1)
- Antacids:** Avoid simultaneous administration. (7.1)
- H₂ Antagonists and Proton Pump Inhibitors:** Avoid coadministration. (7.1)

USE IN SPECIFIC POPULATIONS

- Lactation:** Advise women not to breastfeed. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 6/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

| | | | |
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| 1 | INDICATIONS AND USAGE | 6.1 | Clinical Trials Experience |
| 2 | DOSE AND ADMINISTRATION | 6.2 | Postmarketing Experience |
| 2.1 | Dosage of SPRYCEL in Adult Patients | 7 | DRUG INTERACTIONS |
| 2.2 | Dosage of SPRYCEL in Pediatric Patients with CML or Ph+ ALL | 7.1 | Effect of Other Drugs on Dasatinib |
| 2.3 | Dose Modification | 8 | USE IN SPECIFIC POPULATIONS |
| 2.4 | Dose Escalation in Adults with CML and Ph+ ALL, and Pediatric Patients with CML | 8.1 | Pregnancy |
| 2.5 | Dose Adjustment for Adverse Reactions | 8.2 | Lactation |
| 2.6 | Duration of Treatment | 8.3 | Females and Males of Reproductive Potential |
| 3 | DOSE FORMS AND STRENGTHS | 8.4 | Pediatric Use |
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| 5.1 | Myelosuppression | 11 | DESCRIPTION |
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| 5.8 | Tumor Lysis Syndrome | 14 | CLINICAL STUDIES |
| 5.9 | Embryo-Fetal Toxicity | 14.1 | Newly Diagnosed Chronic Phase CML in Adults |
| 5.10 | Effects on Growth and Development in Pediatric Patients | 14.2 | Imatinib-Resistant or -Intolerant CML or Ph+ ALL in Adults |
| 6 | ADVERSE REACTIONS | 14.3 | CML in Pediatric Patients |
| | | 14.4 | Ph+ ALL in Pediatric Patients |

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

SPRYCEL (dasatinib) is indicated for the treatment of adult patients with

- newly diagnosed Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase.
- chronic, accelerated, or myeloid or lymphoid blast phase Ph+ CML with resistance or intolerance to prior therapy including imatinib.
- Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) with resistance or intolerance to prior therapy.

SPRYCEL (dasatinib) is indicated for the treatment of pediatric patients 1 year of age and older with:

- Ph+ CML in chronic phase.
- newly diagnosed Ph+ ALL in combination with chemotherapy.

2 DOSE AND ADMINISTRATION

2.1 Dosage of SPRYCEL in Adult Patients

The recommended starting dosage of SPRYCEL for chronic phase CML in adults is 100 mg administered orally once daily. The recommended starting dosage of SPRYCEL for accelerated phase CML, myeloid or lymphoid blast phase CML, or Ph+ ALL in adults is 140 mg administered orally once daily. Tablets should not be crushed, cut, or chewed; they should be swallowed whole. SPRYCEL can be taken with or without a meal, either in the morning or in the evening.

2.2 Dosage of SPRYCEL in Pediatric Patients with CML or Ph+ ALL

The recommended starting dosage for pediatrics is based on body weight as shown in Table 1. The recommended dose should be administered orally once daily with or without food. Recalculate the dose every 3 months based on changes in body weight, or more often if necessary.

Do not crush, cut or chew tablets. Swallow tablets whole. There are additional administration considerations for pediatric patients who have difficulty swallowing tablets whole [see Use in Specific Populations (8.4) and Clinical Pharmacology (12.3)].

Table 1: Dosage of SPRYCEL for Pediatric Patients^a

| Body Weight (kg) ^b | Daily Dose (mg) |
|-------------------------------|-----------------|
| 10 to less than 20 | 40 mg |
| 20 to less than 30 | 60 mg |
| 30 to less than 45 | 70 mg |
| at least 45 | 100 mg |

^a For pediatric patients with Ph+ ALL, begin SPRYCEL therapy on or before day 15 of induction chemotherapy, when diagnosis is confirmed and continue for 2 years.

^b Tablet dosing is not recommended for patients weighing less than 10 kg.

16 REFERENCES 17 HOW SUPPLIED/STORAGE AND HANDLING 18 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

Refer to Section 2.4 for recommendations on dose escalation in adults with CML and Ph+ ALL, and pediatric patients with CML.

2.3 Dose Modification

Strong CYP3A4 Inducers

Avoid the use of concomitant strong CYP3A4 inducers and St. John's wort. If patients must be coadministered a strong CYP3A4 inducer, consider a SPRYCEL dose increase. If the dose of SPRYCEL is increased, monitor the patient carefully for toxicity [see Drug Interactions (7.1)].

Strong CYP3A4 Inhibitors

Avoid the use of concomitant strong CYP3A4 inhibitors and grapefruit juice. Recommend selecting an alternate concomitant medication with no or minimal enzyme inhibition potential, if possible. If SPRYCEL must be administered with a strong CYP3A4 inhibitor, consider a dose decrease to:

- 40 mg daily for patients taking SPRYCEL 140 mg daily.
- 20 mg daily for patients taking SPRYCEL 100 mg daily.
- 20 mg daily for patients taking SPRYCEL 70 mg daily.

For patients taking SPRYCEL 60 mg or 40 mg daily, consider interrupting SPRYCEL until the inhibitor is discontinued. Allow a washout period of approximately 1 week after the inhibitor is stopped before reinitiating SPRYCEL.

These reduced doses of SPRYCEL are predicted to adjust the area under the curve (AUC) to the range observed without CYP3A4 inhibitors; however, clinical data are not available with these dose adjustments in patients receiving strong CYP3A4 inhibitors. If SPRYCEL is not tolerated after dose reduction, either discontinue the strong CYP3A4 inhibitor or interrupt SPRYCEL until the inhibitor is discontinued. Allow a washout period of approximately 1 week after the inhibitor is stopped before the SPRYCEL dose is increased [see Drug Interactions (7.1)].

2.4 Dose Escalation in Adults with CML and Ph+ ALL, and Pediatric Patients with CML

For adult patients with CML and Ph+ ALL, consider dose escalation to 140 mg once daily (chronic phase CML) or 180 mg once daily (advanced phase CML and Ph+ ALL) in patients who do not achieve a hematologic or cytogenetic response at the recommended starting dosage. For pediatric patients with CML, consider dose escalation to 120 mg once daily (see Table 2 below) if escalation is not recommended for pediatric patients with Ph+ ALL, who are administered in combination with chemotherapy.

Escalate the SPRYCEL dose as shown in Table 2 in pediatric patients who do not achieve a hematologic or cytogenetic response at the recommended starting dosage.

Table 2: Dose Escalation for Pediatric CML

| Formulation | Dose (maximum dose) | |
|-------------|---------------------|--|
| | Starting Dose | |
| Tablets | 40 mg | |
| | 60 mg | |
| | 70 mg | |
| | 100 mg | |

Table 7: Adverse Reactions Reported in ≥10% of Adult Patients with Newly Diagnosed Chronic Phase CML in the SPRYCEL-Treated Arm (n=258)

| Adverse Reaction | Minimum of 1 Year Follow-up | | Minimum of 5 Years Follow-up | |
|---|-----------------------------|-----------|------------------------------|-----------|
| | All Grades | Grade 3/4 | All Grades | Grade 3/4 |
| Fluid retention | 19 | 1 | 38 | 5 |
| Pleural effusion | 10 | 0 | 28 | 3 |
| Superficial localized edema | 9 | 0 | 14 | 0 |
| Pulmonary hypertension | 1 | 0 | 5 | 1 |
| Generalized edema | 2 | 0 | 4 | 0 |
| Pericardial effusion | 1 | <1 | 4 | 1 |
| Congestive heart failure/cardiac dysfunction ^a | 2 | <1 | 2 | <1 |
| Pulmonary edema | <1 | 0 | 1 | 0 |
| Diarrhea | 17 | <1 | 22 | 1 |
| Musculoskeletal pain | 11 | 0 | 14 | 0 |
| Rash ^b | 11 | 0 | 14 | 0 |
| Headache | 12 | 0 | 14 | 0 |
| Abdominal pain | 7 | 0 | 11 | 0 |
| Fatigue | 8 | <1 | 11 | <1 |
| Nausea | 8 | 0 | 10 | 0 |

^a Includes cardiac failure acute, cardiac failure congestive, cardiomyopathy, diastolic dysfunction, ejection fraction decreased, and left ventricular dysfunction.

^b Includes erythema, erythema multiforme, rash, rash generalized, rash macular, rash papular, rash pustular, skin exfoliation, and rash vesicular.

At 60 months, there were 26 deaths in dasatinib-treated patients (10.1%) and 26 deaths in imatinib-treated patients (10.1%); 1 death in each group was assessed by the investigator as related to study therapy.

Table 8: Adverse Reactions Reported in ≥10% of Adult Patients with Chronic Phase CML Resistant or Intolerant to Prior Imatinib Therapy (minimum of 84 months follow-up)

| Adverse Reaction | 100 mg Once Daily Chronic (n=165) | |
|-----------------------------|-----------------------------------|-----------|
| | All Grades | Grade 3/4 |
| Fluid retention | 48 | 7 |
| Superficial localized edema | 22 | 0 |
| Pleural effusion | 28 | 5 |
| Generalized edema | 4 | 0 |
| Pericardial effusion | 3 | 1 |
| Pulmonary hypertension | 2 | 1 |
| Headache | 33 | 1 |

Table 8: Adverse Reactions Reported in ≥10% of Adult Patients with Chronic Phase CML Resistant or Intolerant to Prior Imatinib Therapy (minimum of 84 months follow-up)

| Adverse Reaction | 100 mg Once Daily Chronic (n=165) | |
|---|-----------------------------------|-----------|
| | All Grades | Grade 3/4 |
| Diarrhea | 28 | 2 |
| Fatigue | 26 | 4 |
| Dyspnea | 24 | 2 |
| Musculoskeletal pain | 22 | 2 |
| Nausea | 18 | 1 |
| Skin rash ^a | 18 | 2 |
| Myalgia | 13 | 0 |
| Arthralgia | 13 | 1 |
| Infection (including bacterial, viral, fungal, and non-specified) | 13 | 1 |
| Abdominal pain | 12 | 1 |
| Hemorrhage | 12 | 1 |
| Gastrointestinal bleeding | 2 | 1 |
| Pruritus | 12 | 1 |
| Pain ^c | 11 | 1 |
| Constipation | 10 | 1 |

^a Includes drug eruption, erythema, erythema multiforme, erythrodermia, exfoliative rash, generalized erythema, genital rash, heat rash, milia, rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, skin exfoliation, skin irritation, urticaria vesiculosa, and rash vesicular.

Cumulative rates of selected adverse reactions that were reported over time in patients treated with the 100 mg once daily recommended starting dose in a randomized dose-optimization trial of imatinib-resistant or -intolerant patients with chronic phase CML are shown in Table 9.

Table 9: Selected Adverse Reactions Reported in Adult Dose Optimization Trial (Imatinib-Intolerant or -Resistant Chronic Phase CML)^a

| Adverse Reaction | Minimum of 2 Years Follow-up | | Minimum of 5 Years Follow-up | | Minimum of 7 Years Follow-up | |
|---------------------------|------------------------------|-----------|------------------------------|-----------|------------------------------|-----------|
| | All Grades | Grade 3/4 | All Grades | Grade 3/4 | All Grades | Grade 3/4 |
| Diarrhea | 27 | 2 | 28 | 2 | 28 | 2 |
| Fluid retention | 34 | 4 | 42 | 6 | 48 | 7 |
| Superficial edema | 18 | 0 | 21 | 0 | 22 | 0 |
| Pleural effusion | 18 | 2 | 24 | 4 | 28 | 5 |
| Generalized edema | 3 | 0 | 4 | 0 | 4 | 0 |
| Pericardial effusion | 2 | 1 | 2 | 1 | 3 | 1 |
| Pulmonary hypertension | 0 | 0 | 0 | 0 | 2 | 1 |
| Hemorrhage | 11 | 1 | 11 | 1 | 12 | 1 |
| Gastrointestinal bleeding | 2 | 1 | 2 | 1 | 2 | 1 |

^a Randomized dose-optimization trial results reported in the recommended starting dose of 100 mg once daily (n=165) population.

Table 10: Adverse Reactions Reported in ≥10% of Adult Patients with Advanced Phase CML Resistant or Intolerant to Prior Imatinib Therapy

| Adverse Reaction | 140 mg Once Daily | | | | | |
|--|---------------------|-----------|----------------------|-----------|-----------------------|-----------|
| | Accelerated (n=157) | | Myeloid Blast (n=74) | | Lymphoid Blast (n=33) | |
| | All Grades | Grade 3/4 | All Grades | Grade 3/4 | All Grades | Grade 3/4 |
| Fluid retention | 35 | 8 | 34 | 7 | 21 | 6 |
| Superficial localized edema | 18 | 1 | 14 | 0 | 3 | 0 |
| Pleural effusion | 21 | 7 | 20 | 7 | 21 | 6 |
| Generalized edema | 1 | 0 | 3 | 0 | 0 | 0 |
| Pericardial effusion | 3 | 1 | 0 | 0 | 0 | 0 |
| Congestive heart failure/cardiac dysfunction | 0 | 0 | 4 | 0 | 0 | 0 |
| Diarrhea | 1 | 0 | 4 | 3 | 0 | 0 |
| Fatigue | 27 | 1 | 18 | 1 | 15 | 3 |
| Dyspnea | 31 | 3 | 20 | 5 | 18 | 0 |
| Musculoskeletal pain | 19 | 2 | 20 | 1 | 9 | 3 |
| Nausea | 20 | 3 | 15 | 3 | 3 | 3 |
| Headache | 11 | 0 | 8 | 1 | 0 | 0 |
| Rash | 19 | 1 | 23 | 1 | 21 | 3 |
| Arthralgia | 15 | 0 | 16 | 1 | 21 | 0 |
| Infection | 10 | 0 | 5 | 1 | 0 | 0 |

Table 10: Adverse Reactions Reported in ≥10% of Adult Patients with Advanced Phase CML Resistant or Intolerant to Prior Imatinib Therapy

| Adverse Reaction | 140 mg Once Daily | | | | | |
|---|---------------------|-----------|----------------------|-----------|-----------------------|-----------|
| | Accelerated (n=157) | | Myeloid Blast (n=74) | | Lymphoid Blast (n=33) | |
| | All Grades | Grade 3/4 | All Grades | Grade 3/4 | All Grades | Grade 3/4 |
| Infection (including bacterial, viral, fungal, and non-specified) | 10 | 6 | 14 | 7 | 9 | 0 |
| Hemorrhage | 26 | 8 | 19 | 9 | 24 | 9 |
| Gastrointestinal bleeding | 8 | 6 | 9 | 7 | 9 | 3 |
| CNS bleeding | 1 | 1 | 0 | 0 | 3 | 3 |
| Vomiting | 11 | 1 | 12 | 0 | 15 | 0 |
| Pyrexia | 11 | 2 | 18 | 3 | 6 | 0 |
| Febrile neutropenia | 4 | 4 | 12 | 12 | 12 | 12 |

^a Includes ventricular dysfunction, cardiac failure, cardiac failure congestive, cardiomyopathy, congestive cardiomyopathy, diastolic dysfunction, ejection fraction decreased, and ventricular failure.

^b Includes drug eruption, erythema, erythema multiforme, erythrodermia, exfoliative rash, generalized erythema, genital rash, heat rash, milia, rash, rash erythematous, rash follicular, rash generalized, rash macular, rash maculopapular, rash papular, rash pruritic, rash pustular, skin exfoliation, skin irritation, urticaria vesiculosa, and rash vesicular.

Table 11: Adverse Reactions Reported in ≥10% of Dasatinib-Treated Pediatric Patients with Chronic Phase CML (n=97)

| Adverse Reaction | Percent (%) of Patients | |
|-------------------|-------------------------|-----------|
| | All Grades | Grade 3/4 |
| Headache | 28 | 3 |
| Nausea | 20 | 0 |
| Diarrhea | 21 | 0 |
| Skin rash | 19 | 0 |
| Vomiting | 13 | 0 |
| Pain in extremity | 19 | 1 |
| Abdominal pain | 16 | 0 |
| Fatigue | 10 | 0 |
| Arthralgia | 10 | 1 |

Adverse reactions associated with bone growth and development were reported in 2 (5.2%) of pediatric patients with chronic phase CML [see Warnings and Precautions (5.10)].

Laboratory Abnormalities

Myelosuppression was commonly reported in all patient populations. The frequency of Grade 3 or 4 neutropenia, thrombocytopenia, and anemia was higher in patients with advanced phase CML than in chronic phase CML (Tables 12 and 13). Myelosuppression was reported in patients with normal baseline laboratory values as well as in patients with pre-existing laboratory abnormalities.

In patients who experienced severe myelosuppression, recovery generally occurred following dose interruption or reduction; permanent discontinuation of treatment occurred in 2% of adult patients with newly diagnosed chronic phase CML and 5% of adult patients with resistance or intolerance to prior imatinib therapy [see Warnings and Precautions (5.1)].

Grade 3 or 4 elevations of transaminases or bilirubin and Grade 3 or 4 hypocalcemia, hypokalemia, and hypophosphatemia were reported in patients with all phases of CML but were reported with an increased frequency in patients with myeloid or lymphoid blast phase CML. Elevations in transaminases or bilirubin were usually managed with dose reduction or interruption. Patients developing Grade 3 or 4 hypocalcemia during SPRYCEL therapy often had recovery with oral calcium supplementation.

Laboratory abnormalities reported in adult patients with newly diagnosed chronic phase CML are shown in Table 12. There were no discontinuations of SPRYCEL therapy in this patient population due to biochemical laboratory parameters.

Table 12: CTC Grade 3/4 Laboratory Abnormalities in Adult Patients with Newly Diagnosed Chronic Phase CML (minimum of 60 months follow-up)

| Hematology Parameters | Percent (%) of Patients | | |
|-------------------------|-------------------------|------------------|----|
| | SPRYCEL (n=258) | Imatinib (n=258) | |
| Neutropenia | 29 | 24 | |
| Thrombocytopenia | 22 | 14 | |
| Anemia | 13 | 9 | |
| Biochemistry Parameters | Percent (%) of Patients | | |
| | Hypophosphatemia | 7 | 31 |
| | Hypokalemia | 0 | 3 |
| | Hypocalcemia | 4 | 3 |
| | Elevated SGPT (ALT) | <1 | 2 |
| | Elevated SGOT (AST) | <1 | 1 |
| | Elevated Bilirubin | 1 | 0 |
| Elevated Creatinine | 1 | 1 | |

CTC grades: neutropenia (Grade 3 ≥0.5-1.0 × 10⁹/L, Grade 4 <0.5 × 10⁹/L); thrombocytopenia (Grade 3 ≥25-50 × 10⁹/L, Grade 4 <25 × 10⁹/L); anemia (hemoglobin Grade 3 ≥65-80 g/L, Grade 4 <65 g/L); elevated creatinine (Grade 3 >3-6 × upper limit of normal range (ULN), Grade 4 >6 × ULN); elevated bilirubin (Grade 3 >3-10 × ULN, Grade 4 >10 × ULN); elevated SGOT or SGPT (Grade 3 >5-20 × ULN, Grade 4 >20 × ULN); hypocalcemia (Grade 3 <7.0-6.0 mg/dL, Grade 4 <6.0 mg/dL); hypophosphatemia (Grade 3 <2.0-1.0 mg/dL, Grade 4 <1.0 mg/dL); hypokalemia (Grade 3 <3.0-2.5 mmol/L, Grade 4 <2.5 mmol/L).

Laboratory abnormalities reported in patients with CML resistant or intolerant to imatinib who received the recommended starting doses of SPRYCEL are shown by disease phase in Table 13.

Table 13: CTC Grade 3/4 Laboratory Abnormalities in Clinical Studies of CML in Adults: Resistance or Intolerance to Prior Imatinib Therapy

| Adverse Reaction | Chronic Phase CML 100 mg Once Daily (n=165) | Advanced Phase CML 140 mg Once Daily | | |
|--------------------------------|---|---|----------------------------------|-----------------------------------|
| | | Accelerated Phase (n=157) | Myeloid Blast Phase (n=74) | Lymphoid Blast Phase (n=33) |
| Percent (%) of Patients | | | | |
| Hematology Parameters* | | | | |
| Neutropenia | 36 | 58 | 77 | 79 |
| Thrombocytopenia | 24 | 63 | 78 | 85 |
| Anemia | 13 | 47 | 74 | 52 |
| Biochemistry Parameters | | | | |
| Hypophosphatemia | 10 | 13 | 12 | 18 |
| Hypokalemia | 2 | 7 | 11 | 15 |
| Hypocalcemia | <1 | 4 | 9 | 12 |
| Elevated SGPT (ALT) | 0 | 2 | 5 | 3 |
| Elevated SGOT (AST) | <1 | 0 | 4 | 3 |
| Elevated Bilirubin | <1 | 1 | 3 | 6 |
| Elevated Creatinine | 0 | 2 | 8 | 0 |

CTC grades: neutropenia (Grade 3 ≥0.5-1.0 × 10⁹/L, Grade 4 <0.5 × 10⁹/L); thrombocytopenia (Grade 3 ≥25-50 × 10⁹/L, Grade 4 <25 × 10⁹/L); anemia (hemoglobin Grade 3 ≥65-80 g/L, Grade 4 <65 g/L); elevated creatinine (Grade 3 >3-6 × upper limit of normal range (ULN), Grade 4 >6 × ULN); elevated bilirubin (Grade 3 >3-10 × ULN, Grade 4 >10 × ULN); elevated SGOT or SGPT (Grade 3 >5-20 × ULN, Grade 4 >20 × ULN); hypocalcemia (Grade 3 <7.0-6.0 mg/dL, Grade 4 <6.0 mg/dL); hypophosphatemia (Grade 3 <2.0-1.0 mg/dL, Grade 4 <1.0 mg/dL); hypokalemia (Grade 3 <3.0-2.5 mmol/L, Grade 4 <2.5 mmol/L).

* Hematology parameters for 100 mg once-daily dosing in chronic phase CML reflects 60-month minimum follow-up.

Among adult patients with chronic phase CML with resistance or intolerance to prior imatinib therapy, cumulative Grade 3 or 4 cytopenias were similar at 2 and 5 years including: neutropenia (36% vs 36%), thrombocytopenia (23% vs 24%), and anemia (13% vs 13%).

In the pediatric studies in CML, the rates of laboratory abnormalities were consistent with the known profile for laboratory parameters in adults.

Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ ALL) in Adults

A total of 135 adult patients with Ph+ ALL were treated with SPRYCEL in clinical studies. The median duration of treatment was 3 months (range 0.03-31 months). The safety profile of patients with Ph+ ALL was similar to those with lymphoid blast phase CML. The most frequently reported adverse reactions included fluid retention events, such as pleural effusion (24%) and superficial edema (19%), and gastrointestinal disorders, such as diarrhea (31%), nausea (24%), and vomiting (16%). Hemorrhage (19%), pyrexia (17%), rash (16%), and dyspnea (16%) were also frequently reported. Serious adverse reactions reported in ≥5% of patients included pleural effusion (11%), gastrointestinal bleeding (7%), febrile neutropenia (6%), and infection (5%).

Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia (Ph+ ALL) in Pediatric Patients

The safety of SPRYCEL administered continuously in combination with multiagent chemotherapy was determined in a multicohort study of 81 pediatric patients with newly diagnosed Ph+ ALL. [see Clinical Studies (14.4)]. The median duration of therapy was 24 months (range 2 to 27 months).

Fatal adverse reactions occurred in 3 patients (4%), all of which were due to infections. Eight (10%) patients experienced adverse reactions leading to treatment discontinuation, including fungal sepsis, hepatotoxicity in the setting of graft versus host disease, thrombocytopenia, CMV infection, pneumonia, nausea, enteritis and drug hypersensitivity.

The most common serious adverse reactions (incidence ≥10%) were pyrexia, febrile neutropenia, mucositis, diarrhea, sepsis, hypotension, infections (bacterial, viral and fungal), hypersensitivity, vomiting, renal insufficiency, abdominal pain, and musculoskeletal pain.

The incidence of common adverse reactions (incidence ≥20%) on study are shown in Table 14:

Table 14: Adverse Reactions Reported in ≥20% of Pediatric Patients with Ph+ ALL Treated with SPRYCEL in Combination with Chemotherapy CA180372 (N=81)

| Adverse Reaction | Percent (%) of Patients | |
|----------------------|-------------------------|-----------|
| | All Grades | Grade 3/4 |
| Mucositis | 93 | 60 |
| Febrile neutropenia | 86 | 86 |
| Pyrexia | 85 | 17 |
| Diarrhea | 84 | 31 |
| Nausea | 84 | 11 |
| Vomiting | 83 | 17 |
| Musculoskeletal pain | 83 | 25 |
| Abdominal pain | 78 | 17 |
| Cough | 78 | |
| Headache | 77 | |
| Rash | 68 | |
| Fatigue | 59 | |
| Constipation | 57 | |
| Arrhythmia | 47 | |
| Hypertension | 47 | |



Table 14: Adverse Reactions Reported in ≥10% of Pediatric Patients with Ph+ ALL Treated with SPRYCEL in Combination with Chemotherapy CA180372 (N=81)

| | | |
|--|-----|----|
| Edema | 47 | 6 |
| Viral infection | 40 | 12 |
| Hypotension | 40 | 26 |
| Decreased appetite | 38 | 22 |
| Hypersensitivity | 36 | 20 |
| Upper respiratory tract infection | 36 | 10 |
| Dyspnea | 35 | 10 |
| Epistaxis | 31 | 6 |
| Peripheral neuropathy | 31 | 7 |
| Sepsis (excluding fungal) | n/a | 31 |
| Altered state of consciousness | 30 | 4 |
| Fungal infection | 30 | 11 |
| Pneumonia (excluding fungal) | 28 | 25 |
| Pruritus | 28 | - |
| Clostridial infection (excluding sepsis) | 25 | 14 |
| Urinary Tract Infection | 24 | 14 |
| Bacteremia (excluding fungal) | 22 | 20 |
| Erythema | 22 | 6 |
| Chills | 21 | - |
| Pleural effusion | 21 | 9 |
| Sinusitis | 21 | 10 |
| Dehydration | 20 | 9 |
| Renal insufficiency | 20 | 9 |
| Visual impairment | 20 | - |

The incidence of common adverse reactions attributed by the investigator to SPRYCEL (reported at a frequency of ≥10%, all grades and grade 3/4, respectively) on study (N=81), included febrile

neutropenia (23%, 23%), nausea (21%, 4%), vomiting (19%, 4%), mucositis (17%, 6%), musculoskeletal pain (17%, 2%), abdominal pain (16%, 5%), diarrhea (16%, 7%), rash (15%, 0%), fatigue (12%, 0%), pyrexia (12%, 6%), and headache (12%, 5%).

CTCAE grade 3/4 laboratory abnormalities in pediatric patients with Ph+ ALL treated with SPRYCEL in combination with chemotherapy are shown in Table 15.

Table 15: CTCAE Grade 3/4 Laboratory Abnormalities in ≥10% of Pediatric Patients with Ph+ ALL Treated with SPRYCEL in Combination with Chemotherapy CA180372 (N=81)

| | Percent (%) of Patients |
|--------------------------------|-------------------------|
| Hematology Parameters | |
| Neutropenia | 96 |
| Thrombocytopenia | 88 |
| Anemia | 82 |
| Biochemistry Parameters | |
| Elevated SGPT (ALT) | 47 |
| Hypokalemia | 40 |
| Elevated SGOT (AST) | 26 |
| Hypocalcemia | 19 |
| Hyponatremia | 19 |
| Elevated Bilirubin | 11 |
| Hypophosphatemia | 11 |

Toxicity grading is per CTCAE version 4.

Additional Pooled Data from Clinical Trials

The following additional adverse reactions were reported in adult and pediatric patients (n=2809) in SPRYCEL CML clinical studies and adult patients in Ph+ ALL clinical studies at a frequency of ≥10%, 1%–<10%, 0.1%–<1%, or <0.1%. These adverse reactions are included based on clinical relevance.

Gastrointestinal Disorders: 1%–<10% – mucosal inflammation (including mucositis/stomatitis), dyspepsia, abdominal distension, constipation, gastritis, colitis (including neutropenic colitis), oral soft tissue disorder, 0.1%–<1% – ascites, dysphagia, anal fissure, upper gastrointestinal ulcer, esophagitis, pancreatitis, gastroesophageal reflux disease; <0.1% – protein losing gastroenteropathy, ileus, acute pancreatitis, anal fistula.

General Disorders and Administration-Site Conditions: ≥10% – peripheral edema, face edema, 1%–<10% – asthenia, chest pain, chills, 0.1%–<1% – malaise, other superficial edema, peripheral swelling; <0.1% – gut disturbance.

Hepatobiliary Disorders: 0.1%–<1% – cholestasis, cholecystitis, hepatitis

Renal and Urinary Disorders: 0.1%–<1% – urinary frequency, renal failure, proteinuria; <0.1% – renal impairment.

Immune System Disorders: 0.1%–<1% – hypersensitivity (including erythema nodosum).

Endocrine Disorders: 0.1%–<1% – hypothyroidism, <0.1% – hyperthyroidism, thyroiditis.

6.2 Postmarketing Experience

The following additional adverse reactions have been identified during post approval use of SPRYCEL. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Infections: hepatitis B virus reactivation

Cardiac disorders: atrial fibrillation/atrial flutter

Respiratory, thoracic, and mediastinal disorders: interstitial lung disease

Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome

Renal and urinary disorders: nephrotic syndrome

Blood and lymphatic system disorders: thrombotic microangiopathy

7 DRUG INTERACTIONS

7.1 Effect of Other Drugs on Dasatinib

Strong CYP3A4 Inhibitors

The coadministration with strong CYP3A inhibitors may increase dasatinib concentrations [see *Clinical Pharmacology (12.3)*]. Increased dasatinib concentrations may increase the risk of toxicity. Avoid concomitant use of strong CYP3A4 inhibitors. If concomitant administration of a strong CYP3A4 inhibitor cannot be avoided, consider a SPRYCEL dose reduction [see *Dosage and Administration (2.5)*].

Strong CYP3A4 Inducers

The coadministration of SPRYCEL with strong CYP3A inducers may decrease dasatinib concentrations [see *Clinical Pharmacology (12.3)*]. Decreased dasatinib concentrations may reduce efficacy. Consider alternative drugs with less enzyme induction potential. If concomitant administration of a strong CYP3A4 inducer cannot be avoided, consider a SPRYCEL dose increase.

Gastric Acid Reducing Agents

The coadministration of SPRYCEL with a gastric acid reducing agent may decrease the concentrations of dasatinib. Decreased dasatinib concentrations may reduce efficacy.

Do not administer H₂ antagonists or proton pump inhibitors with SPRYCEL. Consider the use of antacids in place of H₂ antagonists or proton pump inhibitors. Administer the antacid at least 2 hours prior to or 2 hours after the dose of SPRYCEL. Avoid simultaneous administration of SPRYCEL with antacids.

Skin and Subcutaneous Tissue Disorders: 1%–<10% – alopecia, acne, dry skin, hyperhidrosis, urticaria, dermatitis (including eczema), 0.1%–<1% – pigmentation disorder, skin ulcer, bullous conditions, photosensitivity, nail disorder, neutrophilic dermatosis, panniculitis, palmar-plantar erythrodysesthesia syndrome, hair disorder; <0.1% – leukocytoclastic vasculitis, skin fibrosis.

Respiratory, Thoracic, and Mediastinal Disorders: 1%–<10% – lung infiltration, pneumonia, cough, 0.1%–<1% – asthma, bronchospasm, dysphonia, pulmonary arterial hypertension; <0.1% – acute respiratory distress syndrome, pulmonary embolism.

Nervous System Disorders: 1%–<10% – neuropathy (including peripheral neuropathy), dizziness, dysgeusia, somnolence, 0.1%–<1% – amnesia, tremor, syncope, balance disorder; <0.1% – convulsion, cerebrovascular accident, transient ischemic attack, optic neuritis, VIIIth nerve paralysis, dementia, ataxia.

Blood and Lymphatic System Disorders: 0.1%–<1% – lymphadenopathy, lymphopenia; <0.1% – aplasia pure red cell.

Musculoskeletal and Connective Tissue Disorders: 1%–<10% – muscular weakness, musculoskeletal stiffness; 0.1%–<1% – rhabdomyolysis, tendonitis, muscle inflammation, osteonecrosis, arthritis; <0.1% – epiphyses delayed fusion (reported at 1%–<10% in the pediatric studies), growth retardation (reported at 1%–<10% in the pediatric studies).

Investigations: 1%–<10% – weight increased, weight decreased; 0.1%–<1% – blood creatine phosphokinase increased, gamma-glutamyltransferase increased.

Infections and Infestations: 1%–<10% – pneumonia (including bacterial, viral, and fungal), upper respiratory tract infection/inflammation, herpes virus infection, enterocolitis infection, sepsis (including fatal outcomes [0.2%]).

Metabolism and Nutrition Disorders: 1%–<10% – appetite disturbances, hyperuricemia, 0.1%–<1% – hypoalbuminemia, tumor lysis syndrome, dehydration, hypercholesterolemia; <0.1% – diabetes mellitus.

Cardiac Disorders: 1%–<10% – arrhythmia (including tachycardia), palpitations, 0.1%–<1% – angina pectoris, cardiomegaly, pericarditis, ventricular arrhythmia (including ventricular tachycardia), electrocardiogram T-wave abnormal, troponin increased; <0.1% – cor pulmonale, myocardial infarction, acute coronary syndrome, cardiac arrest, electrocardiogram PR prolongation, coronary artery disease, pleuropericarditis.

Visual Disorders: 1%–<10% – visual disorder (including visual disturbance, vision blurred, and reduced), dry eye, 0.1%–<1% – conjunctivitis, visual impairment, lacrimation; <0.1% – photophobia.

Vascular Disorders: 1%–<10% – flushing, hypertension, 0.1%–<1% – hypotension, thrombosis; <0.1% – livedo reticularis, deep vein thrombosis, embolism.

Psychiatric Disorders: 1%–<10% – insomnia, depression; 0.1%–<1% – anxiety, affect lability, decreased.

Perinatal Conditions: <0.1% – abortion.

Genitourinary Disorders: 0.1%–<1% – gynecostasia, menstrual disorder.

Local Site Reactions: 1%–<10% – contusion.

Other Complications: 1%–<10% – tinnitus, 0.1%–<1% – vertigo, hearing loss.

...ing a single dose of 100 mg by 14% ... was 98.5 kcal. The calories derived from fat ... and 14% for the high-fat meal. ... was approximately 96% and ... (CV% 81.5%). ... is 3 hours to 5 hours. The mean ... is metabolized in humans, primarily by CYP3A4 ... for the formation of the active metabolite, ... of dasatinib metabolites.

The exposure of the active metabolite, which is equipotent to dasatinib, represents approximately 5% of the AUC of dasatinib. The active metabolite of dasatinib is unlikely to play a major role in the observed pharmacology of the drug. Dasatinib also has several other inactive oxidative metabolites.

Excretion

Elimination is primarily via the feces. Following a single radiolabeled dose of oral dasatinib, 4% of the administered radioactivity was recovered in the urine and 85% in the feces within 10 days. Unchanged dasatinib accounted for 0.1% of the administered dose in the urine and 19% of the administered dose in the feces with the remainder of the dose being metabolites.

Specific Populations

Age (15 to 86 years old), sex, and renal impairment (creatinine clearance 21.6 mL/min to 342.3 mL/min as estimated by Cockcroft Gault) have no clinically relevant effect on the pharmacokinetics of dasatinib.

Pediatric Patients

The pharmacokinetics of dasatinib were evaluated in 43 pediatric patients with leukemia or solid tumors at oral doses ranging from 60 mg/m² to 120 mg/m² once daily, taken with or without food. The pharmacokinetics showed dose proportionality with a dose-related increase in exposure. The mean T_{max} was observed between 0.5 hours and 6 hours and the mean half-life was 2 hours to 5 hours. The geometric mean (CV%) of body weight normalized clearance in these 43 pediatric patients is 5.98 (41.5%) L/h/kg. In pediatric patients with a dosing regimen of 60 mg/m², the model simulated geometric mean (CV%) steady-state plasma average concentrations of dasatinib were 14.7 (64.6%) ng/mL (for 2 to <6 years old), 16.3 (97.5%) ng/mL (for 6 to <12 years old), and 18.2 (67.7%) ng/mL (for 12 years and older) [see Dosage and Administration (2.2)]. Dasatinib clearance and volume of distribution change with body weight in pediatric patients. Dasatinib has not been studied in patients < 1 year old.

The bioavailability of dispersed tablets in pediatric patients was estimated to be 36% lower than that of intact tablets.

Patients with Hepatic Impairment

Compared to subjects with normal liver function, patients with moderate hepatic impairment (Child Pugh B) had decreases in mean C_{max} by 47% and mean AUC by 8%. Patients with severe hepatic impairment (Child Pugh C) had decreases in mean C_{max} by 43% and in mean AUC by 28% compared to the subjects with normal liver function.

Drug Interaction Studies

Cytochrome P450 Enzymes

The coadministration of ketoconazole (strong CYP3A4 inhibitor) twice daily increased the mean C_{max} of dasatinib by 4-fold and the mean AUC of dasatinib by 5-fold following a single oral dose of 20 mg.

The coadministration of rifampin (strong CYP3A4 inducer) once daily decreased the mean C_{max} of dasatinib by 81% and the mean AUC of dasatinib by 82%.

Dasatinib is a time-dependent inhibitor of CYP3A4. Dasatinib does not inhibit CYP1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, or 2E1. Dasatinib does not induce CYP enzymes.

Gastric Acid Reducing Agents

were Asian. At baseline, the distribution of Hasford scores was similar in the SPRYCEL and imatinib treatment groups (low risk: 33% and 34%; intermediate risk: 48% and 47%; high risk: 19% and 19%, respectively). With a minimum of 12 months follow-up, 85% of patients randomized to SPRYCEL and 81% of patients randomized to imatinib were still on study.

With a minimum of 24 months follow-up, 77% of patients randomized to SPRYCEL and 75% of patients randomized to imatinib were still on study and with a minimum of 60 months follow-up, 61% and 62% of patients, respectively, were still on treatment at the time of study closure.

Efficacy results are summarized in Table 16.

Table 16: Efficacy Results in a Randomized Newly Diagnosed Chronic Phase CML Trial

| | SPRYCEL (n=259) | Imatinib (n=260) |
|---|--------------------|---------------------|
| Confirmed CCyR^a | | |
| Within 12 months (95% CI) | 76.8% (71.2–81.8) | 66.2% (60.1–71.9) |
| P-value | | 0.007 ^b |
| Major Molecular Response^b | | |
| 12 months (95% CI) | 52.1% (45.9–58.3) | 33.8% (28.1–39.9) |
| P-value | | <0.0001 |
| 60 months (95% CI) | 76.4% (70.8–81.5) | 64.2% (58.1–70.1) |

^a Confirmed CCyR is defined as a CCyR noted on two consecutive occasions at least 28 days apart.
^b Major molecular response (at any time) was defined as BCR-ABL ratios $\leq 0.1\%$ by RQ-PCR in peripheral blood samples standardized on the International scale. These are cumulative rates representing minimum follow up for the time frame specified.
^c Adjusted for Hasford score and indicated statistical significance at a pre-defined nominal level of significance.
 CI = confidence interval.

The confirmed CCyR within 24, 36, and 60 months for SPRYCEL versus imatinib arms were 80% versus 74%, 83% versus 77%, and 83% versus 79%, respectively. The MMR at 24 and 36 months for SPRYCEL versus imatinib arms were 65% versus 50% and 69% versus 56%, respectively.

After 60 months follow-up, median time to confirmed CCyR was 3.1 months in 215 SPRYCEL responders and 5.8 months in 204 imatinib responders. Median time to MMR after 60 months follow-up was 9.3 months in 198 SPRYCEL responders and 15.0 months in 167 imatinib responders.

At the end of the study, 8 patients (3%) on the dasatinib arm progressed to either accelerated phase or blast phase and 15 patients (6%) on the imatinib arm progressed to either accelerated phase or blast phase.

At the end of the study, 8 patients (3%) on the dasatinib arm progressed to either accelerated phase or blast phase and 15 patients (6%) on the imatinib arm progressed to either accelerated phase or blast phase.

At the end of the study, 8 patients (3%) on the dasatinib arm progressed to either accelerated phase or blast phase and 15 patients (6%) on the imatinib arm progressed to either accelerated phase or blast phase.

At the end of the study, 8 patients (3%) on the dasatinib arm progressed to either accelerated phase or blast phase and 15 patients (6%) on the imatinib arm progressed to either accelerated phase or blast phase.

At the end of the study, 8 patients (3%) on the dasatinib arm progressed to either accelerated phase or blast phase and 15 patients (6%) on the imatinib arm progressed to either accelerated phase or blast phase.

At the end of the study, 8 patients (3%) on the dasatinib arm progressed to either accelerated phase or blast phase and 15 patients (6%) on the imatinib arm progressed to either accelerated phase or blast phase.

At the end of the study, 8 patients (3%) on the dasatinib arm progressed to either accelerated phase or blast phase and 15 patients (6%) on the imatinib arm progressed to either accelerated phase or blast phase.

The administration of 30 mL of aluminum hydroxide/magnesium hydroxide 2 hours prior to a single dose of SPRYCEL was associated with no relevant change in the mean AUC of dasatinib; however, the mean C_{max} of dasatinib was increased by 26%.

The simultaneous administration of 30 mL of aluminum hydroxide/magnesium hydroxide with a single dose of SPRYCEL was associated with a 55% reduction in the mean AUC of dasatinib and a 58% reduction in the mean C_{max} of dasatinib.

The administration of a single dose of SPRYCEL 10 hours following famotidine (H₂ antagonist) reduced the mean AUC of dasatinib by 61% and the mean C_{max} of dasatinib by 63%.

The administration of a single 100 mg dose of SPRYCEL 22 hours following a 40 mg dose of omeprazole (proton pump inhibitor) at steady state reduced the mean AUC of dasatinib by 43% and the mean C_{max} of dasatinib by 42%.

Transporters

Dasatinib is not an inhibitor of P-gp *in vitro*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year carcinogenicity study, rats were administered oral doses of dasatinib at 0.3, 1, and 3 mg/kg/day. The highest dose resulted in a plasma drug exposure (AUC) level approximately 60% of the human exposure at 100 mg once daily. Dasatinib induced a statistically significant increase in the combined incidence of squamous cell carcinomas and papillomas in the uterus and cervix of high-dose females and prostate adenoma in low-dose males.

Dasatinib was clastogenic when tested *in vitro* in Chinese hamster ovary cells, with and without metabolic activation. Dasatinib was not mutagenic when tested in an *in vitro* bacterial cell assay (Ames test) and was not genotoxic in an *in vivo* rat micronucleus study.

Dasatinib did not affect mating or fertility in male and female rats at plasma drug exposure (AUC) similar to the human exposure at 100 mg daily. In repeat dose studies, administration of dasatinib resulted in reduced size and secretion of seminal vesicles, and immature prostate, seminal vesicle, and testis. The administration of dasatinib resulted in uterine inflammation and mineralization in monkeys, and cystic ovaries and ovarian hypertrophy in rodents.

14 CLINICAL STUDIES

14.1 Newly Diagnosed Chronic Phase CML in Adults

DASISION (Dasatinib vs Imatinib Study in Treatment-Naive Chronic Myeloid Leukemia Patients) (NCT00481247) was an open-label, multicenter, international, randomized trial conducted in adult patients with newly diagnosed chronic phase CML. A total of 519 patients were randomized to receive either SPRYCEL 100 mg once daily or imatinib 400 mg once daily. Patients with a history of cardiac disease were included in this trial except those who had a myocardial infarction within 6 months, congestive heart failure within 3 months, significant arrhythmias, or QTc prolongation. The primary endpoint was the rate of confirmed complete cytogenetic response (CCyR) within 12 months. Confirmed CCyR was defined as a CCyR noted on two consecutive occasions (at least 28 days apart).

Median age was 46 years in the SPRYCEL group and 49 years in the imatinib groups, with 10% and 11% of patients ≥ 65 years of age, respectively. There were slightly more male than female patients in both groups (59% vs 41%). Fifty-three percent of all patients were Caucasian and 39%

the imatinib arm, the rate of MMR at any time in each risk group determined by Hasford score was 69% (low risk), 65% (intermediate risk), and 54% (high risk).

BCR-ABL sequencing was performed on blood samples from patients in the newly diagnosed trial who discontinued dasatinib or imatinib therapy. Among dasatinib-treated patients the mutations detected were T315I, F317L, and V299L.

Dasatinib does not appear to be active against the T315I mutation, based on *in vitro* data.

14.2 Imatinib-Resistant or -Intolerant CML or Ph+ ALL in Adults

The efficacy and safety of SPRYCEL were investigated in adult patients with CML or Ph+ ALL whose disease was resistant to or who were intolerant to imatinib. 1158 patients had chronic phase CML, 858 patients had accelerated phase, myeloid blast phase, or lymphoid blast phase CML, and 130 patients had Ph+ ALL. In a clinical trial in chronic phase CML, resistance to imatinib was defined as failure to achieve a complete hematologic response (CHR) after 3 months, major cytogenetic response (MCyR) after 6 months, or complete cytogenetic response (CCyR) after 12 months; or loss of a previous molecular response (with concurrent $\geq 10\%$ increase in Ph+ metaphases), cytogenetic response, or hematologic response. Imatinib intolerance was defined as inability to tolerate 400 mg or more of imatinib per day or discontinuation of imatinib because of toxicity.

Results described below are based on a minimum of 2 years follow-up after the start of SPRYCEL therapy in patients with a median time from initial diagnosis of approximately 5 years. Across all studies, 48% of patients were women, 81% were white, 15% were black or Asian, 25% were ≥ 65 years of age or older, and 5% were 75 years of age or older. Most patients had long disease histories with extensive prior treatment, including imatinib, cytotoxic chemotherapy, interferon, and stem cell transplant. Overall, 80% of patients had imatinib-resistant disease and 20% of patients were intolerant to imatinib. The maximum imatinib dose had been 400–600 mg/day in about 60% of the patients and >600 mg/day in 40% of the patients.

The primary efficacy endpoint in chronic phase CML was MCyR, defined as elimination (CCyR) or substantial diminution (by at least 65%, partial cytogenetic response) of Ph+ hematopoietic cells. The primary efficacy endpoint in accelerated phase, myeloid blast phase, lymphoid blast phase CML, and Ph+ ALL was major hematologic response (MaHR), defined as either a CHR or no evidence of leukemia (NEL).

Chronic Phase CML

Dose-Optimization Trial: A randomized, open-label trial (NCT00123474) was conducted in adult patients with chronic phase CML to evaluate the efficacy and safety of SPRYCEL administered once daily compared with SPRYCEL administered twice daily. Patients with significant cardiac diseases, including myocardial infarction within 6 months, congestive heart failure within 3 months, significant arrhythmias, or QTc prolongation were excluded from the trial. The primary efficacy endpoint was MCyR in patients with imatinib-resistant CML. A total of 670 patients, of whom 497 had imatinib-resistant disease, were randomized to the SPRYCEL 100 mg once-daily, 140 mg once-daily, 50 mg twice-daily, or 70 mg twice-daily group. Median duration of treatment was 22 months.

Efficacy was achieved across all SPRYCEL treatment groups with the once-daily schedule demonstrating comparable efficacy (non-inferiority) to the twice-daily schedule on the primary

How Supplied

SPRYCEL® (dasatinib) tablets are available as described in Table 21.

Table 21: SPRYCEL Trade Presentations

| NDC Number | Strength | Description | Tablets per Bottle |
|--------------|----------|---|--------------------|
| 0003-0527-11 | 20 mg | white to off-white, biconvex, round, film-coated tablet with "BMS" debossed on one side and "527" on the other side | 60 |
| 0003-0528-11 | 50 mg | white to off-white, biconvex, oval, film-coated tablet with "BMS" debossed on one side and "528" on the other side | 60 |
| 0003-0524-11 | 70 mg | white to off-white, biconvex, round, film-coated tablet with "BMS" debossed on one side and "524" on the other side | 60 |
| 0003-0855-22 | 80 mg | white to off-white, biconvex, triangle, film-coated tablet with "BMS" and "80" (BMS over 80) debossed on one side and "855" on the other side | 30 |
| 0003-0852-22 | 100 mg | white to off-white, biconvex, oval, film-coated tablet with "BMS 100" debossed on one side and "852" on the other side | 30 |
| 0003-0857-22 | 140 mg | white to off-white, biconvex, round, film-coated tablet with "BMS" and "140" (BMS over 140) debossed on one side and "857" on the other side | 30 |

Storage

SPRYCEL tablets should be stored at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature].

Handling and Disposal

SPRYCEL is an antineoplastic product. Follow special handling and disposal procedures.¹

Personnel who are pregnant should avoid exposure to crushed or broken tablets.

SPRYCEL tablets consist of a core tablet, surrounded by a film coating to prevent exposure of healthcare professionals to the active substance. The use of latex or nitrile gloves for appropriate disposal when handling tablets that are inadvertently crushed or broken is recommended, to minimize the risk of dermal exposure.

17 PATIENT COUNSELING INFORMATION

Inform the patient to read the FDA-approved patient labeling (Patient Information).

Myelosuppression

Inform patients of the possibility of developing low blood cell counts. Advise patients to immediately report fever particularly in association with any suggestion of infection [see Warnings and Precautions (5.1)].

Advise patients using antacids to avoid taking SPRYCEL and antacids less than 2 hours apart [see Drug Interactions (7.1)].

Pain

Inform patients that they may experience headache or musculoskeletal pain with SPRYCEL. Advise patients to seek medical attention if these symptoms are bothersome or persistent.

Fatigue

Inform patients that they may experience fatigue with SPRYCEL. Advise patients to seek medical attention if this symptom is bothersome or persistent.

Rash

Inform patients that they may experience skin rash with SPRYCEL. Advise patients to seek medical attention if this symptom is bothersome or persistent.

Lactose

Inform patients that SPRYCEL contains 135 mg of lactose monohydrate in a 100-mg daily dose and 189 mg of lactose monohydrate in a 140-mg daily dose.

Instructions for Taking SPRYCEL**Missed Dose**

Advise patients that if they miss a dose of SPRYCEL, they should take the next scheduled dose at its regular time. The patient should not take two doses at the same time.

Grapefruit Juice

Advise patients not to drink grapefruit juice as it may increase the amount of SPRYCEL in their blood and therefore increase their risk of adverse reactions.

Distributed by:
Bristol-Myers Squibb Company
Princeton, NJ 08543 USA

Bleeding

Inform patients of the possibility of serious bleeding and to report immediately any signs or symptoms suggestive of hemorrhage (unusual bleeding or easy bruising) [see Warnings and Precautions (5.2)].

Fluid Retention

Patients should be informed of the possibility of developing fluid retention (swelling, weight gain, dry cough, chest pain on respiration, or shortness of breath) and advised to seek medical attention promptly if those symptoms arise [see Warnings and Precautions (5.3)].

Cardiovascular Toxicity

Inform patients of the possibility of developing cardiovascular toxicity, including cardiac ischemic events, cardiac-related fluid retention, conduction abnormalities, and TIAs. Advise patients to seek immediate medical attention if symptoms suggestive of cardiovascular toxicity occur, such as chest pain, shortness of breath, palpitations, transient vision problems, or slurred speech [see Warnings and Precautions (5.4)].

Pulmonary Arterial Hypertension

Inform patients of the possibility of developing pulmonary arterial hypertension (dyspnea, fatigue, hypoxia, and fluid retention) and advise them to seek medical attention promptly if those symptoms arise [see Warnings and Precautions (5.5)].

Tumor Lysis Syndrome

Inform patients to immediately report and seek medical attention for any symptoms such as nausea, vomiting, weakness, edema, shortness of breath, muscle cramps, and seizures, which may indicate tumor lysis syndrome [see Warnings and Precautions (5.8)].

Growth and Development in Pediatric Patients

Inform pediatric patients and their caregivers of the possibility of developing bone growth abnormalities, bone pain, or gynecomastia and advise them to seek medical attention promptly if those symptoms arise [see Warnings and Precautions (5.10)].

Embryo-Fetal Toxicity

- Advise pregnant women of the potential risk to a fetus [see Warnings and Precautions (5.9) and Use in Specific Populations (8.1)].
- Advise females of reproductive potential and males with female partners of reproductive potential to use effective contraception during treatment with SPRYCEL and for 30 days after the last dose. Advise females to contact their healthcare provider if they become pregnant, or if pregnancy is suspected, while taking SPRYCEL [see Warnings and Precautions (5.9) and Use in Specific Populations (8.1, 8.3)].

Lactation

- Advise women that breastfeeding is not recommended during treatment with SPRYCEL and for 2 weeks after the final dose [see Use in Specific Populations (8.2)].

Gastrointestinal Complaints

Inform patients that they may experience nausea, vomiting, or diarrhea with SPRYCEL. Advise patients to seek medical attention if these symptoms are bothersome or persistent.

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| PATIENT INFORMATION SPRYCEL® (Spry-sell) (dasatinib) tablets |
|--|
| <p>What is SPRYCEL? SPRYCEL is a prescription medicine used to treat:</p> <ul style="list-style-type: none"> adults with newly diagnosed Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic phase. adults with Ph+ CML who no longer benefit from, or did not tolerate, other treatment, including imatinib. adults with Ph+ acute lymphoblastic leukemia (Ph+ ALL) who no longer benefit from, or did not tolerate, other treatment. children 1 year of age and older with Ph+ CML in chronic phase. children 1 year of age and older with newly diagnosed Ph+ ALL in combination with chemotherapy. <p>It is not known if SPRYCEL is safe and effective in children under 1 year of age.</p> |
| <p>Before taking SPRYCEL, tell your healthcare provider about all of your medical conditions, including if you:</p> <ul style="list-style-type: none"> have problems with your immune system have heart problems, including a condition called congenital long QT syndrome have low potassium or low magnesium levels in your blood are lactose (milk sugar) intolerant are pregnant or plan to become pregnant. SPRYCEL can harm your unborn baby. <p>Females who can become pregnant:</p> <ul style="list-style-type: none"> You should not become pregnant during treatment with SPRYCEL. You should use effective birth control (contraception) during treatment and for 30 days after your last dose of SPRYCEL. Talk to your healthcare provider right away if you become pregnant or think you may be pregnant during treatment with SPRYCEL. <p>Males with female partners who can become pregnant:</p> <ul style="list-style-type: none"> You should use effective birth control (contraception) during treatment and for 30 days after your last dose of SPRYCEL. Your female partner should call her healthcare provider if she becomes pregnant or thinks she is pregnant during your treatment with SPRYCEL. <ul style="list-style-type: none"> are breastfeeding or plan to breastfeed. It is not known if SPRYCEL passes into your breast milk. You should not breastfeed during treatment and for 2 weeks after your last dose of SPRYCEL. <p>Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, antacids, and herbal supplements. If you take an antacid medicine, take it 2 hours before or 2 hours after your dose of SPRYCEL.</p> |
| <p>How should I take SPRYCEL?</p> <ul style="list-style-type: none"> Take SPRYCEL exactly as your healthcare provider tells you to take it. Your healthcare provider may change your dose of SPRYCEL or temporarily stop treatment with SPRYCEL. Do not change your dose or stop taking SPRYCEL without first talking to your healthcare provider. Take SPRYCEL 1 time a day. Take SPRYCEL with or without food, either in the morning or in the evening. Swallow SPRYCEL tablets whole. Do not crush, cut or chew the tablets. <ul style="list-style-type: none"> If your child cannot swallow tablets whole, talk with your healthcare provider. You should not drink grapefruit juice during treatment with SPRYCEL. If you miss a dose of SPRYCEL, take your next scheduled dose at your regular time. Do not take two doses at the same time. If you take too much SPRYCEL, call your healthcare provider or go to the nearest hospital emergency room right away. |
| <p>What are the possible side effects of SPRYCEL? SPRYCEL may cause serious side effects, including:</p> <ul style="list-style-type: none"> Low blood cell counts. Low blood cell counts are common with SPRYCEL and can be severe, including low red blood cell counts (anemia), low white blood cell counts (neutropenia), and low platelet counts (thrombocytopenia). Your healthcare provider will do blood tests to check your blood cell counts regularly during your treatment with |

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SPRYCEL. Call your healthcare provider right away if you have a fever or any signs of an infection during treatment with SPRYCEL.

- **Bleeding problems.** Bleeding problems are common with SPRYCEL. Sometimes these bleeding problems can be serious and lead to death. Call your healthcare provider right away if you have:
 - unusual bleeding or bruising of your skin
 - bright red or dark tar-like stools
 - decreased alertness, headache, or change in speech
- **Your body may hold too much fluid (fluid retention).** Fluid retention is common with SPRYCEL and can sometimes be severe. In severe cases, fluid may build up in the lining of your lungs, the sac around your heart, or your stomach cavity. Call your healthcare provider right away if you get any of these symptoms during treatment with SPRYCEL:
 - swelling all over your body
 - weight gain
 - shortness of breath, especially if this happens with low levels of physical activity or at rest
 - dry cough
 - chest pain when taking a deep breath
- **Heart and blood vessel (cardiovascular) problems.** SPRYCEL may cause heart problems, including an abnormal heart rate, a heart attack, or small strokes that last only a few minutes or a few hours, called transient ischemic attacks (TIAs). TIAs are often a warning sign that you are at risk for a more serious stroke. Your healthcare provider will monitor the potassium and magnesium levels in your blood and your heart function. Get medical help right away if you develop any of the following symptoms during treatment with SPRYCEL:
 - chest pain
 - shortness of breath
 - feeling like your heart is beating too fast or you feel abnormal heart beats
 - vision changes that may last for a short time
 - slurred speech
- **Pulmonary Arterial Hypertension (PAH).** SPRYCEL may cause high blood pressure in the vessels of your lungs. PAH may happen at any time during your treatment with SPRYCEL. Your healthcare provider should check your heart and lungs before and during treatment with SPRYCEL. Call your healthcare provider right away if you have shortness of breath, tiredness, or swelling all over your body (fluid retention).
- **Severe skin reactions.** SPRYCEL may cause skin reactions that can sometimes be severe. Get medical help right away if you get a skin reaction with fever, sore mouth or throat, or blistering or peeling of your skin or in the mouth.
- **Tumor Lysis Syndrome (TLS).** TLS is caused by a fast breakdown of cancer cells. TLS can cause you to have kidney failure and the need for dialysis treatment, and an abnormal heartbeat. Your healthcare provider may do blood tests to check you for TLS. Call your healthcare provider or get emergency medical help right away if you develop any of these symptoms during treatment with SPRYCEL:
 - nausea
 - shortness of breath
 - vomiting
 - muscle cramps
 - weakness
 - seizures
 - swelling
- **Slowing of growth and development in children.** Effects on bone growth and development in children have happened with SPRYCEL and can sometimes be severe. Your healthcare provider will monitor your child's bone growth and development during treatment with SPRYCEL. Get medical help right away if your child develops bone pain.

The most common side effects of SPRYCEL in adults and children receiving SPRYCEL alone include:

- diarrhea
- headache
- skin rash
- shortness of breath
- tiredness
- nausea
- muscle pain

The most common side effects of SPRYCEL in children receiving SPRYCEL with chemotherapy include:

- swelling, pain and redness of the lining of your mouth, throat, stomach and bowel (mucositis)
- low white blood cell counts with fever
- fever
- diarrhea
- nausea
- tiredness
- constipation
- abnormal heart rate
- high blood pressure (hypertension)
- swelling
- infections
- low blood pressure

- vomiting
- muscle pain
- stomach-area (abdominal) pain
- cough
- headache
- rash
- decreased appetite
- allergic reactions
- shortness of breath
- nose bleed
- numbness or tingling of your hands and feet
- feeling confused or disoriented

SPRYCEL may cause fertility problems in males and females. Talk to your healthcare provider if this is a concern for you.

Tell your healthcare provider if you have any side effect that bothers you or that does not go away. These are not all of the possible side effects of SPRYCEL.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store SPRYCEL?

- Store SPRYCEL at room temperature between 68°F to 77°F (20°C to 25°C).
- Ask your healthcare provider or pharmacist about the right way to throw away expired or unused SPRYCEL.
- Wear latex or nitrile gloves when handling tablets that have accidentally been crushed or broken.
- Females who are pregnant should not handle crushed or broken SPRYCEL tablets.

Keep SPRYCEL and all medicines out of the reach of children.

General information about the safe and effective use of SPRYCEL.

Medicines are sometimes prescribed for purposes other than those listed in a Patient Information leaflet. Do not use SPRYCEL for a condition for which it is not prescribed. Do not give SPRYCEL to other people even if they have the same symptoms you have. It may harm them. You can ask your healthcare provider or pharmacist for information about SPRYCEL that is written for health professionals.

What are the ingredients in SPRYCEL?

Active ingredient: dasatinib

Inactive ingredients: lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, hydroxypropyl cellulose, and magnesium stearate. The tablet coating consists of hypromellose, titanium dioxide, and polyethylene glycol.

Distributed by: Bristol-Myers Squibb Company, Princeton, NJ 08543 USA

For more information, go to www.sprycel.com or call 1-800-332-2556

This Patient Information has been approved by the U.S. Food and Drug Administration

Revised: June 2011

CERTIFICATE OF A PHARMACEUTICAL PRODUCT

Sprycel® (dasatinib) Tablets
NDA 21-986/S-003; Approval Date: May 30, 2008

| Ingredient | 100 mg |
|--|---------------|
| Dasatinib ^a | 100.0 |
| Lactose Monohydrate ^b | 135.0 |
| Microcrystalline Cellulose | 135.0 |
| Hydroxypropyl Cellulose | 12.0 |
| Croscarmellose Sodium | 16.0 |
| Magnesium Stearate | 2.0 |
| Opadry® White, YS-1-18177-A ^c | 12.0 |
| Purified Water ^d | — |

^a The amount shown is based on a theoretical Assay of 100% for dasatinib on an anhydrous basis. The exact amount will vary depending on the assay "as is" of dasatinib.

^b The amount of lactose monohydrate will vary depending upon the amount of dasatinib used.

^c Opadry® White YS-1-18177-A contains hypromellose 6 cP (59.8% w/w), titanium dioxide (31.2% w/w), and polyethylene glycol 400 (9.0% w/w).

^d Removed during processing.

US storage conditions and shelf life: Storage at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]
Shelf life-36 months

TRADUCCIÓN PÚBLICA

APOSTILLA

(Convención de la Haya del 5 de octubre de 1961)

1. País: **Estados Unidos de Norte América**
2. El presente documento público ha sido firmado por: **Carole Jones**
3. quien actúa en calidad de: **Directora de División, Departamento de Cumplimiento de Exportaciones**
4. y está revestido del sello / timbre del **Ministerio de Salud y Servicios Humanos de los Estados Unidos**

Certificado

5. en: **Washington, DC**
6. el: **30 de octubre de 2021**
7. por el: **Subsecretario de Legalizaciones del Departamento de Estado de los Estados Unidos**
8. con el número: **22003824-17**
9. Sello / timbre: (En blanco)
10. Firma: (Sigue una firma ilegible). **Fernesia T. Crawford.**

ADMINISTRACIÓN DE MEDICAMENTOS Y ALIMENTOS DE LOS ESTADOS UNIDOS -----

Centro de Evaluación e Investigación de Medicamentos -----

10903 New Hampshire Ave., Silver Spring, MD 20993, Estados Unidos de América. -----

CDERExportCertificateProgram@fda.hhs.gov – Teléfono: (301) 796-4950 -----

Certificado de un Producto Farmacéutico – Fabricante Extranjero-----

Fecha de emisión del certificado: **29 de septiembre de 2021** -----

Certificado Número: **VXRM-ETMY** -----

Fecha de Vencimiento del Certificado: **28 de septiembre de 2023** -----

País Importador: **Argentina** -----

País Exportador: **Estados Unidos de América** -----

1. Nombre Comercial del Medicamento, Denominación común Internacional o Nacional (según corresponda) y forma farmacéutica: **SPRYCEL®, Comprimido**-----

1.1 Principio(s) Activo(s) y cantidad(es) por unidad de dosis (se prefiere la composición cuantitativa completa): **dasatinib 100 MG** -----

1.2. ¿Este producto cuenta con la licencia para colocarlo en el mercado y utilizarlo en el país exportador? **SI** -----

1.3 ¿Este producto está en el mercado en el país exportador? **SI** -----

2.A.1. Número de licencia del producto y fecha de emisión: **021986 28/06/2006** -----

2.A.2. Nombre y dirección del titular de la licencia del producto: **Bristol-Myers Squibb Company, Casilla de Correo 4000, Princeton, NJ 08543 Estados Unidos de América**-----

2.A.3. Estado del titular de la licencia del producto: **Ninguna.** -----

2.A.3.1. Nombre y dirección del fabricante: **Patheon Inc., 2100 Syntex Court, Mississauga, Ontario L5N 7K9 CANADÁ** -----

2.A.4 ¿Se encuentra adjunto el resumen aprobado? **No** -----

2.A.5 ¿Está adjunta la información sobre el producto oficialmente completa y de conformidad con la licencia? **SI** -----

2.A.6 Nombre y dirección del solicitante del certificado (si difiere del titular de la licencia): **Bristol Myers Squibb. 4931 George Road, Tampa, FL 33634 Estados Unidos de América**-----

2.B.4 Observaciones: Acondicionador: **AndersonBrecon Inc., 4545 Assembly Drive, Rockford, IL 61109.** -----

Esta certificación de la FDA corresponde al producto comercializados en los Estados Unidos de América. -----

3. ¿La autoridad certificadora organiza inspecciones periódicas de la planta de fabricación en la cual se produce la forma farmacéutica? **SI** -----

3.1. Periodicidad de las inspecciones de rutina (años): **De conformidad con la sección 510(h)(3) de la Ley Federal de Alimentos Fármacos y Cosméticos, las inspecciones tendrán lugar de conformidad a un esquema basado en el riesgo** -----

3.2. ¿Se ha inspeccionado la fabricación de este tipo de forma farmacéutica? **SI** -----

3.3. ¿Las instalaciones y las operaciones cumplen con las normas de Buenas Prácticas de Fabricación tal como recomienda la Organización Mundial de la Salud? (Las Buenas Prácticas de Fabricación incluido el Código de Regulaciones Federales 21 partes 210, 211 o ICH Q7A): **SI, al momento de la inspección, el centro cumple con las cGMP de la FDA.**

3.4. ¿La información presentada por el solicitante satisface a la autoridad certificadora con respecto a todos los aspectos de Fabricación del producto a los que se comprometió la otra parte? **SI** -----

Aparece una firma ilegible y debajo se lee: Carole Jones, Directora de División, Departamento de Cumplimiento de Exportaciones -----

El presente certificado es emitido de conformidad al formato recomendado por la Organización Mundial de la Salud revisado el 1º de octubre de 1997. Sitio web: www.who.int. -----

Aparece una estampilla dorada donde se lee: Departamento de Salud y Servicios Humanos - Estados Unidos. -----

ALTO RIESGO
AGENCIA PÚBLICA
INGLÉS
ES - CAP. FEDERAL
PORTUGUES
ES - CAP. FEDERAL
C.B.A. N° 2047

-----CERTIFICADO DE PRODUCTO FARMACÉUTICO-----

-----Sprycel® (dasatinib) Comprimidos-----

-----NDA 21-986/S-003; Fecha de Aprobación: 30 de mayo de 2008-----

| Principio | |
|---|--------|
| Dasatinib ^a | 100 mg |
| | 100,0 |
| Lactosa Monohidrato ^b | 135,0 |
| Celulosa microcristalina | 135,0 |
| Hidroxipropilcelulosa | 12,0 |
| Croscarmelosa de sodio | 16,0 |
| Estearato de magnesio | 2,0 |
| Opadry® Blanco, YS-1-18177-A ^c | 12,0 |
| Agua Purificada ^d | ----- |

a La cantidad indicada se basa en un ensayo teórico del 100% para dasatinib en base anhidra. La cantidad exacta variará según el Ensayo "tal como está" de dasatinib-----

b La cantidad de lactosa monohidrato variará en función de la cantidad de dasatinib utilizada. -----

c Opadry® Blanco YS-1-18177-A contiene hipromelosa 6 cP (59,8% p/p), dióxido de titanio (31,2% p/p) y polietilenglicol 400 (9,0% p/p). -----

d Eliminado durante el procesamiento. -----

Condiciones de conservación y vida útil en los Estados Unidos: Conservar a 20°C a 25°C (68°F a 77°F); se permiten excursiones entre 15°C y 30°C (59°F y 86°F) [ver USP Temperatura ambiente controlada]. -----

Vida útil-36 meses -----

ES TRADUCCIÓN FIEL DEL INGLÉS AL ESPAÑOL (4 PÁGINAS) DE LA PARTE PERTINENTE DEL DOCUMENTO QUE TUVE A LA VISTA Y AL QUE ME REMITO. EN BUENOS AIRES, A LOS 08 DÍAS DEL MES DE NOVIEMBRE DE 2021.

Adriana Luis Riesgo

ADRIANA LUIS RIESGO
TRADUCTORA PÚBLICA
IDIOMA INGLÉS
MAT. T° VIII - F° 425 - CAP. FEDERAL
IDIOMA PORTUGUES
MAT. T° XVIII F° 008 - CAP. FEDERAL
INSCRIP. C.T.P.C.B.A. N° 2047

COLEGIO DE TRADUCTORES PUBLICOS
DE LA CIUDAD DE BUENOS AIRES
Corresponde a la Legalización
N° 70642/2021
JACOB...

ADRIANA LUIS RIESGO
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COLEGIO DE TRADUCTORES PÚBLICOS DE LA CIUDAD DE BUENOS AIRES

República Argentina
Ley 20305

LEGALIZACIÓN

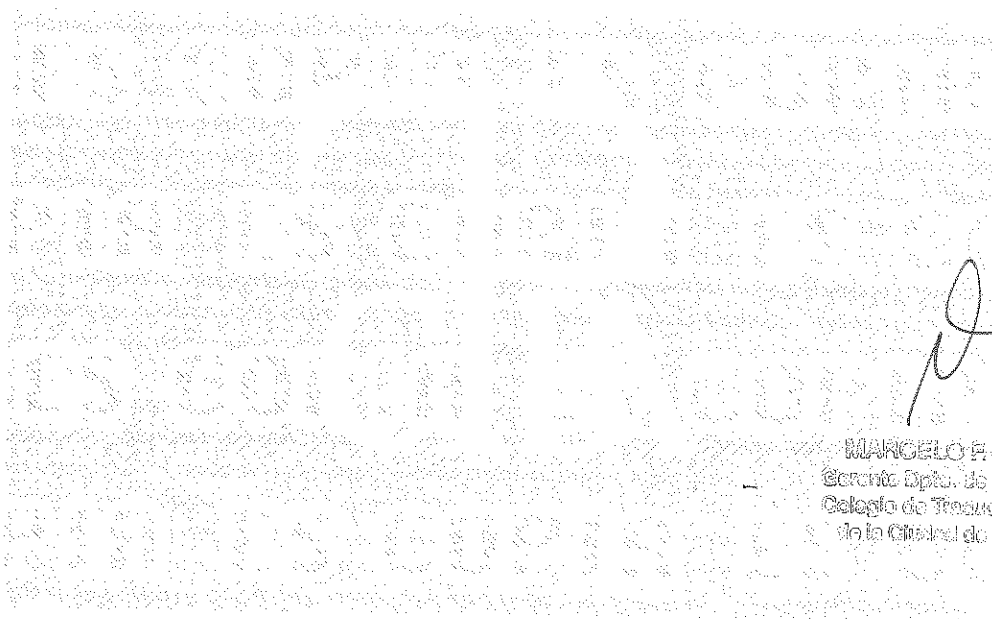
Por la presente, el COLEGIO DE TRADUCTORES PÚBLICOS DE LA CIUDAD DE BUENOS AIRES, en virtud de la facultad que le confiere el artículo 10 inc. d) de la ley 20305, certifica únicamente que la firma y el sello que aparecen en la traducción adjunta concuerdan con los correspondientes

al/a la Traductor/a Público/a **LUIS RIESGO, ADRIANA**

que obran en los registros de esta institución, en el folio **425** del Tomo **8** en el idioma **INGLÉS**

Legalización número: **70642**

Buenos Aires, 10/11/2021



MARCELO E. SIGALOFF
Gerente Dpto. de Legalización
Colegio de Traductores Públicos
de la Ciudad de Buenos Aires

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THIS CERTIFICATION WILL BE VALID ONLY IF IT BEARS THE PERTINENT CHECK STAMP ON THE LAST PAGE OF THE ATTACHED TRANSLATION.

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