SPECIAL REPORT

Clinical Pathways
Updates in Multiple Myeloma:
New and Expected Treatments for Refractory and Resistant Multiple Myeloma
IN THE TREATMENT OF RELAPSED REFRACTORY MULTIPLE MYELOMA IN COMBINATION WITH POMALIDOMIDE AND DEXAMETHASONE (Pd)

ACHIEVE GREATER OUTCOMES FOR YOUR PATIENTS

SARCLISA is an anti–CD38 therapy proven to deliver superior PFS (median PFS of 11.53 months with SARCLISA + Pd vs 6.47 months with Pd alone, HR=0.596, 95% CI: 0.44, 0.81, P=0.0010).

SARCLISA also demonstrated a significant increase in ORR (60.4% with SARCLISA + Pd [95% CI: 52.2%, 68.2%] vs 35.3% with Pd alone [95% CI: 27.8%, 43.4%], P<0.0001)\*.

\*ORR included sCR, CR, VGPR, and PR. sCR, CR, VGPR, and PR were evaluated by an IRC using the IMWG response criteria.1

CR=complete response; IMWG=International Myeloma Working Group; IRC=independent response committee; mAb=monoclonal antibody; ORR=overall response rate; PFS=progression-free survival; PR=partial response; sCR=stringent complete response; VGPR=very good partial response.

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**NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)**

Preferred Category 1 recommendation for isatuximab-irfc (SARCLISA)

Isatuximab-irfc (SARCLISA), in combination with pomalidomide and dexamethasone, is a Preferred Category 1 option for previously treated multiple myeloma by the National Comprehensive Cancer Network® (NCCN®).1

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**Indication**

SARCLISA (isatuximab-irfc) is indicated, in combination with pomalidomide and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor.

**Important Safety Information**

**CONTRAINDICATIONS**

SARCLISA is contraindicated in patients with severe hypersensitivity to isatuximab-irfc or to any of its excipients.

**WARNINGS AND PRECAUTIONS**

**Infusion-Related Reactions**

Infusion-related reactions (IRRs) have been observed in 39% of patients treated with SARCLISA. All IRRs started during the first SARCLISA infusion and resolved on the same day in 98% of the cases. The most common symptoms of an IRR included dyspnea, cough, chills, and nausea. The most common severe signs and symptoms included hypertension and dyspnea.

To decrease the risk and severity of IRRs, premedicate patients prior to SARCLISA infusion with acetaminophen, H₂ antagonists, diphenhydramine or equivalent, and dexamethasone. Monitor vital signs frequently during the entire SARCLISA infusion. For patients with grade 1 or 2 reactions, interrupt SARCLISA infusion and provide appropriate medical support. If symptoms improve, restart SARCLISA infusion at half of the initial rate, with supportive care as needed, and closely monitor patients. If symptoms do not recur after 30 minutes, the infusion rate may be increased to the initial rate, and then increased incrementally. In case symptoms do not improve or recur after interruption, permanently discontinue SARCLISA and institute appropriate management. Permanently discontinue SARCLISA if a grade 3 or higher IRR occurs and institute appropriate emergency medical management.

Please see Important Safety Information throughout, and accompanying brief summary of full Prescribing Information.
SARCLISA + Pd extended median PFS to ~1 year
Superior PFS with SARCLISA + Pd vs Pd alone

The median duration of treatment was 41 weeks with SARCLISA + Pd vs 24 weeks with Pd. At a median follow-up time of 11.6 months, 43 patients (27.9%) receiving SARCLISA + Pd and 56 patients (36.6%) receiving Pd had died. Median OS was not reached for either treatment group at interim analysis. The OS results at interim analysis did not reach statistical significance.

SARCLISA + Pd showed a significant increase in ORR

<table>
<thead>
<tr>
<th>SARCLISA + Pd (n=154)</th>
<th>Pd (n=153)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>60.4%</strong> ORR</td>
<td><strong>35.3%</strong> ORR</td>
</tr>
<tr>
<td><strong>31.8%</strong> ≥VGPR</td>
<td><strong>8.5%</strong> ≥VGPR</td>
</tr>
<tr>
<td><strong>35</strong> days</td>
<td><strong>58</strong> days</td>
</tr>
</tbody>
</table>

*ORR included sCR, CR, VGPR, and PR. ORR: SARCLISA + Pd (95% CI: 52.2%, 68.2%), Pd (95% CI: 27.8%, 43.4%).

STUDY DESIGN: ICARIA-MM (NCT02990338), a multicenter, open-label, randomized, phase 3 study, evaluated the efficacy and safety of SARCLISA in 307 patients with relapsed refractory multiple myeloma who had received at least 2 prior therapies, including lenalidomide and a PI. Patients received either SARCLISA 10 mg/kg administered as an IV infusion in combination with Pd (n=154) or Pd alone (n=153), administered in 28-day cycles until disease progression or unacceptable toxicity. SARCLISA was given weekly in the first cycle and every 2 weeks thereafter. Pomalidomide 4 mg was taken orally once daily from day 1 to day 21 of each 28-day cycle. Low-dose dexamethasone (orally or IV) 40 mg (20 mg for patients ≥75 years of age) was given on days 1, 8, 15, and 22 for each 28-day cycle. PFS was the primary endpoint. ORR and OS were key secondary endpoints. PFS results were assessed by an IRC, based on central laboratory data for M-protein, and central radiologic imaging review using the IMWG criteria. Median follow-up was 11.6 months.
Important Safety Information (cont’d)

Neutropenia
SARCLISA may cause neutropenia. Neutropenia (reported as laboratory abnormality) occurred in 96% of patients and grade 3–4 neutropenia occurred in 85% of patients treated with SARCLISA, pomalidomide, and dexamethasone (Isa-Pd). Febrile neutropenia occurred in 12% of patients and neutropenic infections, defined as infection with concurrent grade ≥3 neutropenia, occurred in 25% of patients treated with Isa-Pd. The most frequent neutropenic infections included those of upper respiratory tract (10%), lower respiratory tract (9%), and urinary tract (3%).

Monitor complete blood counts periodically during treatment. Consider the use of antibiotics and antiviral prophylaxis during treatment. Monitor patients with neutropenia for signs of infection. In case of grade 4 neutropenia, delay SARCLISA dose until neutrophil count recovery to at least 1.0 x 10^9/L, and provide supportive care with growth factors, according to institutional guidelines. No dose reductions of SARCLISA are recommended.

Second Primary Malignancies
Second primary malignancies were reported in 39% of patients in the SARCLISA, pomalidomide, and dexamethasone (Isa-Pd) arm and in 0.7% of patients in the pomalidomide and dexamethasone (Pd) arm, and consisted of skin squamous cell carcinoma (2.6% of patients in the Isa-Pd arm and in 0.7% of patients in the Pd arm), breast angiosarcoma (0.7% of patients in the Isa-Pd arm), and myelodysplastic syndrome (0.7% of patients in the Isa-Pd arm). With the exception of the patient with myelodysplastic syndrome, patients were able to continue SARCLISA treatment. Monitor patients for the development of second primary malignancies.

Laboratory Test Interference
Interference with Serological Testing (Indirect Antiglobulin Test)
SARCLISA binds to CD38 on red blood cells (RBCs) and may result in a false positive indirect antiglobulin test (indirect Coombs test). In ICARIA-multiple myeloma (MM), the indirect antiglobulin test was positive during SARCLISA treatment in 67.7% of the tested patients. In patients with a positive indirect antiglobulin test, blood transfusions were administered without evidence of hemolysis. ABO/RhD typing was not affected by SARCLISA treatment. Before the first SARCLISA infusion, conduct blood type and screen tests on SARCLISA-treated patients. Consider phenotyping prior to starting SARCLISA treatment. If treatment with SARCLISA has already started, inform the blood bank that the patient is receiving SARCLISA and SARCLISA interference with blood compatibility testing can be resolved using dithiothreitol-treated RBCs. If an emergency transfusion is required, non-cross-matched ABO/RhD-compatible RBCs can be given as per local blood bank practices.

Interference with Serum Protein Electrophoresis and Immunofixation Tests
SARCLISA is an IgG kappa monoclonal antibody that can be incidentally detected on both serum protein electrophoresis and immunofixation assays used for the clinical monitoring of endogenous M-protein. This interference can impact the accuracy of the determination of complete response in some patients with IgG kappa myeloma protein.

Embryo-Fetal Toxicity
Based on the mechanism of action, SARCLISA can cause fetal harm when administered to a pregnant woman. SARCLISA may cause fetal immune cell depletion and decreased bone density. Advise pregnant women of the potential risk to a fetus. Advise females with reproductive potential to use an effective method of contraception during treatment with SARCLISA and for at least 5 months after the last dose. The combination of SARCLISA with pomalidomide is contraindicated in pregnant women because pomalidomide may cause birth defects and death of the unborn child. Refer to the pomalidomide prescribing information on use during pregnancy.

ADVERSE REACTIONS
The most common adverse reactions (≥20%) were neutropenia (laboratory abnormality, 96% Isa-Pd vs 92% Pd), infusion-related reactions (38% Isa-Pd vs 0% Pd), pneumonia (31% Isa-Pd vs 23% Pd), upper respiratory tract infections (57% Isa-Pd vs 42% Pd), and diarrhea (26% with Isa-Pd vs 19% Pd). Serious adverse reactions occurred in 62% of patients receiving SARCLISA. Serious adverse reactions in >5% of patients who received Isa-Pd included pneumonia (26%), upper respiratory tract infections (7%), and febrile neutropenia (7%). Fatal adverse reactions occurred in 11% of patients (those that occurred in more than 1% of patients were pneumonia and other infections [3%]).

USE IN SPECIAL POPULATIONS
Because of the potential for serious adverse reactions in the breastfed child from isatuximab-irfc administered in combination with Pd, advise lactating women not to breastfeed during treatment with SARCLISA.

Please see accompanying brief summary of full Prescribing Information.

SARCLISA® Rx Only (isatuximab-irfc) injection, for intravenous use
Brief Summary of Prescribing Information
1 INDICATIONS AND USAGE
SARCLISA is indicated in combination with pomalidomide and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor.

2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dosage
Administer the recommended premedication agents 15 to 60 minutes premedication and of the backbone treatment, before the above recommended dose of dexamethasone.

2.2 Recommended Premedication
Administer the following premedications prior to SARCLISA infusion: for the risk and severity of infusion-related reactions (see Warnings and Precautions (5.1)).

• Dexamethasone 40 mg orally or intravenously (or 20 mg every 6 hours for patients ≥75 years of age).
• Acetylsalicylic acid 650 mg to 1000 mg orally (or equivalent).
• H2 antagonists.
• Diphenhydramine 25 mg to 50 mg orally or intravenously (or equivalent). The intravenous route is preferred for at least the first 4 infusions.
• The above recommended dose of dexamethasone (orally or intravenously) corresponds to the total dose to be administered only once before infusion as part of the premedication and of the backbone treatment, before SARCLISA and pomalidomide administration.

Administer the recommended premedication agents 15 to 60 minutes prior to starting a SARCLISA infusion.

2.3 Dose Modifications
No dose reduction of SARCLISA is recommended. Dose delay may be necessary for recovery of all blood counts.

For other medicinal products that are administered with SARCLISA in combination with pomalidomide and dexamethasone.

2.4 Preparation
For infusion using aseptic technique as follows:

1. Prepare the solution for infusion using aseptic technique as follows:

2. Withdraw the necessary volume of SARCLISA injection according, maintaining the treatment interval.

Table 1: SARCLISA Dosing Schedule in Combination With Pomalidomide and Dexamethasone

<table>
<thead>
<tr>
<th>Cycle</th>
<th>Dosing schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cycle 1</td>
<td>Days 1, 8, 15, and 22 (weekly)</td>
</tr>
<tr>
<td>Cycle 2 and beyond</td>
<td>Days 1, 15 (every 2 weeks)</td>
</tr>
</tbody>
</table>

Each treatment cycle consists of a 28-day period. Treatment is repeated until disease progression or unacceptable toxicity. SARCLISA is used in combination with pomalidomide and dexamethasone.

Maximum Dose
A planned dose of SARCLISA is missed, administer the dose as soon as possible and adjust the treatment schedule accordingly, maintaining the treatment interval.

2.5 Administration
Administer the solution by intravenous infusion using an intravenous tubing infusion set (in PE, PVC with or without DEHP polybutylen (PB0), or polyurethane (PU)) with a 0.22 micron in-line filter (polyethersulfone (PES), polysulfonic acid (PVA), or cellulose (CPL)).

• The infusion solution should be administered for a period of time that will depend on the infusion rate (see Table 2).

Use prepared SARCLISA infusion solution within 48 hours when stored refrigerated at 2°C–8°C, followed by 6 hours (including the infusion time) at room temperature. Do not administer a solution that is congealed in the same intravenous line with other agents.

Infusion Rates
Following dilution, administer the SARCLISA infusion solution intravenously at the infusion rates presented in Table 2. Incrementation of the infusion rate should be considered only in the absence of infusion-related reactions (see Warnings and Precautions (5.1) and Adverse Reactions (6.1)).

Table 2: Infusion Rates of SARCLISA Administration

<table>
<thead>
<tr>
<th>Infusion Rate</th>
<th>Volume/Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>First infusion</td>
<td>250 mL over 60 minutes</td>
</tr>
<tr>
<td>Second infusion</td>
<td>50 mL/hour</td>
</tr>
<tr>
<td>Subsequent infusions</td>
<td>200 mL/hour</td>
</tr>
</tbody>
</table>

4 CONTRAINDICATIONS
SARCLISA is contraindicated in patients with severe hypersensitivity to isatuximab-irfc or any of its excipients (see Warnings and Precautions (5.1)).

5 WARNINGS AND PRECAUTIONS
5.1 Infusion-Related Reactions
Infusion-related reactions have been observed in 39% of patients treated with SARCLISA (see Adverse Reactions (6.1)). All infusion-related reactions started during the first SARCLISA infusion and resolved on the same day in 88% of the cases. The most common symptoms of an infusion-related reaction included dyspnea, cough, chills, and nausea. The most common severe signs and symptoms included hypotension and dyspnea (see Adverse Reactions (6.1)). To decrease the risk and severity of infusion-related reactions, predilute medication prior to SARCLISA infusion with acetylsalicylic acid, H2 antagonists, diphenhydramine, or equivalent; dexamethasone (see Dosage and Administration (2.2)). Monitor vital signs frequently during the entire SARCLISA infusion. For patients with grade 1 or 2 reactions, interrupt SARCLISA infusion and provide appropriate medical support. If symptoms improve, restart SARCLISA infusion at half the initial infusion rate, with supportive care as needed, and closely monitor patients. If symptoms do not recur after 30 minutes, the infusion rate may be increased to the initial rate, and then increased incrementally, as shown in Table 2 (see Dosage and Administration (2.2)).

2.7 Discontinuation of SARCLISA therapy if a grade 3 or higher infusion-related reaction occurs and institute appropriate medical management.

5.2 Neutropenia
SARCLISA may cause neutropenia. Neutropenia (reported as laboratory abnormality) occurred in 96% of patients and grade ≥3 neutropenia occurred in 85% of patients treated with SARCLISA, pomalidomide, and dexamethasone (Isa-Pd). Fibrile neutropenia occurred in 12% of patients and neutropenic infections, defined as infection with concurrent grade ≥3 neutropenia, occurred in 25% of patients treated with Isa-Pd. The most frequent neutropenic infections included those of upper respiratory tract (10%), lower respiratory tract (9%), and urinary tract (3%) (see Adverse Reactions (6.1)).

Monitor complete blood cell counts periodically during treatment. Consider the use of antibiotics and antiviral prophylaxis during treatment. Monitor patients with neutropenia for signs of infection. In case of grade 4 neutropenia delay SARCLISA dose until neutrophil count recovery to at least 1.0 x 10⁹/L and provide supportive care with growth factors, according to institutional guidelines. No dose reductions of SARCLISA are recommended.

5.3 Secondary Malignancies
Second primary malignancies were reported in 3.9% of patients in the SARCLISA, pomalidomide and dexamethasone (Isa-Pd) arm and in 0.7% of patients in the pomalidomide and dexamethasone (Pd) arm, and consisted of skin squamous cell carcinoma (Isa-Pd arm) and II carcinoma (Pd arm) and 0.7% of patients in the Pd arm). Breast angiosarcoma (0.7% of patients in the Isa-Pd arm) and myelodysplastic syndrome (0.7% of patients in the Isa-Pd arm). With the exception of the patient with myelodysplastic syndrome, the patient remained stable and was able to continue SARCLISA treatment. Monitor patients for the development of secondary primary malignancies, as per International Myeloma Working Group (IMWG) guidelines.

5.4 Laboratory Test Interference
Interference with Serological Testing
SARCLISA binds to CD38 on red blood cells (RBCs) and may result in a false positive indirect antiglobulin test (ISAT-Pd) arm and in 0.7% of patients in the pomalidomide and dexamethasone (Pd) arm group. The indirect antiglobulin test was positive during SARCLISA treatment in 7% of patients. In this case, the patient was treated with a positive indirect antiglobulin test, blood transfusions were administered without evidence of hemolysis. ABO/Rh typing was affected by SARCLISA treatment and permanent SARCLISA infusion, conduct blood type and screen tests on SARCLISA-treated patients. Consider phenotyping prior to starting SARCLISA treatment. If treatment with SARCLISA has already started, inform the blood bank that the patient is receiving SARCLISA and SARCLISA interference with blood compatibility testing can be resolved using diamidine-treated RBCs. If an emergency transfusion is required, non–cross-matched ABO-compatible RBCs can be given per local blood bank practices (see Drug Interactions (7.1)).

6 ADVERSE REACTIONS
The following clinically significant adverse reactions from SARCLISA are also described in some other sections of the labeling.

• Infusion-Related Reactions (see Warnings and Precautions (5.1)).
• Neutropenia (see Warnings and Precautions (5.2)).
• Secondary Malignancies (see Warnings and Precautions (5.3)).

6.1 Clinical Trials Experience
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.

1.1. The efficacy of SARCLISA was evaluated in ICARIA-MM, a randomized, open-label clinical trial in patients with previously treated multiple myeloma. ICARIA-MM used a dose of 13.5 mg/kg for inclusion if they had ECOG status of 0–2, platelets ≥75,000 cells/mm³, absolute neutrophil count ≥1 x 10⁹/L, creatinine clearance ≥30 mL/min (MEROX term), and AST and/or ALT ≤3 x ULN. Patients received SARCLISA 10 mg/kg intravenously, weekly in the first cycle and every two weeks thereafter, in combination with pomalidomide and low-dose dexamethasone (Isa-Pd) (n=152) or pomalidomide and low-dose dexamethasone (Pd) (n=149) (see Clinical Studies (14) in the full prescribing information). Among patients receiving Isa-Pd, 66% were exposed to SARCLISA for 6 months or longer and 24% were exposed for greater than 12 months or longer. The median age of patients who received Isa-Pd was 68 years (range 36–83); 58% male, 76% white, and 14% Asian. Serious adverse reactions occurring in ≥6% of patients receiving Isa-Pd were neutropenia (28%), platelet disorders (9%), and upper respiratory tract infections (7%). Serious adverse reactions in ≥5% of patients who received Isa-Pd included pneumonia (26%), upper respiratory tract infections (7%), and fever (7%). Fatal adverse reactions occurred in 11% of patients (those that occurred in more than 1% of patients were pneumonia and other infections (3%).

2.5 Permanent discontinuation due to an adverse reaction (grades 3–4) occurred in 3% of patients receiving Isa-Pd. The most frequent adverse reactions requiring permanent discontinuation in patients who received Isa-Pd were infections (2.1%). In addition, SARCLISA was temporarily discontinued in 3% of patients due to infusion-related reactions. Dosage interruptions due to an adverse reaction occurred in 11% of patients who received SARCLISA and the most frequent adverse reaction requiring dosage interruption was infusion-related reaction (28%).

SARCLISA® Rx Only (isatuximab-irfc) injection, for intravenous use
The most common adverse reactions (>20%) were neutropenia, infusion-related reactions, pyrexia, upper respiratory tract infection, and diarrhea. Table 3 summarizes the adverse reactions in ICARIA-MM.

### Table 3: Adverse Reactions (≥10%) in Patients Receiving SARCLISA, Pomalidomide, and Dexamethasone with a Difference Between Arms of ≥5% Compared to Control Arm in ICARIA-MM Trial

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>SARCLISA + Pomalidomide + Dexamethasone (Isa-Pd) (N=152)</th>
<th>Pomalidomide + Dexamethasone (Pd) (N=149)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grade 3 (%)</td>
</tr>
<tr>
<td>Injection-related reaction</td>
<td>38.1</td>
<td>1.3</td>
</tr>
<tr>
<td>Infections</td>
<td>31.2</td>
<td>22.3</td>
</tr>
</tbody>
</table>

**Upper respiratory tract infection**

- 57.9 %
- 5.9 %
- 42.0 %

**Blood and lymphatic system disorders**

- Fatigue
  - 12.0 %
  - 11.0 %
  - 2.0 %
  - 0.7 %

- Respiratory, thoracic, and mediastinal disorders
  - Fatigue
    - 12.0 %
    - 11.0 %
    - 2.0 %
    - 0.7 %

- Gastrointestinal disorders
  - Diarrhea
    - 18.6 %
    - 9.0 %
    - 11.0 %

- Vomiting
  - 12.0 %
  - 1.0 %
  - 3.4 %

Table 4 summarizes the hematologic laboratory abnormalities in ICARIA-MM.

### Table 4: Treatment Emergent Hematology Laboratory Abnormalities in Patients Receiving Isa-Pd Treatment vs Pd Treatment – ICARIA-MM

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>All Grades</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anaemia</td>
<td>151 (45)</td>
<td>46 (13)</td>
<td>0</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>140 (46)</td>
<td>37 (11)</td>
<td>9 (3)</td>
</tr>
<tr>
<td>Lymphopenia</td>
<td>139 (45)</td>
<td>54 (15)</td>
<td>19 (6)</td>
</tr>
<tr>
<td>Transferrin</td>
<td>127 (38)</td>
<td>27 (8)</td>
<td>22 (7)</td>
</tr>
</tbody>
</table>

**Description of Selected Adverse Reactions**

**Infusion-related reactions** in ICARIA-MM, infusion-related reactions (defined as adverse reactions associated with the SARCLISA infusions, with an onset typically within 24 hours from the start of the infusion) were reported in 58 patients (38%) treated with SARCLISA. All patients who experienced infusion-related reactions, experienced them during the first infusion of SARCLISA, with 3 patients (2%) also having infusion-related reactions at their 2nd infusion, and 2 patients (1.3%) at their 4th infusion. Grade 1 infusion-related reactions were reported in 9%, Grade 2 in 36%, Grade 3 in 1.3%, and Grade 4 in 1.3% of the patients. Signs and symptoms of Grade 3 or higher infusion-related reactions included dyspnea, hypotension, and bronchospasm. The incidence of infusion interruptions because of infusion-related reactions was 29.8%. The median time to infusion interruption was 65 minutes. In a separate study (TCD 14079 Pan B) with SARCLISA 10 mg/kg administered from a 250 mL fixed-volume infusion in combination with Pd, infusion-related reactions (all Grade 2) were reported in 40% of patients, at the first administration, the day of the infusion. Overall, the infusion-related reactions of SARCLISA 10 mg/kg administered as a 250 mL fixed-volume infusion was similar to that of SARCLISA as administered in ICARIA-MM.

**Infections**

- In ICARIA-MM, the incidence of Grade 3 or higher infections was 43% in Isa-Pd group. Pneumonia was the most commonly reported severe infection with Grade 3 reported in 22% of patients in Isa-Pd group compared to 16% in Pd group, and Grade 4 in 3.3% of patients in Isa-Pd group compared to 2.7% in Pd group. Discontinuations from treatment due to infection with Grade 3 or higher in 2.6% of patients in Isa-Pd group compared to 5.4% in Pd group. Fatal infections were reported in 3.3% of patients in Isa-Pd group and in 4% in Pd group.

**Immunogenicity**

- As with all therapeutic proteins, there is a potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the presence of antibodies (including neutralizing antibody positivity) in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described above with the incidence of antibodies in other studies or to other isatuximab-irfc products may be misleading.

**Respiratory, thoracic, and mediastinal disorders**

- Diarrhea
  - 26.5 %
  - 19.0 %

- Nausea
  - 15.0 %

- Vomiting
  - 12.1 %

**Gastrointestinal disorders**

- Abdominal pain
  - 7.8 %
  - 5.6 %

**Hematologic laboratory abnormalities**

- Anaemia
  - 151 (45)
  - 46 (13)

**Allergic reactions**

- Eosinophilia
  - 3.0 %

**Contraindications**

- There are no available data on the presence of isatuximab-irfc in human milk, milk production, or the effects on the breastfed child. Maternal immunoglobulin G is known to be present in human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed infant to SARCLISA are unknown. Because of the potential for serious adverse reactions in the breastfed child from isatuximab-irfc administered in combination with pomalidomide and dexamethasone, advise lactating women not to breastfeed during treatment with SARCLISA. Refer to pomalidomide prescribing information for additional information.

**8.3 Females and Males of Reproductive Potential**

- Pregnancy
  - Risk Summary
    - SARCLISA can cause fetal harm when administered to a pregnant woman.
    - Use in Specific Populations
      - Pregnancy
        - See Use in Specific Populations (8.4).
  - Contraception
    - Females
      - SARCLISA can cause fetal harm when administered to a pregnant woman.
      - Use in Specific Populations
        - Pregnancy
          - See Use in Specific Populations (8.4).
      - Male
        - Refer to the pomalidomide prescribing information.

**8.4 Pediatric Use**

- Safety and effectiveness in pediatric patients have not been established.

**8.5 Geriatric Use**

- Of the total number of subjects in clinical studies of SARCLISA, 53% (390 patients) were 65 or over, while 14% (92 patients) were 75 or over. No overall differences in safety or effectiveness were observed between subjects 65 and over and younger subjects, and other reported clinical experience has not identified differences in responses between the adults 65 years and over and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

**10 OVERDOSAGE**

- There is no known specific antitoxin for SARCLISA overdose.
- In the event of overdose of SARCLISA, monitor the patients for signs or symptoms of adverse effects and take all appropriate measures immediately.

**SARCLISA**

(isatuximab-irfc) injection, for intravenous use

**Data**

- Animal data
  - Mice that were genetically modified to eliminate all CD38 expression (CD38 knockout mice) had reduced bone density which recovered 5 months after birth. Data from studies using CD38 knockout animal models also suggest the involvement of CD38 in regulating humoral immune responses (mice) and early embryonic development (trops).

8.2 Lactation

- Risk Summary
  - There are no available data on the presence of isatuximab-irfc in human milk, milk production, or the effects on the breastfed child. Maternal immunoglobulin G is known to be present in human milk. The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed infant to SARCLISA are unknown. Because of the potential for serious adverse reactions in the breastfed child from isatuximab-irfc administered in combination with pomalidomide and dexamethasone, advise lactating women not to breastfeed during treatment with SARCLISA. Refer to pomalidomide prescribing information for additional information.

**Manufactured by**

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ISA-BPLR-SA-MAR20
Revised: March 2020
SPECIAL REPORT

Clinical Pathways
Updates in Multiple Myeloma:
New and Expected Treatments for Refractory and Resistant Multiple Myeloma

EXECUTIVE SUMMARY

The overall survival rate of patients with multiple myeloma (MM) has increased greatly over the past 30 years. The initial treatment of MM has become largely standardized, making the first step in the treatment process and maintenance therapy relatively easy to follow. Treatment of MM becomes more challenging in patients who have relapsed or who have refractory multiple myeloma (RRMM). As treatments continue to be developed, more options are becoming available for patients with RRMM. In 2020, 3 new treatments were approved for MM. One was a new agent for patients with RRMM, one was a new combination treatment, and the third was a new dosage formulation. More treatments for MM are in the pipeline, both for the initial treatment of MM and for treatment of RRMM. In addition to initial, maintenance, and relapsed/refractory treatment, supportive care of patients with MM should also be addressed. Additionally, one of the biggest challenges faced by MM patients in 2020 was treatment during the time of COVID-19. The 5-year survival rate for MM continues to improve, more drugs are available to treat newly diagnosed patients and patients with RRMM, and promising treatments are in development.

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December 2020 • Multiple Myeloma Special Report 5
Multiple myeloma (MM) is caused by abnormal plasma cell growth in bone marrow and results in marrow failure, production of an abnormal antibody called M protein that can cause tumors and impair immune function, and bone destruction. MM is relatively rare, representing only 1.8% of all new cancer cases,1 18% of all hematologic cancers,2 and 2.1% of all cancer deaths1 in the United States. An estimated 140,779 US people in 2017 were living with MM,1 and approximately 12,830 people are expected to have died from the disease in 2020.3 An estimated 32,270 new cases were diagnosed in 2019, with a median age at diagnosis of 69 years and with diagnoses most commonly occurring between 65 and 74 years.1

The number of MM diagnoses increased globally from 1990 to 2016, with aging contributing to 52.9% of cases and population growth contributing to 40.4% of cases.4 MM has a 53.9% 5-year survival rate,1 with the latest available data from the federal Surveillance, Epidemiology, and End Results Program (SEER) showing an upward trend over time.1 The 5-year relative survival rate for MM when SEER data were first collected between 1975 and 1977 was 24.6%.5 This rate increased by approximately 2% every 2 years until 2005. Between 2002 and 2004, the 5-year survival percentage was 42.5%, which increased to 46.4% between 2005 and 2007 and increased even further to 52.4% between 2008 and 2018.5

While there is no cure for MM, a number of treatments are in the research and development pipeline. Clinicians are particularly challenged to treat relapsed or refractory MM (RRMM); the goal of treatment in patients with relapse is to alleviate symptoms and prevent progressive organ damage.6 First-line treatment options are generally standardized, but with extensive options for subsequent therapy and multiple patient factors to consider, each line of therapy (LOT) becomes more complicated. Drug resistance in MM is greatly influenced by genetics, which contributes to a patient’s predisposition to drug resistance and relapse.7 Patients typically experience fewer complete responses (CRs) to each LOT. In a retrospective cohort study utilizing electronic health record data from 10,553 patients at more than 280 US cancer clinics from 2011 to 2019, approximately 65% of patients survived until the end of follow-up.8 The overall median survival decreased with each additional LOT patients received. The median overall survival in patients receiving first-line therapy was 60 months, which decreased to 48, 36, 29, and 23 months for the second, third, fourth, and fifth-plus LOTs, respectively.8

### INITIAL TREATMENT
For more than 30 years, autologous stem-cell transplant (ASCT) has remained the standard initial treatment of MM. According to the American Society of Clinical Oncology (ASCO) and Cancer Care Ontario guidelines, patients should be referred to transplant centers to determine their transplant eligibility.9 Eligibility for ASCT is affected by age, performance status, and comorbidities.10 A patient’s performance status is determined by how much the cancer affects the patient’s daily living abilities in terms of caring for themselves, daily activity, and physical ability. Prior to stem-cell transplant, 3 to 4 cycles of induction therapy are recommended.9 Induction therapy should include an immunomodulating drug, a proteasome inhibitor (PI), and a corticosteroid.9 According to guidelines from the National Comprehensive Cancer Network (NCCN), the preferred regimens for primary induction therapy in transplant-eligible candidates are bortezomib + lenalidomide + dexamethasone (VRd) or bortezomib + cyclophosphamide + dexamethasone (CyBorD) (Table 1). Other options include carfilzomib + lenalidomide + dexamethasone (KRd) and ixazomib + lenalidomide + dexamethasone (IRd).11 For nontransplant candidates, the preferred treatments are VRd, daratumumab + lenalidomide + dexamethasone (D-Rd), lenalidomide + low-dose dexamethasone (Rd), and CyBorD. There are 3 other accepted regimens, as well.11

### MAINTENANCE THERAPY
**Lenalidomide.** The NCCN Panel recommends lenalidomide as first-line maintenance therapy, regardless of whether a patient has received ASCT.11 This recommendation was based on the results of 2 randomized phase 3 studies. In the
Call for Papers!

Journal of Clinical Pathways invites prospective authors to submit research, quality improvement, and perspectives manuscripts. Articles detailing field implementation of clinical pathways or other value-based care initiatives are particularly encouraged.

Manuscript topics may include but are not limited to:
- Challenges and solutions in the delivery of novel therapies
- Leveraging pathways in alternative payment models
- Use and operationalization of clinical pathways in community cancer centers
- Integrating real-world data and genomics in clinical practice
- Comparative-effectiveness research
- HEOR research

Email your article proposal or manuscript submission to Amanda Del Signore at adelsignore@hmpglobal.com
CALGB 100104 trial, patients received either maintenance therapy with lenalidomide or placebo following ASCT. At a median follow-up of 34 months, 37% of the patients who had received lenalidomide experienced disease progression or died compared with 58% of patients who had received placebo. The median time to progression for patients receiving lenalidomide was 46 months compared with 27 months in the placebo group. Data from IFM 2005-02, an international, double-blind, randomized trial, demonstrated that patients who received lenalidomide as consolidation therapy following ASCT and then continued to receive lenalidomide as maintenance therapy had improved responses. At the median follow-up of 30 months, 104 patients treated with lenalidomide experienced disease progression compared with 160 patients in the placebo group. Patients who received lenalidomide had a mean progression-free survival of 41 months compared with 23 months in the placebo group.

**Bortezomib.** Bortezomib is another recommended maintenance therapy in both transplant-eligible and transplant-ineligible patients. This recommendation is based on the results of the phase 3 UPFRONT study. Patients who were newly diagnosed with MM were treated with bortezomib-based primary regimens and then received maintenance therapy with bortezomib. The study demonstrated improved response rates in all treatment arms with no increase in the incidence of peripheral neuropathy.

**Ixazomib.** Ixazomib is recommended as maintenance therapy in patients who are transplant-eligible. The TOUR-MALINE-MM3 trial, which studied patients receiving ixazomib or placebo over the course of 2 years and who achieved at least partial response following induction therapy and ASCT, demonstrated improved progression-free survival. The median progression-free survival in patients who received ixazomib was 26.5 months compared with 21.3 months in the placebo group.

**TREATMENT AFTER RELAPSE**
While initial therapy is well-defined by current guidelines, additional LOTs following relapse can prove more difficult, since treatment is not as straightforward. Numerous options are available for the treatment of patients with relapsed MM (Table 3), including newly approved medications and medications with newly approved indications by the Food and Drug Administration (FDA) over the past few years. Treatment of patients with relapsed MM should be individualized—physicians need to consider prior treatment, cytogenetic risk, comorbidities, myeloma markers, frailty, and patient preference. Generally, a triplet regimen, consisting of 2 novel agents (PI, immunomodulatory drug, or monoclonal antibody) in combination with a corticosteroid, is preferred. In patients who have not yet undergone ASCT, or who underwent ASCT previously and experienced prolonged remission, ASCT should be considered as salvage therapy. If a patient experiences relapse more than

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**TABLE 1. INITIAL THERAPY FOR MULTIPLE MYELOMA**

<table>
<thead>
<tr>
<th>Transplant-Eligible Patients</th>
<th>Bortezomib + Lenalidomide + Dexamethasone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bortezomib + Cyclophosphamide + Dexamethasone</td>
</tr>
<tr>
<td></td>
<td>Carfilzomib + Lenalidomide + Dexamethasone</td>
</tr>
<tr>
<td></td>
<td>Ixazomib + Lenalidomide + Dexamethasone</td>
</tr>
<tr>
<td></td>
<td>Daratumumab + Lenalidomide + Bortezomib + Dexamethasone</td>
</tr>
<tr>
<td>Transplant-Ineligible Patients</td>
<td>Bortezomib + Lenalidomide + Dexamethasone</td>
</tr>
<tr>
<td></td>
<td>Daratumumab + Lenalidomide + Dexamethasone</td>
</tr>
<tr>
<td></td>
<td>Lenalidomide + Low-Dose Dexamethasone</td>
</tr>
<tr>
<td></td>
<td>Bortezomib + Cyclophosphamide + Dexamethasone</td>
</tr>
<tr>
<td></td>
<td>Carfilzomib + Lenalidomide + Dexamethasone</td>
</tr>
<tr>
<td></td>
<td>Ixazomib + Lenalidomide + Dexamethasone</td>
</tr>
<tr>
<td></td>
<td>Daratumumab + Bortezomib + Melphalan + Prednisone</td>
</tr>
<tr>
<td></td>
<td>Daratumumab + Cyclophosphamide + Bortezomib + Dexamethasone</td>
</tr>
</tbody>
</table>

**TABLE 2. MAINTENANCE THERAPY FOR TRANSPLANT-ELIGIBLE AND TRANSPLANT-INELEGIBLE PATIENTS**

<table>
<thead>
<tr>
<th>Preferred Regimens</th>
<th>Lenalidomide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other Recommended Regimens</td>
<td>Ixazomib [transplant-eligible patients only]</td>
</tr>
<tr>
<td></td>
<td>Bortezomib</td>
</tr>
</tbody>
</table>
In 2020, 3 new treatments were FDA-approved for MM: a first-in-class drug, a monoclonal antibody, and a new formulation of a previously approved medication. Additionally, new treatment regimens were FDA-approved. In August, the FDA approved carfilzomib + daratumumab + dexamethasone for patients with RRMM who have failed 1 to 3 previous LOTs.

Belantamab mafodotin-blmf. The FDA granted accelerated approval to belantamab mafodotin-blmf (Blenrep) in August 2020 for RRMM patients who received at least 4 prior therapies, including an anti-CD38 monoclonal antibody, a PI, and an immunomodulatory agent.16 The FDA granted this approval based on results of the phase 2 DREAMM 2 trial. Belantamab mafodotin-blmf is the first approved anti–B-cell maturation antigen (BCMA). The drug is available through a Risk Evaluation and Mitigation Strategy program, since it may cause serious changes to the cornea, leading to worsening or loss of vision.16

Isatuximab-irfc. The combination of isatuximab-irfc (Sarcis), pomalidomide, and dexamethasone was approved in 2020 for RRMM after 2 or more prior therapies (including lenalidomide and a PI).17 Isatuximab-irfc is an anti-CD38 monoclonal antibody. Patients who received the combination of isatuximab-irfc, pomalidomide, and dexamethasone experienced a 40% reduction in risk of disease progression or death compared with patients who received only pomalidomide and dexamethasone.17

Daratumumab and hyaluronidase-fihj. Subcutaneous daratumumab (daratumumab and hyaluronidase-fihj) was granted FDA approval in May 2020 for adults with newly diagnosed or relapsed or refractory MM.18 Efficacy was evaluated in the COLUMBA trial, an open-label noninferiority trial in which 263 patients were randomly assigned to receive daratumumab and hyaluronidase-fihj (Darzalex Faspro) and 259 patients were randomly assigned to receive intravenous daratumumab (Darzalex). The overall response rate was 41.1% for subcutaneous daratumumab and hyaluronidase-fihj and 37.1% for intravenous daratumumab.19 On average, the first infusion of daratumumab lasts 7 hours, and infusions thereafter last 3 to 5 hours; subcutaneous administration drastically reduces this time of administration.

THE MM TREATMENT PIPELINE

Other new treatments, indications, and combinations are on the horizon for treating MM.

Venetoclax. Venetoclax, approved by the FDA for the treatment of chronic lymphocytic leukemia, small lymphocytic lymphoma, and acute myelogenous leukemia, is a BCL-2 inhibitor that induces cell death in MM cells. In the BELLINI trial, RRMM patients received venetoclax plus bortezomib and dexamethasone or placebo plus bortezomib and dexamethasone. The trial was put on partial clinical hold in March 2019 due to safety concerns. The partial clinical hold was removed in July after the trial was modified to ensure patient safety.20

Melflufen. This drug is activated by aminopeptidase, an enzyme of which persons with MM have high levels. The FDA granted priority review to melflufen in combination with dexamethasone for the treatment of patients with RRMM who have been treated with at least one PI, one immunomodulatory agent, and one anti-CD38 monoclonal antibody. The targeted date of review is February 28, 2021.21 The is based on the not yet posted results of a phase 2 clinical trial evaluating melflufen plus dexamethasone in adults with MM refractory to pomalidomide and/or an anti-CD38 monoclonal antibody.22

Iberdomide. Iberdomide (formerly CC-220) is being studied in a phase Ib/IIa clinical trial to determine dose, safety, tolerability, and efficacy.23 Iberdomide is a cereblon E3 ligase modulator and would provide a new immunomodulatory treatment option to patients whose cancer is resistant to lenalidomide and pomalidomide.

Chimeric antigen receptor (CAR) T-cell therapy. The CAR T-cell therapy closest to FDA approval targets BCMA (which is also the target of newly approved belantamab mafodotin-blmf). Researchers are utilizing γ-secretase inhibitors to increase the amount of BCMA produced by MM cells. If the myeloma cells express more BCMA, it will be easier for the CAR T cells to recognize and target the cancer.24 However, not all patients with MM express BCMA. The CD229 (Ly9) receptor has been shown to be a target for CAR T-cell therapy. Results from a small study of 20 patients with MM showed that CD229 was heavily expressed on the surface of MM cells, both in patients who were newly diagnosed and in patients with RRMM.25

Bispecific T-cell engager (BiTE). BiTE antibodies bind to 2 separate CD3 molecule clusters on tumor-specific T cells and a specific antigen on myeloma cells.26 Binding to

Table 3. Treatment of Progressive or Relapsed Multiple Myeloma

<table>
<thead>
<tr>
<th>Preferred Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bortezomib + Lenalidomide + Dexamethasone</td>
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</tr>
<tr>
<td>Daratumumab + Bortezomib + Dexamethasone</td>
</tr>
<tr>
<td>Daratumumab + Carfilzomib + Dexamethasone</td>
</tr>
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<td>Daratumumab + Lenalidomide + Dexamethasone</td>
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<tr>
<td>Isatuximab-irfc + Pomalidomide + Dexamethasone</td>
</tr>
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</tr>
<tr>
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</tr>
<tr>
<td>Pomalidomide + Bortezomib + Dexamethasone</td>
</tr>
</tbody>
</table>

6 months after stopping initial therapy, the first LOT may be restarted.20 Of the preferred regimens recommended by the NCCN for previously treated MM, 6 of the 8 are triplet therapy.
these 2 epitopes leads to T-cell–dependent destruction of the myeloma cells. Only one BiTE antibody, blinatumomab, has been approved, and it is used to treat relapsed or refractory B-cell acute lymphoblastic leukemia. BiTE antibodies are in early development to target BCMA and CD3 in MM, with 5 phase 1 clinical trials under way. In 42 MM patients with 4 previous LOTs, 31% responded to treatment with the BiTE antibody AMG 420, with CR in 14.2% of those patients, very good partial response in 5%, and partial response in 5%. Based on these results, the FDA granted fast-track status to AMG 420 anti-CD3/BCMA BiTE.

**MEASURING MINIMAL RESIDUAL DISEASE**

Minimal residual disease (MRD) is the measurable number of myeloma cells that remain in the bone marrow following MM treatment. In January 2020, the FDA released recommendations regarding the development of MRD tests. Current MM-associated MRD data mostly evaluate newly diagnosed patients after ASCT. The FDA states that, in the development of new drug products that reference MRD, the relationship between MRD and clinical benefit of the drug should reflect all disease settings (RRMM, newly diagnosed MM, nontransplant eligible). MRD should only be measured in patients who have achieved complete remission.

**USE OF IMAGING**

ASCO guidelines recommended the use of whole-body low-dose computed tomography (CT), with fluorodeoxyglucose positron emission tomography (FDG-PET) or magnetic resonance imaging (MRI) as alternatives. The NCCN recommends either whole-body low-dose CT or FDG-PET/CT for initial diagnosis and whole-body FDG-PET/CT, low-dose CT scan, or whole-body MRI without contrast for advanced imaging.

**SUPPORTIVE CARE**

**Bone disease.** All patients undergoing primary treatment for MM should receive a bisphosphonate or denosumab. Additionally, it is recommended that patients receive a baseline dental examination. Treatment with a bisphosphonate or denosumab should be continued for up to 2 years. Patients should be monitored for osteonecrosis of the jaw, as well as for renal dysfunction if receiving bisphosphonate therapy. Radiation therapy can be used for palliation in patients with MM, including those with uncontrolled pain, impending pathologic fracture, or impending cord compression. Patients with impending or actual long-bone fractures, bony compressions of the spinal cord, or vertebral column instability should receive orthopedic consultation. Vertebroplasty or kyphoplasty should be considered for patients with symptomatic vertebral compression fractures.

**Hypercalcemia.** The NCCN panel recommends hydration, bisphosphonates (with zoledronic acid preferred), denosumab, steroids, and/or calcitonin for the management of hypercalcemia.

**Blood hyperviscosity.** Plasmapheresis should be utilized as adjunctive therapy in patients with symptomatic blood hyperviscosity.

**Anemia.** Erythropoietin can be considered for use in patients with MM with anemia. The NCCN panel recommends utilizing the NCCN Guidelines for Hematopoietic Growth Factors.

**Infection.** If a patient with MM is experiencing recurrent serious infections, intravenous immunoglobulin therapy can be considered. Patients should receive the pneumococcal conjugate vaccine followed by the pneumococcal polysaccharide vaccine 1 year later. If a patient is at high risk for infection at diagnosis, 3 months of antibiotic prophylaxis should be considered. Patients receiving high-dose dexamethasone should receive prophylaxis for *Pneumocystis jiroveci* pneumonia, herpes zoster, and fungal infections. All patients treated with PIs, daratumumab, isatuximab-irc, or elotuzumab should receive herpes zoster prophylaxis. For more in-depth recommendations, the NCCN panel recommends utilizing the NCCN Guidelines for Prevention and Treatment of Cancer-Related Infections.

**Kidney dysfunction.** Patients with MM and kidney disease should have their serum creatinine, electrolyte, and uric acid levels routinely tested. Patients’ urine should also be monitored for protein. Treatment option recommendations change for patients with renal dysfunction. A bortezomib-based regimen is recommended, dexamethasone should be pulsed, and a third drug (cyclophosphamide, thalidomide, anthracycline, or daratumumab) may be considered. If a patient will be receiving lenalidomide, there are dose adjustments based on kidney function (Table 4). The NCCN MM guidelines contain in-depth management recommendations.

**Coagulation/thrombosis.** Aspirin (dosed at 81–325 mg) is recommended for patients receiving immunomodulator-based therapy. Patients who are at high risk for thrombosis

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**TABLE 4. LENALIDOMIDE RENAL DOSE ADJUSTMENTS**

<table>
<thead>
<tr>
<th>Category</th>
<th>Creatinine Clearance</th>
<th>Lenalidomide Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate Kidney Impairment</td>
<td>≥30 mL/min to &lt;60 mL/min</td>
<td>10 mg every 24 hours</td>
</tr>
<tr>
<td>Severe Kidney Impairment</td>
<td>&lt;30 mL/min [not requiring dialysis]</td>
<td>15 mg every 48 hours</td>
</tr>
<tr>
<td>Kidney Failure</td>
<td>&lt;30 mL/min [requiring dialysis]</td>
<td>5 mg once daily [administered postdialysis on dialysis days]</td>
</tr>
</tbody>
</table>

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**Category Creatinine Clearance Lenalidomide Dose**

<table>
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<td>5 mg once daily [administered postdialysis on dialysis days]</td>
</tr>
</tbody>
</table>
Should You Join the Clinical Pathways Forum?

The Clinical Pathways Forum is a multidisciplinary community of pathways professionals from more than 12 institutions in the United States and Canada who are utilizing clinical pathways in their practices and institutions to improve cancer care.

Forum leader Mishellene McKinney, MHA, RN, OCN, organizes quarterly conference calls with Forum members to facilitate discussion of shared experiences and lessons learned regarding pathway use as clinical pathways become more prevalent and evolve to meet the needs of value-based health care systems and reimbursement models.

Want to Know More?

Contact Ms. McKinney for more information about the Forum and/or how to become a member at mishellene.mckinney@roswellpark.org
CONTINUED CHALLENGES

MM, a challenging cancer manage on its own, has become even more difficult to manage during the COVID-19 pan-
demic. Coronavirus infection is dangerous for any person but particularly for those with cancer. Patients with MM receive treatment that can cause immunosuppression and increase the risk of infection. Immunomodulatory drugs can cause neutropenia, which also increases the risk of infection. In combination with PIs and corticosteroids, these therapies increase the infection risk even further.28 When possible, utilization of oral-only treatment regimens can decrease the risk of exposure in patients who otherwise would have gone to the hospital or oncology clinic for administration of an intravenous treatment regimen.28

The 5-year survival rate for MM continues to improve, more drugs are available to treat newly diagnosed patients and patients with RRMM, and promising treatments are in development.11

References
4. Cost is another concern in the treatment of MM. The annual cost of the 3-drug combinations recommended by the NCCN for RRMM is estimated at $220,000 to $300,000.29 While no cure exists for MM, patients may be able to discontinue treatment if the cancer goes into remission. New therapies have increased the survival rate after relapse, and as a result a large proportion of disease costs, resource use, and time occur in the setting of RRMM.30 Patients beginning their fourth or fifth LOT can be financially exhausted.

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INDICATIONS AND USAGE

BLENREP is indicated for the treatment of adults with relapsed or refractory multiple myeloma who have received at least 4 prior therapies, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent.

This indication is approved under accelerated approval based on response rate to a combination of a proteasome inhibitor, an immunomodulatory agent, and BLENREP. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial(s).

DOSAGE AND ADMINISTRATION

2.1 Important Safety Information

Perform an ophthalmic exam prior to initiation of BLENREP and during treatment [see Warnings and Precautions (5.1)].

Advise patients to use preservative-free lubricant eye drops and avoid contact lenses unless directed by an ophthalmologist [see Warnings and Precautions (5.1)].

2.2 Recommended Dosage

The recommended dosage of BLENREP is 2.5 mg/kg of actual body weight given as an intravenous infusion over approximately 30 minutes once every 3 weeks until disease progression or unacceptable toxicity.

2.3 Dosage Modifications for Adverse Reactions

The recommended dose reduction for adverse reactions is:

• BLENREP 1.9 mg/kg intravenously once every 3 weeks.

Discontinue BLENREP in patients who are unable to tolerate a dose of 1.9 mg/kg (see Tables 1 and 2).

Corneal Adverse Reactions

The recommended dosage modifications for corneal adverse reactions, based on both corneal examination findings and changes in best-corrected visual acuity (BCVA), are provided in Table 1 (see Warnings and Precautions (5.1)). Determine the recommended dosage modification of BLENREP based on the worst finding in the worst affected eye.

Withhold BLENREP until improvement in both corneal examination findings and change in BCVA to Grade 1 or better and resume at reduced dose.

Table 1. Dosage Modifications for Corneal Adverse Reactions per the KVA Scale

<table>
<thead>
<tr>
<th>Corneal Adverse Reaction</th>
<th>Recommended Dosage Modifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td></td>
</tr>
<tr>
<td>Corneal examination finding(s): Mild superficial keratopathy*</td>
<td>Continue treatment at current dose.</td>
</tr>
<tr>
<td>Change in BCVA:* Decline from baseline of 1 line on Snellen Visual Acuity</td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td></td>
</tr>
<tr>
<td>Corneal examination finding(s): Moderate superficial keratopathy</td>
<td>Withhold BLENREP until improvement in both corneal examination findings and change in BCVA to Grade 1 or better and resume at reduced dose.</td>
</tr>
<tr>
<td>Change in BCVA:* Decline from baseline of 2 or 3 lines on Snellen Visual Acuity and not worse than 20/200</td>
<td></td>
</tr>
</tbody>
</table>

* Mild superficial keratopathy (documented worsening from baseline), with or without symptoms.

Table 2. Dosage Modifications for Other Adverse Reactions

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Severity</th>
<th>Recommended Dosage Modifications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia [see Warnings and Precautions (5.3)]</td>
<td>Platelet count 25,000 to less than 50,000/μL</td>
<td>Consider withholding BLENREP and/or reducing the dose of BLENREP.</td>
</tr>
<tr>
<td>Infusion-related reactions [see Warnings and Precautions (5.4)]</td>
<td>Grade 2 (moderate) or Grade 3 (severe)</td>
<td>Interrupt infusion and provide supportive care. Once symptoms resolve, resume at lower infusion rate; reduce the infusion rate by at least 50%.</td>
</tr>
<tr>
<td>Other Adverse Reactions [see Adverse Reactions (6.1)]</td>
<td>Grade 4 (life-threatening)</td>
<td>Permanently discontinue BLENREP and provide emergency care.</td>
</tr>
<tr>
<td>Other Adverse Reactions</td>
<td>Grade 3</td>
<td>Withhold BLENREP until improvement to Grade 1 or better. Consider resuming at a reduced dose.</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Withhold BLENREP until improvement to Grade 1 or better. Consider resuming at a reduced dose.</td>
<td></td>
</tr>
</tbody>
</table>

2.4 Preparation and Administration

BLENREP is a hazardous drug. Follow applicable special handling and disposal procedures.

Calculate the dose (mg), total volume (mL) of solution required, and the number of vials of BLENREP needed based on the patient’s actual body weight. More than 1 vial may be needed for a full dose. Do not round down for partial vials.

Reconstitution

• Remove the vial(s) of BLENREP from the refrigerator and allow to stand for approximately 10 minutes to reach room temperature (68°F to 77°F [20°C to 25°C]).

• Reconstitute each 100-mg vial of BLENREP with 2 mL of Sterile Water for Injection, USP, to obtain a final concentration of 50 mg/mL. Gently swirl the vial to aid dissolution. Do not shake.

• If the reconstituted solution is not used immediately, store refrigerated at 36°F to 46°F (2°C to 8°C) or at room temperature (68°F to 77°F [20°C to 25°C]) for up to 4 hours in the original container. Discard if not diluted within 4 hours. Do not freeze.
Withdraw the calculated volume of BLENREP from the appropriate number of vials and dilute in a 250-ml infusion bag of 0.9% Sodium Chloride Injection, USP, to a final concentration of 0.2 mg/mL to 2 mg/mL. The infusion bags must be made of polyvinylchloride (PVC) or polyolefin (PO).

Mix the diluted solution by gentle inversion. Do not shake.

Discard any unused reconstituted solution of BLENREP left in the vial(s).

If the diluted infusion solution is not used immediately, store refrigerated at 36ºF to 46ºF (2ºC to 8ºC) for up to 24 hours. Do not freeze. Once removed from refrigeration, administer the diluted infusion solution of BLENREP within 6 hours (including infusion time).

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The reconstituted solution should be clear to opalescent, colorless to yellow to brown liquid. Discard if extraneous particulate matter is observed.

**Dilution**

- If refrigerated, allow the diluted infusion solution to equilibrate to room temperature (68ºF to 77ºF [20ºC to 25ºC]) prior to administration. Diluted infusion solution may be kept at room temperature for no more than 6 hours (including infusion time).
- Administer by intravenous infusion over approximately 30 minutes using an infusion set made of polyvinyl chloride (PVC) or polyolefin (PO).
- Filtration of the diluted solution is not required; however, if the diluted solution is filtered, use a polyethersulfone (PES)-based filter (0.2 micron).

Do not mix or administer BLENREP as an infusion with other products. The product does not contain a preservative.

**4 CONTRAINDICATIONS**

None.

**5 WARNINGS AND PRECAUTIONS**

**5.1 Ocular Toxicity**

Ocular adverse reactions occurred in 77% of the 218 patients in the pooled safety population. Ocular adverse reactions included keratopathy (76%), changes in visual acuity (55%), blurred vision (27%), and dry eye (19%) [see Adverse Reactions (6.1)]. Among patients with keratopathy (n = 169), 45% had ocular symptoms, 65% had clinically relevant visual acuity changes (decline of 2 or more lines on Snellen Visual Acuity in any eye), and 34% had both ocular symptoms and visual acuity changes.

**Keratopathy**

Keratopathy was reported as Grade 1 in 7% of patients, Grade 2 in 22%, Grade 3 in 45%, and Grade 4 in 0.5% per the KVA scale. Cases of corneal ulcer (ulcerative and infective keratitis) have been reported. Most keratopathy events developed within the first 2 treatment cycles (cumulative incidence of 65% by Cycle 2). Of the patients with Grade 2 to 4 keratopathy (n = 149), 39% of patients recovered to Grade 1 or lower after median follow-up of 6.2 months. Of the 61% who had ongoing keratopathy, 28% were still on treatment, 9% were in follow-up, and in 24% the follow-up ended due to death, study withdrawal, or lost to follow up. For patients in whom treatment resolved, the median time to resolution was 2 months (range: 11 days to 6.3 months).

**Visual Acuity Changes**

A clinically significant decrease in visual acuity of worse than 20/40 in the better-seeing eye was observed in 19% of the 218 patients and of 20/20 or worse in the better-seeing eye in 1.4%. Of the patients with decreased visual acuity of worse than 20/40, 86% resolved and the median time to resolution was 22 days (range: 7 days to 4.2 months). Of the patients with decreased visual acuity of 20/200 or worse, all resolved and the median duration was 22 days (range: 15 to 22 days).

**Monitoring and Patient Instruction**

Conduct ophthalmic examinations (visual acuity and slit lamp) at baseline, prior to each dose, and promptly for worsening symptoms. Perform baseline examinations within 3 weeks prior to the first dose. Perform each follow-up examination at least 1 week after the previous dose and within 2 weeks prior to the next dose. Withhold BLENREP until improvement and resume at same or reduced dose, or consider permanently discontinuing based on severity [see Dosage and Administration (2.3)].

Advise patients to use preservative-free lubricant eye drops at least 4 times a day starting with the first infusion. Discontinue until end of treatment. Avoid use of contact lenses unless directed by an ophthalmologist [see Dosage and Administration (2.1)].

Changes in visual acuity may be associated with difficulty for driving and reading. Advise patients to use caution when driving or operating machinery.

BLENREP is only available through a restricted program under a REMS [see Warnings and Precautions (5.2)]

**5.2 BLENREP REMS**

BLENREP is available only through a restricted program under a REMS called the BLENREP REMS because of the risks of ocular toxicity [see Warnings and Precautions (5.1)].

Notable requirements of the BLENREP REMS include the following:

- Prescribers must be certified with the program by enrolling and completing training in the BLENREP REMS.
- Prescribers must counsel patients receiving BLENREP about the risk of ocular toxicity and the need for ophthalmic examinations prior to each dose.
- Patients must be enrolled in the BLENREP REMS and comply with monitoring.
- Healthcare facilities must be certified with the program and verify that patients are authorized to receive BLENREP.
- Wholesalers and distributors must only distribute BLENREP to certified healthcare facilities.

Further information is available, at www.BLENPREPREMS.com and 1-855-209-9188.

**5.3 Thrombocytopenia**

Thrombocytopenia occurred in 69% of 218 patients in the pooled safety population, including Grade 2 in 13%, Grade 3 in 10%, and Grade 4 in 17% [see Adverse Reactions (6.1)]. The median time to onset of the first thrombocytopenic event was 26.5 days. Thrombocytopenia resulted in dose reduction, dose interruption, or discontinuation in 9%, 2.8%, and 0.5% of patients, respectively.

Grade 3 to 4 bleeding events occurred in 6% of patients, including Grade 4 in 1 patient. Fetal adverse reactions included cerebral hemorrhage in 2 patients.

Perform complete blood cell counts at baseline and during treatment as clinically indicated. Consider withholding and/or reducing the dose based on severity [see Dosage and Administration (2.3)].

**5.4 Infusion-Related Reactions**

Infusion-related reactions occurred in 18% of 218 patients in the pooled safety population, including Grade 3 in 1.8% [see Adverse Reactions (6.1)]. Monitor patients for infusion-related reactions. For Grade 2 or 3 reactions, interrupt the infusion and provide supportive treatment. Once symptoms resolve, resume at a lower infusion rate [see Dosage and Administration (2.3)]. Administer premedication for all subsequent infusions. Discontinue BLENREP for life-threatening infusion-related reactions and provide appropriate emergency care.

**5.5 Embryo-Fetal Toxicity**

Based on its mechanism of action, BLENREP can cause fetal harm when administered to a pregnant woman because it contains a genotoxic compound (the microtubule inhibitor, monomethyl auristatin F [MMAF]) and it targets actively dividing cells.

Advise pregnant women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with BLENREP and for 4 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with BLENREP and for 6 months after the last dose [see Use in Specific Populations (8.1, 8.3)].

**6 ADVERSE REACTIONS**

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Ocular toxicity [see Warnings and Precautions (5.1)].
- Thrombocytopenia [see Warnings and Precautions (5.3)].
- Infusion-related reactions [see Warnings and Precautions (5.4)].

**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 with rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The pooled safety population described in Warnings and Precautions reflects exposure to BLENREP at a dosage of 2.5 mg/kg or 3.4 mg/kg (1.4 times the recommended dose) administered intravenously once every 3 weeks in 218 patients in DREAMM-2. Of these patients, 194 received a liquid formulation (not the approved dosage form) rather than the lyophilized powder. Among the 218 patients, 24% were exposed for 6 months or longer.

(continued on next page)
Relapsed or Refractory Multiple Myeloma

The safety of BLENREP as a single agent was evaluated in DREAMM-2 [see Clinical Studies (14.1) of full Prescribing Information]. Patients received BLENREP at the recommended dosage of 2.5 mg/kg administered intravenously once every 3 weeks (n = 95). Among these patients, 22% were exposed for 6 months or longer. Serious adverse reactions occurred in 40% of patients who received BLENREP. Serious adverse reactions in ≥3% of patients included pneumonia (7%), pyrexia (6%), renal impairment (4.2%), sepsis (4.2%), hypercalcemia (4.2%), and infusion-related reactions (3.2%). Fatal adverse reactions occurred in 3.2% of patients, including sepsis (1%), cardiac arrest (1%), and lung infection (1%).

Permanent discontinuation due to an adverse reaction occurred in 8% of patients who received BLENREP: keratopathy (2.1%) was the most frequent adverse reaction resulting in permanent discontinuation.

Dosage interruptions due to an adverse reaction occurred in 54% of patients who received BLENREP: Adverse reactions which required a dosage interruption in ≥3% of patients included keratopathy (47%), blurred vision (3%), dry eye (3.2%), and pneumonia (3.2%).

Dose reductions due to an adverse reaction occurred in 29% of patients. Adverse reactions which required a dose reduction in ≥3% of patients included keratopathy (23%) and thrombocytopenia (5%).

The most common adverse reactions (≥20%) were keratopathy, decreased visual acuity, nausea, blurred vision, pyrexia, infusion-related reactions, and fatigue. The most common Grade 3 or 4 (≥5%) laboratory abnormalities were lymphocytes decreased, platelets decreased, hemoglobin decreased, neutrophils decreased, creatinine increased, and gamma-glutamyl transferase increased.

Table 3 summarizes the adverse reactions in DREAMM-2 for patients who received the recommended dosage of 2.5 mg/kg once every 3 weeks.

Table 3. Adverse Reactions (≥10%) in Patients Who Received BLENREP in DREAMM-2

<table>
<thead>
<tr>
<th>Laboratory Abnormality</th>
<th>BLENREP N = 95</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
</tr>
<tr>
<td>Platelets decreased</td>
<td>62 21</td>
</tr>
<tr>
<td>Lymphocytes decreased</td>
<td>49 22</td>
</tr>
<tr>
<td>Hemoglobin decreased</td>
<td>32 18</td>
</tr>
<tr>
<td>Neutrophils decreased</td>
<td>28 9</td>
</tr>
<tr>
<td><strong>Chemistry</strong></td>
<td></td>
</tr>
<tr>
<td>Aspartate aminotransferase increased</td>
<td>57 2</td>
</tr>
<tr>
<td>Albumin decreased</td>
<td>43 4</td>
</tr>
<tr>
<td>Glucose decreased</td>
<td>38 3</td>
</tr>
<tr>
<td>Creatinine increased</td>
<td>28 5</td>
</tr>
<tr>
<td>Alkaline phosphatase increased</td>
<td>26 1</td>
</tr>
<tr>
<td>Gamma-glutamyl transferase increased</td>
<td>25 5</td>
</tr>
<tr>
<td>Creatine phosphokinase increased</td>
<td>22 1</td>
</tr>
<tr>
<td>Sodium decreased</td>
<td>21 2</td>
</tr>
<tr>
<td>Potassium decreased</td>
<td>20 2</td>
</tr>
</tbody>
</table>

6.2 Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies in the studies described below with the incidence of antibodies in other studies or to other products may be misleading.

The immunogenicity of BLENREP was evaluated using an electrochemiluminescence (ECL)-based immunoassay to test for anti-belantamab mafodotin antibodies. In clinical studies of BLENREP, 2/274 patients (<1%) tested positive for anti-belantamab mafodotin antibodies after treatment. One of the 2 patients tested positive for neutralizing anti-belantamab-mafodotin antibodies following 4 weeks on therapy. Due to the limited number of patients with antibodies against belantamab mafodotin-blmf, no conclusions can be drawn concerning a potential effect of immunogenicity on pharmacokinetics, efficacy, or safety.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Based on its mechanism of action, BLENREP can cause fetal harm when administered to a pregnant woman, because it contains a genotoxic compound (the microtubule inhibitor, MMAF) and it targets actively dividing cells [see Clinical Pharmacology (12.1), Nonclinical Toxicology (13.1) of full Prescribing Information]. Human immunoglobulin G (IgG) is known to cross the placenta; therefore, belantamab mafodotin-blmf has the potential to be transmitted from the mother to the developing fetus. There are no available data on the use of BLENREP in pregnant women to evaluate for drug-associated risk. No animal reproduction studies were conducted with BLENREP. Advise pregnant women of the potential risk to a fetus. The estimated background risk of major birth defects and miscarriage for the indicated population is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcome. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.

Data

Animal Data: Animal reproductive or developmental toxicity studies were not conducted with belantamab mafodotin-blmf. The cytotoxic component of BLENREP, MMAF, disrupts microtubule function, is genotoxic, and can be toxic to rapidly dividing cells, suggesting it has the potential to cause embryotoxicity and teratogenicity.
8.2 Lactation

Risk Summary

There is no data on the presence of belantamab mafodotin-blmf in human milk or the effects on the breastfed child or milk production. Because of the potential for serious adverse reactions in the breastfed child, advise women not to breastfeed during treatment with BLENREP and for 3 months after the last dose.

8.3 Females and Males of Reproductive Potential

BLENREP can cause fetal harm when administered to pregnant women [see Use in Specific Populations (8.1)].

Pregnancy Testing

Pregnancy testing is recommended for females of reproductive potential prior to initiating BLENREP.

Contraception

Females: Advise women of reproductive potential to use effective contraception during treatment and for 4 months after the last dose.

Males: Because of the potential for genotoxicity, advise males with female partners of reproductive potential to use effective contraception during treatment with BLENREP and for 6 months after the last dose [see Nonclinical Toxicology (13.1) of full Prescribing Information].

Infertility

Based on findings in animal studies, BLENREP may impair fertility in females and males. The effects were not reversible in male rats, but were reversible in female rats [see Nonclinical Toxicology (13.1) of full Prescribing Information].

8.4 Pediatric Use

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

8.5 Geriatric Use

Of the 218 patients who received BLENREP in DREAMM-2, 43% were aged 65 to less than 75 years and 17% were aged 75 years and older. Clinical studies of BLENREP did not include sufficient numbers of patients aged 65 and older to determine whether they respond differently compared with younger patients.

Keratopathy occurred in 80% of patients aged less than 65 years and 73% of patients aged 65 years and older. Among the patients who received BLENREP at the 2.5-mg/kg dose in DREAMM-2 (n = 95), keratopathy occurred in 67% of patients aged less than 65 years and 73% of patients aged 65 years and older. Clinical studies did not include sufficient numbers of patients 75 years and older to determine whether they respond differently compared with younger patients.

8.6 Renal Impairment

No dose adjustment is recommended for patients with mild or moderate renal impairment (estimated glomerular filtration rate [eGFR] 30 to 69 mL/min/1.73 m²) as estimated by the Modification of Diet in Renal Disease (MDRD) equation [see Clinical Pharmacology (12.3) of full Prescribing Information]. The recommended dosage has not been established in patients with severe renal impairment (eGFR 15 to 29 mL/min/1.73 m²) or end-stage renal disease (ESRD) with eGFR <15 mL/min/1.73 m² not on dialysis or requiring dialysis [see Clinical Pharmacology (12.3) of full Prescribing Information].

8.7 Hepatic Impairment

No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin < upper limit of normal [ULN] and aspartate aminotransferase [AST] >ULN or total bilirubin >1.5 × ULN and any AST).

The recommended dosage of BLENREP has not been established in patients with moderate or severe hepatic impairment (total bilirubin >1.5 × ULN and any AST) [see Clinical Pharmacology (12.3) of full Prescribing Information].

15 REFERENCES

1. “OSHA Hazardous Drugs.” OSHA

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Ocular Toxicity

• Advise patients that ocular toxicity may occur during treatment with BLENREP [see Warnings and Precautions (5.1)].
• Advise patients to administer preservative-free lubricant eye drops as recommended during treatment and to avoid wearing contact lenses during treatment unless directed by a healthcare professional [see Dosage and Administration (2.3), Warnings and Precautions (5.1)].
• Advise patients to use caution when driving or operating machinery as BLENREP may adversely affect their vision [see Warnings and Precautions (5.1)].
BLENREP
belantamab mafodotin-blnmf
for injection 100 mg

NOW APPROVED

Please see following pages for Brief Summary of full Prescribing Information, including BOXED WARNING

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