PNH: A CASCADE OF DEVASTATING

References:
CONSEQUENCES\textsuperscript{1-3} 

In PNH, chronic hemolysis leads to systemic, progressive, and life-threatening manifestations.\textsuperscript{1-3}

Early diagnosis and intervention are critical\textsuperscript{1,4}

- 64\% of patients with PNH have chronic kidney disease (CKD)\textsuperscript{5}
- Nearly 50\% of patients with PNH have evidence of pulmonary hypertension\textsuperscript{6}
- 40\% to 67\% of deaths are due to venous or arterial thrombosis\textsuperscript{7}
- Thrombosis and renal failure are leading causes of death\textsuperscript{2,5}

To learn more, visit www.PNHSource.com or call OneSource\textsuperscript{™} at 1-888-765-4747

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In Ph+ CML

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Ph+ CML, Philadelphia chromosome–positive chronic myeloid leukemia; NCCN®, National Comprehensive Cancer Network®, RQ-PCR, real-time quantitative polymerase chain reaction.


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Janssen Ibrutinib (Bruton’s Tyrosine Kinase (BTK) Inhibitor) Trials
MCL, CLL and FL ENROLLING NOW DBL ENROLLING SOON

A Study of Ibrutinib vs. Temsirolimus in Patients with Relapsed or Refractory Mantle Cell Lymphoma Who Have Received at Least One Prior Therapy
MCL3001 (RAY)
N=280
KEY ELIGIBILITY CRITERIA
- At least one prior rituximab-containing chemotherapy regimen
- Active disease (at least one of the IWCLL 2008 criteria for requiring treatment)
- Relapsed or refractory MCL following at least 1 prior chemotherapy-containing regimen
- No prior treatment with temsirolimus, other mTOR inhibitors, ibritinib, or other BTK inhibitors

For more information visit: www.clinicaltrials.gov (NCT01646021)

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
- Active disease (at least one of the IWCLL 2008 criteria for requiring treatment)
- 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 (NCT01776840)

A Study of Ibrutinib in Combination with Bendamustine and Rituximab in Patients with Relapsed or Refractory Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma
CLL3001 (HELIOS)
N=580
KEY ELIGIBILITY CRITERIA
- Active disease (at least one of the IWCLL 2008 criteria for requiring treatment)
- Relapsed or refractory CLL following at least 1 prior chemotherapy-containing regimen
- No presence of deletion of the short arm of chromosome 17, i.e., del (17p13.1)

For more information visit: www.clinicaltrials.gov (NCT01611090)

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)

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

For more information visit: www.clinicaltrials.gov (NCT01855750)

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BD Biosciences
2350 Qume Drive
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NOW APPROVED
in pediatric patients
4 months and older

The #1 used echinocandin for candidemia in
adults* is now indicated for use in pediatric
patients 4 months and older†

*With the experience of patient-days, derived from
the calculation of total milligrams sold/average
grams per day. Information provided by Wolters
Kluwer Pharma Solutions, Source Non-Retail,
†Safety and effectiveness in pediatric patients
younger than 4 months of age have not been
established.

INDICATIONS
MYCAMINE is indicated in adult and pediatric
patients 4 months and older for:
• Treatment of candidemia, acute disseminated
candidiasis, Candida peritonitis, and abscesses
  — MYCAMINE has not been adequately studied in
  patients with endocarditis, osteomyelitis, and
  meningitis due to Candida infections
• Treatment of patients with esophageal candidiasis
• Prophylaxis of Candida infections in patients
  undergoing hematopoietic stem cell transplantation

NOTE: The efficacy of MYCAMINE against infections
caused by fungi other than Candida has not been
established.

IMPORTANT SAFETY INFORMATION
MYCAMINE is contraindicated in patients with known
hypersensitivity to micafungin, any component of
MYCAMINE, or other echinocandins.

Isolated cases of serious hypersensitivity (anaphylaxis
and anaphylactoid) reactions (including shock) have
been reported in patients receiving MYCAMINE. In
these cases, MYCAMINE should be discontinued and
appropriate treatment administered.

Elevations in BUN and creatinine, and isolated
cases of clinically significant hepatic dysfunction,
hepatitis, hepatic failure, renal dysfunction, acute
renal failure, hemolysis, or hemolytic anemia have
occurred in some patients who have received
MYCAMINE. Patients who develop these conditions,
or abnormal liver or renal function tests, should
be monitored closely for worsening function
and evaluated for risk/benefit of continuing
MYCAMINE therapy.

In clinical trials, possible histamine-mediated
symptoms have been reported with MYCAMINE
(including rash, pruritus, facial swelling, and
vasodilatation).

In clinical trials, the most common treatment-
emergent adverse reactions in adults for all
indications included diarrhea, nausea, vomiting,
pyrexia, thrombocytopenia, and headache.
The most common treatment-emergent adverse
reactions observed in pediatric patients 4 months
and older included vomiting, diarrhea, pyrexia,
nausea, abdominal pain, and thrombocytopenia.

Please see the adjacent pages for the brief
summary of full prescribing information.
**MYCAMINE®**
(micafungin sodium) for injection

**INTRAVENTOUS INFUSION (not for IV bolus injection)**

**Brief Summary of Prescribing Information**

**INDICATIONS AND USAGE**

MYCAMINE is an echinocandin indicated in adult and pediatric patients 4 months and older for:

- **Treatment of Patients with Candidemia, Acute Disseminated Candidiasis, Candida Peritonitis and Abscesses**
- **Prophylaxis of Candida Infections in Patients Undergoing Hematopoietic Stem Cell Transplantation**

**NOTE:** The efficacy of MYCAMINE against infections caused by fungi other than Candida has not been established.

**CONTRAINDICATIONS**

MYCAMINE is contraindicated in persons with known hypersensitivity to micafungin, any component of MYCAMINE, or other echinocandins.

**WARNINGS AND PRECAUTIONS**

**Hypersensitivity Reactions**
Isolated cases of serious hypersensitivity (anaphylaxis and anaphylactoid reactions including shock) have been reported in patients receiving MYCAMINE. If these reactions occur, MYCAMINE infusion should be discontinued and appropriate treatment administered.

**Hematological Effects**
Acute intravascular hemolysis and hemoglobinuria was seen in a healthy volunteer during infusion of MYCAMINE (200 mg) and oral prednisolone (20 mg). This reaction was transient, and the subject did not develop significant anemia. Isolated cases of significant hemolysis and hemolytic anemia have also been reported in patients treated with MYCAMINE. Patients who develop clinical or laboratory evidence of hemolysis or hemolytic anemia during MYCAMINE therapy should be monitored closely for evidence of worsening of these conditions and evaluated for the risk/benefit of continuing MYCAMINE therapy.

**Renal Effects**
Laboratory abnormalities in liver function tests have been seen in healthy volunteers and patients treated with MYCAMINE. In some patients with serious underlying conditions who were receiving MYCAMINE along with multiple concomitant medications, clinical hepatic abnormalities have occurred, and isolated cases of significant hepatic impairment, hepatitis, and hepatic failure have been reported. Patients who develop abnormal liver function tests during MYCAMINE therapy should be monitored for evidence of worsening hepatic function and evaluated for the risk/benefit of continuing MYCAMINE therapy.

**Hepatic Effects**

Laboratory abnormalities in liver function tests have been seen in healthy volunteers and patients treated with MYCAMINE. In some patients with serious underlying conditions who were receiving MYCAMINE along with multiple concomitant medications, clinical hepatic abnormalities have occurred, and isolated cases of significant hepatic impairment, hepatitis, and hepatic failure have been reported. Patients who develop abnormal liver function tests during MYCAMINE therapy should be monitored for evidence of worsening hepatic function and evaluated for the risk/benefit of continuing MYCAMINE therapy.

**ADVERSE REACTIONS**
The overall safety of MYCAMINE was assessed in 3227 adult and pediatric patients and 520 volunteers in 46 clinical trials, including the invasive candidiasis, esophageal candidiasis, and prophylaxis trials, who received single or multiple doses of MYCAMINE, ranging from 0.75 mg/kg to 10 mg/kg in pediatric patients and 12.5 mg to 150 mg/day or greater in adult patients. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of MYCAMINE cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does provide a basis for identifying adverse events that appear to be related to drug use and for approximating rates.

**Infiltration Reactions**
Possible histamine-mediated symptoms have been reported with MYCAMINE, including rash, pruritus, facial swelling, and vasodilatation.

**Clinical Trials Experience in Adults**

In all clinical trials with MYCAMINE, 2497/2748 (91%) adult patients experienced at least one treatment-emergent adverse reaction.

**Selected Treatment-emergent adverse reactions, those occurring in 5% or more of the patients and more frequently in a MYCAMINE treatment group are shown in Table 3.**

**Table 3. Selected Treatment-Emergent Adverse Reactions in Adult Patients with Candidemia and Other Candida Infections**

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Mycamine 100 mg n (%)</th>
<th>Mycamine 150 mg n (%)</th>
<th>Caspofungin n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>200</td>
<td>202</td>
<td>193</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>81 (41)</td>
<td>89 (44)</td>
<td>76 (39)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>15 (8)</td>
<td>26 (13)</td>
<td>14 (7)</td>
</tr>
<tr>
<td>Nausea</td>
<td>19 (10)</td>
<td>15 (7)</td>
<td>20 (10)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>18 (9)</td>
<td>15 (7)</td>
<td>16 (8)</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td>77 (39)</td>
<td>83 (41)</td>
<td>73 (38)</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>12 (6)</td>
<td>14 (7)</td>
<td>9 (5)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>8 (4)</td>
<td>13 (6)</td>
<td>8 (4)</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>10 (5)</td>
<td>8 (4)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>General Disorders/ Administration Site Conditions</td>
<td>59 (30)</td>
<td>56 (28)</td>
<td>51 (26)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>14 (7)</td>
<td>22 (11)</td>
<td>15 (8)</td>
</tr>
<tr>
<td>Investigations</td>
<td>36 (18)</td>
<td>49 (24)</td>
<td>37 (19)</td>
</tr>
<tr>
<td>Blood Alkaline Phosphatase Increased</td>
<td>11 (6)</td>
<td>16 (8)</td>
<td>8 (4)</td>
</tr>
<tr>
<td>Cardiac Disorders</td>
<td>35 (18)</td>
<td>48 (24)</td>
<td>36 (19)</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>5 (3)</td>
<td>10 (5)</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 4. Selected Treatment-Emergent Adverse Reactions in Adult Patients with Esophageal Candidiasis**

<table>
<thead>
<tr>
<th>System Organ Class (Preferred Term)</th>
<th>Mycamine 150 mg/day n (%)</th>
<th>Fluconazole 200 mg/day n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>260</td>
<td>258</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>84 (32)</td>
<td>93 (36)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>27 (10)</td>
<td>29 (11)</td>
</tr>
<tr>
<td>Nausea</td>
<td>20 (8)</td>
<td>23 (9)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>17 (7)</td>
<td>17 (7)</td>
</tr>
<tr>
<td>General Disorders/ Administration Site Conditions</td>
<td>52 (20)</td>
<td>45 (17)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>34 (13)</td>
<td>21 (8)</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>42 (16)</td>
<td>48 (16)</td>
</tr>
<tr>
<td>Headache</td>
<td>22 (9)</td>
<td>20 (8)</td>
</tr>
<tr>
<td>Vascular Disorders</td>
<td>54 (21)</td>
<td>21 (8)</td>
</tr>
<tr>
<td>Phlebitis</td>
<td>49 (19)</td>
<td>13 (5)</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td>36 (14)</td>
<td>26 (10)</td>
</tr>
<tr>
<td>Rash</td>
<td>14 (5)</td>
<td>6 (2)</td>
</tr>
</tbody>
</table>

**Table 5. Selected Adverse Reactions in Adult Patients During Prophylaxis of Candida Infection in Hematopoietic Stem Cell Transplant Recipients**

<table>
<thead>
<tr>
<th>System Organ Class (Preferred Term)</th>
<th>Mycamine 50 mg/day n (%)</th>
<th>Fluconazole 400 mg/day n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of Patients</td>
<td>382</td>
<td>409</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>377 (99)</td>
<td>404 (99)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>294 (77)</td>
<td>327 (80)</td>
</tr>
</tbody>
</table>
**Clinical Trials Experience in Pediatric Patients**

The selected treatment-emergent adverse reactions, those occurring in 15% or more of the patients and more frequently in the MYCAMINE group, for all MYCAMINE pediatric studies and for the two comparative studies (candidemia and prophylaxis) are shown in Table 6.

---

### Table 5 Continued

<table>
<thead>
<tr>
<th>System Organ Class* (Preferred Term)</th>
<th>Mycamine 50 mg/day n (%)</th>
<th>Fluconazole 400 mg/day n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>270 (71)</td>
<td>290 (71)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>252 (66)</td>
<td>274 (67)</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>100 (26)</td>
<td>93 (23)</td>
</tr>
<tr>
<td>Blood and Lymphatic System Disorders</td>
<td>368 (96)</td>
<td>385 (94)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>288 (75)</td>
<td>297 (73)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>286 (75)</td>
<td>280 (69)</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td>257 (67)</td>
<td>275 (67)</td>
</tr>
<tr>
<td>Rash</td>
<td>95 (25)</td>
<td>91 (22)</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>250 (65)</td>
<td>254 (62)</td>
</tr>
<tr>
<td>Headache</td>
<td>169 (44)</td>
<td>154 (38)</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>233 (61)</td>
<td>235 (58)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>142 (37)</td>
<td>140 (34)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>84 (22)</td>
<td>87 (21)</td>
</tr>
<tr>
<td>Cardiac Disorders</td>
<td>133 (35)</td>
<td>138 (34)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>99 (26)</td>
<td>91 (22)</td>
</tr>
</tbody>
</table>

*Patient base: all randomized adult patients who received at least 1 dose of trial drug

---

### Table 6 Continued

<table>
<thead>
<tr>
<th>System Organ Class* (Preferred Term)</th>
<th>All Micafungin- treated Patients n = 479 n (%)</th>
<th>C/I/C</th>
<th>Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal disorders</td>
<td>285 (60)</td>
<td>22 (40)</td>
<td>18 (32)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>146 (31)</td>
<td>10 (18)</td>
<td>8 (14)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>106 (22)</td>
<td>4 (7)</td>
<td>5 (9)</td>
</tr>
<tr>
<td>Nausea</td>
<td>91 (19)</td>
<td>4 (7)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>76 (16)</td>
<td>2 (4)</td>
<td>2 (4)</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>29 (6)</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td>256 (53)</td>
<td>14 (25)</td>
<td>14 (25)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>103 (22)</td>
<td>5 (9)</td>
<td>9 (16)</td>
</tr>
<tr>
<td>Infusion related reaction</td>
<td>24 (5)</td>
<td>0 (0)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>197 (41)</td>
<td>11 (20)</td>
<td>8 (14)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>54 (11)</td>
<td>0 (0)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Rash</td>
<td>55 (12)</td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Urticaria</td>
<td>24 (5)</td>
<td>0 (0)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td>194 (41)</td>
<td>9 (16)</td>
<td>13 (23)</td>
</tr>
</tbody>
</table>

*Patient base: all randomized patients who received at least one dose of trial drug

---

### Table 7

<table>
<thead>
<tr>
<th>System Organ Class* (Preferred Term)</th>
<th>Mycamine n = 56 n (%)</th>
<th>AmBisome n = 56 n (%)</th>
<th>Mycamine n = 43 n (%)</th>
<th>Fluconazole n = 48 n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epistaxis</td>
<td>45 (9)</td>
<td>0 (0)</td>
<td>4 (9)</td>
<td>8 (17)</td>
</tr>
<tr>
<td>Blood and lymphatic system disorders</td>
<td>161 (34)</td>
<td>17 (30)</td>
<td>13 (23)</td>
<td>40 (93)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>70 (15)</td>
<td>5 (9)</td>
<td>3 (5)</td>
<td>31 (72)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>61 (13)</td>
<td>3 (5)</td>
<td>4 (7)</td>
<td>33 (77)</td>
</tr>
<tr>
<td>Anemia</td>
<td>63 (13)</td>
<td>10 (18)</td>
<td>6 (11)</td>
<td>22 (51)</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>23 (5)</td>
<td>0 (0)</td>
<td>7 (16)</td>
<td>7 (15)</td>
</tr>
<tr>
<td>Investigations</td>
<td>191 (40)</td>
<td>12 (21)</td>
<td>8 (14)</td>
<td>24 (56)</td>
</tr>
<tr>
<td>Alamineaminotransferase increased</td>
<td>45 (10)</td>
<td>0 (0)</td>
<td>7 (16)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Urine output decreased</td>
<td>18 (4)</td>
<td>0 (0)</td>
<td>10 (23)</td>
<td>7 (15)</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>97 (20)</td>
<td>7 (13)</td>
<td>3 (5)</td>
<td>10 (23)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>47 (10)</td>
<td>2 (4)</td>
<td>4 (7)</td>
<td>16 (37)</td>
</tr>
<tr>
<td>Hematuria</td>
<td>18 (4)</td>
<td>0 (0)</td>
<td>10 (23)</td>
<td>7 (15)</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>80 (17)</td>
<td>3 (6)</td>
<td>1 (2)</td>
<td>20 (47)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>35 (7)</td>
<td>0 (0)</td>
<td>10 (23)</td>
<td>3 (6)</td>
</tr>
</tbody>
</table>

*Patient base: all randomized patients who received at least one dose of trial drug

---

**Postmarketing Adverse Reactions**

The following adverse reactions have been identified during the post-approval use of micafungin sodium for injection. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

- **Blood and lymphatic system disorders:** disseminated intravascular coagulation
- **Hepatobiliary disorders:** hepatic disorder
- **Renal and urinary disorders:** renal impairment
- **Skin and subcutaneous tissue disorders:** Stevens-Johnson syndrome, toxic epidermal necrolysis
- **Vascular disorders:** shock

**DRUG INTERACTIONS**

Monitor for sirolimus, itraconazole or nifedipine toxicity, and dosage of sirolimus, itraconazole or nifedipine should be reduced, if necessary.

**USE IN SPECIFIC POPULATIONS**

**Pregnancy**

Pregnancy Category C. No human data. Adverse effects in animals. Use if potential benefits of treatment outweigh potential fetal risk.

**Nursing Mothers**

Caution should be exercised if administered to a nursing woman.

**Pediatric Use**

Safety and effectiveness in pediatric patients younger than 4 months of age have not been established.

**Product of Japan**

Manufactured by: Astellas Pharma Tech Co., Takaoka city, Toyama 939-1118, Japan

Marketed by: Astellas Pharma US, Inc., Northbrook, IL 60062 USA

Revised: June 2013

MYCAMINE is a registered trademark of Astellas Pharma, Inc., Tokyo, Japan.
Ibrutinib Expanded Access Treatment Protocol

Ibrutinib is an investigational agent for the treatment of relapsed or refractory Mantle Cell Lymphoma*

PCI-32765 MCL4001
An Open-Label Treatment Use Protocol for Ibrutinib in Subjects with Relapsed or Refractory Mantle Cell Lymphoma

OBJECTIVE

To provide early access to ibrutinib and to collect safety data in patients with relapsed or refractory Mantle Cell Lymphoma, who do not meet the enrollment criteria for any other ibrutinib clinical trial

KEY ENTRY CRITERIA

- Patients, 18 years of age and older, with MCL who have progressive disease after prior therapy are eligible.
- Patients eligible for enrollment in any other ongoing clinical study of ibrutinib are not eligible.
- Patients previously treated with ibrutinib are not eligible.
- Patients enrolled in another interventional clinical study with therapeutic intent are not eligible.

For additional information about this US only study:

Call: 1-855-ibrutinib
Email: medinfo@pcyc.com
Visit: www.clinicaltrials.gov (NCT 01833039)

*This compound is an investigational agent and its safety and efficacy have not been determined.
Hear important educational updates and review the latest scientific discoveries

55th ASH® Annual Meeting and Exposition
The world’s premier hematology meeting is coming to New Orleans.

December 7-10, 2013
Ernest N. Morial Convention Center
New Orleans, LA

- Over 3,000 scientific abstracts
- Global community of more than 20,000 hematology professionals
- Groundbreaking advances in patient care
- Networking opportunities with colleagues and top leaders in the field

Look for the latest updates on the meeting at www.hematology.org/55AnnualMeeting.
Because of the risk of embryo-fetal toxicity, REVLIMID is only available through a restricted program called the REVLIMID 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 REVLIMID. 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)].
- REVLIMID is available only from pharmacies that are certified in REVLIMID REMS™ program. Provide patients with the telephone number and website for information on how to obtain the product.

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

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

Allergic Reactions
Inform patients of the potential for allergic reactions including hypersensitivity, angioedema, Stevens Johnsons 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.

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.

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

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

Instruct patients that if they miss a dose of REVLIMID, 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 REVLIMID 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

REVLIMID®, RevAssist®, and THALOMID® are registered trademarks of Celgene Corporation.

REVLIMID 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; 7,468,363; 7,465,800; 7,855,217; 7,968,569
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REV_COMBO_HCP_B Sv.001 06/13
Until recently, research of B-cell malignancies has been focused primarily on the B cell itself. However, new insights have revealed that there are important interactions between the B cell and the extracellular microenvironment that are dependent on intracellular signaling pathways mediated by various kinases including Bruton’s tyrosine kinase (BTK). These interactions suggest an important role in B-cell homing, adhesion, and migration. Further elucidation of these processes could change how we view and approach B-cell malignancies.

Pharmacyclics, Inc., and Janssen Biotech, Inc., are currently investigating BTK in search of insights that could improve the lives of patients with B-cell malignancies. Visit us at www.BCellSignals.com.
Prosurvival Signals

Normal and malignant B cells rely on multiple prosurvival pathways to avoid apoptosis.\(^6\) In B-cell malignancies, microenvironmental cues may inappropriately initiate signaling cascades through several kinases, including BTK, driving uncontrolled growth and survival of malignant B cells.\(^5,10-13\)

B-Cell Homing

Cells in the microenvironment secrete chemotaxant factors to promote the homing of B cells to lymphoid tissue.\(^14\) These factors act via signaling pathways involving BTK and other kinases.\(^4,15\)

Adhesion and Migration

The upregulation and increased migration of B cells may lead to retention of malignant cells in proliferative environments and the promotion of chemoresistance.\(^16-18\) BTK is an essential mediator of multiple adhesion and migration processes.\(^4\)

References:
POMALYST® (pomalidomide) is indicated for patients with multiple myeloma who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy. Approval is based on response rate. Clinical benefit, such as improvement in survival or symptoms, has not been verified.

Overall response rate (ORR) of 29.2% was achieved with all-oral POMALYST + low-dose dex

Study design: A Phase II, multicenter, randomized open-label study in patients who were refractory to their last myeloma therapy and had received lenalidomide and bortezomib. The safety and efficacy of POMALYST 4 mg 21/28 days until disease progression was evaluated alone and in combination with low-dose dex: 40 mg per day (patients ≤75 years) or 20 mg per day (patients >75 years) only on Days 1, 8, 15, and 22 for each 28-day cycle. Patients in the POMALYST alone arm were allowed to add low-dose dex upon disease progression.

ORR did not differ based on type of prior anti-myeloma therapy.

Help give your patients a chance for response

7.4-month median duration of response (n=33; 95% CI, 5.1 to 9.2) vs NE for POMALYST + low-dose dex and POMALYST, respectively

NE, not established (the median has not yet been reached).
CONTRAINDICATIONS

Pregnancy
POMALYST can cause fetal harm when administered to a pregnant female. POMALYST is contraindicated in females who are pregnant. Pomalidomide is a thalidomide analogue, and is teratogenic in both rats and rabbits when administered during the period of organogenesis. 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.

POMALYST is only available under a restricted distribution program, POMALYST REMS™.

Please see brief summary of full Prescribing Information, including Boxed WARNINGS, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and ADVERSE REACTIONS, and Important Safety Information on following pages.
POMALYST® (pomalidomide) is indicated for patients with multiple myeloma who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy. Approval is based on response rate. Clinical benefit, such as improvement in survival or symptoms, has not been verified.

**Important Safety Information**

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

**Embryo-Fetal Toxicity**
- POMALYST is contraindicated in pregnancy. POMALYST is a thalidomide analogue. Thalidomide is a known human teratogen that causes severe birth defects or embryo-fetal death. In females of reproductive potential, obtain 2 negative pregnancy tests before starting POMALYST treatment.
- Females of reproductive potential must use 2 forms of contraception or continuously abstain from heterosexual sex during and for 4 weeks after stopping POMALYST treatment.

POMALYST is only available through a restricted distribution program called POMALYST REMS™.

**Venous Thromboembolism**
- Deep Venous Thrombosis (DVT) and Pulmonary Embolism (PE) occur in patients with multiple myeloma treated with POMALYST. Prophylactic anti-thrombotic measures were employed in the clinical trial. Consider prophylactic measures after assessing an individual patient’s underlying risk factors.

**CONTRAINDICATIONS: Pregnancy**
- POMALYST can cause fetal harm and 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 a fetus.
- Pomalidomide is a thalidomide analogue and is teratogenic in both rats and rabbits when administered during the period of organogenesis.

**WARNINGS AND PRECAUTIONS**

**Embryo-Fetal Toxicity**
- **Females of Reproductive Potential:** Must avoid pregnancy while taking POMALYST and for at least 4 weeks after completing therapy. Must commit either to abstain continuously from heterosexual sexual intercourse or to use 2 methods of reliable birth control, beginning 4 weeks prior to initiating treatment with POMALYST, during therapy, during dose interruptions and continuing for 4 weeks following discontinuation of POMALYST therapy. Must obtain 2 negative pregnancy tests prior to initiating therapy.
- **Males:** Pomalidomide 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 POMALYST and for up to 28 days after discontinuing POMALYST, even if they have undergone a successful vasectomy. Males must not donate sperm.
- **Blood Donation:** Patients must not donate blood during treatment with POMALYST 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 POMALYST.

**POMALYST REMS Program**

Because of the embryo-fetal risk, POMALYST is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called “POMALYST REMS.” Prescribers and pharmacists must be certified with the program; patients must sign an agreement form and comply with the requirements. Further information about the POMALYST REMS program is available at [celgeneriskmanagement.com](http://celgeneriskmanagement.com) or by telephone at 1-888-423-5436.

**Venous Thromboembolism:** Patients receiving POMALYST have developed venous thromboembolic events reported as serious adverse reactions. In the trial, all patients were required to receive prophylaxis or antithrombotic treatment. The rate of DVT or PE was 3%. Consider anticoagulation prophylaxis after an assessment of each patient’s underlying risk factors.

**Hematologic Toxicity:** Neutropenia of any grade was reported in 50% of patients and was the most frequently reported Grade 3/4 adverse event, followed by anemia and thrombocytopenia. Monitor patients for hematologic toxicities, especially neutropenia, with complete blood counts weekly for the first 8 weeks and monthly thereafter. Treatment is continued or modified for Grade 3 or 4 hematologic toxicities based upon clinical and laboratory findings. Dosing interruptions and/or modifications are recommended to manage neutropenia and thrombocytopenia.

**Hypersensitivity Reactions:** Patients with a prior history of serious hypersensitivity associated with thalidomide or lenalidomide were excluded from studies and may be at higher risk of hypersensitivity.
WARNINGS AND PRECAUTIONS (continued)

Dizziness and Confusional State: 18% of patients experienced dizziness and 12% of patients experienced a confusional state; 1% of patients experienced grade 3/4 dizziness, and 3% of patients experienced grade 3/4 confusional state. Instruct patients to avoid situations where dizziness or confusion may be a problem and not to take other medications that may cause dizziness or confusion without adequate medical advice.

Neuropathy: 18% of patients experienced neuropathy (approximately 9% peripheral neuropathy). There were no cases of grade 3 or higher neuropathy adverse reactions reported.

Risk of Second Primary Malignancies: Cases of acute myelogenous leukemia have been reported in patients receiving POMALYST as an investigational therapy outside of multiple myeloma.

ADVERSE REACTIONS

In the clinical trial of 219 patients who received POMALYST alone (n=107) or POMALYST + low-dose dexamethasone (low-dose dex) (n=112), all patients had at least one treatment-emergent adverse reaction.

- In the POMALYST alone versus POMALYST + low dose dexamethasone arms, respectively, most common adverse reactions (≥30%) included fatigue and asthenia (55%, 63%), neutropenia (52%, 47%), anemia (38%, 39%), constipation (36%, 35%), nausea (36%, 22%), diarrhea (34%, 33%), dyspnea (34%, 45%), upper respiratory tract infection (32%, 25%), back pain (32%, 30%), and pyrexia (19%, 30%)
- 90% of patients treated with POMALYST alone and 88% of patients treated with POMALYST + low-dose dex had at least one treatment-emergent NCI CTC Grade 3 or 4 adverse reaction
- In the POMALYST alone versus POMALYST + low dose dexamethasone arms, respectively, most common Grade 3/4 adverse reactions (≥15%) included neutropenia (47%, 38%), anemia (22%, 21%), thrombocytopenia (22%, 19%), and pneumonia (16%, 23%). For other Grade 3 or 4 toxicities besides neutropenia and thrombocytopenia, hold treatment and restart treatment at 1 mg less than the previous dose when toxicity has resolved to less than or equal to Grade 2 at the physician's discretion
- 67% of patients treated with POMALYST and 62% of patients treated with POMALYST + low-dose dex had at least one treatment-emergent serious adverse reaction
- In the POMALYST alone versus POMALYST + low dose dexamethasone arms, respectively, most common serious adverse reactions (≥5%) were pneumonia (14%, 19%), renal failure (8%, 6%), dyspnea (5%, 6%), sepsis (6%, 3%), pyrexia (3%, 5%) dehydration (5%, 3%), hypercalcemia (5%, 2%), urinary tract infection (0%, 5%), and febrile neutropenia (5%, 1%)

DRUG INTERACTIONS

No formal drug interaction studies have been conducted with POMALYST. Pomalidomide is primarily metabolized by CYP1A2 and CYP3A. Pomalidomide is also a substrate for P-glycoprotein (P-gp). Co-administration of POMALYST with drugs that are strong inhibitors or inducers of CYP1A2, CYP3A, or P-gp should be avoided. Cigarette smoking may reduce pomalidomide exposure due to CYP1A2 induction. Patients should be advised that smoking may reduce the efficacy of pomalidomide.

USE IN SPECIFIC POPULATIONS

Pregnancy: If pregnancy does occur during treatment, immediately discontinue the drug and refer patient to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. Report any suspected fetal exposure to POMALYST 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 if pomalidomide is excreted in human milk. Pomalidomide was excreted in the milk of lactating rats. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from POMALYST, 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: Safety and effectiveness of POMALYST in patients under the age of 18 have not been established.

Geriatric Use: No dosage adjustment is required for POMALYST based on age. Patients greater than or equal to 65 years of age were more likely than patients less than or equal to 65 years of age to experience pneumonia.

Renal and Hepatic Impairment: Pomalidomide is metabolized in the liver. Pomalidomide and its metabolites are primarily excreted by the kidneys. The influence of renal and hepatic impairment on the safety, efficacy, and pharmacokinetics of pomalidomide has not been evaluated. Avoid POMALYST in patients with a serum creatinine >3.0 mg/dL. Avoid POMALYST in patients with serum bilirubin >2.0 mg/dL and AST/ALT >3.0 x ULN.

Please see full Prescribing Information, including Boxed WARNINGS, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and ADVERSE REACTIONS.
This brief summary does not include all the information needed to use POMALYST® (pomalidomide) safely and effectively. See full prescribing information for POMALYST.

WARNING: EMBRYO-FETAL TOXICITY and VENOUS THROMBOEMBOLISM

Embryo-Fetal Toxicity
- POMALYST is contraindicated in pregnancy. POMALYST is a thalidomide analogue. Thalidomide is a known human teratogen that causes severe birth defects or embryo-fetal death. In females of reproductive potential, obtain 2 negative pregnancy tests before starting POMALYST treatment.
- Females of reproductive potential must use 2 forms of contraception or continuously abstain from sexual intercourse during therapy and for 4 weeks after stopping POMALYST treatment (see Contraindications (4), Warnings and Precautions (5.1), and Use in Specific Populations (8.1, 8.6)).
- POMALYST is only available through a restricted distribution program called POMALYST REMS (see Warnings and Precautions (5.2)).
- Venous Thromboembolism
  - Deep Venous Thrombosis (DVT) and Pulmonary Embolism (PE) occur in patients with multiple myeloma treated with POMALYST. Prophylactic anti-thrombotic measures were employed in the clinical trial. Consider prophylactic measures after assessing an individual patient’s underlying risk factors (see Warnings and Precautions (5.3)).

1 INDICATIONS AND USAGE 1.1 Multiple Myeloma POMALYST is indicated for patients with multiple myeloma who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy. Approval is based on response rate (see Clinical Studies (14.1)). Clinical benefit, such as improvement in survival or symptoms, has not been verified.

2 DOSAGE AND ADMINISTRATION 2.1 Multiple Myeloma Females of reproductive potential must have negative pregnancy testing and use contraception methods before initiating POMALYST (see Warnings and Precautions (5.1) and Use in Specific Populations (8.6)). The recommended starting dose of POMALYST is 4 mg once daily orally on Days 1-21 of repeated 28-day cycles until YST is 4 mg once daily (see Warnings and Precautions (5.1) and Use in Specific Populations (8.1)). POMALYST is contraindicated in females who are pregnant. Pomalidomide is a thalidomide analogue, and is teratogenic in both rats and rabbits when administered during the period of organogenesis. 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.

5 WARNINGS AND PRECAUTIONS 5.1 Embryo-Fetal Toxicity POMALYST is a thalidomide analogue and is contraindicated for use during pregnancy. Thalidomide is a known human teratogen that causes severe birth defects or embryo-fetal death (see Use in Specific Populations (8.1)). POMALYST is only available through the POMALYST REMS program (see Warnings and Precautions (5.2)). Females of Reproductive Potential Females of reproductive potential must avoid pregnancy while taking POMALYST 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 POMALYST, during therapy, during dose interruptions and continuing for 4 weeks following discontinuation of POMALYST 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 POMALYST 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)). Patients must not donate blood during treatment with POMALYST and for 6 weeks after discontinuing POMALYST, even if they have undergone a successful vasectomy. Male patients taking POMALYST must not donate sperm (see Use in Specific Populations (8.6)). Blood Donation Patients must not donate blood during treatment with POMALYST 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 POMALYST.

5.2 POMALYST REMS™ Program Because of the embryo-fetal risk (see Warnings and Precautions (5.1)), POMALYST is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called “POMALYST REMS.” Required components of the POMALYST REMS program include the following:
- Prescribers must be certified with the POMALYST 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 POMALYST REMS program, must only dispense to patients enrolled in POMALYST and comply with REMS requirements.

Further information about the POMALYST REMS program is available at [celgenskinsmanagement.com] or by telephone at 1-888-423-5436.

Venous Thromboembolism Patients receiving POMALYST have developed venous thromboembolic events (Venous Thromboembolism [VTEs]) reported as serious adverse reactions. In the trial, all patients were required to receive prophylaxis or anti-thrombotic treatment; 8% used warfarin, 16% heparin, and 3% clopidogrel. The rate of deep vein thrombosis or pulmonary embolism was 3%. Consider anti-coagulation prophylaxis after an assessment of each patient’s underlying risk factors.

5.4 Hematologic Toxicity Neutropenia was the most frequently reported Grade 3/4 adverse event (AE), followed by anemia and thrombocytopenia. Neutropenia of any grade was reported in 50% of patients in the trial. The rate of Grade 3/4 neutropenia was 43%. The rate of deep vein thrombosis was 3%. Monitor patients for hematologic toxicities, especially neutropenia. Monitor complete blood counts weekly for the first 8 weeks and monthly thereafter. Patients may require dose interruption and/or modification (see Dosage and Administration (2.2)).

5.5 Hypersensitivity Reactions. Patients with a history of serious hypersensitivity reactions associated with thalidomide or lenalidomide were excluded from studies and may be at higher risk of hypersensitivity.

5.6 Dizziness and Confusional State. In the trial, 18% of patients experienced dizziness and 12% of patients experienced a confusional state; 1% of patients experienced grade 3/4 dizziness, and 3% of patients experienced grade 3/4 confusional state. Instruct patients to avoid situations where dizziness or confusion may be a problem and not to take other medications that may cause dizziness or confusion without adequate medical advice.

5.7 Neuropathy In the trial, 18% of patients experienced neuropathy, with approximately 9% of the patients experiencing peripheral neuropathy. There were no cases of grade 3 or higher neuropathy adverse reactions reported.

5.8 Risk of Second Primary Malignancies Cases of acute myelogenous leukemia have been reported in patients receiving POMALYST as an investigational therapy outside of multiple myeloma.

6 ADVERSE REACTIONS The following adverse reactions are described in detail in other labeling sections:
- Neutropenia (seeWARNINGS AND PRECAUTIONS (5.1))
- Neutropenic infections (see WARNINGS AND PRECAUTIONS (5.1))
- Venous Thromboembolism (see WARNINGS AND PRECAUTIONS (5.3))
- Hematologic Toxicity (see WARNINGS AND PRECAUTIONS (5.4))
- Hypersensitivity Reactions (see WARNINGS AND PRECAUTIONS (5.5))
- Fetal Risk (seeBoxed Warnings, Warnings and Precautions (5.1, 5.2))
- Venous Thromboembolism (see Boxed Warnings, Warnings and Precautions (5.3))
- Hematologic Toxicity (see WARNINGS AND PRECAUTIONS (5.4))
- Hypersensitivity Reactions (see WARNINGS AND PRECAUTIONS (5.5))

Determine and report adverse events to [celgenskinsmanagement.com] or by telephone at 1-888-423-5436.
6.1 Clinical Trials Experience in Multiple Myeloma

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. In clinical trial 1, data were evaluated from 219 patients (safety population) who received treatment with POMALYST® + Low Dose Dexamethasone (Dex) (112 patients) or POMALYST alone (107 patients). Median number of treatment cycles was 5. Sixty three percent of patients in the study had a dose interruption of either drug due to adverse reactions. Thirty seven percent of patients in the study had a dose reduction of either drug due to adverse reactions. The discontinuation rate due to treatment-related adverse reaction was 3%. Tables 2, 3, and 4 summarize all treatment-emergent adverse reaction rates observed in POMALYST® + Low dose Dex and POMALYST alone groups regardless of attribution of relatedness to pomalidomide. In the absence of a randomized comparator arm, it is often not possible to distinguish adverse events that are drug-related and those that reflect the patient’s underlying disease.

In the clinical trial of 219 patients who received POMALYST alone* (n=107) or POMALYST + Low dose Dex (n=112), all patients had at least one treatment-emergent adverse reaction. Adverse reactions ≥10% in either arm, respectively, included: General disorders and administration site conditions: Fatigue and asthenia (55%, 63%), Pyrexia (19%, 30%), Edema (23%, 16%), Chills (9%, 11%), Pain (6%, 5%); Blood and lymphatic system disorders: Neutropenia (52%, 47%), Thrombocytopenia (25%, 23%), Leukopenia (11%, 18%), Lymphopenia (4%, 15%); Gastrointestinal disorders: Constipation (36%, 35%), Diarrhea (34%, 33%), Nausea (36%, 22%), Vomiting (14%, 13%); Infections and infestations: Pneumonia (16%, 14%); Respiratory, thoracic and mediastinal disorders: Dyspnea (24%, 45%), Cough (14%, 21%), Epistaxis (15%, 11%); Metabolism and nutritional disorders: Decreased appetite (22%, 18%), Hyperglycermia (12%, 15%), Hypoatremia (10%, 13%), Hypocalcemia (21%, 12%), Hypokalemia (6%, 12%), Hypoglycemia (11%, 11%); Skin and subcutaneous tissue disorders: Hyperhidrosis (6%, 16%), Rash (22%, 16%), Night sweats (5%, 13%), Dry skin (9%, 11%), Pruritus (15%, 11%); Nervous system disorders: Dizziness (20%, 17%), Tremor (9%, 13%), Headache (13%, 8%); Neoplasms: Breast, ovary, and prostate (0%, 0%); Breast and connective tissue disorders: Fatigue and asthenia (11%, 12%); Infections and infestations: Pneumonia (16%, 14%); Neutropenia (52%, 47%), Thrombocytopenia (25%, 23%)...

### Grade 3/4 Adverse Reactions

#### Grade 3

- Fatigue and asthenia
- Hyperglycermia
- Hypocalcemia
- Hypoatremia
- Hypokalemia

### Grade 4

- Neutropenia
- Thrombocytopenia
- Leukopenia
- Lymphopenia

### Risk Summary

POMALYST can cause embryo-fetal harm when administered to a pregnant female and is contraindicated during pregnancy. POMALYST 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, extremal ear abnormalities (anatomical, microphthalmia, small or absent external auditory canals), facial palsy, eye abnormalities (anophthalmos, microphthalmos), and congenital heart defects. Alimentary tract, urinary tract, and genital malformations have also been reported, and mortality at or shortly after birth has been reported in about 40% of infants. Pomalidomide was teratogenic in both rats and rabbits when administered during the period of organogenesis. If the drug is used during pregnancy 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 a reproductive toxicologist experienced in reproductive toxicity for further evaluation and counseling. Report any suspected fetal exposure to POMALYST to the FDA via the MedWatch program at 1-800-FDA-1088 and also to Celgene Corporation at 1-888-423-5436.

### Animal Data

Pomalidomide was teratogenic in both rats and rabbits in the embryofetal developmental studies, when administered during the period of organogenesis. In rats, pomalidomide was administered orally to pregnant animals at doses of 25 to 1000 mg per kg per day. Malformations of absence of urinary bladder, absence of thyroid gland, and fusion and misalignment of lumbar and thoracic vertebral elements (vertebral, central, and/or neural arches) were observed at all dose levels. There was no maternal toxicity observed in this study. The lowest dose in rats resulted in an exposure (AUC) approximately 85-fold of the human exposure at the recommended dose of 4 mg per day. Other embryofetotoxicities included increased resorptions leading to decreased number of viable fetuses. In rabbits, pomalidomide was administered orally to pregnant animals at doses of 10 to 250 mg per kg per day. Increased cardiometabolic abnormalities such as interventricular septal defect were seen at all doses with significant increases at 250 mg per kg per day. Additional malformations observed at 250 mg per kg per day included anomalies in limbs (flexed and/or rotated fore- and hind limbs) and absent digit, and associated skeletal malformations (not ossified metacarpal, misaligned phalanx and metacarpal, absent digit, not ossified phalanx, and short not ossified or bent tibia), moderate dilation of the lateral ventricle in the brain, abnormal placement of the right subclavian artery, absent intermediate lobe in the lungs, low-set kidney, altered liver morphology, incompletely or not ossified pelvis, an increased average for supernumerary thoracic ribs and a reduced number of ribs, and associated tarsals. No maternal toxicity was observed at the low dose (10 mg per kg per day) that resulted in cardiac anomalies in fetuses; this dose resulted in an exposure (AUC) approximately 50-fold of the human exposure reported in humans at the recommended dose of 4 mg per day. Additional embryofetotoxicity included increased resorption.

### 8.3 Nursing mothers

It is not known if pomalidomide 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 POMALYST, 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 of POMALYST in patients below the age of 18 have not been established.

### Additional Information

- **7 Drug Interactions:** No formal drug interaction studies have been conducted with POMALYST.
- **8.1 Pregnancy:** Safety and effectiveness of POMALYST in patients below the age of 18 have not been established.
- **8.2 Lactation:** Safety and effectiveness of POMALYST in patients below the age of 18 have not been established.
- **8.3 Nursing mothers:** It is not known if pomalidomide 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 POMALYST, 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 of POMALYST in patients below the age of 18 have not been established.
8.5 Geriatric use No dosage adjustment is required for POMALYST based on age. The total number of patients in clinical studies of POMALYST, 41 percent were 65 and over, while 12 percent were 75 and over. No overall differences in effectiveness were observed between these patients and younger patients. In this study, patients greater than or equal to 65 years of age were more likely than patients less than or equal to 65 years of age to experience procedures.

8.6 Females of Reproductive Potential and Males POMALYST can cause fetal harm when administered during pregnancy [see Use in Specific Populations (8.6)]. The influence of POMALYST on the safety of females of reproductive potential should be referred to a qualified provider of contraceptive advice. Females who are of reproductive potential must have negative pregnancy tests before initiating treatment with POMALYST. The test should be performed within 10-14 days, and the second test within 24 hours prior to prescribing POMALYST. Once treatment has started and during dose interruptions, pregnancy testing for females of reproductive potential should be performed 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 menstrual period, or if there is any abnormality in her menstrual bleeding. POMALYST treatment must be discontinued during this evaluation. Males Pomalidomide is present in the semen of males who take POMALYST. Therefore, males must always use a highly effective form of contraception and avoid sexual contact with females of reproductive potential while taking POMALYST and for up to 28 days after discontinuing POMALYST, even if they have undergone a successful vasectomy. Male patients taking POMALYST must not donate sperm.

8.7 Renal Impairment Pomalidomide and its metabolites are primarily excreted by the kidneys [see Clinical Pharmacology (12.3)]. The influence of renal impairment on the safety, efficacy, and pharmacokinetics of pomalidomide has not been evaluated. Patients with serum creatinine greater than 3.0 mg/dL were excluded in clinical studies. Avoid POMALYST in patients with a serum creatinine greater than 3.0 mg/dL.

8.8 Hepatic Impairment Pomalidomide is metabolized in the liver [see Clinical Pharmacology (12.3)]. The influence of hepatic impairment on the safety, efficacy, and pharmacokinetics of pomalidomide has not been evaluated. Patients with serum bilirubin greater than 2.0 mg/dL and AST/ALT greater than 3.0 x upper limit normal (ULN) were excluded in clinical studies. Avoid POMALYST in patients with serum bilirubin greater than 2.0 mg/dL and AST/ALT greater than 3.0 x ULN.

10 OVERDOSAGE No specific information is available for overdose of pomalidomide, and it is unknown whether pomalidomide or its metabolites are dialyzable.

13 NONCLINICAL TOXICOLOGY 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility Studies examining the carcinogenic potential of pomalidomide have not been conducted. One of twelve mouse strains dosed with pomalidomide (an exposure approximately 15-fold of the exposure in patients at the recommended dose of 4 mg/per day) developed acute myeloid leukemia in a 9-month repeat-dose toxicity study. Pomalidomide is clastogenic in a battery of tests, including the bacteria reverse mutation assay (Ames test), the in vitro assay using human peripheral blood lymphocytes and the micronucleus test in orally treated rats administered doses up to 2000 mg/kg/day. In a fertility and early embryonic development study in rats, drug-treated males were mated with untreated or treated females. Pomalidomide was administered to males and females at doses of 25 to 1000 mg/kg/day. When treated males were mated with treated females, there was an increase in post-implantation loss and a decrease in mean number of viable embryos at all dose levels. There were no other effects on reproductive functions or the number of pregnancies. The lowest dose tested in animals resulted in a decrease in the number of pregnancies. The lowest dose tested in animals resulted in an exposure (AUC) approximately 100-fold of the exposure in patients at the recommended dose of 4 mg/day. When drug-treated males were mated with untreated females, all uterine parameters were comparable to the controls. Based on these results, the observed effects were attributed to the treatment of females.

17 PATIENT COUNSELING INFORMATION See FDA-approved Patient labeling (Medication Guide) Embryo-Fetal Toxicity Advise patients that POMALYST is contraindicated in pregnancy [see Contraindications (4)]. POMALYST is a thalidomide analog and may 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 POMALYST and for at least 4 weeks after completing therapy. Initiate POMALYST 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 simultaneously during POMALYST therapy; during therapy interruption days after she has completed finishing taking POMALYST. 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.

18.1 Patient Information Advise patients that if their doctor is not available, they may contact their health care provider for further evaluation. Second Primary Malignancies Inform patients of the potential risk of developing acute myelogenous leukemia during treatment with POMALYST is unknown.

Dosing Instructions Inform patients on how to take POMALYST [see Dosage and Administration (2.1)] POMALYST should be taken once daily at about the same time each day. POMALYST should be taken without food (at least 2 hours before or 2 hours after a meal). The capsules should not be opened, broken, or chewed. POMALYST should be swallowed whole with water.

Inform patients that if they miss a dose of POMALYST, 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 POMALYST at the usual time. Warn patients not to take 2 doses to make up for the one that they missed.

Other Information Advise patients who smoke to stop because smoking may reduce the efficacy of pomalidomide [see Drug Interactions (7.2)].

Manufactured for: Celgene Corporation Summit, NJ 07901

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U.S. Pat. Nos. 5,635,517; 6,045,501; 6,315,784; 6,316,471; 6,476,052; 6,561,976; 6,561,977; 6,755,784; 6,908,432; 8,158,653; 8,198,262; 8,204,763; 8,315,886

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This is a 2-armed, randomized, open-label, phase 3 study designed to evaluate the hematologic remission rate (CR + CRi) with inotuzumab ozogamicin compared with investigators’ choice of FLAG, cytarabine combined with mitoxantrone, or HIDAC.

**Selected inclusion criteria**
- Relapsed or refractory CD22-positive ALL due to receive salvage 1 or salvage 2 therapy
- Ph+ ALL patients must have failed treatment with at least 1 second-generation tyrosine kinase inhibitor
- Bone marrow involvement with ≥5% lymphoblasts
- Aged 18 years or older
- ECOG performance status 0–2
- Adequate liver function

**Selected exclusion criteria**
- Isolated extramedullary relapse, Burkitt’s lymphoma or mixed-lineage leukemia, or active central nervous system leukemia
- Active heart disease
- Prior chemotherapy ≤2 weeks prior to randomization and/or patients not recovered from acute toxicity
- Prior treatment with monoclonal antibodies ≤6 weeks before randomization
- Prior allogeneic hematopoietic stem cell transplant ≤4 months before randomization
- Peripheral lymphoblasts >10,000/µL

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For more information about this trial, please visit [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (NCT01564784)
or call: 1-877-369-9753 in the United States and Canada (toll-free)
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Reference: ClinicalTrials.gov Web site.

**Inotuzumab ozogamicin is an investigational compound.**
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