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Start With SPRYCEL (dasatinib)

SPRYCEL: Superior Response Rates vs Imatinib
- Phase III, open-label, international, multicenter, randomized* study of SPRYCEL 100 mg once daily (n=259) vs imatinib 400 mg once daily (n=260) in adults with newly diagnosed Ph+ CML in chronic phase (N=519) at a minimum follow-up of 12 months
  - Primary endpoint was confirmed complete cytogenetic response (CCyR) by 12 months

Among responders, median time to MMR was 6.3 months with SPRYCEL (n=135) vs 9.2 months with imatinib (n=88)
- Primary endpoint: A significantly higher rate of patients on SPRYCEL (77%) (95% CI, 71-82) achieved confirmed CCyR by 12 months vs 66% (95% CI, 60-72) of patients on imatinib (P=0.007)
- Among responders, median time to confirmed CCyR with SPRYCEL was 3.1 months (n=199) vs 5.6 months with imatinib (n=177)

Select Important Safety Information
- SPRYCEL is associated with the following warnings and precautions: myelosuppression; bleeding-related events; fluid retention; QT prolongation; congestive heart failure, left ventricular dysfunction, and myocardial infarction; pulmonary arterial hypertension; and use in pregnancy
- The most frequently reported serious adverse events in patients with newly diagnosed CP CML included pleural effusion (2%), hemorrhage (2%), congestive heart failure (1%), and pyrexia (1%)
- The most frequently reported adverse reactions reported in ≥10% of patients with newly diagnosed CP CML included myelosuppression, fluid retention events (pleural effusion, superficial localized edema, generalized edema), diarrhea, headache, musculoskeletal pain, and rash
- Please see detailed Important Safety Information on adjacent pages

Indication
SPRYCEL® (dasatinib) is indicated for the treatment of adults with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML) in chronic phase. The effectiveness of SPRYCEL is based on cytogenetic and major molecular response rates. The trial is ongoing and further data will be required to determine long-term outcome.
Now Enrolling

Investigating Everolimus* in Diffuse Large B-cell Lymphoma

Study Description
Phase III, double-blind study in poor-risk patients with diffuse large B-cell lymphoma (DLBCL) following complete response to rituximab-containing chemotherapy

Study Design†

Primary Endpoint
Disease-free survival

For more information
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*This is an investigational study; there is no guarantee that everolimus will become commercially available for this indication.
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Start With Convenient Once-Daily Dosing

1 pill
100 mg
1 time per day

One tablet taken consistently, either in the morning or in the evening
Tablets should not be crushed or cut; they should be swallowed whole

• In clinical studies, treatment with SPRYCEL was continued until disease progression or until no longer tolerated by the patient¹

SPRYCEL Can Be Taken Either With or Without Food¹

SPRYCEL—the only treatment for adults with newly diagnosed Ph+ CML in chronic phase with:
• No fasting requirements
• No need to alter meal schedules
• No need to take with food

Important Safety Information About Drug Interactions

• Use of concomitant strong CYP3A4 inducers may decrease plasma concentrations of SPRYCEL and should be avoided
• Strong CYP3A4 inhibitors may increase plasma concentrations of SPRYCEL and should be avoided
• Grapefruit juice may increase plasma concentrations of SPRYCEL and should be avoided
• Concomitant use of H₂ antagonists or proton pump inhibitors with SPRYCEL is not recommended
• Antacids should be considered instead. Antacids may decrease SPRYCEL drug levels. If antacid therapy is needed, the dose should be given 2 hours before or after SPRYCEL

¹Stratified by Hasford risk score.²
¹Confirmed CCyR is defined as a CCyR (0% Ph+ metaphases) noted on 2 consecutive assessments at least 28 days apart.¹
²MMR (at any time) was defined as BCR-ABL ratios ≤0.1% by real-time quantitative polymerase chain reaction (RQ-PCR) in peripheral blood samples standardized on the International Scale.¹
³Adjusted for Hasford score and indicated statistical significance at a pre-defined nominal level of significance.¹

Please see detailed Important Safety Information, including Important Safety Information on Drug Interactions, on adjacent pages.
Join the experts to learn about the newest treatment options for hematologic malignancies and thrombotic disorders.

Program Co-Chairs:
Nancy Bartlett, MD, Washington University
Thomas Ortel, MD, PhD, Duke University

www.hematology.org/SAS
Important Safety Information

Myelosuppression:
- Treatment with SPRYCEL® (dasatinib) can cause severe (NCI CTC Grade 3/4) thrombocytopenia, neutropenia, and anemia. Myelosuppression was reported in patients with normal baseline laboratory values as well as in patients with pre-existing laboratory abnormalities.
  - Perform complete blood counts (CBCs) weekly for the first 2 months and then monthly thereafter, or as clinically indicated.
  - Myelosuppression was generally reversible and usually managed by dose interruption, dose reduction, or discontinuation.
  - Hematopoietic growth factor has been used in patients with resistant myelosuppression.

Bleeding-Related Events:
- SPRYCEL caused platelet dysfunction in vitro and thrombocytopenia in humans.
  - In all clinical trials, severe central nervous system (CNS) hemorrhage, including fatalities, occurred in 1% of patients. Severe gastrointestinal (GI) hemorrhage, including fatalities, occurred in 4% of patients receiving SPRYCEL, which generally required treatment interruptions and transfusions. Other cases of severe hemorrhage occurred in 2% of patients.
- Most bleeding events were associated with severe thrombocytopenia.
  - Exercise caution in patients required to take medications that inhibit platelet function or anticoagulants.

Fluid Retention:
- SPRYCEL is associated with fluid retention.
  - In clinical trials, fluid retention was severe in up to 10% of patients. Ascites (<1%), generalized edema (<1%), and severe pulmonary edema (1%) were also reported.
  - Patients who develop symptoms suggestive of pleural effusion such as dyspnea or dry cough should be evaluated by chest X-ray.
  - Severe pleural effusion may require thoracentesis and oxygen therapy.
  - Fluid retention was typically managed by supportive care measures that included diuretics or short courses of steroids.

QT Prolongation:
- In vitro data suggest that SPRYCEL has the potential to prolong cardiac ventricular repolarization (QT interval).
  - In 865 patients with leukemia treated with SPRYCEL in five phase 2 single-arm studies, the maximum mean changes in QTcF (90% upper bound CI) from baseline ranged from 7.0 ms to 13.4 ms.
  - In clinical trials of patients treated with SPRYCEL (N=2440), 15 patients (<1%) had QTc prolongation as an adverse reaction. Twenty-two patients (1%) experienced a QTcF >500 ms.
  - Administer SPRYCEL with caution to patients who have or may develop prolongation of QTc, including patients with hypokalemia, hypomagnesemia, or congenital long QT syndrome and patients taking anti-arrhythmic drugs, other medicinal products that lead to QT prolongation, and cumulative high-dose anthracycline therapy.
    - Correct hypokalemia or hypomagnesemia prior to SPRYCEL administration.

Congestive Heart Failure, Left Ventricular Dysfunction, and Myocardial Infarction:
Cardiac adverse reactions were reported in 5.8% of 258 patients taking SPRYCEL, including 1.6% of patients with cardiomyopathy, heart failure congestive, diastolic dysfunction, fatal myocardial infarction, and left ventricular dysfunction. Monitor patients for signs or symptoms consistent with cardiac dysfunction and treat appropriately.

Pulmonary Arterial Hypertension (PAH):
SPRYCEL may increase the risk of developing PAH, which may occur anytime after initiation, including after more than one year of treatment. Manifestations include dyspnea, fatigue, hypoxia, and fluid retention. 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.

Use in Pregnancy:
SPRYCEL may cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of SPRYCEL in pregnant women. Women of childbearing potential should be advised of the potential hazard to the fetus and to avoid becoming pregnant when taking SPRYCEL.

Nursing Mothers:
It is unknown whether SPRYCEL is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue SPRYCEL.
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**Drug Interactions:**

SPRYCEL (dasatinib) is a CYP3A4 substrate and a weak time-dependent inhibitor of CYP3A4.

- **Drugs that may increase SPRYCEL plasma concentrations are:**
  - **CYP3A4 inhibitors:** Concomitant use of SPRYCEL and drugs that inhibit CYP3A4 should be avoided. If administration of a potent CYP3A4 inhibitor cannot be avoided, close monitoring for toxicity and a SPRYCEL dose reduction or temporary discontinuation should be considered
    - Strong CYP3A4 inhibitors (eg, ketoconazole, itraconazole, clarithromycin, atazanavir, indinavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, voriconazole). If SPRYCEL must be administered with a strong CYP3A4 inhibitor, a dose decrease should be considered
    - Grapefruit juice may also increase plasma concentrations of SPRYCEL and should be avoided

- **Drugs that may decrease SPRYCEL plasma concentrations are:**
  - **CYP3A4 inducers:** If SPRYCEL must be administered with a CYP3A4 inducer, a dose increase in SPRYCEL should be considered
    - Strong CYP3A4 inducers (eg, dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, phenobarbital) should be avoided. Alternative agents with less enzyme induction potential should be considered. If the dose of SPRYCEL is increased, the patient should be monitored carefully for toxicity
    - St John’s Wort may decrease SPRYCEL plasma concentrations unpredictably and should be avoided

- **Antacids:** Antacids may decrease SPRYCEL drug levels. Simultaneous administration of SPRYCEL and antacids should be avoided. If antacid therapy is needed, the antacid dose should be administered at least 2 hours prior to or 2 hours after the dose of SPRYCEL

- **H₂ antagonists/proton pump inhibitors,** such as famotidine and omeprazole. Long-term suppression of gastric acid secretion by use of H₂ antagonists or proton pump inhibitors is likely to reduce SPRYCEL exposure. Therefore, concomitant use of H₂ antagonists or proton pump inhibitors with SPRYCEL is not recommended

- **Drugs that may have their plasma concentration altered by SPRYCEL are:**
  - **CYP3A4 substrates,** such as simvastatin. CYP3A4 substrates with a narrow therapeutic index should be administered with caution in patients receiving SPRYCEL

**Adverse Reactions:**

The safety data reflect exposure to SPRYCEL in 258 patients with newly diagnosed chronic phase CML in a clinical study (median duration of therapy was 18 months).

The majority of SPRYCEL-treated patients experienced adverse reactions at some time. Patients aged 65 years and older are more likely to experience toxicity. In the newly diagnosed chronic phase CML study, SPRYCEL was discontinued for adverse reactions in 6% of patients.

- In newly diagnosed chronic phase CML patients:
  - The most frequently reported serious adverse reactions included pleural effusion (2%), hemorrhage (2%), congestive heart failure (1%), and pyrexia (1%)
  - The most frequently reported adverse reactions (reported in ≥10% of patients) included myelosuppression, fluid retention events (pleural effusion, superficial localized edema, generalized edema), diarrhea, headache, musculoskeletal pain, and rash
  - Grade 3/4 laboratory abnormalities included neutropenia (22%), thrombocytopenia (19%), anemia (11%), hypophosphatemia (5%), hypocalcemia (3%), and elevated bilirubin (1%)
  - Grade 3/4 elevations of transaminase or bilirubin and Grade 3/4 hypocalcemia, hypokalemia, and hypophosphatemia were reported in patients with all phases of CML
    - Elevations in transaminase or bilirubin were usually managed with dose reduction or interruption
    - Patients developing Grade 3/4 hypocalcemia during the course of SPRYCEL therapy often had recovery with oral calcium supplementation

Please see brief summary of full Prescribing Information on adjacent pages.

**References:**

1. SPRYCEL® (dasatinib) full Prescribing Information. Bristol-Myers Squibb.

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For more information online, visit www.sprycel.com.
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Severe pulmonary edema was reported in 1% of patients. Patients who develop symptoms suggestive of QT Prolongation:
Perform complete blood counts weekly for the first 2 months and then monthly thereafter, or as clinically
Care measures that include diuretics or short courses of steroids. In dose-optimization studies, fluid retention
In the imatinib resistant or intolerant CML or Ph+ ALL clinical trials, patients had a minimum of 2 years
Myelosuppression:
• QT prolongation
• newly diagnosed Philadelphia chromosome-positive (Ph+) chronic myeloid leukemia (CML) in chronic
Congestive Heart Failure, Left Ventricular Dysfunction, and Myocardial Infarction:
• Bleeding related events
[see Warnings and Precautions].
SPRYCEL® (dasatinib) Tablet for Oral Use
CML or Ph+ ALL than in chronic phase CML. In a dose-optimization study in patients with resistance or
Myelosuppression was, generally reversible and usually managed by withholding SPRYCEL temporarily or dose reduction [see Dose and Administration (2.3) in Full Prescribing Information and Adverse
Adverse reactions are reported in 5.8% of 258 patients taking SPRYCEL, including 1.6% of patients with cardiomyopathy, heart failure (including acute, congestive, or cardiac failure), peripheral edema, and left ventricular dysfunction. Monitor patients for signs or symptoms consistent with cardiac dysfunction and treat appropriately.
Pulmonary Arterial Hypertension: SPRYCEL may increase the risk of developing pulmonary arterial hypertension (PAH) which may occur anytime after initiation, including after more than one year of treatment. Manifestations include dyspnea, fatigue, hypoaemia, and fluid retention. PAH may be reversible on discontinuation of SPRYCEL. Patients with symptoms consistent with PAH should be referred to a pulmonary hypertension specialist for evaluation and therapy.
Other bleeding:
Pulmonary hypertension
Pericardial effusion
Congestive heart failure and Left Ventricular dysfunction, and Myocardial infarction: [see Warnings and Precautions].
Pulmonary Arterial Hypertension: [see Warnings and Precautions].
Myelosuppression: [see Dose and Administration (2.3) in Full Prescribing Information and Warnings and Precautions].
Bleeding related events: [see Warnings and Precautions].
Fluid retention: [see Warnings and Precautions].
Pulmonary Arterial Hypertension: [see Warnings and Precautions].
Congestive heart failure, left ventricular dysfunction, and myocardial infarction: [see Warnings and Precautions].
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 in clinical studies including 258 patients with newly
diagnosed chronic phase CML and in 2182 patients with imatinib resistant or intolerant CML or Ph+ ALL.
In the newly diagnosed chronic phase CML trial, the median duration of therapy was 18 months; the median average dose was 109 mg. In the imatinib resistant or intolerant CML or Ph+ ALL clinical trials, patients had a minimum of 2 years follow-up. Median duration of therapy with SPRYCEL was 100 mg once daily (range 3–140 mg) and 140 mg once daily, 50 mg twice daily, or 70 mg twice daily. Among patients with chronic phase CML, resistance and intolerance to prior imatinib therapy, the median duration of treatment with SPRYCEL 100 mg once daily was 24 months (range 1–33 months). The median duration of SPRYCEL 140 mg once daily was 15 months (range 0.3–36 months) for accelerated phase CML or 3 months (range 0.3–29 months) for myeloid blast phase CML and 3 months (range 0.3–20 months) for lymphoid blast CML.
The majority of SPRYCEL-treated patients experienced adverse reactions at some time. In the newly
diagnosed chronic phase CML trial, treatment was discontinued for adverse reactions (Tables 1 and 2). Among patients with resistance or intolerance to prior imatinib therapy, the rates of discontinuation for adverse reaction were 15% in chronic phase CML, 16% in accelerated phase CML, 15% in myeloid blast phase CML, 13% in lymphoid blast phase CML, 10% in patients treated for 90 days or less at 60 mg/day and 1% in patients treated for 90 days or more at 60 mg/day. Among patients with resistance or intolerance to prior imatinib therapy and chronic phase CML, the rate for discontinuation of adverse reaction was lower in patients treated with SPRYCEL for 90 days or more at 60 mg/day treated with dose monitoring than in patients treated with SPRYCEL temporarily or dose reduction (Table 1).
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In patients who experienced severe myelosuppression, recovery generally occurred following dose interruption or reduction. Recovery was maintained in 5% of patients who received the same dose of SPRYCEL (dasatinib) for 3 or 4 cycles without interruption. Ellis et al.

Laboratory abnormalities were reported in patients with newly diagnosed chronic phase CML, as shown in Table 3. There were no disconnections of SPRYCEL therapy in this patient population due to biochemical laboratory parameters.

<table>
<thead>
<tr>
<th>Arborality Parameters</th>
<th>Percent (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>22</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>13</td>
</tr>
<tr>
<td>Anemia</td>
<td>11</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Biochemistry Parameters</th>
<th>Percent (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypophosphatemia</td>
<td>5</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>24</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>3</td>
</tr>
<tr>
<td>Elevated AST (ALT)</td>
<td>1</td>
</tr>
<tr>
<td>Elevated Bilirubin</td>
<td>1</td>
</tr>
<tr>
<td>Elevated Creatinine</td>
<td>5</td>
</tr>
</tbody>
</table>

Laboratory abnormalities were reported in patients with chronic phase CML who received the recommended dosage of SPRYCEL. The incidence of biochemical laboratory abnormalities in patients who experienced treatment failure is shown in Table 3.

### Postmarketing Experience

The following additional adverse reactions have been identified during post-approval use of SPRYCEL (dasatinib).


<table>
<thead>
<tr>
<th>Drugs That May Decrease Dasatinib Plasma Concentrations</th>
</tr>
</thead>
</table>
| **CYFRA4 Inducers**: Dasatinib is a CYP3A4 substrate. In a study of 18 patients with solid tumors, 20 mg SPRYCEL was administered once daily without concomitant with 500 mg of ketoconazole twice daily increased the dasatinib dose by 55%, and a 5% decrease in CYP3A4 activity was observed in patients receiving SPRYCEL and atorvastatin. The effect of fumaric acid ester on the pharmacokinetics of dasatinib is unknown.

<table>
<thead>
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</tr>
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### Table 3: CTC Grade 3/4 Laboratory Abnormalities in Patients with Newly Diagnosed Chronic Phase CML

<table>
<thead>
<tr>
<th>Laboratory Abnormalities</th>
<th>Percent (%) of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1%–&lt;1%</td>
<td>10</td>
</tr>
<tr>
<td>1%–&lt;10%</td>
<td>3</td>
</tr>
<tr>
<td>≥10%</td>
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</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Laboratory Abnormalities</th>
<th>Percent (%) of Patients</th>
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<td>0.1%–&lt;1%</td>
<td>36</td>
</tr>
<tr>
<td>1%–&lt;10%</td>
<td>32</td>
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<tr>
<td>≥10%</td>
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</tbody>
</table>

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

A total of 157 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 lymphoblastic 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 (21%), nausea (22%), and vomiting (16%). Hemorrhage (19%), pyrexia (17%), rash (16%), and dysesthesia (16%) were also frequently reported. The most frequently reported serious adverse reactions included pleural effusion (11%), gastrointestinal bleeding (7%), febrile neutropenia (6%), infection (5%), pyrexia (4%), pneumonia (9%), diarrhea (3%), nausea (5%), vomiting (3%), and colitis (5%).

### Additional Data From Clinical Trials

The following adverse reactions were reported in patients in the SPRYCEL clinical studies at a frequency of 1%–10%: 0.1%–<1%, or <0.1%. These events are included on the basis of clinical relevance.
Check out
ASH’s VIDEO LIBRARY
for Useful Teaching Tools

ASH offers a number of FREE videos that are perfect for students. ASH’s video library includes films on a variety of topics including:

- Cancer Cells vs. Healthy Cells
- Hereditary Spherocytosis
- How Lymphoma Develops
- How a Clot Becomes a Pulmonary Embolism
- The Components of Blood
- The Problem With Sickled Cells
- The Role of Proteins in Blood Clotting
- The Role of Red Blood Cells in Anemia
- Von Willebrand Factor and ADAMTS13

Additionally, this library includes short videos about patients dealing with various hematologic disorders, excerpted from the film “Blood Detectives.”

www.hematology.org/videolibrary

AMERICAN SOCIETY
of HEMATOLOGY
INotuzumab Ozogamicin trial to inVestigAte Tolerability and Efficacy

A randomized, phase 3 trial in patients with CD22-positive aggressive non-Hodgkin lymphoma (NHL) who are not candidates for intensive high-dose chemotherapy

Selected inclusion criteria

- Relapsed/refractory/persistent CD20+/CD22+ aggressive NHL (DLBCL, transformed indolent lymphoma with DLBCL, primary mediastinal large B-cell lymphomas)
- Up to 3 prior regimens containing cytotoxic chemotherapies
- Not candidates for intensive high-dose chemotherapy, with or without an autologous stem cell transplant

Selected exclusion criteria

- Any prior allogeneic hematopoietic stem cell transplant; autotransplant within prior 4 months
- Anti-CD22 treatment or radioimmunotherapy within prior 6 months
- Contraindication to both investigator choice regimens
- Chronic liver disease, history of veno-occlusive disease


Inotuzumab ozogamicin is an investigational compound.
This information is current as of April 3, 2012.
Flow cytometry allows you to analyze multiple parameters simultaneously—and by adding more colors you can open up a whole new world of information and insight. BD Biosciences makes it easy for you with our ever-expanding portfolio of high-quality conjugated antibody specificities that offer a full spectrum of color choices including our new BD Horizon™ V500-C violet-laser dyes to simplify work and speed results.

BD Biosciences reagents are part of the building blocks to support patient care for blood cell disorders. Go to bdbiosciences.com/go/color to learn more about our proven solution, try our BD FACSelect™ tools, and download a free product catalog.
Resistance to CML therapy may occur. In some cases, repeatedly.

Even today, with a number of available options for treating refractory CML, a gap in therapy exists. One post-imatinib study found 65% of patients discontinued dasatinib as a second-line therapy after 5 years.1 Another post-imatinib study found 70% of patients discontinued nilotinib after 4 years.2 Additionally, a small study showed approximately a quarter of patients responded when treated sequentially with 2 second-generation tyrosine kinase inhibitors (TKIs) after imatinib. But in those patients that did respond, the median response rate was 16 months.3 It’s clear that for refractory patients, unmet medical needs persist.

Blood Classified Advertising

Blood will accept advertisements for its Classified Advertising section only if they substantially relate to and further the American Society of Hematology’s tax-exempt purpose. ASH’s purpose is to engage exclusively in charitable, scientific, and educational activities and endeavors, including promoting and fostering, among the many scientific and clinical disciplines, the exchange and diffusion of information and ideas relating to blood and blood-forming tissues and encouraging investigations of hematologic matters.

Examples of advertisements that substantially relate to ASH’s purposes include advertisements for hematology-related employment at academic institutions that involve a research and/or an educational component, and advertisements for symposia and meetings that relate to furthering the exchange of hematology-related information and ideas.

To place an advertisement in Blood’s Classified Advertising section, please contact Valerie Marvin at the following address: Blood, 180 Old Tappan Road, Old Tappan, NJ 07675. Phone: 201-767-4170; fax: 201-767-8065; e-mail: vmarvin@cunnasso.com.

Save the Date
2nd International Workshop
Biology, Prevention, and Treatment of Relapse After Allogeneic Hematopoietic Stem Cell Transplantation
November 5-6, 2012
Natcher Auditorium
Bethesda, MD, USA

The primary goal of this Workshop is to develop multicenter clinical trials related to relapse after SCT.
Abstract submission deadline August 20, 2012

Organizing Committee
Michael Bishop, MD
Sergio Giralt, MD
Nicolaus Kröger, MD
Alan Wayne, MD

For more information visit:
https://ccrod.cancer.gov/confluence/display/2012NCIRelapse/Home

Now Enrolling
Two Phase III Studies of Elotuzumab in Multiple Myeloma

Bristol-Myers Squibb and Abbott are conducting the ELOQUENT Program to evaluate the safety and efficacy of elotuzumab in various multiple myeloma settings.

ELOQUENT-1
A phase III, randomized, open-label study of lenalidomide/dexamethasone with or without elotuzumab in subjects with previously untreated multiple myeloma

ELOQUENT-2
A phase III, randomized, open-label study of lenalidomide/dexamethasone with or without elotuzumab in relapsed or refractory multiple myeloma

To learn more about this study please go to
www.MMStudies.com
or visit www.ClinicalTrials.gov

Bristol-Myers Squibb
Abbott Oncology
Editor Search Announcement for the Hematology Education Program Book

The American Society of Hematology is in the initial stage of the selection process for the next Executive Editor of the Hematology Education Program Book (term: 2013-2015).

Candidates with an M.D., M.D./Ph.D. or equivalent should demonstrate a broad and comprehensive knowledge of translational research and clinical investigation in hematology and its subspecialty areas; a distinguished research and publication record; high standing among peers; and proven editing, writing, and reviewing skills.

There are responsibilities throughout the year, but the majority of the required duties occur between May and October. An honorarium will be provided.

Members of ASH are encouraged to submit a letter of intent if they are interested in the position or provide the name of a potential candidate. Nominations should be accompanied by a description of the candidate’s editorial experience and a short, informal endorsement. Nominations must be received on or before June 1, 2012. Please submit nominations via e-mail to:

Editor Search Committee
Hematology Education Program Book
editorsearch@hematology.org
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Your classified advertisement in **Blood** gives you more exposure than you think. When you place a print advertisement, you will also receive a free 30-day* posting on the American Society of Hematology’s online Job Bank. This employment resource is located at www.hematology.org and is free for all job seekers.

For more information on submitting a classified ad in **Blood**, contact Valerie Marvin at vmarvin@cunnasso.com or at 201-767-4170.

*Your 30-day online posting will start when your print advertisement first appears in **Blood**.

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**Now Recruiting……**

A New Clinical Trial for Patients with High-risk Smoldering Multiple Myeloma

**About Smoldering Multiple Myeloma (SMM)**

Smoldering multiple myeloma (SMM) is an asymptomatic condition that over time will transition into the malignant disease of multiple myeloma (MM).

**Study Overview**

Janssen Research, a unit of Centocor Research and Development, Inc., is conducting a study on SMM. In a global study 50 high-risk SMM subjects will be randomized to study drug and 50 subjects will be randomized to placebo (same drug without active ingredient). The study is double-blind, that is both doctors and patients will not know if the study drug or placebo will be given. The study intends to evaluate and/or follow subjects for 4-5 years.

**Primary Objective**

The primary objective of the study is to evaluate the 1-year progression-free survival (PFS) rate in patients with smoldering multiple myeloma (MM) with an investigational medication.

**Major Inclusion Criteria**

- Diagnosis of SMM for < 4 years
- Diagnosis of high-risk SMM;
- ECOG Performance score of 0 or 1

**About the Investigative Medication**

The investigational medication is a monoclonal antibody that binds to IL-6.

For more information, please email: ckopaczy@its.jnj.com or btromp@its.jnj.com
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Scan the QR code below for more information, or search "Blood Journal" in the Apple App Store to download.

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** After August 1, 2012 access to full content we be limited to ASH Members and *Blood* Subscribers.
Important Safety Information

WARNINGS AND PRECAUTIONS:

- Treatment with ISTODAX has been associated with thrombocytopenia, leukopenia (neutropenia and lymphopenia), and anemia; therefore, monitor these hematological parameters during treatment with ISTODAX and modify the dose as necessary.
- Serious and sometimes fatal infections have been reported during treatment and within 30 days after treatment with ISTODAX and the risk of life-threatening infections may be higher in patients with a history of extensive or intensive chemotherapy.
- Electrocardiographic (ECG) changes have been observed with ISTODAX.
- In patients with congenital long QT syndrome, a history of significant cardiovascular disease, and patients taking anti-arrhythmic medicines or medicinal products that lead to significant QT prolongation, appropriate cardiovascular monitoring precautions should be considered, such as monitoring electrolytes and ECGs at baseline and periodically during treatment.
- Ensure that potassium and magnesium are within the normal range before administration of ISTODAX.
- Tumor lysis syndrome has been reported during treatment with ISTODAX. Patients with advanced stage disease and/or high tumor burden should be closely monitored and appropriate precautions taken, and treatment should be instituted as appropriate.
- ISTODAX may cause fetal harm when administered to a pregnant woman. Advise women to avoid pregnancy while receiving ISTODAX. If this drug is used during pregnancy, or if the patient becomes pregnant while taking ISTODAX, the patient should be apprised of the potential hazard to the fetus (Pregnancy Category D).

ADVERSE REACTIONS:

Peripheral T-Cell Lymphoma
The most common Grade 3/4 adverse reactions (≥5%) regardless of causality in Study 3 (n=131) were thrombocytopenia (24%), neutropenia (20%), anemia (11%), asthenia/fatigue (8%), and leukopenia (6%), and in Study 4 (n=47) were neutropenia (47%), leukopenia (45%), thrombocytopenia (36%), anemia (28%), asthenia/fatigue (19%), pyrexia (17%), vomiting (9%), and nausea (6%).

Infections were the most common type of serious adverse event reported in Study 3 (n=131) and Study 4 (n=47). In Study 3, 25 patients (19%) experienced a serious infection, including 6 patients (5%) with serious treatment-related infections. In Study 4, 11 patients (23%) experienced a serious infection, including 8 patients (17%) with serious treatment-related infections.

The most common adverse reactions regardless of causality in Study 3 (n=131) were nausea (59%), asthenia/fatigue (55%), thrombocytopenia (41%), vomiting (39%), diarrhea (36%), and pyrexia (35%), and in Study 4 (n=47) were asthenia/fatigue (77%), nausea (75%), thrombocytopenia (72%), neutropenia (66%), anemia (62%), leukopenia (55%), pyrexia (47%), anorexia (45%), vomiting (40%), constipation (40%), and diarrhea (36%).

Cutaneous T-Cell Lymphoma
The most common Grade 3/4 adverse reactions (≥5%) regardless of causality in Study 1 (n=102) were infections (11%) and asthenia/fatigue (8%), and in Study 2 (n=83) were lymphopenia (37%), infections (33%), neutropenia (27%), leukopenia (22%), anemia (16%), asthenia/fatigue (14%), thrombocytopenia (14%), hypophosphatemia (10%), vomiting (10%), dermatitis/exfoliative dermatitis (8%), hypermagnesemia (8%), hyperuricemia (8%), hypocalcemia (6%), nausea (6%), and pruritus (6%).

Infections were the most common type of serious adverse event reported in both Study 1 (n=102) and Study 2 (n=83) with 8 patients (8%) in Study 1 and 26 patients (31%) in Study 2 experiencing a serious infection.

The most common adverse reactions regardless of causality in Study 1 (n=102) were nausea (56%), asthenia/fatigue (53%), infections (46%), vomiting (34%), and anorexia (23%) in Study 2 (n=83) were nausea (86%), asthenia/fatigue (77%), anemia (72%), thrombocytopenia (65%), ECG ST-T wave changes (63%), neutropenia (57%), lymphopenia (57%), infections (54%), anorexia (54%), vomiting (52%), hypocalcemia (52%), hyperglycemia (51%), hypoaalbuminemia (48%), leukopenia (46%), dysgeusia (40%), and constipation (39%).

DRUG INTERACTIONS:

- ISTODAX is metabolized by CYP3A4. Avoid concomitant use with strong CYP3A4 inhibitors and potent CYP3A4 inducers if possible.
- Caution should also be exercised with concomitant use of moderate CYP3A4 inhibitors and P-glycoprotein (P-gp, ABCB1) inhibitors.
- Physicians should carefully monitor prothrombin time (PT) and International Normalized Ratio (INR) in patients concurrently administered ISTODAX and warfarin sodium derivatives.

USE IN SPECIFIC POPULATIONS:

- Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from ISTODAX, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.
- Patients with moderate and severe hepatic impairment and/or patients with end-stage renal disease should be treated with caution.

Please see full Prescribing Information, including WARNINGS AND PRECAUTIONS and ADVERSE REACTIONS.
INDICATIONS

- Treatment of peripheral T-cell lymphoma (PTCL) in patients who have received at least one prior therapy
- Treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy

These indications are based on response rate. Clinical benefit such as improvement in overall survival has not been demonstrated.
ISTODAX® (romidepsin) for injection

For intravenous infusion only

The following is a brief summary only; see full prescribing information for complete product information.

1 INDICATIONS AND USAGE
ISTODAX is indicated for:
- Treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy.
- Treatment of peripheral T-cell lymphoma (PTCL) in patients who have received at least one prior therapy.

These indications are based on response rate. Clinical benefit such as improvement in overall survival has not been demonstrated.

2 DOSAGE AND ADMINISTRATION

2.1 Dosing Information

The recommended dose of romidepsin is 14 mg/m² administered intravenously over a 4-hour period on days 1, 8 and 15 of a 28-day cycle. Cycles should be repeated every 28 days provided that the patient continues to benefit from and tolerates the drug.

2.2 Dose Modification

Nonhematologic toxicities except alopecia
- Grade 2 or 3 toxicity: Treatment with romidepsin should be delayed until toxicity returns to ≤ Grade 1 or baseline, then therapy may be restarted at 14 mg/m². If Grade 3 toxicity recurs, treatment with romidepsin should be delayed until toxicity returns to ≤ Grade 1 or baseline and the dose should be permanently reduced to 10 mg/m².
- Grade 4 toxicity: Treatment with romidepsin should be delayed until toxicity returns to ≤ Grade 1 or baseline, then the dose should be permanently reduced to 10 mg/m².
- Romidepsin should be discontinued if Grade 3 or 4 toxicities recur after dose reduction.

Hematologic toxicities
- Grade 3 or 4 neutropenia or thrombocytopenia: Treatment with romidepsin should be delayed until the specific cytopenia returns to ANC ≥ 1.5×10⁹/L and/or platelet count ≥75×10⁹/L or baseline, then therapy may be restarted at 14 mg/m².
- Grade 4 febrile (≥38.5°C) neutropenia or thrombocytopenia that requires platelet transfusion: Treatment with romidepsin should be delayed until the specific cytopenia returns to ≤ Grade 1 or baseline, and then the dose should be permanently reduced to 10 mg/m².

2.3 Instructions for Preparation and Intraavenous Administration

ISTODAX should be handled in a manner consistent with recommended safe procedures for handling cytotoxic drugs.

5 WARNINGS AND PRECAUTIONS

5.1 Hematologic

Treatment with ISTODAX can cause thrombocytopenia, leukopenia (neutropenia and lymphopenia), and anemia; therefore, these hematological parameters should be monitored during treatment with ISTODAX, and the dose should be modified, as necessary [See Dosage and Administration (2.2) and Adverse Reactions (6)].

5.2 Infection

Serious and sometimes fatal infections, including pneumonia and sepsis, have been reported in clinical trials with ISTODAX. These can occur during treatment and within 30 days after treatment, and the risk of life-threatening infections may be higher in patients with a history of extensive or intensive chemotherapy [See Adverse Reactions (6)].

5.3 Electrocardiographic Changes

Several treatment-emergent morphological changes in ECGs (including T-wave and ST-segment changes) have been reported in clinical studies. The clinical significance of these changes is unknown [See Adverse Reactions (6)].

In patients with congenital long QT syndrome, patients with a history of significant cardiovascular disease, and patients taking anti-arrhythmic medicines or medicinal products that lead to significant QT prolongation, appropriate cardiovascular monitoring precautions should be considered, such as the monitoring of electrolytes and ECGs at baseline and periodically during treatment.

Potassium and magnesium should be within the normal range before administration of ISTODAX [See Adverse Reactions (6)].

5.4 Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) has been reported to occur in 1% of patients with tumor stage CTCL and 2% of patients with Stage III/IV PTCL. Patients with advanced stage disease and/or high tumor burden should be closely monitored, appropriate precautions should be taken, and treatment should be instituted as appropriate.

5.5 Use in Pregnancy

There are no adequate and well-controlled studies of ISTODAX in pregnant women. However, based on its mechanism of action and findings in animals, ISTODAX may cause fetal harm when administered to a pregnant woman. In an animal reproductive study, romidepsin was embryocidal and resulted in adverse effects on the developing fetus at exposures below those in patients at the recommended dose of 14 mg/m²/week. If this drug is used during pregnancy, or if the patient becomes pregnant while taking ISTODAX, the patient should be apprised of the potential hazard to the fetus [See Use in Specific Populations (8.1)].

6 ADVERSE REACTIONS

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.

Cutaneous T-Cell Lymphoma

The safety of ISTODAX was evaluated in 185 patients with CTCL in 2 single arm clinical studies in which patients received a starting dose of 14 mg/m². The mean duration of treatment in these studies was 5.8 months (range: <1 to 83.4 months).

Common Adverse Reactions

Table 1 summarizes the most frequent adverse reactions (>20%) regardless of causality using the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE, Version 3.0). Due to methodological differences between the studies, the AE data are presented separately for Study 1 and Study 2. Adverse reactions are ranked by their incidence in Study 1. Laboratory abnormalities commonly reported (>20%) as adverse reactions are included in Table 1.

Table 1. Adverse Reactions Occurring in ≥20% of Patients in Either CTCL Study (N=185)

<table>
<thead>
<tr>
<th>Adverse Reactions n (%)</th>
<th>Study 1 (n=102)</th>
<th>Study 2 (n=83)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse reaction</td>
<td>99 (97)</td>
<td>83 (100)</td>
</tr>
<tr>
<td>Nausea</td>
<td>57 (56)</td>
<td>71 (86)</td>
</tr>
<tr>
<td>Asthenia/Fatigue</td>
<td>54 (53)</td>
<td>64 (77)</td>
</tr>
<tr>
<td>Infections</td>
<td>47 (46)</td>
<td>45 (54)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>35 (34)</td>
<td>43 (52)</td>
</tr>
<tr>
<td>Anorexia</td>
<td>23 (23)</td>
<td>45 (54)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>22 (22)</td>
<td>23 (28)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>20 (20)</td>
<td>22 (27)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>20 (20)</td>
<td>19 (23)</td>
</tr>
<tr>
<td>Anemia</td>
<td>19 (19)</td>
<td>60 (72)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>11 (11)</td>
<td>47 (57)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>7 (7)</td>
<td>19 (23)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>7 (7)</td>
<td>26 (31)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>6 (6)</td>
<td>17 (20)</td>
</tr>
<tr>
<td>Dermatitis/Exfoliative</td>
<td>4 (4)</td>
<td>43 (52)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>4 (4)</td>
<td>38 (46)</td>
</tr>
<tr>
<td>Alanolaminotransferase</td>
<td>3 (3)</td>
<td>22 (27)</td>
</tr>
<tr>
<td>Aspartateaminotransferase</td>
<td>3 (3)</td>
<td>23 (28)</td>
</tr>
<tr>
<td>Electrocardiogram</td>
<td>2 (2)</td>
<td>42 (51)</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>2 (2)</td>
<td>17 (20)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1 (&lt;1)</td>
<td>22 (27)</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>0</td>
<td>22 (27)</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>0</td>
<td>8 (10)</td>
</tr>
<tr>
<td>Hyperuricemia</td>
<td>0</td>
<td>7 (8)</td>
</tr>
</tbody>
</table>
Serious Adverse Reactions

Infections were the most common type of SAE reported. In Study 3, 25 patients (19%) experienced a serious infection, including 6 patients (5%) with serious treatment-related infections. In Study 4, 11 patients (23%) experienced a serious infection, including 8 patients (17%) with serious treatment-related infections. Serious adverse reactions reported in ≥ 2% of patients in Study 3 were pyrexia (7%), pneumonia, sepsis, vomiting (5%), cellulitis, deep vein thrombosis, (4%), febrile neutropenia, abdominal pain (3%), chest pain, neutropenia, pulmonary embolism, dyspnea, and dehydration (2%). In Study 4, serious adverse reactions in ≥ 2% of patients were pyrexia (17%), aspartate aminotransferase increased, hypotension (13%), anemia, thrombocytopenia, alanine aminotransferase increased (11%), infection, dehydration, dyspnea (9%), lymphopenia, neutropenia, hyperbilirubinemia, hypocalcemia, hypoglycemia (6%), febrile neutropenia, leukemia, ventricular arrhythmia, vomiting, hypersensitivity, catheter related infection, hyperuricemia, hypocalcemia, syncope, pneumonitis, packed red blood cell transfusion, and platelet transfusion (4%). Deaths due to all causes within 30 days of the last dose of ISTODAX occurred in 7% of patients in Study 3 and 17% of patients in Study 4. In Study 3, there were 5 deaths unrelated to disease progression that were due to infections, including multi-organ failure/sepsis, pneumonia, septic shock, candida sepsis, and sepsis/cardiovascular shock. In Study 4, there were 3 deaths unrelated to disease progression that were due to sepsis, aspartate aminotransferase elevation in the setting of Epstein Barr virus reactivation, and death of unknown cause.

Discontinuations

Discontinuation due to an adverse event occurred in 19% of patients in Study 3 and in 28% of patients in Study 4. Discontinuation due to an adverse event occurred in ≥ 2% of patients in either study included infecion, fatigue, dyspnea, QT prolongation, and hypomagnesemia.

Peripheral T-Cell Lymphoma

The safety of ISTODAX was evaluated in 178 patients with PTCL in a sponsor-conducted pivotal study (Study 3) and a secondary NCI-sponsored study (Study 4) in which patients received a starting dose of 14 mg/m². The mean duration of treatment and number of cycles in these studies were 5.6 months and 6 cycles.

Common Adverse Reactions

Table 2 summarizes the most frequent adverse reactions (≥ 10%) regardless of causality, using the NCI-CTCAE, Version 3.0. The AE data are presented separately for Study 3 and Study 4. Laboratory abnormalities commonly reported (≥ 10%) as adverse reactions are included in Table 2.

Table 2. Adverse Reactions Occurring in ≥ 10% of Patients with PTCL in Study 3 and Corresponding Incidence in Study 4 (N=178)

<table>
<thead>
<tr>
<th>Adverse Reactions n (%)</th>
<th>Study 3 (N=131)</th>
<th>Study 4 (N=47)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>Grade 3 or 4</td>
<td>All Grade 3 or 4</td>
</tr>
<tr>
<td>Any adverse reactions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>77 (59)</td>
<td>35 (75)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>51 (39)</td>
<td>19 (40)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>47 (36)</td>
<td>17 (36)</td>
</tr>
<tr>
<td>Constipation</td>
<td>39 (30)</td>
<td>19 (40)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>18 (14)</td>
<td>6 (13)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>13 (10)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenia/Fatigue</td>
<td>72 (55)</td>
<td>36 (77)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>46 (35)</td>
<td>22 (47)</td>
</tr>
<tr>
<td>Chills</td>
<td>14 (11)</td>
<td>8 (17)</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>13 (10)</td>
<td>3 (6)</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>53 (41)</td>
<td>34 (72)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>39 (30)</td>
<td>31 (66)</td>
</tr>
<tr>
<td>Anemia</td>
<td>32 (24)</td>
<td>29 (62)</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>16 (12)</td>
<td>26 (55)</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia</td>
<td>37 (28)</td>
<td>21 (45)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>14 (11)</td>
<td>8 (17)</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypotension</td>
<td>27 (21)</td>
<td>13 (28)</td>
</tr>
<tr>
<td>Headache</td>
<td>19 (15)</td>
<td>16 (34)</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>23 (18)</td>
<td>10 (21)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>17 (13)</td>
<td>10 (21)</td>
</tr>
<tr>
<td>Investigations</td>
<td>13 (10)</td>
<td>7 (15)</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>13 (10)</td>
<td>0</td>
</tr>
</tbody>
</table>

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D [See Warnings and Precautions (5.5)].

There are no adequate and well-controlled studies of ISTODAX in pregnant women. However, based on its mechanism of action and findings in animals, ISTODAX may cause fetal harm when administered to a pregnant woman.

ISTODAX may cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of ISTODAX in pregnant women. However, based on its mechanism of action and findings in animals, ISTODAX may cause fetal harm when administered to a pregnant woman. ISTODAX is classified as Pregnancy Category D [See Warnings and Precautions (5.5)].

ISTODAX is administered intravenously to rats during the period of organogenesis at doses of 0.1, 0.2, or 0.5 mg/kg/day. Substantial resorption or post-implantation loss was observed at the high-dose of 0.5 mg/kg/day, a maternally toxic dose. Adverse embryo-fetal effects were noted at rodent doses of ≥0.1 mg/kg/day, with systemic exposures...
the recommended dose of 14 mg/m²/dose. Maturation arrest of ovarian follicles and decreased weight of ovaries were observed in a separate study in rats, atrophy was seen in the ovary, uterus, vagina and mammary gland of females administered doses as low as 0.1 mg/kg/dose (0.6 mg/m²/dose) following the clinical dosing schedule. This dose resulted in AUC₀–∞ values that were 0.3% of those in patients receiving the recommended dose of 14 mg/m²/dose. A similar effect was seen in mice after 4 weeks of drug administration at higher doses. Seminal vesicle and prostate organ weights were decreased in a separate study in rats after 4 weeks of daily drug administration at 0.1 mg/kg/day (0.6 mg/m²/day), approximately 30% the estimated human daily dose based on body surface area. Romidepsin was not clastogenic in an in vitro in the bacterial reverse mutation assay (Ames test) or the mouse lymphoma assay. Romidepsin was not mutagenic in vitro in the bacterial reverse mutation assay. Romidepsin was not mutagenic in vitro in the bacterial reverse mutation assay.

10 OVERDOSAGE
No specific information is available on the treatment of overdosage of ISTODAX.

Toxicities in a single-dose study in rats or dogs, at intravenous romidepsin doses up to 2.2 fold the recommended human dose based on the body surface area, included irregular respiration, irregular heart beat, staggering gait, tremor, and tonic convulsions. In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., clinical monitoring and supportive therapy, if required. There is no known antidote for ISTODAX and it is not known if ISTODAX is dialyzable.

11 PATIENT COUNSELING INFORMATION

11.1 Instructions
- Nausea and Vomiting
  Nausea and vomiting are common following treatment with ISTODAX. Prophylactic antiemetics are recommended to be used in all patients. Patients should be instructed to report fever, cough, shortness of breath with or without chest pain, burning on urination, flu-like symptoms, muscle aches, or worsening skin problems.

- Infections
  Patients should be informed that infections may occur during treatment with ISTODAX. Patients should be instructed to report fever, cough, shortness of breath with or without chest pain, burning on urination, flu-like symptoms, muscle aches, or worsening skin problems.

- Tumor Lysis Syndrome
  Patients at risk of tumor lysis syndrome (i.e., those with advanced stage disease and/or high tumor burden) should be monitored closely for TLS and appropriate measures taken if symptoms are observed.

- Use in Pregnancy
  If pregnancy occurs during treatment with ISTODAX, female patients should be advised to seek immediate medical advice and counseling.

- Patients should be instructed to read the patient insert carefully.

Manufactured for:
Celgene Corporation
Summit, NJ 07901

Manufactured by:
Ben Venue Laboratories, Inc.
Bedford, OH 44146

17 PATIENT COUNSELING INFORMATION

See FDA-approved patient labeling.

17.1 Instructions
- Nausea and Vomiting
  Nausea and vomiting are common following treatment with ISTODAX. Prophylactic antiemetics are recommended to be used in all patients.
  Patients should be instructed to report fever, cough, shortness of breath with or without chest pain, burning on urination, flu-like symptoms, muscle aches, or worsening skin problems.

- Infections
  Patients should be informed that infections may occur during treatment with ISTODAX. Patients should be instructed to report fever, cough, shortness of breath with or without chest pain, burning on urination, flu-like symptoms, muscle aches, or worsening skin problems.

- Tumor Lysis Syndrome
  Patients at risk of tumor lysis syndrome (i.e., those with advanced stage disease and/or high tumor burden) should be monitored closely for TLS and appropriate measures taken if symptoms are observed.

- Use in Pregnancy
  If pregnancy occurs during treatment with ISTODAX, female patients should be advised to seek immediate medical advice and counseling.

- Patients should be instructed to read the patient insert carefully.

Manufactured for:
Celgene Corporation
Summit, NJ 07901

Manufactured by:
Ben Venue Laboratories, Inc.
Bedford, OH 44146

ISTODAX® is a registered trademark of Celgene Corporation
U.S. Patents: 4,977,138; 7,608,280; 7,611,724
ISTBVPI.1003/PP1.003 09/11
TRTH is being made possible by a generous unrestricted educational grant from the Wallace H. Coulter Foundation.

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**FOR ADULT PATIENTS NEWLY DIAGNOSED WITH Ph+ CML IN CHRONIC PHASE (CP)**

Choose TASIGNA first

TASIGNA provides superior MMR* rates vs imatinib at 12 months and <1% progression to AP/BC†

(44% [95% CI, 38%-50%] vs 22% [95% CI, 18%-28%], P<0.0001)†

*Major molecular response (MMR)=≥3 logs below baseline [≤0.1% international scale [IS]].

†Progression to accelerated phase or blast crisis (AP/BC) includes patients with clonal evolution and CML-related death.

**INDICATION AND BOXED WARNING**

TASIGNA (nilotinib) is indicated for the treatment of adult patients with newly diagnosed Philadelphia chromosome positive chronic myeloid leukemia (Ph+ CML) in chronic phase. The effectiveness of TASIGNA is based on major molecular response and cytogenetic response rates. The study is ongoing and further data will be required to determine long-term outcome.

**WARNING: QT PROLONGATION AND SUDDEN DEATHS**

- TASIGNA prolongs the QT interval. Prior to TASIGNA administration and periodically, monitor for hypokalemia or hypomagnesemia and correct deficiencies. Obtain ECGs to monitor the QTc at baseline, 7 days after initiation, and periodically thereafter, and follow any dose adjustments.
- Sudden deaths have been reported in patients receiving nilotinib. Do not administer TASIGNA to patients with hypokalemia, hypomagnesemia, or long QT syndrome.
- Avoid use of concomitant drugs known to prolong the QT interval and strong CYP3A4 inhibitors.
- Patients should avoid food 2 hours before and 1 hour after taking dose.

Please see Important Safety Information, including Boxed WARNING, and brief summary of Prescribing Information on the following pages.
IN THE TREATMENT OF ADULT PATIENTS NEWLY DIAGNOSED WITH Ph+ CML-CP
Less than 1% of TASIGNA patients progressed to AP/BC¹

Progression to AP/BC at 24 months

2
vs
17

0.7%
TASIGNA 300 mg bid (n=282)

6%
Imatinib 400 mg qd (n=283)

- TASIGNA significantly improved the rate of MMR compared with imatinib at 12 months—the primary end point of the ENESTnd trial (44% [95% CI, 38%-50%] vs 22% [95% CI, 18%-28%], P<0.0001)¹

ENESTnd study design: A randomized, controlled, open-label, multicenter Phase III trial of 866 patients with newly diagnosed Ph+ CML-CP. Patients were randomized to receive either TASIGNA 400 mg bid (n=281), TASIGNA 300 mg bid (n=282), or imatinib 400 mg qd (n=283). The daily dose of imatinib could be escalated to 800 mg (400 mg bid), but no dose escalation was permitted with TASIGNA. A centralized laboratory was used for RQ-PCR testing. The primary end point was MMR at 12 months.¹²

IMPORTANT SAFETY INFORMATION

- Treatment with TASIGNA can cause Grade 3/4 thrombocytopenia, neutropenia, and anemia. Complete blood counts should be performed every 2 weeks for the first 2 months and then monthly thereafter
- Caution is recommended in patients with a history of pancreatitis
- The use of TASIGNA may result in elevations in bilirubin, AST/ALT, and alkaline phosphatase
- TASIGNA can cause hypophosphatemia, hypokalemia, hyperkalemia, hypocalcemia, and hyponatremia (see Boxed WARNING)
- The concomitant use of strong CYP3A4 inhibitors or anti-arrhythmic drugs [including, but not limited to, amiodarone, disopyramide, procainamide, quinidine, and sotalol] and other drugs that may prolong the QT interval [including, but not limited to, chloroquine, clarithromycin, haloperidol, methadone, moxifloxacin, and pimozide] should be avoided. Grapefruit products should also be avoided
- The concomitant use of strong CYP3A4 inducers should be avoided [including, but not limited to, dexamethasone, phenytoin, carbamazepine, rifampin, rifabutin, rifapentin, phenobarbital, and St. John’s wort]
- TASIGNA must not be taken with food
- TASIGNA exposure is increased in patients with impaired hepatic function

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080
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3/12
AM7-1033710
TASIGNA maintained the difference in MMR rates through 24 months\(^1,2\)

- At 12 months
  - TASIGNA 300 mg bid (n=282)
  - 44% (95% CI, 38%-50%) (P<0.0001)
  - Imatinib 400 mg qd (n=283)
  - 22% (95% CI, 18%-28%)
  - Δ22%

- At 24 months
  - TASIGNA 300 mg bid (n=282)
  - 62% (95% CI, 56%-67%)
  - Imatinib 400 mg qd (n=283)
  - 38% (95% CI, 32%-43%)
  - Δ26%

- In newly diagnosed Ph+ CML-chronic phase, the most commonly reported nonhematologic adverse drug reactions (>10%) were rash, pruritus, headache, nausea, fatigue, and myalgia.
- TASIGNA may need to be temporarily withheld and/or dose reduced for QT prolongation, hematologic toxicities that are not related to underlying leukemia, clinically significant moderate or severe nonhematologic toxicities, laboratory abnormalities, or concomitant use of strong CYP3A4 inhibitors.

Cases of tumor lysis syndrome have been reported in TASIGNA-treated patients with resistant or intolerant CML. Due to potential for tumor lysis syndrome, maintain adequate hydration and correct uric acid levels prior to initiating therapy with TASIGNA.

The exposure of TASIGNA is reduced in patients with total gastrectomy.

Since the capsules contain lactose, TASIGNA is not recommended for patients with rare hereditary problems of galactose intolerance, severe lactase deficiency with a severe degree of intolerance to lactose-containing products, or of glucose-galactose malabsorption.

Women of childbearing potential should avoid becoming pregnant while taking TASIGNA and should be advised of the potential hazard to the fetus if they do. The safety and effectiveness of TASIGNA in pediatric patients have not been established.

References:
1. TASIGNA (nilotinib) capsules prescribing information. East Hanover, NJ: Novartis Pharmaceuticals Corporation; November 2011.

Please see Important Safety Information, including Boxed WARNING, and brief summary of Prescribing Information on adjacent pages.
**WARNINGS AND PRECAUTIONS**

5.7 Drug Interactions

The administration of Tasigna with agents that are strong CYP34A inhibitors or anti-arrhythmic drugs (including, but not limited to amiodarone, disopyramide, procainamide, quinidine and sotalol) and other drugs that may prolong QT interval (including, but not limited to chloroquine, clarithromycin, haloperidol, methadone, moxifloxacin and pimozide) should be avoided.

5.8 Food Effects

The bioavailability of nilotinib is increased with food. Tasigna must not be taken with food. No food should be taken at least 2 hours before and at least one hour after the dose is taken. Grapefruit products and other foods that are known to inhibit CYP34A should be avoided. [see Boxed Warning, Drug Interactions (7.2) and Clinical Pharmacology (12.3) in the full prescribing information].

5.9 Hepatic Impairment

Nilotinib exposure is increased in patients with impaired hepatic function. A lower starting dose is recommended for patients with mild to severe hepatic impairment (at baseline) and QT interval should be monitored closely [see Dosage and Administration (2.2) and Use in Specific Populations (8.7) in the full prescribing information].

5.10 Tumor Lysis Syndrome

Cases of tumor lysis syndrome have been reported in Tasigna treated patients with resistant or intolerant CML. Malignant disease progression, high WBC counts and/or dehydration were present in the majority of these cases. Due to potential for tumor lysis syndrome, maintain adequate hydration and correct uric acid levels prior to initiating therapy with Tasigna.

5.11 Total Gastrectomy

The exposure of nilotinib is reduced in patients with total gastrectomy. More frequent follow-up of these patients should be considered. Dose increase or alternative therapy may be considered in patients with total gastrectomy [see Clinical Pharmacology (12.3) in the full prescribing information].

5.12 Lactose

Since the capsules contain lactose, Tasigna is not recommended for patients with rare hereditary problems of galactose intolerance, severe lactase deficiency with a severe degree of intolerance to lactose-containing products or of glucose-galactose malabsorption.

5.13 Monitoring Laboratory Tests

Complete blood counts should be performed every two weeks for the first two months and then monthly thereafter. Chemistry panels, including the lipid profile, should be checked periodically. ECGs should be obtained at baseline, seven days after initiation and periodically thereafter, as well as following dose adjustments [see Warnings and Precautions (5.7, 5.8)]. Laborator y monitoring for patients receiving Tasigna may need to be performed more or less frequently at the physician’s discretion.

5.14 Use in Pregnancy

There are no adequate and well controlled studies of Tasigna in pregnant women. However, Tasigna may cause fetal harm when administered to a pregnant woman. Nilotinib caused embryo-fetal toxicities in animals at maternal exposures that were lower than the expected human exposure at the recommended doses of nilotinib. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of child-bearing potential should avoid becoming pregnant while taking Tasigna [see Use in Specific Populations (8.1) in the full prescribing information].

5.4 Elevated Serum Lipase

The use of Tasigna can cause increases in serum lipase. Caution is recommended in patients with a previous history of pancreatitis. If lipase elevations are accompanied by abdominal symptoms, interrupt dosing and consider appropriate diagnostics to exclude pancreatitis. Test serum lipase levels monthly or as clinically indicated.

5.5 Hepatotoxicity

The use of Tasigna may result in elevations in bilirubin, AST/ALT, and alkaline phosphatase. Hepatic function tests should be checked monthly or as clinically indicated [see Warnings and Precautions (5.12)].
6 ADVERSE REACTIONS

The following serious adverse reactions can occur with Tasigna and are discussed in greater detail in other sections of the package insert [see Boxed Warning, Warnings and Precautions (5)].

Myelosuppression [see Warnings and Precautions (5.1)]

QT prolongation [see Boxed Warning, Warnings and Precautions (5.2)]

Sudden deaths [see Boxed Warning, Warnings and Precautions (5.3)]

Elevated serum lipase [see Warnings and Precautions (5.4)]

Hepatotoxicity [see Warnings and Precautions (5.5)]

Electrolyte abnormalities [see Boxed Warning, Warnings and Precautions (5.6)]

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.

Newly diagnosed Ph+ CML-CP

The data below reflect exposure to Tasigna from a randomized trial in newly diagnosed patients with Ph+ CML in chronic phase treated at the recommended dose of 300 mg twice daily (n=279). The median time on treatment in the nilotinib 300 mg twice daily group was 25 months (range 0.1 – 35.4 months).

The median actual dose intensity was 594 mg/day in the nilotinib 300 mg twice daily group.

The most common (>10%) non-hematologic adverse drug reactions were rash, pruritus, headache, nausea, fatigue and myalgia. Upper abdominal pain, alopecia, constipation, diarrhea, dry skin, muscle spasms, arthralgia, abdominal pain, peripheral edema, vomiting and anemia were observed less commonly (<10% and >5%) and have been of mild to moderate severity, manageable and generally did not require dose reduction. Pleural and pericardial effusions occurred in 1% of patients. Gastrointestinal hemorrhage was reported in 2.5% of patients.

Increase in QTcF >60 msec from baseline was observed in 4 patients (<1%) [see Boxed Warning, Warnings and Precautions (5)].

Increase in QTcF >500 msec while on study drug.

In patients with CML-AP, the most commonly reported non-hematologic adverse drug reactions (all grades) were myelosuppression including: thrombocytopenia (17%), neutropenia (15%) and anemia (7%). See Table 7 for Grade 3/4 laboratory abnormalities.

The median cumulative exposure in days for CML-CP and CML-AP patients is 561 (range 1-1096) and 264 (range 2-1160), respectively. The median actual dose intensity for patients with CML-CP and CML-AP is 789 mg/day (range 1-1096) and 264 (range 2-1160), respectively. The median time on treatment in the nilotinib 300 mg twice daily group was 25 months (range 0.1 – 35.4 months).

The median duration of exposure in days for CML-CP and CML-AP patients is 561 (range 1-1096) and 264 (range 2-1160), respectively. The median actual dose intensity for patients with CML-CP and CML-AP is 789 mg/day (range 151-1110) and 780 mg/day (range 150-1149), respectively and corresponded to the planned 400 mg twice daily dosing.

The median cumulative exposure in days for dose interruptions for the CML-CP patients was 20 (range 1-345), and the median duration in days of dose interruptions for the CML-AP patients was 23 (range 1-234).

In patients with CML-CP, the most commonly reported non-hematologic adverse drug reactions (≥10%) were rash, pruritus, nausea, fatigue, headache, constipation, diarrhea, vomiting and myalgia. The common serious drug-related adverse reactions (≥1% and <10%) were thrombocytopenia, neutropenia and anemia.

In patients with CML-AP, the most commonly reported non-hematologic adverse drug reactions (≥10%) were rash, pruritus and fatigue. The common serious adverse drug reactions (<1% and <10%) were thrombocytopenia, neutropenia, febrile neutropenia, pneumonia, leukopenia, intracranial hemorrhage, elevated lipase and pyrexia.

Sudden deaths and QT prolongation were reported. The maximum mean QTcF change from baseline at steady-state was 10 msec. Increase in QTcF >60 msec from baseline was observed in 4.1% of the patients and QTcF >500 msec was observed in 4 patients (<1%) [see Boxed Warning, Warnings and Precautions (5.2, 5.3), Clinical Pharmacology (12.4) in the full prescribing information].

Discontinuation due to drug-related adverse reactions was observed in 16% of CML-CP and 10% of CML-AP patients.

6.2 Clinical Trials Experiences

Resistant or intolerant Ph+ CML-CP and CML-AP

In the single open-label multicenter clinical trial, a total of 458 patients with Ph+ CML-CP and CML-AP resistant to or intolerant to at least one prior therapy including imatinib were treated (CML-CP:321, CML-AP:137) at the recommended dose of 400 mg twice daily.

Most Frequently Reported Adverse Reactions in Patients with Resistant or Intolerant Ph+ CML-CP (≥10% in any Group)a

<table>
<thead>
<tr>
<th>Patients with Newly Diagnosed Ph+ CML-CP</th>
<th>N=279</th>
<th>N=280</th>
<th>N=279</th>
<th>N=280</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body System and Preferred Term</strong></td>
<td>All Grades (%)</td>
<td>CTC Grades 3 / 4 (%)</td>
<td>All Grades (%)</td>
<td>CTC Grades 3 / 4 (%)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash 37</td>
<td>18 &lt;1 2</td>
<td>Pruritus 20</td>
<td>7 &lt;1 0</td>
</tr>
<tr>
<td></td>
<td>Alopecia 11</td>
<td>6 0 0</td>
<td>Periorbital edema &lt;1</td>
<td>15 0 0</td>
</tr>
<tr>
<td>Gastro-intestinal disorders</td>
<td>Nausea 20</td>
<td>39 1 1</td>
<td>Constipation 17</td>
<td>6 0 0</td>
</tr>
<tr>
<td></td>
<td>Diarrhea 14</td>
<td>40 &lt;1 2</td>
<td>Vomiting 11</td>
<td>24 &lt;1 0</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain upper Abdominal pain 15</td>
<td>11 &lt;1 1</td>
<td>14</td>
<td>10 1 0</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headache 30</td>
<td>18 3 &lt;1</td>
<td>21</td>
<td>16 1 1</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>Fatigue 11</td>
<td>10 &lt;1 0</td>
<td>Pyrexia 11</td>
<td>12 &lt;1 0</td>
</tr>
<tr>
<td></td>
<td>Azthenna 11</td>
<td>10 &lt;1 0</td>
<td>Abdominal edema, peripheral Face edema &lt;1</td>
<td>11 0 &lt;1</td>
</tr>
<tr>
<td>Musculo-skeletal and connective tissue disorders</td>
<td>Myalgia 14</td>
<td>18 &lt;1 0</td>
<td>Arthralgia 17</td>
<td>13 &lt;1 1</td>
</tr>
<tr>
<td></td>
<td>Muscle spasms 11</td>
<td>31 0 &lt;1</td>
<td>Pain in extremity 11</td>
<td>13 &lt;1 1</td>
</tr>
<tr>
<td></td>
<td>Back pain 14</td>
<td>11 &lt;1 1</td>
<td>14</td>
<td>11 &lt;1 1</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Cough 14</td>
<td>9 0 0</td>
<td>14</td>
<td>9 0 0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Nasopharyngitis 22</td>
<td>17 0 0</td>
<td>Upper respiratory tract infection 14</td>
<td>10 &lt;1 0</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Eyelid edema 1</td>
<td>16 0 &lt;1</td>
<td>14</td>
<td>11 0 &lt;1</td>
</tr>
</tbody>
</table>

aExcluding laboratory abnormalities

*NCI Common Terminology Criteria for Adverse Events, Version 3.0

Table 6: Most Frequently Reported Non-hematologic Adverse Reactions in Patients with Resistant or Intolerant Ph+ CML-CP (≥10% in any Group)a

<table>
<thead>
<tr>
<th>Body System and Preferred Term</th>
<th>All Grades (%)</th>
<th>CTC Grades 3 / 4 (%)</th>
<th>All Grades (%)</th>
<th>CTC Grades 3 / 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Rash 36</td>
<td>2 29 0</td>
<td>Pruritus 32</td>
<td>1 20 0</td>
</tr>
<tr>
<td></td>
<td>Night sweat 12</td>
<td>1 27 0</td>
<td>Alopecia 11</td>
<td>0 12 0</td>
</tr>
</tbody>
</table>

(continued)
### Table 6: Most Frequently Reported Non-hematologic Adverse Reactions in Patients with Resistant or Intolerant Ph+ CML Receiving Tasigna 400 mg Twice Daily (Regardless of Relationship to Study Drug) (≥10% in any Group)*

<table>
<thead>
<tr>
<th>Body System and Preferred Term</th>
<th>CML-CP</th>
<th>CML-AP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>37%</td>
<td>22%</td>
</tr>
<tr>
<td>Constipation</td>
<td>28%</td>
<td>19%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>28%</td>
<td>24%</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>29%</td>
<td>13%</td>
</tr>
<tr>
<td>Abdominal pain upper</td>
<td>15%</td>
<td>16%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>14%</td>
<td>12%</td>
</tr>
<tr>
<td>Back pain</td>
<td>10%</td>
<td>4%</td>
</tr>
<tr>
<td>General disorders and site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>35%</td>
<td>20%</td>
</tr>
<tr>
<td>General disorders and site</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone pain</td>
<td>17%</td>
<td>15%</td>
</tr>
<tr>
<td>Muscle, skeletal and connective tissue disorders</td>
<td>16%</td>
<td>12%</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>26%</td>
<td>16%</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>13%</td>
<td>15%</td>
</tr>
<tr>
<td>Bone pain</td>
<td>14%</td>
<td>15%</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>20%</td>
<td>18%</td>
</tr>
<tr>
<td>Back pain</td>
<td>17%</td>
<td>15%</td>
</tr>
<tr>
<td>Muscle-skeletal pain</td>
<td>11%</td>
<td>12%</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>27%</td>
<td>18%</td>
</tr>
<tr>
<td>Cough</td>
<td>15%</td>
<td>9%</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>11%</td>
<td>7%</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>24%</td>
<td>15%</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>12%</td>
<td>10%</td>
</tr>
<tr>
<td>Metabolism and nutritional disorders</td>
<td>12%</td>
<td>15%</td>
</tr>
<tr>
<td>Anorexia</td>
<td>12%</td>
<td>15%</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>12%</td>
<td>7%</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>10%</td>
<td>11%</td>
</tr>
</tbody>
</table>

* Excluding laboratory abnormalities
*NCTI Common Terminology Criteria for Adverse Events, version 3.0

### Table 7: Percent Incidence of Clinically Relevant Grade 3/4* Laboratory Abnormalities

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>Newley Diagnosed Ph+ CML-CP</th>
<th>Resistant or Intolerant Ph+</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=279</td>
<td>N=280</td>
</tr>
<tr>
<td>TASIGNA 300 mg</td>
<td>Imatinib 400 mg</td>
<td>TASIGNA 400 mg</td>
</tr>
<tr>
<td>Twice daily</td>
<td>Once daily</td>
<td>Twice daily</td>
</tr>
<tr>
<td>(%)</td>
<td>(%)</td>
<td>(%)</td>
</tr>
<tr>
<td>Biochemistry Parameters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated lipase</td>
<td>7%</td>
<td>3%</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>6%</td>
<td>0%</td>
</tr>
<tr>
<td>Hypophosphatemia</td>
<td>5%</td>
<td>8%</td>
</tr>
<tr>
<td>Elevated bilirubin (total)</td>
<td>4%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Elevated SGPT (ALT)</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>&lt;1%</td>
<td>2%</td>
</tr>
<tr>
<td>Elevated SGOT (AST)</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Decreased albumin</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Hypocalcemia</td>
<td>&lt;1%</td>
<td>0%</td>
</tr>
<tr>
<td>Elevated alkaline phosphatase</td>
<td>0%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Elevated creatinine</td>
<td>0%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

* Excluding laboratory abnormalities
*NCTI Common Terminology Criteria for Adverse Events, version 3.0

6.2 Additional Data from Clinical Trials

The following adverse drug reactions were reported in patients in the Tasigna clinical studies at the recommended doses. These adverse drug reactions are ranked under a heading of frequency, the most frequent first using the following convention: common (≥1% and <10%), uncommon (≥0.1% and <1%), and unknown frequency (single events). For adverse drug reactions listed under “Investigations”, very common events (≥10%), which were not included in Tables 5 and 6, are also reported. These adverse reactions are included based on clinical relevance and ranked in order of decreasing seriousness within each category.

### Laboratory Abnormalities

Table 7 shows the percentage of patients experiencing treatment-emergent Grade 3/4 laboratory abnormalities in patients who received at least one dose of Tasigna.

<table>
<thead>
<tr>
<th>Hematologic Parameters</th>
<th>Newley Diagnosed Ph+ CML-CP</th>
<th>Resistant or Intolerant Ph+</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=279</td>
<td>N=280</td>
</tr>
<tr>
<td>TASIGNA 300 mg</td>
<td>Imatinib 400 mg</td>
<td>TASIGNA 400 mg</td>
</tr>
<tr>
<td>Twice daily</td>
<td>Once daily</td>
<td>Twice daily</td>
</tr>
<tr>
<td>(%)</td>
<td>(%)</td>
<td>(%)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>10%</td>
<td>9%</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>12%</td>
<td>21%</td>
</tr>
<tr>
<td>Anemia</td>
<td>4%</td>
<td>5%</td>
</tr>
</tbody>
</table>

* Excluding laboratory abnormalities
*NCTI Common Terminology Criteria for Adverse Events, version 3.0

Eye Disorders: Common: eye hemorrhage, peribulbar edema, eye pruritus, conjunctivitis, dry eye. Uncommon: vision impairment, vision blurred, visual acuity reduced, photopsia, hyperemia (scleral, conjunctival, ocular), eye irritation. Unknown frequency: papilloedema, diplopia, photophobia, eye swelling, blepharitis, eye pain, choristomatous, conjunctival hemorrhage, conjunctivitis allergic, ocular surface disease.
Ear and Labyrinth Disorders: Common: vertigo. Unknown frequency: hearing impaired, ear pain, tinnitus.

Cardiac Disorders: Common: angina pectoris, arrhythmia (including atrioventricular block, cardiac flutter, extrasystoles, atrial fibrillation, tachycardia, bradycardia), palpitations, electrocardiogram QT prolonged. Uncommon: cardiac failure, pericardial effusion, coronary artery disease, cyanosis, cardiac murmur. Unknown frequency: myocardial infarction, ventricular dysfunction, pericarditis, ejection fraction decrease.


Skin and Subcutaneous Tissue Disorders: Common: night sweats, eczema, urticaria, erythema, hyperhidrosis, contusion, acne, dermatitis (including allergic and acneiform), dry skin. Uncommon: exfoliative rash, drug eruption, pain of skin, ecchymosis, swelling of face. Unknown frequency: erythema multiforme, erythema nodosum, skin ulcer, palmar-plantar erythrodysesthesia syndrome, petechiae, photosensitivity, blister, dermal cyst, sebaceous hyperplasia, skin atrophy, skin discoloration, skin exfoliation, skin hyperpigmentation, skin hypertrophy.


General Disorders and Administration Site Conditions: Common: pyrexia, chest pain (including non-cardiac chest pain), pain (including neck pain and back pain), chest discomfort, malaise. Uncommon: face edema, gravitational edema, influenza-like illness, chills, feeling body temperature change (including feeling hot, feeling cold). Unknown frequency: localized edema.

Investigations: Common: hemoglobin decreased, blood amylase increased, gamma-glutamyltransferase increased, blood creatinine phosphokinase increased, blood alkaline phosphatase increased, weight decreased, weight increased. Uncommon: blood lactate dehydrogenase increased, blood urea increased. Unknown frequency: troponin increased, blood bilirubin unconjugated increased, blood insulin increased, lipoprotein increased (including very low density and high density), blood parathyroid hormone increased.

10 OVERDOSAGE
Overdose with nilotinib has been reported, where an unspecified number of Tasigna capsules were ingested in combination with alcohol and other drugs. Events included neutropenia, vomiting, and drowsiness. In the event of overdose, the patient should be observed and appropriate supportive treatment given.

Manufactured by: Novartis Pharma Stein AG
Stein, Switzerland
Distributed by: Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936
(C) Novartis
T2011-126
November 2011
Important Safety Information

BOXED WARNING
Progressive multifocal leukoencephalopathy (PML): JC virus infection resulting in PML and death can occur in patients receiving ADCETRIS™ (brentuximab vedotin).

Contraindication:
Concomitant use of ADCETRIS and bleomycin is contraindicated due to pulmonary toxicity.

Warnings and Precautions:

- Peripheral neuropathy: ADCETRIS treatment causes a peripheral neuropathy that is predominantly sensory. Cases of peripheral motor neuropathy have also been reported. ADCETRIS-induced peripheral neuropathy is cumulative. Treating physicians should monitor patients for symptoms of neuropathy, such as hypoesthesia, hyperesthesia, paresthesia, discomfort, a burning sensation, neuropathic pain or weakness and institute dose modifications accordingly.

- Infusion reactions: Infusion-related reactions, including anaphylaxis, have occurred with ADCETRIS. Monitor patients during infusion. If an infusion reaction occurs, the infusion should be interrupted and appropriate medical management instituted. If anaphylaxis occurs, the infusion should be immediately and permanently discontinued and appropriate medical management instituted.

- Neutropenia: Monitor complete blood counts prior to each dose of ADCETRIS and consider more frequent monitoring for patients with Grade 3 or 4 neutropenia. If Grade 3 or 4 neutropenia develops, manage by dose delays, reductions or discontinuation. Prolonged (>1 week) severe neutropenia can occur with ADCETRIS.

- Tumor lysis syndrome: Patients with rapidly proliferating tumor and high tumor burden are at risk of tumor lysis syndrome and these patients should be monitored closely and appropriate measures taken.
Indicated for the treatment of:

- **Hodgkin lymphoma (HL)** after failure of autologous stem cell transplant (ASCT)\(^1\)
- **HL** in patients who are not ASCT candidates after failure of at least 2 multiagent chemotherapy regimens\(^1\)

**HL: 73%** objective response rate (ORR) \((95\% \text{ CI: 65\%-83\%)})\(^1\)

<table>
<thead>
<tr>
<th></th>
<th>Complete Remission</th>
<th>Partial Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>32%</strong></td>
<td>(95% CI: 23%-42%)(^1)</td>
<td><strong>40%</strong></td>
</tr>
</tbody>
</table>

\(N = 102, 15-77\) years (median: 31 years)\(^1\)

- **Systemic anaplastic large cell lymphoma (sALCL)** after failure of at least 1 multiagent chemotherapy regimen\(^1\)

**sALCL: 86\% ORR (95\% CI: 77\%-95\%)\(^1\)

<table>
<thead>
<tr>
<th></th>
<th>Complete Remission</th>
<th>Partial Remission</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>57%</strong></td>
<td>(95% CI: 44%-70%)(^1)</td>
<td><strong>29%</strong></td>
</tr>
</tbody>
</table>

\(N = 58, 14-76\) years (median: 52 years)\(^1\)

The indications for ADCETRIS™ (brentuximab vedotin) are based on response rate. There are no data available demonstrating improvement in patient-reported outcomes or survival with ADCETRIS.\(^1\)

**Important Safety Information (continued)**

- **Progressive multifocal leukoencephalopathy (PML):** JC virus infection resulting in PML and death has been reported in ADCETRIS™ (brentuximab vedotin)-treated patients. In addition to ADCETRIS therapy, other possible contributory factors include prior therapies and underlying disease that may cause immunosuppression. Consider the diagnosis of PML in any patient presenting with new-onset signs and symptoms of central nervous system abnormalities. Evaluation of PML includes, but is not limited to, consultation with a neurologist, brain MRI, and lumbar puncture or brain biopsy. Hold ADCETRIS if PML is suspected and discontinue ADCETRIS if PML is confirmed.

- **Stevens-Johnson syndrome:** Stevens-Johnson syndrome has been reported with ADCETRIS. If Stevens-Johnson syndrome occurs, discontinue ADCETRIS and administer appropriate medical therapy.

- **Use in pregnancy:** Fetal harm can occur. Pregnant women should be advised of the potential hazard to the fetus.

**Adverse Reactions:** ADCETRIS was studied as monotherapy in 160 patients in two phase 2 trials. Across both trials, the most common adverse reactions (≥20%), regardless of causality, were neutropenia, peripheral sensory neuropathy, fatigue, nausea, anemia, upper respiratory tract infection, diarrhea, pyrexia, rash, thrombocytopenia, cough and vomiting.

**Drug Interactions:** Patients who are receiving strong CYP3A4 inhibitors concomitantly with ADCETRIS should be closely monitored for adverse reactions.
ADCEITRIS (brentuximab vedotin) is indicated for treatment of patients with Hodgkin lymphoma (HL) or systemic anaplastic large cell lymphoma (sALCL). ACDEITRIS was studied in 58 patients with sALCL in a single arm clinical trial in which the recommended starting dose was 1.8 mg/kg intravenously every 3 weeks. Median duration of treatment was 24 weeks (range, 3 to 56 weeks). The most common adverse reactions (≥20%), regardless of causality, were neutropenia, anemia, peripheral sensory neuropathy, fatigue, nausea, pyrexia, rash, diarrhea, and pain. The most common serious adverse reactions experienced by patients with sALCL were septic shock (3%), supraventricular arrhythmia (3%), pain in extremity (3%), and urinary tract infection (3%).

**Drug interactions**

In vitro data indicate that monomethyl auristatin E (MMAE) is a substrate and an inhibitor of CYP34A4/5.

**Effect of other drugs on ADCEITRIS**

CYP34A4 Inhibitors/Inducers: MMAE is primarily metabolized by CYP3A. Co-administration of ADCEITRIS with ketoconazole, a potent CYP34A inhibitor, increased exposure to MMAE by approximately 46%. Patients who are receiving strong CYP34A inhibitors concomitantly with ADCEITRIS should be monitored for adverse reactions. Co-administration of ADCEITRIS with rifampin, a potent CYP34A inducer, reduced exposure to MMAE by approximately 46%.

**Effect of ADCEITRIS on other drugs**

Co-administration of ADCEITRIS did not affect exposure to midazolam, a CYP34A substrate. MMAE decreased and did not inhibit other CYP substrates at relevant clinical concentrations. ADCEITRIS is not expected to alter the exposure to drugs that are metabolized by CYP34A enzymes.

**Use in specific populations**

**Pregnancy**

Pregnancy Category D. There are no adequate and well-controlled studies with ADCEITRIS in pregnant women. However, based on its mechanism of action and findings in animals, ADCEITRIS can cause fetal harm when administered to a pregnant woman. Brentuximab vedotin caused embryo-fetal toxicities in animals at exposures that were similar to human exposures at the recommended doses for patients with HL and sALCL. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus.

In an embryo-fetal developmental study, pregnant rats received 2 intravenous doses of 0.3, 1, or 10 mg/kg brentuximab vedotin during the period of organogenesis (once each on Pregnancy Days 6 and 13). Drug-induced embryo-fetal toxicities were seen mainly in animals treated with 3 and 10 mg/kg of the drug and included increased early resorption (≥99%), post-implantation loss (≥99%), decreased numbers of live fetuses, and external malformations (i.e., umbilical hernias and malrotated hindlimbs). Systemic exposure in animals at the brentuximab vedotin dose of 3 mg/kg is approximately the same exposure in patients with HL or sALCL who received the recommended dose of 1.8 mg/kg every three weeks.

**Nursing mothers**

Breast milk is known to be excreted in human milk. Due to the potential for serious adverse reactions in nursing infants from ADCEITRIS a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

**Pediatric use**

The safety and effectiveness of ADCEITRIS have not been established in the pediatric population. Clinical trials of ADCEITRIS included only 9 pediatric patients and this number is not sufficient to determine whether they respond differently from adult patients.

**Geriatric use**

Clinical trials of ADCEITRIS did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Safety and efficacy have not been established.

**Renal impairment**

The kidney is a route of excretion for MMAE. The influence of renal impairment on the pharmacokinetics of MMAE has not been determined.

**Hepatic impairment**

The liver is a route of excretion for MMAE. The influence of hepatic impairment on the pharmacokinetics of MMAE has not been determined.

**Overdose**

There is no known antidote for overdosage of ADCEITRIS. In case of overdose, the patient should be closely monitored for adverse reactions, particularly neutropenia, and supportive treatment should be administered.

**Dosage and administration**

**General dosing information**

The recommended dose is 1.8 mg/kg administered only as an intravenous infusion over 30 minutes every 3 weeks. The dose for patients weighing greater than 100 kg should be calculated based on a weight of 100 kg. Do not administer as an intravenous push or bolus. Continue treatment until a maximum of 16 cycles, disease progression or unacceptable toxicity.

**Dose modification**

**Peripheral Neuropathy**

Peripheral neuropathy should be managed using a combination of dose delay and reduction to 1.2 mg/kg. For new or worsening Grade 2 or 3 neuropathy, dosing should be held until neuropathy improves to Grade 1 or baseline and then restarted at 1.2 mg/kg. For Grade 4 neuropathy, ADCEITRIS should be discontinued.

**Neutropenia**

Neutropenia should be managed by dose delays and reductions. The dose of ADCEITRIS should be held for Grade 3 or 4 neutropenia until resolution to baseline or Grade 2 or lower. Growth factor support should be considered for subsequent cycles in patients who experience Grade 3 or 4 neutropenia despite the use of growth factor, or if the patient becomes neutropenic after treatment with ADCEITRIS.
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Indication
ARZERRA (ofatumumab) is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL) refractory to fludarabine and alemtuzumab.

The effectiveness of ARZERRA is based on the demonstration of durable objective responses. No data demonstrate an improvement in disease-related symptoms or increased survival with ARZERRA.

Important Safety Information

Infusion Reactions
ARZERRA can cause serious infusion reactions manifesting as bronchospasm, dyspnea, laryngeal edema, pulmonary edema, flushing, hypertension, hypotension, syncope, cardiac ischemia/infarction, back pain, abdominal pain, pyrexia, rash, urticaria, and angioedema. Infusion reactions occur more frequently with the first 2 infusions. Premedicate with acetaminophen, an antihistamine, and a corticosteroid. Interrupt infusion for infusion reactions of any severity. Institute medical management for severe infusion reactions including angina, or other signs and symptoms of myocardial ischemia. In a study of patients with moderate to severe chronic obstructive pulmonary disease, an indication for which ARZERRA is not approved, 2 of 5 patients developed Grade 3 bronchospasm during infusion. Infusion reactions occurred in 44% of patients on the day of the first infusion (300 mg), 29% on the day of the second infusion (2,000 mg), and less frequently during subsequent infusions.

Cytopenias
Prolonged (≥2 week) severe neutropenia and thrombocytopenia can occur with ARZERRA. Monitor complete blood counts (CBC) and platelet counts at regular intervals during therapy, and increase the frequency of monitoring in patients who develop Grade 3 or 4 cytopenias. Of 108 patients with normal neutrophil counts at baseline, 45 (42%) developed ≥Grade 3 neutropenia. Nineteen (18%) developed Grade 4 neutropenia. Some patients experienced new onset Grade 4 neutropenia >2 weeks in duration.

Progressive Multifocal Leukoencephalopathy
Progressive multifocal leukoencephalopathy (PML), including fatal PML, can occur with ARZERRA. Consider PML in any patient with new onset of or changes in pre-existing neurological signs or symptoms. Discontinue ARZERRA if PML is suspected and initiate evaluation for PML including consultation with a neurologist, brain MRI, and lumbar puncture.

Hepatitis B Infection and Reactivation
Fulminant and fatal hepatitis B virus (HBV) infection and reactivation can occur in patients following treatment with ARZERRA. Screen patients at high risk of HBV infection before initiation of ARZERRA. Closely monitor carriers of hepatitis B for clinical and laboratory signs of active HBV infection during treatment with ARZERRA and for 6 to 12 months following the last infusion of ARZERRA. Discontinue ARZERRA in patients who develop viral hepatitis or

EXPAND YOUR OPTIONS

A study population in need of additional treatment options

5 median prior therapies

- 59% of patients received prior rituximab
- 93% of patients received prior alkylating agents
- 100% of patients received prior fludarabine and alemtuzumab

The following serious adverse events (AEs) are discussed in greater detail below:
Infusion reactions, cytopenias, progressive multifocal leukoencephalopathy, hepatitis B infection and reactivation, and intestinal obstruction.

To learn more, please visit www.ARZERRA.com.

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Progressive multifocal leukoencephalopathy (PML), including fatal PML, can occur with ARZERRA. Consider PML in any patient with new onset of or changes in pre-existing neurological signs or symptoms. Discontinue ARZERRA if PML is suspected and initiate evaluation for PML including consultation with a neurologist, brain MRI, and lumbar puncture.

Hepatitis B Infection and Reactivation
Fulminant and fatal hepatitis B virus (HBV) infection and reactivation can occur in patients following treatment with ARZERRA. Screen patients at high risk of HBV infection before initiation of ARZERRA. Closely monitor carriers of hepatitis B for clinical and laboratory signs of active HBV infection during treatment with ARZERRA and for 6 to 12 months following the last infusion of ARZERRA. Discontinue ARZERRA in patients who develop viral hepatitis or
When treated with ARZERRA monotherapy, 42% of patients with CLL refractory to fludarabine and alemtuzumab achieved a partial response\(^1\)

- Patients had received a median of 5 prior therapies
- The investigator-determined overall response rate in patients with CLL refractory to fludarabine and alemtuzumab was 42% (99% CI: 26, 60)
- There were no complete responses
- The effectiveness of ARZERRA is based on the demonstration of durable objective responses
- No data demonstrate an improvement in disease-related symptoms or increased survival with ARZERRA
- 6.5 months—median duration of response (95% CI: 5.8, 8.3)

reactivation of viral hepatitis, and institute appropriate treatment. Insufficient data exist regarding the safety of administration of ARZERRA in patients with active hepatitis.

**Intestinal Obstruction**
Obstruction of the small intestine can occur in patients receiving ARZERRA. Perform a diagnostic evaluation if obstruction is suspected.

**Immunizations**
The safety of immunization with live viral vaccines during or following administration of ARZERRA has not been studied. Do not administer live viral vaccines to patients who have recently received ARZERRA. The ability to generate an immune response to any vaccine following administration of ARZERRA has not been studied.

**Most Common Adverse Reactions**
In the pivotal study (total population, n=154) the most common adverse reactions (≥10%, all grades) were neutropenia, followed by pneumonia (23%), pyrexia (20%), cough (19%), diarrhea (18%), anemia (16%), fatigue (15%), dyspnea (14%), rash (14%), nausea (11%), bronchitis (11%), and upper respiratory tract infections (11%).

**Most Common Serious Adverse Reactions**
In the pivotal study (total population, n=154), where ARZERRA was administered at 2,000 mg beginning with the second dose for 11 doses, the most common serious adverse reactions were infections (including pneumonia and sepsis), neutropenia, and pyrexia.

A total of 108 patients (70%) experienced bacterial, viral, or fungal infections. A total of 45 patients (29%) experienced ≥Grade 3 infections, of which 19 (12%) were fatal. The proportion of fatal infections in the fludarabine- and alemtuzumab-refractory group was 17%.

Please see Brief Summary of Prescribing Information on adjacent pages.

How Supplied: Available as 2 different single-use glass vials for dilution and intravenous administration. Each vial contains either 100 mg ofatumumab in 5 mL of solution or 1,000 mg ofatumumab in 50 mL of solution.

ARZERRA® (ofatumumab) Injection, for intravenous infusion

The following is a brief summary only; see full prescribing information for complete product information.

1 INDICATIONS AND USAGE

ARZERRA® (ofatumumab) is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL) refractory to fludarabine and alemtuzumab. The effectiveness of ARZERRA is based on the demonstration of durable objective responses [see Clinical Studies (14) of full prescribing information]. No data demonstrate an improvement in disease-related symptoms or increased survival with ARZERRA.

2 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Infusion Reactions ARZERRA can cause serious infusion reactions manifesting as bronchospasm, dyspnea, laryngeal edema, pulmonary edema, flushing, hypotension, syncope, cardiac ischemia/infarction, back pain, abdominal pain, pyrexia, rash, urticaria, and angioedema. Infusion reactions occur more frequently with the first 2 infusions [see Adverse Reactions (6.1)]. Premedicate with acetaminophen, an antihistamine, and a corticosteroid [see Dosage and Administration (2.1, 2.4) of full prescribing information]. Interrupt infusion for infusion reactions of any severity. Institute medical management for severe infusion reactions including angina or other signs and symptoms of myocardial ischemia [see Dosage and Administration (2.3) of full prescribing information]. In a study of patients with moderate to severe chronic obstructive pulmonary disease, an indication for which ARZERRA is not approved, 2 of 5 patients developed Grade 3 bronchospasm during infusion. 5.2 Cytopenias Prolonged (>1 week) severe neutropenia and thrombocytopenia can occur with ARZERRA. Monitor complete blood counts (CBC) and platelet counts at regular intervals during therapy, and increase the frequency of monitoring in patients who develop Grade 3 or 4 cytopenias. 5.3 Progressive Multifocal Leuкоencephalopathy Progressive multifocal leukoencephalopathy (PML), including fatal PML, can occur with ARZERRA. Consider PML in any patient with new onset or changes in pre-existing neurological signs or symptoms. Discontinue ARZERRA if PML is suspected, and initiate evaluation for PML including consultation with a neurologist, brain MRI, and lumbar puncture. 5.4 Hepatitis B Infection and Reactivation Fulminant and fatal hepatitis B virus (HBV) infection and reactivation can occur in patients following treatment with ARZERRA. Screen patients at high risk of HBV infection before initiation of ARZERRA. Closely monitor carriers of hepatitis B for clinical and laboratory signs of active HBV infection during treatment with ARZERRA and for 12 months following the last infusion of ARZERRA. Discontinue ARZERRA in patients who develop viral hepatitis or reactivation of viral hepatitis, and institute appropriate treatment. Insufficient data exist regarding the safety of administration of ARZERRA in patients with active hepatitis. 5.5 Intestinal Obstruction Obstruction of the small intestine can occur in patients receiving ARZERRA. Perform a diagnostic evaluation if obstruction is suspected. 5.6 Immunizations The safety of immunization with live viral vaccines during or following administration of ARZERRA has not been studied. Do not administer live viral vaccines to patients who have recently received ARZERRA. The ability to generate an immune response to any vaccine following administration of ARZERRA has not been studied.

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in other sections of the labeling:

Infusion Reactions [see Warnings and Precautions (5.1)]

Cytopenias [see Warnings and Precautions (5.2)]

Progressive Multifocal Leucoencephalopathy [see Warnings and Precautions (5.3)]

Hepatitis B Reactivation [see Warnings and Precautions (5.4)]

Intestinal Obstruction [see Warnings and Precautions (5.5)]

5.7 Immunogenicity There is a potential for immunogenicity with therapeutic proteins such as ofatumumab. Serum samples from patients with CLL in Study 1 were tested by enzyme-linked immunosorbent assay (ELISA) for anti-ofatumumab antibodies during and after the 24-week treatment period. Results were negative in 46 patients after the 8th infusion and in 33 patients after the 12th infusion. Immunogenicity assay results are highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of incidence of antibodies to ARZERRA with the incidence of antibodies to other products may be misleading.

Table 1. Incidence of All Adverse Reactions Occurring in ≥5% of Patients in Study 1 and in the Fludarabine- and Alemtuzumab-Refractory Subset of Study 1 (MedDRA 9.0)

<table>
<thead>
<tr>
<th>Body System/Adverse Event</th>
<th>All Grades %</th>
<th>Grade ≥3 %</th>
<th>All Grades %</th>
<th>Grade ≥3 %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Infections and infestations</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>23</td>
<td>14</td>
<td>25</td>
<td>15</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>11</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>11</td>
<td>&lt;1</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>Sepsis</td>
<td>8</td>
<td>8</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>8</td>
<td>0</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Herpes zoster</td>
<td>6</td>
<td>1</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td><strong>Blood and lymphatic system disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>16</td>
<td>5</td>
<td>17</td>
<td>8</td>
</tr>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>7</td>
<td>0</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>6</td>
<td>0</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td><strong>Cardiovascular disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>5</td>
<td>0</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Hypotension</td>
<td>5</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>5</td>
<td>&lt;1</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic, and mediastinal disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cough</td>
<td>19</td>
<td>0</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>14</td>
<td>2</td>
<td>19</td>
<td>5</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Diarrhea</td>
<td>18</td>
<td>0</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>11</td>
<td>0</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td><strong>Skin and subcutaneous tissue disorders</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>14</td>
<td>&lt;1</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>Urticaria</td>
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<td>Hyperhidrosis</td>
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<td>0</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
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<td>Back pain</td>
<td>8</td>
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<td>12</td>
<td>2</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>5</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>20</td>
<td>3</td>
<td>25</td>
<td>5</td>
</tr>
<tr>
<td>Fatigue</td>
<td>15</td>
<td>0</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>9</td>
<td>&lt;1</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Chills</td>
<td>8</td>
<td>0</td>
<td>10</td>
<td>0</td>
</tr>
</tbody>
</table>

*Necropsy includes pneumonia, lung infection, lobar pneumonia, and bronchopneumonia.

Sepsis includes sepsis, neutropenic sepsis, bacteremia, and septic shock.

Rash includes rash, rash macular, and rash vesicular.

Infusion Reactions: Infusion reactions occurred in 44% of patients on the day of the first infusion (300 mg), 29% on the day of the second infusion (2,000 mg), and less frequently during subsequent infusions. Infections: A total of 108 patients (70%) experienced bacterial, viral, or fungal infections. A total of 45 patients (29%) experienced ≥Grade 3 infections, of which 19 (12%) were fatal. The proportion of fatal infections in the fludarabine- and alemtuzumab-refractory group was 17%. Neutropenia: Of 108 patients with normal neutrophil counts at baseline, 45 (42%) developed ≥Grade 3 infections, of which 19 (12%) were fatal. The proportion of fatal infections in the fludarabine- and alemtuzumab-refractory group was 17%.
7 DRUG INTERACTIONS
No formal drug-drug interaction studies have been conducted with ARZERRA.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy Pregnancy Category C: There are no adequate or well-controlled studies of ofatumumab in pregnant women. A reproductive study in pregnant cynomolgus monkeys that received ofatumumab at doses up to 3.5 times the recommended human dose of ofatumumab did not demonstrate maternal toxicity or teratogenicity. Ofatumumab crossed the placental barrier, and fetuses exhibited depletion of peripheral B cells and decreased spleen and placental weights. ARZERRA should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus. There are no human or animal data on the potential short- and long-term effects of perinatal B-cell depletion in offspring following in utero exposure to ofatumumab. Ofatumumab does not bind normal human tissues other than B lymphocytes. It is not known if binding occurs to unique embryonic or fetal tissue targets. In addition, the kinetics of B-lymphocyte recovery are unknown in offspring with B-cell depletion [see Nonclinical Toxicology (13.3)].

8.2 Nursing Mothers It is not known whether ofatumumab is secreted in human milk; however, human IgG is secreted in human milk. Published data suggest that neonatal and infant consumption of ofatumumab is secreted in human milk; however, human IgG is secreted in human milk. Published data suggest that neonatal and infant consumption of breast milk does not result in substantial absorption of these maternal antibodies into circulation. Because the effects of local gastrointestinal and limited systemic exposure to ofatumumab are unknown, caution should be exercised when ARZERRA is administered to a nursing woman. 8.4 Pediatric Use Safety and effectiveness of ARZERRA have not been established in children. 8.5 Geriatric Use Clinical studies of ARZERRA did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects [see Clinical Pharmacology (12.3) of full prescribing information].

8.6 Renal Impairment No formal studies of ARZERRA in patients with renal impairment have been conducted [see Clinical Pharmacology (12.3) of full prescribing information].

8.7 Hepatic Impairment No formal studies of ARZERRA in patients with hepatic impairment have been conducted.

10 OVERDOSAGE
No data are available regarding overdosage with ARZERRA.

13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility No carcinogenicity or mutagenicity studies of ofatumumab have been conducted. In a repeat-dose toxicity study, no tumorigenic or unexpected mitogenic responses were noted in cynomolgus monkeys treated for 7 months with up to 3.5 times the human dose of ofatumumab. Effects on male and female fertility have not been evaluated in animal studies. 13.3 Reproductive and Developmental Toxicology Pregnant cynomolgus monkeys dosed with 0.7 or 3.5 times the human dose of ofatumumab weekly during the period of organogenesis (gestation days 20 to 50) had no maternal toxicity or teratogenicity. Both dose levels of ofatumumab depleted circulating B cells in the dams, with signs of initial B cell recovery 50 days after the final dose. Following Caesarean section at gestational day 100, fetuses from ofatumumab-treated dams exhibited decreases in mean peripheral B-cell counts (decreased to approximately 10% of control values), splenic B-cell counts (decreased to approximately 15 to 20% of control values), and spleen weights (decreased by 15% for the low-dose and by 30% for the high-dose group, compared to control values). Fetuses from treated dams exhibiting anti-ofatumumab antibody responses had higher B cell counts and higher spleen weights compared to the fetuses from other treated dams, indicating partial recovery in those animals developing anti-ofatumumab antibodies. When compared to control animals, fetuses from treated dams in both dose groups had a 10% decrease in mean placental weights. A 15% decrease in mean thymus weight compared to the controls was also observed in fetuses from dams treated with 3.5 times the human dose of ofatumumab. The biological significance of decreased placental and thymic weights is unknown. The kinetics of B-lymphocyte recovery and the potential long-term effects of perinatal B-cell depletion in offspring from ofatumumab-treated dams have not been studied in animals.

17 PATIENT COUNSELING INFORMATION
Advise patients to contact a healthcare professional for any of the following:
• Signs and symptoms of infusion reactions including fever, chills, rash, or breathing problems within 24 hours of infusion [see Warnings and Precautions (5.1) and Adverse Reactions (6.1)]
• Bleeding, easy bruising, petechiae, pallor, worsening weakness, or fatigue [see Warnings and Precautions (5.2)]
• Signs of infections including fever and cough [see Warnings and Precautions (5.2) and Adverse Reactions (6.1)]
• New neurological symptoms such as confusion, dizziness or loss of balance, difficulty talking or walking, or vision problems [see Warnings and Precautions (5.3)]
• Symptoms of hepatitis including worsening fatigue or yellow discoloration of skin or eyes [see Warnings and Precautions (5.4)]
• New or worsening abdominal pain or nausea [see Warnings and Precautions (5.5)]
• Pregnancy or nursing [see Use in Specific Populations (8.1, 8.3)]

Advise patients of the need for:
• Periodic monitoring for blood counts [see Warnings and Precautions (5.2)]
• Avoiding vaccination with live viral vaccines [see Warnings and Precautions (5.6)]
Study Description

A multicenter, randomized, double-blind, placebo-controlled clinical trial of deferasirox in patients with myelodysplastic syndromes (MDS) (low/intermediate-1 risk) and transfusional iron overload (Clinical Trial Protocol CICL670A2302).

The purpose of this study is to demonstrate in low/intermediate-1 risk MDS patients, treated as per standard practice, the clinical superiority of deferasirox to placebo, while rigorously monitoring relevant clinical parameters (cardiac and liver function, and transformation to acute leukemia [AML]) potentially affected by iron overload complications.

Study Design

<table>
<thead>
<tr>
<th>Study Arm</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deferasirox</td>
<td>5 y</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
</tr>
</tbody>
</table>

Randomization (2:1=Deferasirox/Placebo)

Expected end of study

The following dosing schedule is to be followed:

- 10 mg/kg/day (once daily) for 2 weeks, followed by 20 mg/kg/day (once daily)
- After 3 months, the dose can be adjusted by 5 mg/kg/day or 10 mg/kg/day up to 40 mg/kg/day based on serum ferritin response

Two interim analyses for safety and efficacy are planned when approximately 50% and 75% of the required number of events (244) have been observed.

Eligibility

**Inclusion criteria:**

- Male or female patients, ≥18 years of age
- Patient must weigh between 35 kg to 135 kg
- Patients with low or intermediate risk MDS, as determined by IPSS score
- Ferritin > 1000 mcg/L and < 3500 mcg/L at screening
- History of transfusion of 15 PRBC to 75 PRBC units annually during the study

**Exclusion criteria:**

- More than 6 months of cumulative iron chelation therapy (such as daily deferasirox or deferiprone or 5×/week deferoxamine)
- More than 3 years since patient began receiving regular transfusions (2 units per 8 weeks or 4 units received in a 3-month period)
- Creatinine clearance < 40 mL/min
- Serum creatinine > 1.2×ULN at screening
- Significant proteinuria
- ECOG performance status > 2
- LVEF < 50% by echocardiography
- History of hospitalization for congestive heart failure
- Systemic diseases which would prevent study treatment (eg, uncontrolled hypertension, cardiovascular, renal, hepatic, metabolic, etc)
- Evidence of active hepatitis B or hepatitis C
- History of HIV-positive test result
- ALT or AST > 2.5×ULN at screening
- Total bilirubin > ULN at screening
- Diagnosis of liver cirrhosis

Primary Endpoint

Composite primary endpoint (event-free survival):

- Death
- Nonfatal event:
  1. Echocardiographic evidence of worsening cardiac function
  2. Hospitalization for congestive heart failure
  3. Liver function impairment
  4. Liver cirrhosis
  5. Progression to AML

For more information

- Call Novartis Oncology at 1-800-340-6843
- Contact your local Novartis Medical Science Liaison (MSL)
- ClinicalTrials.gov identifier: NCT00940602
were considered at least possibly related to drug treatment.

Six patients had fatal events associated with their underlying disease and myelosuppression (anemia, neutropenia, and thrombocytopenia) that discontinued therapy for adverse events; compared to 1 of 81 patients in the supportive care arm.

between patients >65 years of age and younger patients in these myelodysplasia trials. No significant gender differences in safety or efficacy

The following Adverse Events were Reported in ≥5% of Patients in the Dacogen Group and at a Rate Greater than Supportive Care: For Details see Table 1a. Supportive Care (N = 81 (%)) vs Dacogen (N = 83 (%))

The developmental toxicity of decitabine was evaluated in nonclinical testing in mice and rabbits. In utero exposures were from gestation days 9-12, no maternal toxicity was noted at the highest dose level tested (3 mg/m² IP injection on gestation day 9). Decitabine was without adverse effects on growth or development in the offspring up to the highest dose level tested. The NOAEL was the highest dose level tested (6 mg/m² IP injection on gestation day 9). A NOAEL was not established for the lowest dose level tested (0.3 mg/m² IP injection on gestation day 9). The NOAEL for intrauterine growth was 6.0 mg/m².

In contrast to decitabine, qingtongin caused fetal anomalies in mice administered a single 3 mg/m² IP injection on gestation day 9. The NOAEL for fetal anomalies was 1.0 mg/m². No maternal effects were noted at the highest dose level tested. No maternal effects were noted at 0.3 mg/m². The NOAEL was 0.3 mg/m².

The effect of decitabine on postnatal development and reproductive capacity was evaluated in mice administered a single 3 mg/m² IP injection on gestation day 9. No reproductive or postnatal effects were noted at the highest dose level tested. The NOAEL was 6.0 mg/m². No maternal effects were noted at 0.3 mg/m². The NOAEL was 0.3 mg/m².

In conclusion, the data from this study indicate that decitabine is not a teratogen and is probably not a teratogen in the mouse. The NOAEL for intrauterine growth was 6.0 mg/m² IP injection on gestation day 9. The NOAEL for fetal anomalies was 6.0 mg/m² IP injection on gestation day 9. The NOAEL for postnatal development was 6.0 mg/m² IP injection on gestation day 9. The NOAEL for reproductive capacity was 6.0 mg/m² IP injection on gestation day 9.

Men with female partners of childbearing potential should use effective contraception during this time (Use in Specific Populations).

Patients with renal or hepatic dysfunction were not studied. Insufficient numbers of non-white patients were available to draw conclusions about the safety or efficacy of Dacogen in these populations. None of the patients had received chemotherapy or radiotherapy within 3 months of entry into the study.

For cutaneous lesions, the most frequent cause of dose delays and discontinuation was dermatitis—cutaneous disorders—especially cellulitis. Dacogen administration was discontinued in 16 of 83 patients (19%) for dermatitis—cutaneous disorders. In 11 patients, cellulitis was the causative agent. No significant differences in safety or efficacy

Bone marrow suppression was the most frequent cause of dose reduction, delay and discontinuation.

mechanism of action, Dacogen alters DNA synthesis and can cause fetal harm.

WARNINGS AND PRECAUTIONS

Patients who are receiving myelosuppressive therapy and Dacogen should be considered for early institution of hematopoietic growth factors so as to achieve the needed early recovery of growth factors and/or anticoagulants for the prevention or treatment of infections in patients with myelosuppression. Myelosuppression and resulting neutropenia may occur more frequently in the first 2-3 months of therapy and may not be easily reversible.

Dacogen is a cytotoxic drug and caution should be exercised when handling and preparing Dacogen. Procedures for proper handling and disposal of decitabine are detailed in the US prescribing information for decitabine. In addition, decitabine should be disposed of properly in a manner consistent with good laboratory practice. Properly label the product and dispose of it according to the manufacturer's instructions. In addition, decitabine should be stored in such a manner that it is not accessible to children. Do not use an insecticide band to secure the vial. Do not store decitabine in the company's original carton due to the presence of refrigeration equipment. Use only sterile, single-use transfer apparatus.

Women of childbearing potential should be advised to avoid becoming pregnant while receiving Dacogen and for 1 month following completion of their treatment with Dacogen. While the use of oral contraceptives by themselves does not protect against HIV infection, they may reduce the risk of acquiring other STDs. If a woman becomes pregnant while taking Dacogen, the patient should be advised to stop decitabine and begin taking a different antiretroviral regimen immediately.

Patients with severe low white blood counts, neutropenia (23%) and leucopenia (22%). Bone marrow suppression was the most frequent cause of dose reduction, delay and discontinuation.

Men with female partners of childbearing potential should use effective contraception during this time (Use in Specific Populations).
THE ONLY HYPOMETHYLATING AGENT APPROVED FOR 5-DAY DOSING

DACOGEN provides 2 dose options for your patients with myelodysplastic syndromes (MDS).1
• 20 mg/m² by IV over 1 hour repeated daily for 5 days. Repeat cycle every 4 weeks
• 15 mg/m² by IV over 3 hours repeated every 8 hours for 3 days. Repeat cycle every 6 weeks
• With either regimen, it is recommended that the patient be treated for a minimum of 4 cycles. However, a complete or partial response may take longer than 4 cycles

See Important Safety Information below and the Dosage and Administration section of the full Prescribing Information.

DACOGEN is indicated for the treatment of patients with MDS including those who are:
• Previously treated and untreated
• De novo and secondary
  – All FAB subtypes (RA, RARS, RAEB, RAEB-t, CMML)
  – Intermediate-1, Intermediate-2, High-Risk International Prognostic Scoring System groups

Important Safety Information
Treatment with DACOGEN is associated with neutropenia and thrombocytopenia. Complete blood and platelet counts should be performed as needed to monitor response and toxicity but at a minimum prior to each dosing cycle. After administration of the recommended dosage for the first cycle, treatment for subsequent cycles should be adjusted if indicated by dose adjustment guidelines. Clinicians should consider the need for early institution of growth factors and/or antimicrobial agents for the prevention or treatment of infections in patients with MDS.

DACOGEN may cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with DACOGEN and for 1 month following completion of treatment. Women of childbearing potential should be counseled to use effective contraception during this time. Men should be advised not to father a child while receiving treatment with DACOGEN and for 2 months following completion of treatment. DACOGEN may cause fetal harm. Men with female partners of childbearing potential should use effective contraception during this time.

In the phase 3 clinical trial, the highest incidence of Grade 3 or Grade 4 adverse events in the DACOGEN arm was neutropenia (87%), thrombocytopenia (85%), febrile neutropenia (23%), and leukopenia (22%). Bone marrow suppression was the most frequent cause of dose reduction, delay, and discontinuation. Six patients had fatal events associated with their underlying disease and myelosuppression (anemia, neutropenia, and thrombocytopenia) that were considered at least possibly related to drug treatment. Of the 83 DACOGEN-treated patients, 8 permanently discontinued therapy for adverse events compared to 1 of 81 patients in the supportive care arm.

In the single-arm study, the highest incidence of Grade 3 or Grade 4 adverse events was neutropenia (37%), thrombocytopenia (24%), and anemia (22%). Seventy-eight percent of patients had dose delays, the median duration of this delay was 7 days. Hematologic toxicities and infections were the most frequent causes of dose delays and discontinuation. Eight patients had fatal events due to infection and/or bleeding that were considered at least possibly related to drug treatment. Nineteen of 99 patients permanently discontinued therapy for adverse events.

Other commonly occurring reactions include fatigue, pyrexia, nausea, cough, petechiae, constipation, diarrhea, and hyperglycemia.

If hematologic recovery from a previous DACOGEN treatment cycle requires more than 6 weeks when administering the 3-day dosing, then the next DACOGEN cycle should be delayed and dosing temporarily reduced. When administering the 5-day dosing, the DACOGEN cycle should be delayed until there is hematologic recovery. If the following nonhematologic toxicities are present, DACOGEN treatment should not be restarted until the toxicity is resolved: (1) serum creatinine ≥2 mg/dL; (2) SGPT, total bilirubin ≥2 × ULN; and (3) active or uncontrolled infection.

Because there are no data on use of DACOGEN in patients with renal or hepatic dysfunction, DACOGEN should be used with caution in these patients.

Please see the accompanying brief summary of full Prescribing Information on the following page.

Reference: 1. Dacogen (decitabine) for Injection full prescribing information.