EXPAND YOUR OPTIONS

A study population in need of additional treatment options\textsuperscript{1,2}

The following serious adverse reactions are discussed in greater detail below:

Infusion reactions, tumor lysis syndrome, cytopenias, hepatitis B virus reactivation, hepatitis B virus infection, progressive multifocal leukoencephalopathy, intestinal obstruction, and immunizations.

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

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

WARNING: HEPATITIS B VIRUS REACTIVATION AND PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY

- Hepatitis B virus (HBV) reactivation can occur in patients receiving CD20-directed cytolytic antibodies, including ARZERRA, in some cases resulting in fulminant hepatitis, hepatic failure, and death [see Warnings and Precautions (5.4)].
- Progressive multifocal leukoencephalopathy (PML) resulting in death can occur in patients receiving CD20-directed cytolytic antibodies, including ARZERRA [see Warnings and Precautions (5.6)].

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. Administer ARZERRA in an environment where facilities to adequately monitor and treat infusion reactions are available. Premedicate with acetaminophen, an antihistamine, and a corticosteroid. Interrupt infusion with ARZERRA 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.

Tumor Lysis Syndrome
Tumor lysis syndrome (TLS) has occurred in patients treated with CD20-directed cytolytic antibodies, including ARZERRA. Administer aggressive intravenous hydration and anti-hyperuricemic agents, correct electrolyte abnormalities, and monitor renal function.

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.

Hepatitis B Virus Reactivation
Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, has occurred in patients treated with ARZERRA. Cases have been reported in patients who are hepatitis B surface antigen (HBsAg) positive and also in patients who are HBsAg negative but are hepatitis B core antibody (anti-HBc) positive. Reactivation also has occurred in patients who appear to have resolved hepatitis B infection (i.e., HBsAg negative, anti-HBc positive, and hepatitis B surface antibody [anti-HBs] positive).

HBV reactivation is defined as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA level or detection of HBsAg in a person who was previously HBsAg negative and anti-HBc positive. Reactivation of HBV replication is often followed by hepatitis, i.e., increase in transaminase levels and, in severe cases, increase in bilirubin levels, liver failure, and death.

Screen all patients for HBV infection by measuring HBsAg and anti-HBc before initiating treatment with ARZERRA. For patients who show evidence of hepatitis B infection (HBsAg positive [regardless of antibody status] or HBsAg negative but anti-HBc positive) or if patients received prior rituximab

5 median prior therapies

93% | of patients received prior alkylating agents

100% | of patients received prior fludarabine and alemtuzumab

For chronic lymphocytic leukemia (CLL) refractory to fludarabine and alemtuzumab

\textsuperscript{1,2}
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)

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 the full Prescribing Information, including Boxed Warning, for ARZERRA on the following 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

**BRIEF SUMMARY**

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

**WARNING: HEPATITIS B VIRUS REACTIVATION AND PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY**

- Hepatitis B Virus (HBV) reactivation can occur in patients receiving CD20-directed cytolytic antibodies, including ARZERRA, in some cases resulting in fulminant hepatitis, hepatic failure, and death [see Warnings and Precautions (5.4)].
- Progressive Multifocal Leukoencephalopathy (PML) resulting in death can occur in patients receiving CD20-directed cytolytic antibodies, including ARZERRA [see Warnings and Precautions (5.6)].

**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.

**4 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, 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 [see Adverse Reactions (6.2) of full prescribing information]. Interrupt infusion with ARZERRA for infusion reactions of any severity. Institute medical management for severe infusion reactions including anaphylaxis or other signs and symptoms of myocardial ischemia [see Dosage and Administration (2.1, 2.4) of full prescribing information].

**5.2 Tumor Lysis Syndrome**

Tumor lysis syndrome (TLS) has occurred in patients treated with CD20-directed cytolytic antibodies, including ARZERRA. Administer aggressive intravenous hydration and antihyperuricemic agents, correct electrolyte abnormalities, and monitor renal function. [see Adverse Reactions (6.1) of full prescribing information].

**5.3 Cytophenias**

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 cytophenias. [see Adverse Reactions (6.1) of full prescribing information].

**5.4 Hepatitis B Virus Reactivation**

Hepatitis B virus (HBV) reactivation, in some cases resulting in fulminant hepatitis, hepatic failure and death, has occurred in patients treated with ARZERRA. Cases have been reported in patients who are hepatitis B surface antigen (HBsAg) positive and also in patients who are HBsAg negative but are hepatitis B core antibody (anti-HBc) positive. Reactivation has also occurred in patients who appear to have resolved hepatitis B infection (i.e., HBsAg negative, anti-HBc positive, and hepatitis B surface antibody (anti-HBs) positive). HBV reactivation is defined as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA level or detection of HBsAg in a person who was previously HBsAg negative and anti-HBc positive. Reactivation of HBV replication is often followed by hepatitis, i.e., increase in transaminase levels and, in severe cases, increase in bilirubin levels, liver failure, and death. Screen all patients for HBV infection before and after infusion of ARZERRA, and monitor patients with evidence of current or prior HBV infection for clinical and laboratory signs of hepatitis or HBV reactivation during and for several months following treatment with ARZERRA. HBV reactivation has been reported for at least 12 months following completion of therapy. In patients who develop reactivation of HBV while receiving ARZERRA, immediately discontinue ARZERRA and any concomitant chemotherapy, and institute appropriate treatment. Resumption of ARZERRA in patients whose HBV reactivation resolves has been discussed with physicians with expertise in managing hepatitis B. Insufficient data exist regarding the safety of resuming ARZERRA in patients who develop HBV reactivation. 5.5 Hepatitis B Virus Infection

Fetal infection due to hepatitis B in patients who have not been previously infected has been observed with ARZERRA. Monitor patients for clinical and laboratory signs of hepatitis B. 5.6 Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) resulting in death has occurred with ARZERRA. Consider PML in any patient with new onset or of changes in pre-existing neurological signs or symptoms. If PML is suspected, discontinue ARZERRA and initiate evaluation for PML including neurology consultation.

**5.7 Intestinal Obstruction**

Obstruction of the small intestine can occur in patients receiving ARZERRA. Evaluate if symptoms of obstruction such as abdominal pain or repeated vomiting occur. 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)]
- Tumor Lysis Syndrome [see Warnings and Precautions (5.2)]
- Cytophenias [see Warnings and Precautions (5.3)]
- Hepatitis B Virus Reactivation [see Warnings and Precautions (5.4)]
- Hepatitis B Virus Infection [see Warnings and Precautions (5.5)]
- Progressive Multifocal Leukoencephalopathy [see Warnings and Precautions (5.6)]
- Intestinal Obstruction [see Warnings and Precautions (5.7)]

The most common adverse reactions (≥10%) in Study 1 were neutropenia, pneumonia, pyrexia, cough, diarrhea, anemia, fatigue, dyspnea, rash, nausea, bronchitis, and upper respiratory tract infections. The most common serious adverse reactions in Study 1 were infections (including pneumonia and sepsis), neutropenia, and pyrexia. Infections were the most common adverse reactions leading to drug discontinuation in Study 1. 6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. The safety of monotherapy with ARZERRA was evaluated in 181 patients with relapsed or refractory CLL in 2 open-label, non-randomized, single-arm studies. In these studies, ARZERRA was administered at 2,000 mg beginning with the second dose for 11 doses (Study 1 [n = 154]) or 3 doses (Study 2 [n = 27]). The data described in Table 1 and other sections below are derived from 154 patients in Study 1. All patients received 2,000 mg weekly from the second dose onward. Ninety percent of patients received at least 8 infusions of ARZERRA and 55% received all 12 infusions. The median age was 63 years (range: 41 to 86 years). 72% were male, and 97% were White.

**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>Total Population (n = 154)</th>
<th>Fludarabine- and Alemtuzumab-Refractory (n = 59)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td>Infectious and infestations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia*</td>
<td>23</td>
<td>14</td>
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<tr>
<td>Upper respiratory tract infection</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>11</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Sepsis*</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Hepatitis zoster</td>
<td>6</td>
<td>1</td>
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<tr>
<td>Sinusitis</td>
<td>5</td>
<td>2</td>
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<tr>
<td>Blood and lymphatic system disorders</td>
<td></td>
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<tr>
<td>Anemia</td>
<td>16</td>
<td>5</td>
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<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>7</td>
<td>0</td>
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<tr>
<td>Nervous system disorders</td>
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<tr>
<td>Headache</td>
<td>6</td>
<td>0</td>
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<tr>
<td>Cardiovascular disorders</td>
<td></td>
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<tr>
<td>Hypertension</td>
<td>5</td>
<td>0</td>
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<tr>
<td>Hypotension</td>
<td>5</td>
<td>0</td>
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<tr>
<td>Tachycardia</td>
<td>5</td>
<td>&lt;1</td>
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<tr>
<td>Respiratory, thoracic, and mediastinal disorders</td>
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<tr>
<td>Cough</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>11</td>
<td>0</td>
</tr>
</tbody>
</table>

(cont'd)
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) (cont’d)

<table>
<thead>
<tr>
<th>Body System/Adverse Event</th>
<th>Total Population (n = 154)</th>
<th>Fludarabine- and Alemtuzumab-Refractory (n = 59)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades %</td>
<td>Grade ≥3 %</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
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<tr>
<td>Rash 1</td>
<td></td>
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<tr>
<td>Urticaria</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>5</td>
<td>0</td>
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<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>20</td>
<td>3</td>
</tr>
<tr>
<td>Fatigue</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>9</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Chills</td>
<td>8</td>
<td>8</td>
</tr>
</tbody>
</table>

1Pneumonia includes pneumonia, lung infection, lobar pneumonia, and bronchopneumonia.
2Sepsis includes sepsis, neutropenic sepsis, bacteremia, and septic shock.
3 Rash includes rash, rash macular, and rash vesicular.

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 tumorogenic 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. 13.2 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 Caesarian 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 and 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 (5.3)]
- Signs of infections including fever and cough [see Warnings and Precautions (5.3) and Adverse Reactions (6.1)]
- Symptoms of hepatitis including worsening fatigue or yellow discoloration of skin or eyes [see Warnings and Precautions (5.4, 5.5)]
- New neurological symptoms such as confusion, dizziness or loss of balance, difficulty talking or walking, or vision problems [see Warnings and Precautions (5.6)]
- New or worsening abdominal pain or nausea or a significant increase in feeling unwell [see Warnings and Precautions (5.2, 5.7)]
- 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 (5.3)]
- Avoiding vaccination with live viral vaccines [see Warnings and Precautions (5.8)]

ARZERRA is a registered trademark of the GlaxoSmithKline group of companies.

Manufactured by:
GLAXO GROUP LIMITED
Greenford, Middlesex, UB6 0NN, United Kingdom
U.S. Lic. 1809

Distributed by:
GlaxoSmithKline
Research Triangle Park, NC 27709

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September 2013
ARZ-7BRS

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Janssen Ibrutinib (Bruton’s Tyrosine Kinase (BTK) Inhibitor) Trials
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A Study of Ibrutinib in Combination with Bendamustine and Rituximab in Patients With Newly Diagnosed Mantle Cell Lymphoma
MCL3002 (SHINE)
N=520
KEY ELIGIBILITY CRITERIA
• Patients with Newly Diagnosed MCL, 65 years and older
• No prior treatment
• ECOG score of 0 or 1

For more information visit: www.clinicaltrials.gov (NCT01776840). No new sites are being opened; for any questions on the study, please contact: Dr. Aleksandra Rizo at Janssen R&D at arizo@its.jnj.com

A Study of Ibrutinib in Combination with R-CHOP in Patients With Newly Diagnosed Non-Germinal Center B-Cell Subtype of Diffuse Large B-Cell Lymphoma
DBL3001 (PHOENIX)
N=800
KEY ELIGIBILITY CRITERIA
• Patients, 18 years or older, with newly diagnosed, non-GCB DLBCL as determined by central IHC
• Ann Arbor Stage II-IV
• R-IPI score of ≥1
• ECOG 0 – 2

For more information visit: www.clinicaltrials.gov (NCT01855750). No new sites are being opened; for any questions on the study, please contact: Dr. Jessica Vermeulen at JVermeul@its.jnj.com or Kevin Bellew at kbellew2@its.jnj.com

An Open-label, Multicenter, Single-arm, Phase 2 Study of Ibrutinib (PCI-32765) in Subjects with refractory Follicular Lymphoma
FLR2002 (DAWN)
N=110
KEY ELIGIBILITY CRITERIA
• Histologic proof of Grade 1, 2, or 3a FL at initial diagnosis without clinical or pathological evidence of transformation
• Prior therapy includes all of the following criteria:
  a. Previously treated with at least 2 prior lines of therapy,
  b. At least 1 prior rituximab-containing combination chemotherapy regimen
  c. Last prior line of therapy includes an anti CD20 monoclonal antibody-containing chemotherapy regimen
• Resistant disease to the last prior therapy, defined as progression of disease during or within 12 months of the last dose of a CD20 antibody combination chemotherapy regimen

For more information visit: www.clinicaltrials.gov (NCT01779791). No new sites are being opened; for any questions on the study, please contact: Dr. Jessica Vermeulen at JVermeul@its.jnj.com or Dr. Gary Gartenberg at ggartenb@its.jnj.com

A Randomized, Double-blind, Placebo-controlled Phase 3 Study of Ibrutinib in Combination with Either Bendamustine and Rituximab (BR) or Rituximab, Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone (R-CHOP) in Subjects with Previously Treated Indolent Non-Hodgkin Lymphoma (iNHL)
FLR3001 (SELENE)
N=400
KEY ELIGIBILITY CRITERIA
• ≥18 years of age with histologically confirmed diagnosis of either
  a. Follicular lymphoma Grade 1, 2, or 3a
  b. Marginal zone lymphoma (splenic, nodal, or extra-nodal)
• Relapsed or refractory disease
• Received at least one prior chemoimmunotherapy regimen containing a CD20 antibody
• ECOG 0-1

For more information visit: www.clinicaltrials.gov (NCT01974440). No new sites are being opened; for any questions on the study, please contact: Dr. Esther Rose at ERose10@its.jnj.com or Dr. Jessica Vermeulen at JVermeul@its.jnj.com

*The safety and efficacy of the investigational use of this product has not been determined. There is no guarantee that the investigational uses listed will be filed with and/or approved for marketing by any regulatory agency.
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<td>The Safety Net Foundation provides products at no cost to eligible uninsured and underinsured patients</td>
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<td>The NEULASTA/NEUPOGEN FIRST STEP™ Program helps reduce out-of-pocket (OOP) costs for all eligible commercially insured patients. Go to <a href="http://www.amgenfirststep.com">www.amgenfirststep.com</a> for program eligibility and limitations</td>
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REVLIMID is indicated for the treatment of patients with mantle cell lymphoma (MCL) whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib.

REVLIMID is not indicated and not recommended for the treatment of patients with chronic lymphocytic leukemia (CLL) outside of controlled clinical trials.

For patients with

RELAPSED OR REFRACTORY
MANTLE CELL LYMPHOMA

WARNING: EMBRYO-FETAL TOXICITY, HEMATOLOGIC TOXICITY, and VENOUS THROMBOEMBOLISM

See full prescribing information for complete boxed warning.

EMBRYO-FETAL TOXICITY

- Lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study similar to birth defects caused by thalidomide in humans. If lenalidomide is used during pregnancy, it may cause birth defects or embryo-fetal death.
- Pregnancy must be excluded before start of treatment. Prevent pregnancy during treatment by the use of two reliable methods of contraception.

REVLIMID is available only through a restricted distribution program called the REVLIMID REMS™ program (formerly known as the “RevAssist® program”).

HEMATOLOGIC TOXICITY. REVLIMID can cause significant neutropenia and thrombocytopenia.

- For patients with del 5q myelodysplastic syndromes, monitor complete blood counts weekly for the first 8 weeks and monthly thereafter.

VENOUS THROMBOEMBOLISM

- Significantly increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients with multiple myeloma receiving REVLIMID with dexamethasone.

For more information, please visit www.REVLIMID.com or call 1-888-423-5436.

REVLIMID is only available through a restricted distribution program, REVLIMID REMS™.

Please see Brief Summary of full Prescribing Information, including Boxed WARNINGS, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and ADVERSE REACTIONS, and Important Safety Information on the following pages.
Efficacy and safety of REVLIMID were evaluated in pretreated patients with advanced disease

- In a multicenter, single-arm, single-agent, open-label study (N=134)*
- 92% (124/134) of patients had stage III-IV disease; 78% (105/134) of patients had received ≥3 prior systemic therapies; 60% (81/134) of patients were refractory to prior bortezomib; 55% (74/134) of patients were refractory to last prior therapy
- Refractory disease was defined as without any response of PR or better during treatment with bortezomib or a bortezomib-containing regimen; relapsed disease was defined as progression within one year after treatment with bortezomib or a bortezomib-containing regimen†
- Patients received REVLIMID 25 mg orally, once daily for 21 days every 28 days. Treatment was continued until disease progression, unacceptable toxicity, or withdrawal of consent

REVLIMID may help continue the fight against relapsed or refractory MCL‡

<table>
<thead>
<tr>
<th>ORR $\dagger$</th>
<th>CR $\dagger$</th>
</tr>
</thead>
<tbody>
<tr>
<td>26% (34/133)</td>
<td>7% (9/133)</td>
</tr>
</tbody>
</table>

Overall response rate (CR + CRu + PR) (95% CI: 18.4, 33.9)
Complete response rate (CR + CRu) (95% CI: 3.1, 12.5)

Median duration of response (95% CI: 7.7, 26.7) 16.6 months (n=34)

- Median time to response was 2.2 months (range: 1.8 to 13 months)

CI=confidence interval; CR=complete response; CRu=complete response unconfirmed; DOR=duration of response; ORR=overall response rate; PR=partial response.

CONTRAINDICATIONS

Pregnancy:
- REVLIMID can cause fetal harm when administered to a pregnant female. Lenalidomide is contraindicated in females who are pregnant.
- 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

Allergic Reactions:
- REVLIMID is contraindicated in patients who have demonstrated hypersensitivity (e.g., angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis) to lenalidomide

ADVERSE REACTIONS

Mantle Cell Lymphoma
- Grade 3 and 4 adverse events reported in ≥5% of patients treated with REVLIMID in the MCL trial (N=134) included neutropenia (43%), thrombocytopenia (28%), anemia (11%), pneumonia (9%), leukopenia (7%), fatigue (7%), diarrhea (6%), dyspnea (6%), and febrile neutropenia (6%)
- Serious adverse events reported in ≥2 patients treated with REVLIMID monotherapy for MCL included chronic obstructive pulmonary disease, clostridium difficile colitis, sepsis, basal cell carcinoma, and supraventricular tachycardia
- Adverse events reported in ≥15% of patients treated with REVLIMID in the MCL trial included neutropenia (49%), thrombocytopenia (36%), fatigue (34%), anemia (31%), diarrhea (31%), nausea (30%), cough (28%), pyrexia (23%), rash (22%), dyspnea (18%), pruritus (17%), peripheral edema (16%), constipation (16%), and leukopenia (15%)
- Adverse events occurring in patients treated with REVLIMID in the MCL trial resulted in at least one dose interruption in 76 (57%) patients, at least one dose reduction in 51 (38%) patients, and discontinuation of treatment in 26 (19%) patients


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### Important Safety Information

**WARNING: EMBRYO-FETAL TOXICITY, HEMATOLOGIC TOXICITY, and VENOUS THROMBOEMBOLISM**

**Embryo-Fetal Toxicity**

Do not use REVLIMID during pregnancy. Lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study. Thalidomide is a known human teratogen that causes severe life-threatening human birth defects. Iflenalidomide is used during pregnancy, it may cause birth defects or embryo-fetal death. In females of reproductive potential, obtain 2 negative pregnancy tests before starting REVLIMID treatment. Females of reproductive potential must use 2 forms of contraception or continuously abstain from heterosexual sex during and for 4 weeks after REVLIMID treatment. To avoid embryo-fetal exposure to lenalidomide, REVLIMID is only available through a restricted distribution program, the REVLIMID REMS™ program (formerly known as the “RevAssist™” program).

Information about the REVLIMID REMS™ Program is available at www.celgeneriskmanagement.com or by calling the manufacturer's toll-free number 1-888-423-5436.

**Hematologic Toxicity (Neutropenia and Thrombocytopenia)**

REVLIMID can cause significant neutropenia and thrombocytopenia. Eighty percent of patients with del 5q myelodysplastic syndrome (MDS) had to have a dose delay/reduction during the major study. Thirty-four percent of patients had to have a second dose delay/reduction. Grade 3 or 4 hematologic toxicity was seen in 80% of patients enrolled in the study. Patients on therapy for del 5q MDS should have their complete blood counts monitored weekly for the first 8 weeks of therapy and at least monthly thereafter. Patients may require dose interruption and/or reduction. Patients may require use of blood product support and/or growth factors.

**Venous Thromboembolism**

REVLIMID has demonstrated a significantly increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients with multiple myeloma (MM) who were treated with REVLIMID and dexamethasone therapy. Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling. It is not known whether prophylactic anticoagulation or antiplatelet therapy prescribed in conjunction with REVLIMID may lessen the potential for venous thromboembolism. The decision to take prophylactic measures should be done carefully after an assessment of an individual patient’s underlying risk factors.

### CONTRAINDICATIONS

**Pregnancy:**
- REVLIMID can cause fetal harm when administered to a pregnant female. Lenalidomide is contraindicated in females who are pregnant. 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

**Allergic Reactions:**
- REVLIMID is contraindicated in patients who have demonstrated hypersensitivity (e.g., angioedema, Stevens-Johnson syndrome, toxic epidermal necrolysis) to lenalidomide

### WARNINGS AND PRECAUTIONS

**Embryo-Fetal Toxicity:**
- REVLIMID is an analogue of thalidomide, a known human teratogen that causes life-threatening human birth defects or embryo-fetal death. An embryo-fetal development study in monkeys indicated that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy, similar to birth defects observed in humans following exposure to thalidomide during pregnancy
- Females of Reproductive Potential: Must avoid pregnancy for at least 4 weeks before beginning REVLIMID therapy, during therapy, during dose interruptions, and for at least 4 weeks after completing therapy. Must commit either to abstain continuously from heterosexual sexual intercourse or to use two methods of reliable birth control beginning 4 weeks prior to initiating treatment with REVLIMID, during therapy, during dose interruptions and continuing for 4 weeks following discontinuation of REVLIMID therapy. Must obtain 2 negative pregnancy tests prior to initiating therapy
- Males: Lenalidomide is present in the semen of patients receiving the drug. Males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking REVLIMID and for up to 28 days after discontinuing REVLIMID, even if they have undergone a successful vasectomy. Male patients taking REVLIMID must not donate semen
- Blood Donation: Patients must not donate blood during treatment with REVLIMID and for 1 month following discontinuation of the drug because the blood might be given to a pregnant female patient whose fetus must not be exposed to REVLIMID

**REVLIMID REMS Program**

Because of embryo-fetal risk, REVLIMID is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) program. Prescribers and pharmacies must be certified with the program and patients must sign an agreement form and comply with the requirements. Further information about the REVLIMID REMS program is available at www.celgeneriskmanagement.com or by telephone at 1-888-423-5436.

**Hematologic Toxicity:** REVLIMID can cause significant neutropenia and thrombocytopenia. Patients may require dose interruption and/or dose reduction. MCL: Patients taking REVLIMID for MCL should have their complete blood counts monitored weekly for the first cycle (28 days), every 2 weeks during cycles 2-4, and then monthly thereafter. In the MCL trial, Grade 3 or 4 neutropenia was reported in 43% of the patients. Grade 3 or 4 thrombocytopenia was reported in 28% of the patients.

**Venous Thromboembolism:** Venous thromboembolic events (predominantly deep venous thrombosis and pulmonary embolism) have occurred in patients with MCL treated with lenalidomide monotherapy. It is not known whether prophylactic anticoagulation or antiplatelet therapy prescribed in conjunction with REVLIMID may lessen the potential for venous thromboembolism.
Increased Mortality in Patients With CLL: In a clinical trial in the first line treatment of patients with CLL, single agent REVLIMID therapy increased the risk of death as compared to single agent chlorambucil. In an interim analysis, there were 34 deaths among 210 patients on the REVLIMID treatment arm compared to 18 deaths among 211 patients in the chlorambucil treatment arm, and hazard ratio for overall survival was 1.92 [95% CI: 1.08-3.41], consistent with a 92% increase in risk of death. Serious adverse cardiovascular reactions, including atrial fibrillation, myocardial infarction, and cardiac failure occurred more frequently in the REVLIMID treatment arm. REVLIMID is not indicated and not recommended for use in CLL outside of controlled clinical trials.

Second Primary Malignancies: Patients with MM treated with lenalidomide in studies including melphalan and stem cell transplantation had a higher incidence of second primary malignancies, particularly acute myelogenous leukemia (AML) and Hodgkin lymphoma, compared to patients in the control arms who received similar therapy but did not receive lenalidomide. Monitor patients for the development of second malignancies. Take into account both the potential benefit of lenalidomide and the risk of second primary malignancies when considering treatment with lenalidomide.

Hepatotoxicity: Hepatic failure, including fatal cases, has occurred in patients treated with lenalidomide in combination with dexamethasone. The mechanism of drug-induced hepatotoxicity is unknown. Pre-existing viral liver disease, elevated baseline liver enzymes, and concomitant medications may be risk factors. Monitor liver enzymes periodically. Stop REVLIMID upon elevation of liver enzymes. After return to baseline values, treatment at a lower dose may be considered.

Allergic Reactions: Angioedema and serious dermatologic reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported. These events can be fatal. Patients with a prior history of Grade 4 rash associated with thalidomide treatment should not receive REVLIMID. REVLIMID interruption or discontinuation should be considered for Grade 2-3 skin rash. REVLIMID must be discontinued for angioedema, Grade 4 rash, exfoliative or bullous rash, or if SJS or TEN is suspected and should not be resumed following discontinuation for these reactions. REVLIMID capsules contain lactose. Risk-benefit of REVLIMID treatment should be evaluated in patients with lactose intolerance.

Tumor Lysis Syndrome: Fatal instances of tumor lysis syndrome (TLS) have been reported during treatment with lenalidomide. The patients at risk of TLS are those with high tumor burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

Tumor Flare Reaction: Tumor flare reaction (TFR) occurred during investigational use of lenalidomide for CLL and lymphoma, and is characterized by tender lymph node swelling, low grade fever, pain and rash. REVLIMID is not indicated and not recommended for use in CLL outside of controlled clinical trials.

Monitoring and evaluation for TFR is recommended in patients with MCL. Tumor flare may mimic the progression of disease (PD). In patients with Grade 3 or 4 TFR, it is recommended to withhold treatment with lenalidomide until TFR resolves to ≤ Grade 1. In the MCL trial, approximately 10% of subjects experienced TFR; all reports were Grade 1 or 2 in severity. All of the events occurred in cycle 1 and one patient developed TFR again in cycle 11. Lenalidomide may be continued in patients with Grade 1 and 2 TFR without interruption or modification, at the physician’s discretion. Patients with Grade 1 or 2 TFR may also be treated with corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs) and/or narcotic analgesics for management of TFR symptoms. Patients with Grade 3 or 4 TFR may be treated for management of symptoms per the guidance for treatment of Grade 1 and 2 TFR.

ADVERSE REACTIONS

Mantle Cell Lymphoma

- Grade 3 and 4 adverse events reported in ≥5% of patients treated with REVLIMID in the MCL trial (N=134) included neutropenia (43%), thrombocytopenia (28%), anemia (11%), pneumonia (9%), leukopenia (7%), fatigue (7%), diarrhea (6%), dyspnea (6%), and febrile neutropenia (6%)
- Serious adverse events reported in ≥2 patients treated with REVLIMID monotherapy for MCL included chronic obstructive pulmonary disease, clostridium difficile colitis, sepsis, basal cell carcinoma, and supraventricular tachycardia
- Adverse events reported in ≥15% of patients treated with REVLIMID in the MCL trial included neutropenia (49%), thrombocytopenia (36%), fatigue (34%), anemia (31%), diarrhea (31%), nausea (30%), cough (28%), pyrexia (23%), rash (22%), dyspnea (18%), pruritus (17%), peripheral edema (16%), constipation (16%), and leukopenia (15%)
- Adverse events occurring in patients treated with REVLIMID in the MCL trial resulted in at least one dose interruption in 76 (57%) patients, at least one dose reduction in 51 (38%) patients, and discontinuation of treatment in 26 (19%) patients

DRUG INTERACTIONS

Periodic monitoring of digoxin plasma levels, in accordance with clinical judgment and based on standard clinical practice in patients receiving this medication, is recommended during administration of REVLIMID.

USE IN SPECIFIC POPULATIONS

Pregnancy: If pregnancy does occur during treatment, immediately discontinue the drug. Under these conditions, refer patient to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. Any suspected fetal exposure to REVLIMID must be reported to the FDA via the MedWatch program at 1-800-332-1088 and also to Celgene Corporation at 1-888-423-5436.

Nursing Mothers: It is not known whether REVLIMID is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or the drug, taking into account the importance of the drug to the mother.

Pediatric Use: Safety and effectiveness in pediatric patients below the age of 18 have not been established.

Geriatric Use: Since elderly patients are more likely to have decreased renal function, care should be taken in dose selection. Monitor renal function.

Renal Impairment: Since REVLIMID is primarily excreted unchanged by the kidney, adjustments to the starting dose of REVLIMID are recommended to provide appropriate drug exposure in patients with moderate (CLcr 30-60 mL/min) or severe renal impairment (CLcr <30 mL/min) and in patients on dialysis.

REVLIMID is only available through a restricted distribution program, REVLIMID REMS™.

Please see Brief Summary of full Prescribing Information, including Boxed WARNINGS, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and ADVERSE REACTIONS, on the following pages.
INDICATIONS AND USAGE

1. Mantle Cell Lymphoma

REVLIMID® is indicated for the treatment of patients with mantle cell lymphoma (MCL) whose disease has relapsed or progressed after two prior therapies, one of which included bortezomib.

1.4 Limitations of Use:

REVLIMID® is not indicated and is not recommended for the treatment of patients with GLL outside of controlled clinical trials [see Warnings and Precautions (5.5)].

2. DOSAGE AND ADMINISTRATION

REVLIMID® should be taken orally at about the same time each day, either with or without food. REVLIMID capsules should be swallowed whole with water. The capsules should not be opened, broken, or chewed.

2.3 Mantle Cell Lymphoma

The recommended starting dose of REVLIMID® is 25 mg/day orally on Days 1-21 of repeated 28-day cycles for relapsed or refractory mantle cell lymphoma. Treatment should be continued until disease progression or unacceptable toxicity.

Treatment is continued, modified or discontinued based upon clinical and laboratory findings.

Dose Adjustments for Hematologic Toxicities During MCL Treatment

Dose modification guidelines as summarized below are recommended to manage Grade 3 or 4 neutropenia or thrombocytopenia or other Grade 3 or 4 toxicities considered to be related to REVLIMID®.

---

### Platelet counts

<table>
<thead>
<tr>
<th>Thrnombocytopenia during treatment in MCL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>When Platelets</strong></td>
</tr>
<tr>
<td>Fall to &lt; 50,000/mcL</td>
</tr>
<tr>
<td>Return to &lt; 50,000/mcL</td>
</tr>
</tbody>
</table>

### Absolute Neutrophil counts (ANC)

<table>
<thead>
<tr>
<th>Neutropenia during treatment in MCL</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>When Neutrophils</strong></td>
</tr>
<tr>
<td>Fall to &lt; 1000/mcL for at least 7 days OR</td>
</tr>
<tr>
<td>Falls to &lt; 1,000/mcL with an associated temperature ≥ 38.5°C OR</td>
</tr>
<tr>
<td>Falls to &lt; 500/mcL</td>
</tr>
</tbody>
</table>

### Other Grade 3 / 4 Toxicities in MCL

For other Grade 3/4 toxicities judged to be related to REVLIMID®, hold treatment and restart at the physician’s discretion at next lower dose level when toxicity has resolved to ≤ Grade 2.

### Starting Dose Adjustment for Renal Impairment in MCL:

2.4 Starting Dose for Renal Impairment in MCL

Since REVLIMID® is primarily excreted unchanged by the kidney, adjustments to the starting dose of REVLIMID® are recommended to provide appropriate drug exposure in patients with moderate or severe renal impairment and in patients on dialysis. Based on a pharmacokinetic study in patients with renal impairment due to non-malignant conditions, REVLIMID® starting dose adjustment is recommended for patients with CLcr < 60 mL/min. Non-dialysis patients with creatinine clearances less than 11 mL/min and dialysis patients with creatinine clearances less than 7 mL/min have not been studied. The recommendations for initial starting doses for patients with MCL are as follows:

| Table 1: Starting Dose Adjustments for Patients with Renal Impairment in MCL |
|-------------------------------|-----------------|
| Category                      | Renal Function (Cockcroft-Gault) | Dose in MCL |
| Moderate Renal Impairment     | CLcr 30-60 mL/min | 10 mg Every 24 hours |
| Severe Renal Impairment       | CLcr < 30 mL/min (not requiring dialysis) | 15 mg Every 48 hours |
| End Stage Renal Disease       | CLcr < 30 mL/min (requiring dialysis) | 5 mg Once daily. On dialysis days, administer the dose following dialysis. |

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After initiation of REVLIMID® therapy, subsequent REVLIMID® dose modification is based on individual patient treatment tolerance, as described elsewhere (see section 2).
female monkeys who received the drug during pregnancy, similar to birth defects observed in humans following exposure to thalidomide during pregnancy.

REVLIMID is only available through the REVLIMID REMS™ program (formerly known as the “RevAssist™ program”) [see Warnings and Precautions (5.2)].

Females of Reproductive Potential

Females of reproductive potential must avoid pregnancy for at least 4 weeks before initiating REVLIMID therapy, during therapy, during dose interruptions and for at least 4 weeks after completing therapy.

Females must commit either to abstain continuously from heterosexual sexual intercourse or to use two methods of reliable birth control, beginning 4 weeks prior to initiating treatment with REVLIMID, during therapy, during dose interruptions and continuing for 4 weeks following discontinuation of REVLIMID therapy.

Two negative pregnancy tests must be obtained prior to initiating therapy. The first test should be performed within 10-14 days and the second test within 24 hours prior to prescribing REVLIMID therapy and then weekly during the first month, then monthly thereafter in women with regular menstrual cycles or every 2 weeks in women with irregular menstrual cycles [see Use in Specific Populations (8.6)].

Males

Lenalidomide is present in the semen of patients receiving the drug. Therefore, males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking REVLIMID and for up to 28 days after discontinuing REVLIMID, even if they have undergone a successful vasectomy. Male patients taking REVLIMID must not donate sperm [see Use in Specific Populations (8.6)].

Blood Donation

Patients must not donate blood during treatment with REVLIMID and for 1 month following discontinuation of the drug because the blood might be given to a pregnant female patient whose fetus must not be exposed to REVLIMID.

5.2 REVLIMID REMS™ program

Because of the embryo-fetal risk [see Warnings and Precautions (5.1)], REVLIMID is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS), the REVLIMID REMS™ program (formerly known as the “RevAssist™ program”). Required components of the REVLIMID REMS™ program include the following:

- Prescribers must be certified with the REVLIMID REMS™ program by enrolling and complying with the REMS requirements.
- Patients must sign a Patient-Prescriber agreement form and comply with the REMS requirements. In particular, female patients of reproductive potential who are not pregnant must comply with the pregnancy testing and contraception requirements [see Use in Specific Populations (8.6)] and males must comply with contraception requirements [see Use in Specific Populations (8.6)].
- Pharmacies must be certified with the REVLIMID REMS™ program, must only dispense to patients who are authorized to receive REVLIMID and comply with REMS requirements.

Further information about the REVLIMID REMS™ program is available at www.celgenerismanagement.com or by telephone at 1-888-423-5436.

5.3 Hematologic Toxicity

REVLIMID can cause significant neutropenia and thrombocytopenia. Patients taking REVLIMID for MDS should have their complete blood counts monitored weekly for the first 8 weeks and at least monthly thereafter. Patients taking REVLIMID for MM should have their complete blood counts monitored every 2 weeks for the first 12 weeks and then monthly thereafter. Patients taking REVLIMID for MCL should have their complete blood counts monitored weekly for the first cycle (28 days), every 2 weeks during cycles 2-4, and then monthly thereafter. Patients may require dose interruption and/or dose reduction [see Dosage and Administration (2.1, 2.2, 2.3)].

Grade 3 or 4 hematologic toxicity was seen in 80% of patients enrolled in the MDS study. In the 48% of patients who developed Grade 3 or 4 neutropenia, the median time to onset was 42 days (range, 14-411 days), and the median time to documented recovery was 17 days (range, 2-170 days). In the 54% of patients who developed Grade 3 or 4 thrombocytopenia, the median time to onset was 28 days (range, 6-290 days), and the median time to documented recovery was 22 days (range, 5-224 days) [see Boxed Warning and Dosage and Administration (2.1)].

In the pooled MM trials Grade 3 and 4 hematologic toxicities were more frequent in patients treated with the combination of REVLIMID and dexamethasone than in patients treated with dexamethasone alone [see Adverse Reactions (6.1)].

In the MCL trial, Grade 3 or 4 neutropenia was reported in 43% of the patients. Grade 3 or 4 thrombocytopenia was reported in 28% of the patients.

5.4 Venous Thromboembolism

Venous thromboembolic events (predominantly deep venous thrombosis and pulmonary embolism) have occurred in patients with multiple myeloma treated with lenalidomide combined with dexamethasone [see Boxed Warning].

Grade 3 or 4 neutropenia was reported in 28% of the patients. Grade 3 or 4 thrombocytopenia was reported in 28% of the patients.

5.5 Increased Mortality in Patients with CLL

In a prospective randomized (1:1) clinical trial in the first line treatment of patients with chronic lymphocytic leukemia, single-agent dexamethasone plus lenalidomide increased the risk of death as compared to single agent chlorambucil.

In an interim analysis, there were 34 deaths among 210 patients on the REVLIMID treatment arm compared to 18 deaths among 211 patients in the chlorambucil treatment arm, and hazard ratio for overall survival was 1.92 (95% CI: 1.08-3.41), consistent with a 92% increase in the risk of death. The trial was halted for safety in July 2013.

5.6 Second Primary Malignancies

Patients with multiple myeloma treated with lenalidomide in studies including melphalan and stem cell transplantation had a higher incidence of second primary malignancies, particularly acute myelogenous leukemia (AML) and Hodgkin lymphoma, compared to patients in the control arms who received similar therapy but did not receive lenalidomide. Monitor patients for the development of second malignancies. Take into account both the potential benefit of lenalidomide and the risk of second primary malignancies when considering treatment with lenalidomide.

5.7 Hepatotoxicity

Hepatic failure, including fatal cases, has occurred in patients treated with lenalidomide in combination with dexamethasone. In clinical trials, 15% of patients experienced hepatic toxicity (with hepaticcellular, cholestatic and mixed characteristics); 2% of patients with multiple myeloma and 1% of patients with myelodysplasia had severe hepatotoxicity events. The mechanism of drug-induced hepatotoxicity is unknown. Pre-existing viral liver disease, elevated baseline liver enzymes, and concomitant medications may be risk factors. Monitor liver enzymes periodically. Stop REVLIMID upon elevation of liver enzymes. After return to baseline values, treatment at a lower dose may be considered.

5.8 Allergic Reactions

Angioedema and serious dermatologic reactions including melphalan and stem cell transplantation had a higher incidence of second primary malignancies, particularly acute myelogenous leukemia (AML) and Hodgkin lymphoma, compared to patients in the control arms who received similar therapy but did not receive lenalidomide. Monitor patients for the development of second malignancies. Take into account both the potential benefit of lenalidomide and the risk of second primary malignancies when considering treatment with lenalidomide.

5.9 Tumor Lysis Syndrome

Fatal instances of tumor lysis syndrome have been reported during treatment with lenalidomide. The patients at risk of tumor lysis syndrome are those with high tumor burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

5.10 Tumor Flare Reaction

Tumor flare reaction has occurred during investigational use of lenalidomide for CLL and lymphoma, and is characterized by tender lymph node swelling, low grade fever, pain and rash. REVLIMID is not indicated and not recommended for use in CLL outside of controlled clinical trials. Monitoring and evaluation for tumor flare reaction (TFR) is recommended in patients with MCL. Tumor flare reaction may mimic progression of disease (PD). In the MCL trial, 13/134 (10%) of subjects experienced TFR; all reports were Grade 1 or 2 severity. All of the events occurred in cycle 1 and one patient developed TFR again in cycle 11. Lenalidomide may be continued in patients with Grade 1 and 2 TFR without interruption or modification, at the physician’s discretion. Patients with Grade 1 and 2 TFR may also be treated with corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs) and/or narcotic analgesics for management of TFR symptoms. In patients with Grade 3 or 4 TFR, it is recommended to
withhold treatment with lenalidomide until TFR resolves to ≤ Grade 1. Patients with Grade 3 or 4 TFR may be treated for management of symptoms for the guidance of treatment for Grade 1 and 2 TFR.

6 ADVERSE REACTIONS

The following adverse reactions are described in detail in other labeling sections:

- Neutropenia and thrombocytopenia [see Boxed Warnings, Warnings and Precautions (5.3)]
- Deep vein thrombosis and pulmonary embolism [see Boxed Warnings, Warnings and Precautions (5.4)]
- Increased Mortality in Patients with CLL [see Warnings and Precautions (5.5)]
- Second Primary Malignancies [see Warnings and Precautions (5.6)]
- Hepatotoxicity [see Warnings and Precautions (5.7)]
- Allergic Reactions [see Warnings and Precautions (5.8)]
- Tumor lysis syndrome [see Warnings and Precautions (5.9)]
- Tumor flare reactions [see Warnings and Precautions (5.10)]

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.

6.3 Clinical Trials Experience in Mantle Cell Lymphoma

In the MCL trial, a total of 134 patients received at least 1 dose of REVLIMID. Their median age was 67 (range 43-83) years, 128/134 (96%) were Caucasian, 108/134 (81%) were males and 82/134 (61%) had duration of MCL for at least 3 years.

Table 7 summarizes the most frequently observed adverse reactions regardless of relationship to treatment with REVLIMID. Across the 134 patients treated in this study, median duration of treatment was 95 days (1-1002 days). Seventy-eight patients (58%) received 3 or more cycles of therapy, 53 patients (40%) received 6 or more cycles, and 26 patients (19%) received 12 or more cycles. Seventy-six patients (57%) underwent at least one dose interruption due to adverse events, and 51 patients (38%) underwent at least one dose reduction due to adverse events. Twenty-six patients (19%) discontinued treatment due to adverse events.

Table 7: Incidence of Adverse Reactions (≥10%) or Grade 3/4 AE (in at least 2 patients) in Mantle Cell Lymphoma

<table>
<thead>
<tr>
<th>System Organ Class/Preferred Term</th>
<th>All AEs¹ (N=134) n (%)</th>
<th>Grade 3/4 AEs² (N=134) n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General disorders and administration site conditions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>45 (34)</td>
<td>9 (7)</td>
</tr>
<tr>
<td>Pyrexia⁴</td>
<td>31 (23)</td>
<td>3 (2)</td>
</tr>
<tr>
<td>Edema peripheral</td>
<td>21 (16)</td>
<td>0</td>
</tr>
<tr>
<td>Asthenia⁴</td>
<td>19 (14)</td>
<td>4 (3)</td>
</tr>
<tr>
<td>General physical health deterioration</td>
<td>3 (2)</td>
<td>2 (1)</td>
</tr>
<tr>
<td><strong>Gastrointestinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea⁴</td>
<td>42 (31)</td>
<td>8 (6)</td>
</tr>
<tr>
<td>Nausea⁴</td>
<td>40 (30)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Constipation</td>
<td>21 (16)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Vomiting⁴</td>
<td>16 (12)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Abdominal pain⁴</td>
<td>13 (10)</td>
<td>5 (4)</td>
</tr>
<tr>
<td><strong>Musculoskeletal and connective tissue disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Back pain</td>
<td>18 (13)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>17 (13)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>11 (8)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Muscular weakness⁴</td>
<td>8 (6)</td>
<td>2 (1)</td>
</tr>
<tr>
<td><strong>Respiratory, thoracic and mediastinal disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>33 (28)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Dyspnea⁴</td>
<td>24 (18)</td>
<td>8 (6)</td>
</tr>
<tr>
<td>Pleural Effusion</td>
<td>10 (7)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Hypoxia</td>
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<tr>
<td>Pulmonary embolism</td>
<td>3 (2)</td>
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</tr>
<tr>
<td>Respiratory distress⁴</td>
<td>2 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Oropharyngeal pain</td>
<td>13 (10)</td>
<td>0</td>
</tr>
<tr>
<td><strong>Infections and infestations</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia⁵</td>
<td>19 (14)</td>
<td>12 (9)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>17 (13)</td>
<td>0</td>
</tr>
<tr>
<td>Cellulitis⁵</td>
<td>3 (2)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Bacteremia⁴</td>
<td>2 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Staphylococcal sepsis⁴</td>
<td>2 (1)</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Urinary tract infection⁴</td>
<td>5 (4)</td>
<td>2 (1)</td>
</tr>
</tbody>
</table>

(continued)
treatment. Baseline and ongoing monitoring of thyroid function is recommended.

7 Drug Interactions
Results from human in vitro studies show that REVLIMID is neither metabolized by nor inhibits or induces the cytochrome P450 pathway suggesting that lenalidomide is not likely to cause or be subject to P450-based metabolic drug interactions.

In vitro studies demonstrated that REVLIMID is not a substrate of human breast cancer resistance protein (BCRP), multidrug resistance protein (MRP) transporters MRP1, MRP2, or MRP3, organic anion transporters (OAT) OAT1 and OAT3, organic anion transporting polypeptide 1B1 (OATP1B1 or OATP2), organic cation transporters (OCT) OCT1 and OCT2, multidrug and toxin extrusion protein (MATE) MATE1, and organic cation transporters novel (OCTN) OCTN1 and OCTN2.

In vitro, lenalidomide is a substrate, but is not an inhibitor of P-glycoprotein (P-gp).

7.1 Digoxin
When digoxin was co-administered with multiple doses of REVLIMID (10 mg/day) the digoxin Cmax and AUC∞ were increased by 14%. Periodic monitoring of digoxin plasma levels, in accordance with clinical judgment and based on standard clinical practice in patients receiving this medication, is recommended during administration of REVLIMID.

7.2 Warfarin
Co-administration of multiple dose REVLIMID (10 mg) with single dose warfarin (25 mg) had no effect on the pharmacokinetics of total lenalidomide or R- and S-warfarin. Close monitoring of PT and INR is recommended in multiple myeloma patients taking concomitant warfarin.

7.3 Concomitant Therapies That May Increase the Risk of Thrombosis
Erythropoietic agents, or other agents that may increase the risk of thrombosis, are not recommended in multiple myeloma patients taking concomitant warfarin. Dexamethasone and warfarin. Close monitoring of PT and INR is recommended after warfarin administration, but these changes were not affected by concomitant REVLIMID administration. It is not known whether there is an interaction between dexamethasone and warfarin. Close monitoring of PT and INR is recommended in multiple myeloma patients taking concomitant warfarin.

8 Use in Specific Populations
8.1 Pregnancy

Pregnancy Category X (see Boxed Warnings and Contraindications (4.1))

Risk Summary
REVLIMID can cause embryo-fetal harm when administered to a pregnant female and is contraindicated during pregnancy. REVLIMID is a thalidomide analogue.

Thalidomide is a human teratogen, inducing a high frequency of severe and life-threatening birth defects such as amelia (absence of limbs), phocomelia (short limbs), hypoplasia of the bones, absence of bones, external ear abnormalities (including anotia, microtia, small or absent external auditory canals), facial palsy, eye abnormalities (anophthalmos, microphthalmia, and congenital heart defects). Alimentary tract, urinary tract, and genital malformations have also been documented and mortality at or shortly after birth has been reported in about 40% of infants.

Lenalidomide caused thalidomide-type limb defects in monkey offspring. 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 a fetus.

If pregnancy does occur during treatment, immediately discontinue the drug. Under these conditions, refer patient to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. Any suspected fetal exposure to REVLIMID must be reported to the FDA via the MedWatch program at 1-800-332-1088 and also to Celgene Corporation at 1-888-423-5436.

Animal data
In an embryo-fetal developmental toxicity study in monkeys, teratogenicity, including thalidomide-like limb defects, occurred in offspring when pregnant monkeys received oral lenalidomide during organogenesis. Exposure (AUC) in monkeys at the lowest dose was 0.17 times the human exposure at the maximum recommended human dose (MRHD) of 25 mg. Similar studies in pregnant rabbits and rats at 20 times and 200 times the MRHD respectively, produced embryo lethality in rabbits and no adverse reproductive effects in rats.

In a pre- and post-natal development study in rats, animals received lenalidomide from organogenesis through lactation. The study revealed a few adverse effects on the offspring of female rats treated with lenalidomide at doses up to 500 mg/kg (approximately 200 times the human dose of 25 mg based on body surface area). The male offspring exhibited slightly delayed sexual maturation and the female offspring had slightly lower body weight gains during gestation when bred to male offspring. As with thalidomide, the rat model may not adequately address the full spectrum of potential human embryo-fetal developmental effects for lenalidomide.

8.3 Nursing Mothers
It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from lenalidomide, 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.

8.4 Pediatric Use
Safety and effectiveness in pediatric patients below the age of 18 have not been established.

8.5 Geriatric use
REVLIMID has been used in multiple myeloma (MM) clinical trials in patients up to 85 years of age.

Of the 703 MM patients who received study treatment in Studies 1 and 2, 45% were age 65 or over while 12% of patients were age 75 and over. The percentage of patients age 65 or over was not significantly different between the REVLIMID/dexamethasone and placebo/dexamethasone groups. Of the 353 patients who received REVLIMID/dexamethasone, 46% were age 65 and over. In both studies, patients > 65 years of age were more likely than patients ≤ 65 years of age to experience DVT, pulmonary embolism, atrial fibrillation, and renal failure following use of REVLIMID. No differences in efficacy were observed between patients over 65 years of age and younger patients.

REVLIMID has been used in del 5q MDS clinical trials in patients up to 95 years of age.

Of the 148 patients with del 5q MDS enrolled in the major study, 38% were age 65 and over, while 33% were age 75 and over. Although the overall frequency of adverse events (100%) was the same in patients over 65 years of age as in younger patients, the frequency of serious adverse events was higher in patients over 65 years of age than in younger patients (54% vs. 33%). A greater proportion of patients over 65 years of age discontinued from the clinical studies because of adverse events than the proportion of younger patients (27% vs. 16%). No differences in efficacy were observed between patients over 65 years of age and younger patients.

REVLIMID has been used in a mantle cell lymphoma (MCL) clinical trial in patients up to 85 years of age. Of the 134 patients with MCL enrolled in the MCL trial, 63% were age 65 and over, while 22% of patients were age 75 and over. The overall frequency of adverse events was similar in patients over 65 years of age and in younger patients (98% vs. 100%). The overall incidence of grade 3 and 4 adverse events was also similar in these 2 patient groups (79% vs. 78%, respectively). The frequency of serious adverse events was higher in patients over 65 years of age than in younger patients (55% vs. 41%). No differences in efficacy were observed between patients over 65 years of age and younger patients.

Since elderly patients are more likely to have decreased renal function, care should be taken in dose selection. Monitor renal function.

8.6 Females of Reproductive Potential and Males
REVLIMID can cause fetal harm when administered during pregnancy (see Use in Specific Populations (8.1)). Females of reproductive potential must avoid pregnancy 4 weeks before therapy, while taking REVLIMID, during dose interruptions and for at least 4 weeks after completing therapy.

Females
Females of reproductive potential must commit either to abstain continuously from heterosexual sexual intercourse or to use two methods of reliable birth control simultaneously (one highly effective form of contraception – tubal ligation, IUD, hormonal (birth control pills, injections, hormonal patches, vaginal rings or implants) or partner’s vasectomy and one additional effective contraceptive method – male latex or synthetic condom, diaphragm or cervical cap. Contraception must begin 4 weeks prior to initiating treatment with REVLIMID, during therapy, during dose interruptions and continuing for 4 weeks following discontinuation of REVLIMID therapy. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy. Females of reproductive potential should be referred to a qualified provider of contraceptive methods, if needed.

Females of reproductive potential must have 2 negative pregnancy tests before initiating REVLIMID. The first test should be performed within 10-14 days, and the second test within 24 hours prior to prescribing REVLIMID. Once treatment has started and during dose interruptions and continuing for 4 weeks following discontinuation of pregnancy testing for females of reproductive potential should occur weekly during the first 4 weeks of use, then pregnancy testing should be repeated every 4 weeks in females with regular menstrual cycles. If menstrual cycles are irregular, the pregnancy testing should occur every 2 weeks. Pregnancy testing and counseling should be performed if a patient misses her period or if there is any abnormality in her menstrual bleeding. REVLIMID treatment must be discontinued during this evaluation.
Males
Lenalidomide is present in the semen of males who take REVLMID.
Therefore, males must always use a latex or synthetic condom during any
sexual contact with females of reproductive potential while taking
REVLMID, during dose interruptions and for up to 28 days after
discontinuing REVLMID, even if they have undergone a successful
vasectomy. Male patients taking REVLMID must not donate sperm

8.7 Renal Impairment
Since lenalidomide is primarily excreted unchanged by the kidney,
adjustments to the starting dose of REVLMID are recommended to provide
appropriate drug exposure in patients with moderate (CLcr 30-60 mL/min)
or severe renal impairment (CLcr < 30 mL/min) and in patients on dialysis
[see Dosage and Administration (2.4)].

8.8 Hepatic Impairment
No dedicated study has been conducted in patients with hepatic impairment.
The elimination of unchanged lenalidomide is predominantly by the renal
route.

10 OVERDOSE
There is no specific experience in the management of lenalidomide
overdose in patients; although in dose-ranging studies, some patients were
exposed to up to 150 mg and in single-dose studies, some patients were
exposed up to 1000 mg. In studies, the dose-limiting toxicity was essentially hematological. In the event of overdose, supportive care is advised.

13 NONCLINICAL TOXICOLGY
13.1 Carcinogenesis, mutagenesis, impairment of fertility
Carcinogenicity studies with lenalidomide have not been conducted.
Lenalidomide was not mutagenic in the bacterial reverse mutation assay
(Ames test) and did not induce chromosome aberrations in cultured human
peripheral blood lymphocytes, or mutations at the thymidine kinase (tk)
locus of mouse lymphoma L5178Y cells. Lenalidomide did not increase
morphological transformation in Syrian Hamster Embryo assay or induce micronuclei in the polychromatic erythrocytes of the bone marrow of male
rats.
A fertility and early embryonic development study in rats, with administration of lenalidomide up to 500 mg/kg (approximately 200 times
the human dose of 25 mg, based on body surface area) produced no
parental toxicity and no adverse effects on fertility.

17 PATIENT COUNSELING INFORMATION
See FDA-approved Patient labeling (Medication Guide)
Embryo-Fetal Toxicity
Advise patients that REVLMID is contraindicated in pregnancy [see Contraindications (4.1)]. REVLMID is a thalidomide analog and can cause
serious birth defects or death to a developing baby. [see Warnings and
Precautions (5.1) and Use in Specific Populations (8.1)].
• Advise females of reproductive potential that they must avoid pregnancy
while taking REVLMID and for at least 4 weeks after completing therapy.
• Initiate REVLMID treatment in females of reproductive potential only
following a negative pregnancy test.
• Advise females of reproductive potential of the importance of monthly
pregnancy tests and the need to use two different forms of contraception
including at least one highly effective form simultaneously during
REVLMID therapy, during dose interruption and for 4 weeks after she
has completely finished taking REVLMID. Highly effective forms of
contraception other than tubal ligation include IUD and hormonal (birth
control pills, injections, patch or implants) and a partner’s vasectomy.
Additional effective contraceptive methods include latex or synthetic
condom, diaphragm and cervical cap.
• Advise patients not to take REVLMID and contact her doctor
if she becomes pregnant while taking this drug, if she misses
her menstrual period, or experiences unusual menstrual bleeding, if she
stops taking birth control, or if she thinks FOR ANY REASON that she
may be pregnant.
• Advise patients that if her doctor is not available, she can call
1-888-668-2528 for information on emergency contraception [see Warnings and Precautions (5.1) and Use in Specific Populations (8.6)].
• Advise males to always use a latex or synthetic condom during any
sexual contact with females of reproductive potential while taking
REVLMID and for up to 28 days after discontinuing REVLMID, even if
they have undergone a successful vasectomy.
• Advise male patients taking REVLMID that they must not donate sperm
[see Warnings and Precautions (5.1) and Use in Specific Populations (8.6)].
• All patients must be instructed to not donate blood while taking
REVLMID, during dose interruptions and for 1 month following
discontinuation of REVLMID [see Warnings and Precautions (5.1) and
Use in Specific Populations (8.6)].

REVLMID REMS™ program
Because of the risk of embryo-fetal toxicity, REVLMID is only available
through a restricted program called the REVLMID REMS™ program
(formerly known as the “RevAssist®” program) [see Warnings and
Precautions (5.2)].
• Patients must sign a Patient-Prescriber agreement form and comply
with the requirements to receive REVLMID. In particular, females of
reproductive potential must comply with the pregnancy testing,
contraception requirements and participate in monthly telephone
surveys. Males must comply with the contraception requirements [see
Use in Specific Populations (8.6)].
• REVLMID is available only from pharmacies that are certified in
REVLMID REMS™ program. Provide patients with the telephone
number and website for information on how to obtain the product.

Hematologic Toxicity
Inform patients that REVLMID is associated with significant neutropenia
and thrombocytopenia [see Boxed Warnings and Warnings and
Precautions (5.3)].

Venous Thromboembolism
Inform patients that REVLMID/dexamethasone has demonstrated
significant increased risk of DVT and PE in patients with multiple myeloma
[see Boxed Warnings and Warning and Precautions (5.4)].

Increased Mortality in Patients with CLL
Inform patients that REVLMID had increased mortality in patients with CLL
and serious adverse cardiovascular reactions, including atrial fibrillation,
myocardial infarction, and cardiac failure [see Warning and Precautions
(5.5)].

Secondary Primary Malignancies
Inform patients of the potential risk of developing second primary
malignancies during treatment with REVLMID.

Hepatotoxicity
Inform patients of the risk of hepatotoxicity, including hepatic failure and
death, and to report any signs and symptoms associated with this event
to their healthcare provider for evaluation.

Allergic Reactions
Inform patients of the potential for allergic reactions including
hypersensitivity, angioedema, Stevens Johnson Syndrome, or toxic
epidermal necrolysis if they had such a reaction to THALOMID and report
symptoms associated with these events to their healthcare provider for
evaluation.

Tumor Lysis Syndrome
Inform patients of the potential risk of tumor lysis syndrome and to report
any signs and symptoms associated with this event to their healthcare
provider for evaluation.

Tumor Flare Reaction
Inform patients of the potential risk of tumor flare reaction and to report
any signs and symptoms associated with this event to their healthcare
provider for evaluation.

Dosing Instructions
Inform patients to take REVLMID once daily at about the same time each
day, either with or without food. The capsules should not be opened,
broken, or chewed. REVLMID should be swallowed whole with water.

Instruct patients that if they miss a dose of REVLMID, they may still take
it up to 12 hours after the time they would normally take it. If more than
12 hours have elapsed, they should be instructed to skip the dose for that
day. The next day, they should take REVLMID at the usual time. Warn
patients to not take 2 doses to make up for the one that they missed.

Manufactured for: Celgene Corporation
Summit, NJ 07901

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Celgene Corporation.

REVLMID REMS™ is a trademark of Celgene Corporation.

U.S. Pat. Nos. 5,635,517; 6,045,501; 6,281,230; 6,315,720; 6,555,554;
6,561,976; 6,561,977; 6,755,784; 6,908,432; 7,119,106; 7,189,740; 7,468,364;
7,465,800; 7,855,217; 7,968,569

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REV_MCL_HCP_BSv18 11_2013
Take a bite out of G-CSF acquisition costs*

*Based on wholesale acquisition cost (WAC) of all short-acting G-CSF products as of November 11, 2013. WAC represents published catalogue or list prices and may not represent actual transactional prices. Please contact your supplier for actual prices.

Indication

» GRANIX™ (tbo-filgrastim) Injection is a leukocyte growth factor indicated for reduction in the duration of severe neutropenia in patients with nonmyeloid malignancies receiving myelosuppressive anticancer drugs associated with a clinically significant incidence of febrile neutropenia.

Important Safety Information

» **Splenic rupture:** Splenic rupture, including fatal cases, can occur following the administration of human granulocyte colony-stimulating factors (hG-CSFs). Discontinue GRANIX and evaluate for an enlarged spleen or splenic rupture in patients who report upper abdominal or shoulder pain after receiving GRANIX.

» **Acute respiratory distress syndrome (ARDS):** ARDS can occur in patients receiving hG-CSFs. Evaluate patients who develop fever and lung infiltrates or respiratory distress after receiving GRANIX, for ARDS. Discontinue GRANIX in patients with ARDS.

» **Allergic reactions:** Serious allergic reactions, including anaphylaxis, can occur in patients receiving hG-CSFs. Reactions can occur on initial exposure. Permanently discontinue GRANIX in patients with serious allergic reactions. Do not administer GRANIX to patients with a history of serious allergic reactions to filgrastim or pegfilgrastim.
GRANIX™ is another option in short-acting G-CSF therapy

» GRANIX demonstrated a 71% reduction in duration of severe neutropenia (DSN) vs placebo

– GRANIX significantly reduced DSN when compared to placebo (1.1 days vs 3.8 days; \( p<0.001 \))

– Efficacy was evaluated in a multinational, multicenter, randomized, controlled, Phase III study of chemotherapy-naïve patients with high-risk breast cancer receiving doxorubicin (60 mg/m\(^2\) IV bolus)/docetaxel (75 mg/m\(^2\))

» Safety was evaluated in 3 Phase III clinical trials

Important Safety Information (continued)

» Use in patients with sickle cell disease: Severe and sometimes fatal sickle cell crises can occur in patients with sickle cell disease receiving hG-CSFs. Consider the potential risks and benefits prior to the administration of GRANIX in patients with sickle cell disease. Discontinue GRANIX in patients undergoing a sickle cell crisis.

» Potential for tumor growth stimulatory effects on malignant cells: The granulocyte colony-stimulating factor (G-CSF) receptor, through which GRANIX acts, has been found on tumor cell lines. The possibility that GRANIX acts as a growth factor for any tumor type, including myeloid malignancies and myelodysplasia, diseases for which GRANIX is not approved, cannot be excluded.

» Most common treatment-emergent adverse reaction: The most common treatment-emergent adverse reaction that occurred in patients treated with GRANIX at the recommended dose with an incidence of at least 1% or greater and two times more frequent than in the placebo group was bone pain.

Please see brief summary of Full Prescribing Information on adjacent page.

For more information, visit GRANIXhcp.com.

5.1 Warnings and Precautions

5.1.1 Splenic Rupture

Splenic rupture, including fatal cases, can occur following administration of human granulocyte colony-stimulating factors. In patients who report upper abdominal or shoulder pain after receiving GRANIX, discontinue GRANIX and evaluate for an enlarged spleen or splenic rupture.

5.2 Acute Respiratory Distress Syndrome (ARDS)

Acute respiratory distress syndrome (ARDS) can occur in patients receiving human granulocyte colony-stimulating factors. Evaluate patients who develop fever and lung infiltrates or respiratory distress after receiving GRANIX, for ARDS. Discontinue GRANIX in patients with ARDS.

5.3 Allergic Reactions

Serious allergic reactions including anaphylaxis can occur in patients receiving human granulocyte colony-stimulating factors. Reactions can occur on initial exposure. The administration of antihistamines, steroids, bronchodilators, and/or epinephrine may reduce the severity of the reactions. Permanently discontinue GRANIX in patients with serious allergic reactions. Do not administer GRANIX to patients with a history of serious allergic reactions to filgrastim or pegfilgrastim.

5.4 Use in Patients with Sickle Cell Disease

Severe and sometimes fatal sickle cell crises can occur in patients with sickle cell disease receiving human granulocyte colony-stimulating factors. Consider the potential risks and benefits prior to the administration of human granulocyte colony-stimulating factors in patients with sickle cell disease. Discontinue GRANIX in patients undergoing a sickle cell crisis.

5.5 Potential for Tumor Growth Stimulatory Effects on Malignant Cells

The granulocyte colony-stimulating factor (G-CSF) receptor through which GRANIX acts has been found on tumor cell lines. The possibility that GRANIX acts as a growth factor for any tumor type, including myeloid malignancies and myeloid leukemia, is not excluded. Discontinue GRANIX in patients with non-myeloid malignancies receiving myelosuppressive anti-cancer drugs associated with a clinically significant incidence of febrile neutropenia.

6. Adverse Reactions

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

- Splenic Rupture [see Warnings and Precautions (5.1)]
- Acute Respiratory Distress Syndrome [see Warnings and Precautions (5.2)]
- Serious Allergic Reactions [see Warnings and Precautions (5.3)]
- Use in Patients with Sickle Cell Disease [see Warnings and Precautions (5.4)]
- Potential for Tumor Growth Stimulatory Effects on Malignant Cells [see Warnings and Precautions (5.5)]

The most common treatment-emergent adverse reaction that occurred at an incidence of at least 1% or greater in patients treated with GRANIX at the recommended dose and was numerically two times more frequent than in the placebo group was bone pain.

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 clinical practice. GRANIX clinical trials safety data are based upon the results of three randomized clinical trials in patients receiving myeloablative chemotherapy for breast cancer (N=348), lung cancer (N=240) and non-Hodgkin’s lymphoma (N=92). In the breast cancer study, 99% of patients were female, the median age was 50 years, and 86% of patients were Caucasian. In the lung cancer study, 80% of patients were male, the median age was 58 years, and 95% of patients were Caucasian. In the non-Hodgkin’s lymphoma study, 52% of patients were male, the median age was 55 years, and 88% of patients were Caucasian. In all three studies a placebo (Cycle 1 of the breast cancer study only) or a non-US-approved filgrastim product were used as controls. In all studies with GRANIX and the non-US-approved filgrastim product were administered at 5 mcg/kg subcutaneously once daily beginning one day after chemotherapy for at least five days and continued to a maximum of 14 days or until an ANC of ≥10,000 x 10^9/L after nadir was reached.

Bone pain was the most frequent treatment-emergent adverse reaction that occurred in at least 1% or greater in patients treated with GRANIX at the recommended dose and was numerically two times more frequent than in the placebo group. The overall incidence of bone pain in Cycle 1 of treatment was 3.4% (3.4% GRANIX, 1.4% placebo, 7.5% non-US-approved filgrastim product).

5.6.1 Leukocytosis

In clinical studies, leukocytosis (WBC counts > 100,000 x 10^9/L) was observed in less than 1% of patients with non-myeloid malignancies receiving GRANIX. No complications attributable to leukocytosis were reported in clinical studies.

5.7 Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity. The incidence of antibody development in patients receiving GRANIX has not been adequately determined.

7. Drug Interactions

No formal drug interaction studies between GRANIX and other drugs have been performed.

Drugs which may potentiate the release of neutrophils, such as lithium, should be used with caution. Increased hematopoietic activity of the bone marrow in response to growth factor therapy has been associated with transient positive bone imaging changes. This should be considered when interpreting bone-imaging results.

8. Use in Specific Populations

8.1 Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies of GRANIX in pregnant women. In an embryofetal developmental study, treatment of pregnant rabbits with tbo-flgrastim resulted in adverse embryofetal findings, including increased spontaneous abortion and fetal malformations at a maternally toxic dose. GRANIX should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

In the embryofetal developmental study, pregnant rabbits were administered subcutaneous doses of tbo-flgrastim during the period of organogenesis at 1, 10 and 100 mcg/kg/day. Increased abortions were evident in rabbits treated with tbo-flgrastim at 100 mcg/kg/day. This dose was maternally toxic as demonstrated by reduced body weight. Other embryofetal findings at this dose level consisted of post-implantation loss, decrease in mean live litter size and fetal weight, and fetal malformations such as malformed hindlimbs and cleft palate. The dose of 100 mcg/kg/day corresponds to a systemic exposure (AUC0-24) of approximately 50-90 times the exposures observed in patients treated with the clinical tbo-flgrastim dose of 5 mcg/kg/day.

8.3 Nursing Mothers

It is not known whether tbo-flgrastim is secreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when GRANIX is administered to a nursing woman. Other recombinant G-CSF products are poorly secreted in breast milk and G-CSF is not orally absorbed by neonates.

8.4 Pediatric Use

The safety and effectiveness of GRANIX in pediatric patients have not been established.

8.5 Geriatric Use

Among 677 cancer patients enrolled in clinical trials of GRANIX, a total of 111 patients were 65 years of age and older. No overall differences in safety or effectiveness were observed between patients age 65 and older and younger patients.

8.6 Renal Impairment

The safety and efficacy of GRANIX have not been studied in patients with moderate or severe renal impairment. No dose adjustment is recommended for patients with mild renal impairment.

8.7 Hepatic Impairment

The safety and efficacy of GRANIX have not been studied in patients with hepatic impairment.

10. Overdosage

No case of overdose has been reported.
IMBRUVICA™ is indicated for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. This indication is based on overall response rate. An improvement in survival or disease-related symptoms has not been established.

INDICATION - IMBRUVICA™ is indicated for the treatment of patients with chronic lymphocytic leukemia (CLL) who have received at least one prior therapy. This indication is based on overall response rate. An improvement in survival or disease-related symptoms has not been established.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

Hemorrhage –

Five percent of patients with MCL and 6% of patients with CLL had Grade 3 or higher bleeding events (subdural hematoma, ecchymoses, gastrointestinal bleeding, and hematuria). Overall, bleeding events including bruising of any grade occurred in 48% of patients with MCL treated with 560 mg daily and 63% of patients with CLL treated at 420 mg daily.

The mechanism for the bleeding events is not well understood. IMBRUVICA™ may increase the risk of hemorrhage in patients receiving antiplatelet or anticoagulant therapies. Consider the benefit-risk of withholding IMBRUVICA™ for at least 3 to 7 days pre and post-surgery depending upon the type of surgery and the risk of bleeding.

Infections - Fatal and non-fatal infections have occurred with IMBRUVICA™ therapy. At least 25% of patients with MCL and 35% of patients with CLL had infections Grade 3 or greater NCI Common Terminology Criteria for Adverse Events (CTCAE). Monitor patients for fever and infections and evaluate promptly.

Myelosuppression - Treatment-emergent Grade 3 or 4 cytopenias were reported in 41% of patients with MCL and 35% of patients with CLL. These included neutropenia (29%), thrombocytopenia (17%) and anemia (9%) in patients with MCL and neutropenia (27%) and thrombocytopenia (10%) in patients with CLL. Monitor complete blood counts monthly.

Renal Toxicity - Fatal and serious cases of renal failure have occurred with IMBRUVICA™ therapy. Treatment-emergent increases in creatinine levels up to 1.5 times the upper limit of normal occurred in 67% of patients with MCL and 23% of patients with CLL. Increases in creatinine 1.5 to 3 times the upper limit of normal occurred in 9% of patients with MCL and 4% of patients with CLL. Periodically monitor creatinine levels. Maintain hydration.

Second Primary Malignancies - Other malignancies have occurred in 5% of patients with MCL and 10% of patients with CLL who have been treated with IMBRUVICA™. Four percent of patients with MCL had skin cancers, and 1% had other carcinomas. Eight percent of patients with CLL had skin cancers and 2% had other carcinomas.

Embryo-Fetal Toxicity - Based on findings in animals, IMBRUVICA™ can cause fetal harm when administered to a pregnant woman. Advise women to avoid becoming pregnant while taking IMBRUVICA™. 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 a fetus.

ADVERSE REACTIONS –

MCL: The most commonly occurring adverse reactions (≥20%) in the clinical trial were thrombocytopenia*, diarrhea (51%), neutropenia*, anemia*, fatigue (41%), musculoskeletal pain (37%), peripheral edema (35%), upper respiratory tract infection (34%), nausea (31%), bruising (30%), dyspnea (27%), constipation (25%), rash (25%), abdominal pain (24%), vomiting (23%), and decreased appetite (21%).

Treatment-emergent decreases (all grades) of platelets (7%), neutrophils (47%) and hemoglobin (41%) were based on laboratory measurements and adverse reactions.

CYTOKINE REACTIONS –

Five percent of patients discontinued treatment due to adverse reactions in the trial (N=48). These included 3 patients (6%) with infections and 2 patients (4%) with subdural hematomas. Adverse reactions leading to dose reduction occurred in 13% of patients.

DRUG INTERACTIONS

CYP3A Inhibitors - Avoid concomitant administration with strong or moderate inhibitors of CYP3A. If a moderate CYP3A inhibitor must be used, reduce the IMBRUVICA™ dose.

CYP3A Inducers - Avoid co-administration with strong CYP3A inducers.

SPECIAL POPULATIONS - Hepatic Impairment - Avoid use in patients with baseline hepatic impairment.

Please review the Brief Summary of full Prescribing Information on the following page.

Learn more at www.IMBRUVICA.com
Brief Summary of Prescribing Information for IMBRUVICA™ (ibrutinib)
IMBRUVICA™ (ibrutinib) capsules, for oral use

See package insert for Full Prescribing Information

INDICATIONS AND USAGE
IMBRUVICA is indicated for the treatment of patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. This indication is based on overall response rate. An improvement in survival or disease-related symptoms has not been established [see Clinical Studies (14.1) in full Prescribing Information].

CONTRAINDICATIONS
None

WARNINGS AND PRECAUTIONS
Hemorrhage: Five percent of patients with MCL and 6% of patients with CLL had Grade 3 or higher bleeding events (subdural hematoma, ecchymoses, gastrointestinal bleeding, and hematuria). Overall, bleeding events including bruising of any grade occurred in 48% of patients with MCL treated with 560 mg daily and 63% of patients with CLL treated at 420 mg daily. The mechanism for the bleeding events is not well understood. IMBRUVICA may increase the risk of hemorrhage in patients receiving antithrombotic or anticoagulant therapies.

Consider the benefit-risk of withholding IMBRUVICA for at least 3 to 7 days pre and post-surgery depending upon the type of surgery and the risk of bleeding [see Clinical Studies (14.1) in full Prescribing Information].

Infections: Fatal and non-fatal infections have occurred with IMBRUVICA therapy. At least 25% of patients with MCL and 35% of patients with CLL had infections Grade 3 or greater NCI Common Terminology Criteria for Adverse Events (CTCAE) [see Adverse Reactions]. Monitor patients for fever and infections and evaluate promptly.

Myelosuppression: Treatment-emergent Grade 3 or 4 cytopenias were reported in 41% of patients with MCL and 35% of patients with CLL treated. These included neutropenia (29%), thrombocytopenia (17%) and anemia (8%) in patients with MCL and neutropenia (27%) and thrombocytopenia (10%) in patients with CLL.

Monitor complete blood counts monthly.

Renal Toxicity: Fatal and serious cases of renal failure have occurred with IMBRUVICA therapy. Treatment-emergent increases in creatinine levels up to 1.5 times the upper limit of normal occurred in 67% of patients with MCL and 23% of patients with CLL. Increases in creatinine 1.5 to 3 times the upper limit of normal occurred in 9% of patients with MCL and 4% of patients with CLL. Periodically monitor creatinine levels. Maintain hydration.

Second Primary Malignancies: Other malignancies have occurred in 5% of patients with MCL and 10% of patients with CLL who have been treated with IMBRUVICA. Four percent of patients with MCL, had skin cancers and 1% had other carcinomas. Eight percent of patients with CLL had skin cancers and 2% had other carcinomas.

Embryo-Fetal Toxicity: Based on findings in animals, IMBRUVICA can cause fetal harm when administered to a pregnant woman. Ibrutinib causes malformations in rats at exposures 14 times those reported in patients with MCL and 23 times those reported in patients with CLL, receiving the ibrutinib dose of 560 mg per day and 420 mg per day, respectively. Reduced fetal weights were observed at lower exposures. Advise women to avoid becoming pregnant while taking IMBRUVICA. 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 a fetus [see Use in Specific Populations].

ADVERSE REACTIONS
The following adverse reactions are discussed in more detail in other sections of the labeling:

- Hemorrhage [see Warnings and Precautions]
- Infections [see Warnings and Precautions]
- Myelosuppression [see Warnings and Precautions]
- Renal Toxicity [see Warnings and Precautions]
- Second Primary Malignancies [see Warnings and Precautions]

Because clinical trials are conducted under widely variable conditions, adverse event rates observed in clinical trials of a drug cannot be directly compared with rates of clinical trials of another drug and may not reflect the rates observed in practice.

Mantle Cell Lymphoma: The data described below reflect exposure to IMBRUVICA in a clinical trial that included 111 patients with previously treated MCL treated with 560 mg daily with a median treatment duration of 8.3 months.

IMBRUVICA™ (ibrutinib) capsules
The most commonly occurring adverse reactions (≥ 20%) were thrombocytopenia, diarrhea, neutropenia, anemia, fatigue, musculoskeletal pain, peripheral edema, upper respiratory tract infection, nausea, bruising, dyspnea, constipation, rash, abdominal pain, vomiting and decreased appetite (see Tables 1 and 2).

The most common Grade 3 or 4 non-hematological adverse reactions (≥5%) were pneumonia, abdominal pain, atrial fibrillation, diarrhea, fatigue, and skin infections.

Adverse reactions from the MCL trial (N=111) using single agent IMBRUVICA 560 mg daily occurring at a rate of ≥ 10% are presented in Table 1.

Table 1: Non-Hematologic Adverse Reactions in ≥10% of Patients with Mantle Cell Lymphoma (N=111)

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>All Grades (%</th>
<th>Grade 3 or 4 (%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea</td>
<td>51</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>31</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
<td>24</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Stomatitis</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Dysepsis</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Infections and administrative site conditions</td>
<td>Upper respiratory tract infection</td>
<td>34</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Urinary tract infection</td>
<td>14</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Pneumonia</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Skin infections</td>
<td>14</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Sinusitis</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>General disorders and subcutaneous tissue disorders</td>
<td>Fatigue</td>
<td>41</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Periphereral edema</td>
<td>35</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Pyrexia</td>
<td>18</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Anesthesia</td>
<td>14</td>
<td>3</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Bruising</td>
<td>30</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Rash</td>
<td>25</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Petechiae</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Musculoskeletal pain</td>
<td>37</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Muscle spasms</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Arthralgia</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Dyspnea</td>
<td>27</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Cough</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Epistaxis</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Decreased appetite</td>
<td>21</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Dehydration</td>
<td>12</td>
<td>4</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Dizziness</td>
<td>14</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>13</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 2: Treatment-Emergent* Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with MCL (N=111)

<table>
<thead>
<tr>
<th>Percent of Patients (N=111)</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets Decreased</td>
<td>57</td>
<td>17</td>
</tr>
<tr>
<td>Neutrophils Decreased</td>
<td>47</td>
<td>29</td>
</tr>
<tr>
<td>Hemoglobin Decreased</td>
<td>41</td>
<td>9</td>
</tr>
</tbody>
</table>

* Based on laboratory measurements and adverse reactions

Ten patients (9%) discontinued treatment due to adverse reactions in the trial (N=111). The most frequent adverse reaction leading to treatment discontinuation was subdural hematoma (11%). Adverse reactions leading to dose reduction occurred in 14% of patients.

Patients with MCL who develop lymphocytosis greater than 400,000/mL have developed intracranial hemorrhage, lethargy, gait instability, and headache. However, some of these cases were in the setting of disease progression.

Forty percent of patients had elevated uric acid levels on study including 13% with values above 10 mg/dL. Adverse reaction of hyperuricemia was reported for 15% of patients.

Chronic Lymphocytic Leukemia: The data described below reflect exposure to IMBRUVICA in a clinical trial that included 48 patients with previously treated CLL treated with 420 mg daily with a median treatment duration of 15.6 months.
IMBRUVICA™ (ibrutinib) capsules

The most commonly occurring adverse reactions (≥ 20%) were thrombocytopenia, diarrhea, bruising, neutropenia, anemia, upper respiratory tract infection, fatigue, musculoskeletal pain, rash, pyrexia, constipation, peripheral edema, arthralgia, nausea, stomatitis, sinusitis, and dizziness. (See Tables 3 and 4). The most common Grade 3 or 4 non-hematological adverse reactions (≥ 5%) were pneumonia, hypertension, atrial fibrillation, sinusitis, skin infection, dehydration, and musculoskeletal pain.

Adverse reactions from the CLL trial (N=48) using single agent IMBRUVICA 420 mg daily occurring at a rate of ≥ 10% are presented in Table 3.

Table 3: Non-Hematologic Adverse Reactions in ≥ 10% of Patients with Chronic Lymphocytic Leukemia (N=48)

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Preferred Term</th>
<th>All Grades (%)</th>
<th>Grade 3 or 4 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>Diarrhea</td>
<td>63</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Constipation</td>
<td>22</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Nausea</td>
<td>21</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Stomatitis</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Vomiting</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Abdominal pain</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Dyspepsia</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td>Upper respiratory tract infection</td>
<td>48</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Sinusitis</td>
<td>21</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Skin infection</td>
<td>17</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Pneumonia</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>Urinary tract infection</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>General disorders and administrative site conditions</td>
<td>Fatigue</td>
<td>31</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Pyrexia</td>
<td>25</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Peripheral edema</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Asthenia</td>
<td>13</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Chills</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Bruising</td>
<td>54</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Rash</td>
<td>27</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Petechiae</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Cough</td>
<td>19</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Oropharyngeal pain</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Dyspnea</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Musculoskeletal pain</td>
<td>27</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Arthralgia</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Muscle spasms</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Dizziness</td>
<td>21</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Headache</td>
<td>19</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Peripheral neuropathy</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Metabolism and nutrition disorders</td>
<td>Decreased appetite</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>Neoplasms benign, malignant, unspecified</td>
<td>Second malignancies*</td>
<td>10*</td>
<td>0</td>
</tr>
<tr>
<td>Injury, poisoning and procedural complications</td>
<td>Laceration</td>
<td>10</td>
<td>2</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>Anxiety</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Insomnia</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Hypertension</td>
<td>17</td>
<td>8</td>
</tr>
</tbody>
</table>

*One patient death due to histiocytic sarcoma.

Table 4: Treatment-Emergent Decrease of Hemoglobin, Platelets, or Neutrophils in Patients with CLL (N=48)

<table>
<thead>
<tr>
<th></th>
<th>Percent of Patients (N=48)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
</tr>
<tr>
<td>Platelets Decreased</td>
<td>71</td>
</tr>
<tr>
<td>Neutrophils Decreased</td>
<td>54</td>
</tr>
<tr>
<td>Hemoglobin Decreased</td>
<td>44</td>
</tr>
</tbody>
</table>

* Based on laboratory measurements per IWCLL criteria and adverse reactions

IMBRUVICA™ (ibrutinib) capsules

Five patients (10%) discontinued treatment due to adverse reactions in the trial (N=48). These included 3 patients (6%) with infections and 2 patients (4%) with subdural hematomas. Adverse reactions leading to dose reduction occurred in 13% of patients.

Thirty-eight percent of patients had shifts from normal to elevated uric acid levels on study including 4% with values above 10 mg/dL.

DRUG INTERACTIONS

Ibrutinib is primarily metabolized by cytochrome P450 enzyme 3A.

CYP3A Inhibitors: In healthy volunteers, co-administration of ketoconazole, a strong CYP3A inhibitor, increased Cmax and AUC of ibrutinib by 29- and 24-fold, respectively. The highest ibrutinib dose evaluated in clinical trials was 12.5 mg/kg (actual doses of 840 – 1400 mg) given for 28 days with single dose AUC values of 1445 ± 869 ng•h/mL which is approximately 50% greater than steady state exposures seen at the highest indicated dose (560 mg). Avoid concomitant administration of IMBRUVICA with strong or moderate inhibitors of CYP3A. For strong CYP3A inhibitors used short-term (e.g., antifungals and antibiotics for 7 days or less, e.g., ketoconazole, itraconazole, voriconazole, posaconazole, clarithromycin, telithromycin) consider interrupting IMBRUVICA therapy during the duration of inhibitor use. Avoid strong CYP3A inhibitors that are needed chronically. If a moderate CYP3A inhibitor must be used, reduce the IMBRUVICA dose. Patients taking concomitant strong or moderate CYP3A4 inhibitors should be monitored more closely for signs of IMBRUVICA toxicity [see Dosage and Administration (2.4) in full Prescribing Information].

Avoid grapefruit and Seville oranges during IMBRUVICA treatment, as these contain moderate inhibitors of CYP3A [see Dosage and Administration (2.4), and Clinical Pharmacology (12.3) in full Prescribing Information].

CYP3A Inducers: Administration of IMBRUVICA with strong inducers of CYP3A decrease ibrutinib plasma concentrations by approximately 10-fold. Avoid concomitant use of strong CYP3A inducers (e.g., carbamazepine, rifampin, phenytoin and St. John’s Wort). Consider alternative agents with less CYP3A induction [see Clinical Pharmacology (12.3) in full Prescribing Information].

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Category D [see Warnings and Precautions].

Risk Summary: Based on findings in animals, IMBRUVICA can cause fetal harm when administered to a pregnant woman. If IMBRUVICA is used during pregnancy or if the patient becomes pregnant while taking IMBRUVICA, the patient should be apprised of the potential hazard to the fetus.

Animal Data: Ibrutinib was administered orally to pregnant rats during the period of organogenesis at oral doses of 10, 40 and 80 mg/kg/day. Ibrutinib at a dose of 80 mg/kg/day was associated with visceral malformations (heart and major vessels) and increased post-implantation loss. The dose of 80 mg/kg/day in animals is approximately 14 times the exposure (AUC) in patients with MCL and 20 times the exposure in patients with CLL administered the dose of 560 mg daily, respectively. Ibrutinib at doses of 40 mg/kg/day or greater was associated with decreased fetal weights. The dose of 40 mg/kg/day in animals is approximately 6 times the exposure (AUC) in patients with MCL administered the dose of 560 mg daily.

Nursing Mothers: It is not known whether ibrutinib is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from IMBRUVICA, 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 IMBRUVICA in pediatric patients has not been established.

Geriatric Use: Of the 111 patients treated for MCL, 63% were 65 years of age or older. No overall differences in effectiveness were observed between these patients and younger patients. Cardiac adverse events (atrial fibrillation and hypertension), infections (pneumonia and cellulitis) and gastrointestinal events (diarrhea and dehydration) occurred more frequently among elderly patients (80% of patients 65 and older versus 61% of younger patients).

Renal Impairment: Less than 1% of ibrutinib is excreted renally. Ibrutinib exposure is not altered in patients with Creatinine clearance (CLcr) > 25 mL/min. There are no data in patients with severe renal impairment (CLcr < 25 mL/min) or patients on dialysis [see Clinical Pharmacology (12.3) in full Prescribing Information].
**Hepatic Impairment:** Ibrutinib is metabolized in the liver and significant increases in exposure of ibrutinib are expected in patients with hepatic impairment. Patients with serum aspartate transaminase (AST/SGOT) or alanine transaminase (ALT/SGPT) ≥ 3.0 x upper limit of normal (ULN) were excluded from IMBRUVICA clinical trials. There is insufficient data to recommend a dose of IMBRUVICA in patients with baseline hepatic impairment [see Clinical Pharmacology (12.3) in full Prescribing Information].

**Females and Males of Reproductive Potential:** Advise women to avoid becoming pregnant while taking IMBRUVICA because IMBRUVICA can cause fetal harm [see Use in Specific Populations].

**PATIENT COUNSELING INFORMATION**

See FDA-approved patient labeling (Patient Information)

- **Hemorrhage:**
  Inform patients of the possibility of bleeding, and to report any signs or symptoms (blood in stools or urine, prolonged or uncontrolled bleeding). Inform the patient that IMBRUVICA may need to be interrupted for medical or dental procedures [see Warnings and Precautions].

- **Infections:**
  Inform patients of the possibility of serious infection, and to report any signs or symptoms (fever, chills) suggestive of infection [see Warnings and Precautions].

- **Renal toxicity:**
  Inform patients of the possibility of renal toxicity. Advise patients to maintain adequate hydration [see Warnings and Precautions].

- **Second primary malignancies:**
  Inform patients that other malignancies have occurred in patients who have been treated with IMBRUVICA, including skin cancers and other carcinomas [see Warnings and Precautions].

- **Embryo-fetal toxicity:**
  Advise women of the potential hazard to a fetus and to avoid becoming pregnant [see Warnings and Precautions].

- **Inform patients to take IMBRUVICA orally once daily according to their physician’s instructions and that the capsules should be swallowed whole with a glass of water without being opened, broken, or chewed at approximately the same time each day [see Dosage and Administration (2.1) in full Prescribing Information].

- **Advise patients that in the event of a missed daily dose of IMBRUVICA, it should be taken as soon as possible on the same day with a return to the normal schedule the following day. Patients should not take extra capsules to make up the missed dose [see Dosage and Administration (2.5) in full Prescribing Information].

- **Advise patients of the common side effects associated with IMBRUVICA [see Adverse Reactions]. Direct the patient to a complete list of adverse drug reactions in PATIENT INFORMATION.**

- **Advise patients to inform their health care providers of all concomitant medications, including prescription medicines, over-the-counter drugs, vitamins, and herbal products [see Drug Interactions].

- **Advise patients that they may experience loose stools or diarrhea, and should contact their doctor if their diarrhea persists.**

Active ingredient made in China.

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Pharmacyclics, Inc.
Sunnyvale, CA USA 94085
and
Marketed by:
Janssen Biotech, Inc.
Horsham, PA USA 19044

Patent http://www.imbruvica.com

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• Evaluate the role of new diagnostic techniques and therapeutic approaches as applied to the care and management of people with blood diseases
• Discuss new patient management and care strategies with leading faculty in the field

Check the website for updates and to register at www.hematology.org/attendhoala.

CME Credits
This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the American Society of Hematology and the Associação Brasileira de Hematologia, Hemoterapia e Terapia Celular (ABHH). The American Society of Hematology is accredited by the ACCME to provide continuing medical education for physicians.

The American Society of Hematology designates this live educational activity for a maximum of 10 AMA PRA Category 1 Credit(s)™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Brazilian CNA Credits
ABHH is accredited by the CNA (National Accreditation Commission) to provide continuing medical education for physicians that have Specialist Certificates.
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**Important Safety Information**

- Treatment with Jakafi can cause thrombocytopenia, anemia and neutropenia, which are each dose-related effects, with the most frequent being thrombocytopenia and anemia. Perform a pre-treatment complete blood count (CBC) and monitor CBCs every 2 to 4 weeks until doses are stabilized, and then as clinically indicated.
- Thrombocytopenia was generally reversible and was usually managed by reducing the dose or temporarily interrupting Jakafi. Platelet transfusions may be necessary.
- Patients developing anemia may require blood transfusions and/or dose modifications of Jakafi.
- Severe neutropenia (ANC <0.5 × 10^9/L) was generally reversible. Withhold Jakafi until recovery.
- Serious bacterial, mycobacterial, fungal and viral infections may occur. Active serious infections should have resolved before starting Jakafi. Tuberculosis (TB) has been reported; attention should be given to the possibility of latent or active TB. Observe patients receiving Jakafi for signs and symptoms of infection and initiate appropriate treatment promptly.
- Progressive multifocal leukoencephalopathy (PML) has been reported with ruxolitinib treatment for myelofibrosis. If PML is suspected, stop Jakafi and evaluate.

**Indications and Usage**

Jakafi is indicated for treatment of patients with intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis.

**MYELOFIBROSIS** is a serious hematologic malignancy driven by overactive JAK1 and JAK2 signaling."

*Jakafi® is the first and only FDA-approved drug treatment for intermediate or high-risk MYELOFIBROSIS.

**JAK** is Janus-associated kinase.

**JAK**1,2

**COMFORT-I** = COntrolled MyeloFibrosis study with ORal JAK inhibitor Treatment (I); TSS = Total Symptom Score.

**Indications and Usage**

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The first and only FDA-approved drug treatment for intermediate or high-risk MYELOFIBROSIS

Target the JAK pathway—treat the disease

Jakafi inhibits both JAK1 and JAK2 signaling, an underlying mechanism of disease, and significantly improves splenomegaly and symptoms4,5

![Graph showing percentage of patients with ≥35% reduction in spleen volume and ≥50% improvement in TSS](image)

- Advise patients about early signs and symptoms of herpes zoster and to seek early treatment
- The three most frequent non-hematologic adverse reactions were bruising, dizziness and headache
- A dose modification is recommended when administering Jakafi with strong CYP3A4 inhibitors or in patients with renal or hepatic impairment. Patients should be closely monitored and the dose titrated based on safety and efficacy
- Use of Jakafi during pregnancy is not recommended and should only be used if the potential benefit justifies the potential risk to the fetus. Women taking Jakafi should not breast-feed

Please see Brief Summary of Full Prescribing Information for Jakafi on the following page.

Table 2: Worst Hematology Laboratory Abnormalities in the Placebo-controlled Studya

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>All Grades1 (n=155)</th>
<th>Grade 3 (n=3)</th>
<th>Grade 4 (n=4)</th>
<th>All Grades1 (n=151)</th>
<th>Grade 3 (n=4)</th>
<th>Grade 4 (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>60.7</td>
<td>3.9</td>
<td>0.0</td>
<td>61.3</td>
<td>4.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Anemia</td>
<td>96.1</td>
<td>34.2</td>
<td>11.0</td>
<td>96.1</td>
<td>34.2</td>
<td>11.0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>18.7</td>
<td>5.2</td>
<td>1.9</td>
<td>20.8</td>
<td>5.9</td>
<td>1.3</td>
</tr>
</tbody>
</table>

a Presented values were worst Grade values regardless of baseline.

Additional Data from the Placebo-controlled Study: A total of 25.2% of patients treated with Jakafi and 7.3% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in platelet counts (AST), and there was no incidence of greater than Grade 1 abnormalities in platelet counts. Jakafi was associated with a 1.5% incidence of Grade 3 and Grade 4 ATE events. 17.4% of patients treated with Jakafi and 6.0% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in platelet counts. The incidence of Grade 2 ATE events was 0.6% for Jakafi and 0.0% for placebo. 16.8% of patients treated with placebo developed newly occurring or worsening Grade 1 abnormalities in platelet counts. The incidence of Grade 2 ATE events was 0.6% for Jakafi and 0.0% for placebo.

HUG INTERACTIONS Drugs That Affect or Induce Cytochrome P450 Enzymes Ruxolitinib is predominantly metabolized by CYP3A4. Strong CYP3A4 inhibitors increased 33% and 91%, respectively, with Jakafi administration (10 mg single dose) following ketoconazole (50 mg single dose) for four days, completely the clinical exposure at the maximum recommended dose. In prolonged from 3.7 to 6.0 hours with concurrent use of ketoconazole. The change in the pharmacodynamic marker, PSTAT3 inhibition, was consistent with the corresponding ruxolitinib AUC following concurrent administration with ketoconazole. When administering Jakafi with strong CYP3A4 inhibitors a dose reduction is recommended as the exposure increased approximately 3.0-fold compared to receiving Jakafi alone in healthy subjects. In addition, the relative exposure to ruxolitinib’s active metabolites increased approximately 12-fold with concomitant use. The plasma clearance of Jakafi may be markedly reduced with concurrent use of strong CYP3A4 inhibitors, including in pregnant women. In the randomized placebo-controlled study, ruxolitinib was administered in an exposure-adjusted fashion (AUC) that is approximately 4 times the clinical exposure at the maximum recommended dose of 25 mg twice daily. In the placebo-controlled study, ruxolitinib was administered in an exposure-adjusted fashion (AUC) that is approximately 4 times the clinical exposure at the maximum recommended dose of 25 mg twice daily. In the placebo-controlled study, ruxolitinib was administered in an exposure-adjusted fashion (AUC) that is approximately 4 times the clinical exposure at the maximum recommended dose of 25 mg twice daily.

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Share your latest lymphoma-related research

The first ASH Meeting on Lymphoma Biology will bring together world-class experts in lymphoma research to review the state of the science and to identify current challenges and the next steps to move the field forward. The goal of this meeting is to further the understanding of lymphoma pathogenesis and to accelerate new therapies by providing a forum for scientific exchange and by developing a road map for lymphoma research.

The format of the meeting offers many opportunities for close interactions between the participants and discussions of latest results in basic, translational, and early clinical lymphoma research.

Researchers at all career levels interested in lymphoma may submit abstracts by April 29 at www.hematology.org/LymphomaAbstracts

All submitted abstracts will be considered for poster presentation, while authors of the top abstracts will be invited to present their research at an oral session. You may submit your abstract to one of the following ASH Meeting on Lymphoma Biology 2014 Abstract Review Categories:

- Biologic agents
- Chromosomal rearrangements and DNA repair
- Clinical biology, excluding therapy
- Epigenetic regulation
- Experimental therapeutics, drug resistance, and molecular pharmacology
- Genetics
- Metabolism
- Signaling

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The Max Delbrück Center for Molecular Medicine, Berlin, Germany

Program Co-Chairs:
Ari Melnick, MD
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