BLENREP
belantamab
mafodotin

An Overview of BLENREP and Corneal Adverse Reactions for Eye Care Professionals

NX-IL-BLM-BROC-210006

Patients with relapsed or refractory multiple myeloma prescribed BLENREP (belantamab mafodotin) require an eye exam at baseline, before the subsequent 3 treatment cycles, and as clinically indicated while on treatment.[1]

Adverse reactions (ARs) have been reported with BLENREP, including corneal events, during clinical trials.[1] Patients may be referred to you by a haematologyst or may see you directly for their eye exams.

This guide is intended to provide you an overview of why eye exams are required and what corneal ARs could potentially occur with BLENREP.

It is important to communicate these findings to the haematologyst, as findings of the eye exam(s) may impact the patient's treatment.

Corneal ARs are not the only risks associated with BLENREP.[1]

Table of Contents

BLENREP
belantamab
mafodotin

Understanding a Patient With Relapsed/Refractory Multiple Myeloma

Multiple myeloma is a **malignancy of the plasma cells,** resulting in **bone marrow infiltration and monoclonal protein** in serum and/or urine[2]

Multiple myeloma is the third most common haematological malignancy worldwide, **with an estimated 159,985 new multiple myeloma cases** and **106,105 deaths per year**[3]

Multiple myeloma is most frequently diagnosed in older individuals, **with a median age at diagnosis of 72 years**[4]

The highest age-standardised death and incidence rates of multiple myeloma have been observed in countries in **Australasia, North America, and Western Europe,** while Asia, Oceania, and sub-Saharan Africa are regions with the lowest age-standardised incidence of multiple myeloma[5]

The content contained within this section is not specific to product indication and is intended to provide general disease state background on multiple myeloma.

Although currently considered incurable, multiple myeloma is treatable[6]

Due to the relapsing course of multiple myeloma, patients often receive multiple lines of therapy. Most patients receive several courses of therapy that may include[6,7]:

- An immunomodulatory agent
- A proteasome inhibitor (PI) used in combination with either
  - A corticosteroid
  - Anti-CD38 monoclonal antibodies (mAbs)

Advances have been made in the management of multiple myeloma in recent years with the introduction of these novel therapies.[7] Yet the duration of response, time to progression, and survival get shorter with each successive line of therapy.[8-10]

Most patients will eventually progress to relapsed and refractory disease, highlighting the need for new treatments[8]

The addition of BLENREP to the therapeutic landscape is an important option for patients who have[1,6,7]:

- Disease that is refractory or relapsed
- Received at least four prior therapies including:
  - one proteasome inhibitor
  - one immunomodulatory agent
  - an anti-CD38 monoclonal antibody

BLENREP
belantamab mafodotin

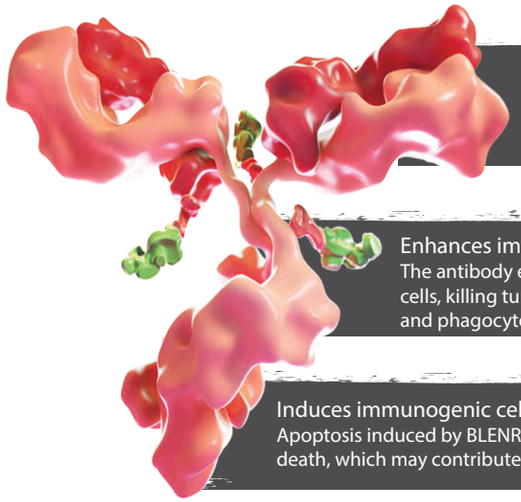
BLENREP, the first BCMA-targeting ADC for relapsed/refractory multiple myeloma[1]

BLENREP is an antibody-drug conjugate (ADC) linking a monoclonal antibody with mafodotin, a toxic payload with known corneal adverse reactions. BLENREP targets B-cell maturation antigen (BCMA), a cell-surface protein expressed on myeloma cells, late-stage B cells, and plasma cells.[1,11]

Study design: DREAMM-2 (Study 205678) was an open-label, 2-arm, multicentre, phase 2 study evaluating BLENREP monotherapy in patients with multiple myeloma who had relapsed following treatment with at least 3 prior therapies, and who were refractory to an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody alone or in combination. Patients were randomised to receive 2.5 mg/kg (n=97) or 3.4 mg/kg (n=99) BLENREP by intravenous infusion every 3 weeks until disease progression or unacceptable toxicity. Data presented throughout this guide are from the 2.5-mg/kg cohort, who received the recommended therapeutic dose based on overall benefit-risk assessment.[1]

BLENREP has multiple mechanisms of action[1]

Upon binding to BCMA, BLENREP is rapidly internalised and proceeds to carry out its multimodal mechanism of action.[1]



Delivers cytotoxic payload
The free cytotoxic agent (cys-monomethyl auristatin F [MMAF]) is released inside the tumour cell, disrupting the microtubule network, leading to cell cycle arrest and apoptosis[1]

Enhances immune-mediated actions
The antibody enhances recruitment and activation of immune effector cells, killing tumour cells by antibody-dependent cellular cytotoxicity and phagocytosis[1]

Induces immunogenic cell death
Apoptosis induced by BLENREP is accompanied by markers of immunogenic cell death, which may contribute to an adaptive immune response to tumour cells[1]

Corneal ARs have been reported with ADCs using the cytotoxic payload mafodotin[12]

In nonclinical studies, BLENREP was taken up into cells throughout the body, including corneal epithelial cells, by a mechanism unrelated to BCMA receptor expression on the cell membrane. Historically, ADCs using this payload are associated with a high incidence of ocular surface adverse reactions, including microcyst-like epithelial changes (MECs).[12]

BLENREP
belantamab
mafodotin

Proposed Pathophysiology of BLENREP MECs

The off-target effect of BLENREP leads to apoptosis of epithelial cells. These epithelial cells are then replaced with new ones, allowing for the resolution of MECs and symptoms after patient's complete treatment.[12]

MECs have been described as multiple, bilateral, microcyst-like lesions in the superficial cornea[12]

Stages of MEC development[12]

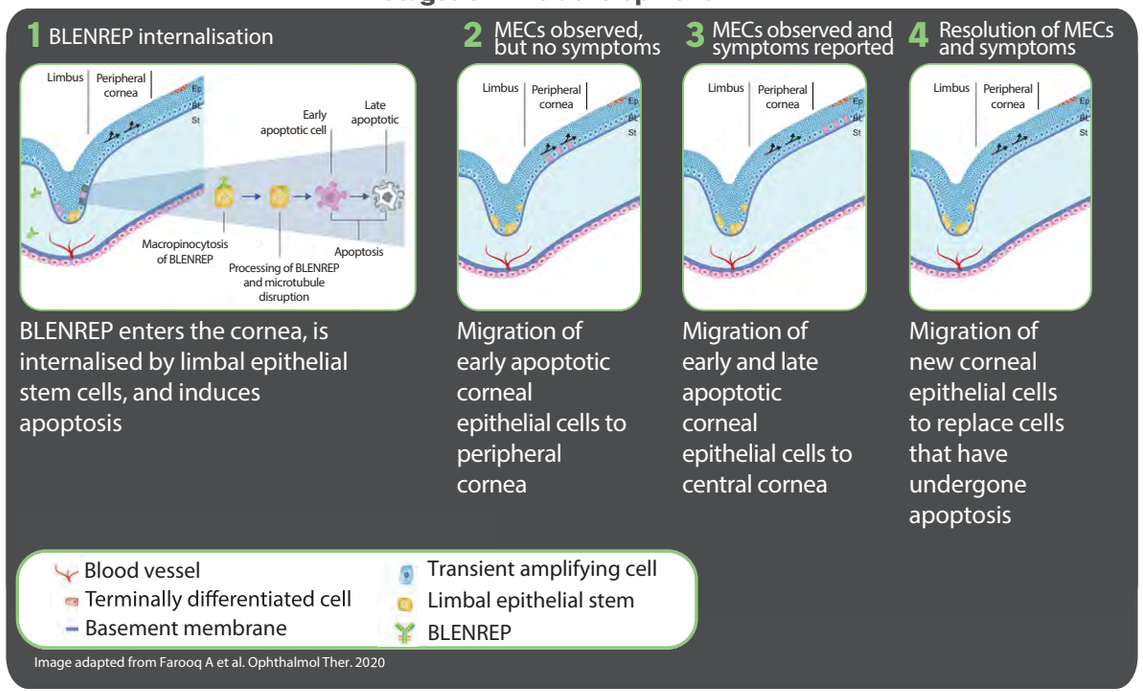


Image adapted from Farooq A et al. Ophthalmol Ther. 2020

The migrating BLENREP-containing cells can be visualised by in vitro confocal microscopy (IVCM) as hyperreflective opacities.[12]

- As they migrate toward the visual axis, patient-reported symptoms of blurred vision and best corrected visual acuity (BCVA) changes occur[12]

MEC findings of BLENREP are consistent with other ADCs[12]

ADCs directed against other targets have demonstrated a high incidence of ocular surface adverse reactions[12]

- MECs are commonly reported with other MMAF-containing ADCs
  - Rates of ocular adverse reactions ranged from 31% to 92%, with Grade 3/4 events occurring

Corneal findings are proposed as an off-target mechanism of ADCs[12]

- This may occur by several mechanisms including Fc-receptor–mediated endocytosis, pinocytosis, and bystander toxicity in which the cytotoxic payload is prematurely cleaved from the linker

"Off-target" toxicity is a cytotoxic effect on (non-cancer) cells that do not express the target antigen[12]

Corneal events observed with ADCs have been described as manageable with dose modifications and supportive care[12]

BLENREP
belantamab
mafodotin

Corneal ARs Observed in the DREAMM-2 (Study 205678) Clinical Trial[1]

Keratopathy or MECs were the most common ARs[1]

- Keratopathy or MECs were characterised as changes in corneal epithelium (as seen on eye examination) with or without changes in visual acuity, blurred vision, and dry eye symptoms[1]
  - Eye disorders (any grade) reported in ≥3% of patients in the clinical trial were keratopathy (71%), blurred vision events (25%), dry eye events (15%), photophobia (4%), and eye irritation (3%)[1]
- Patients with a history of dry eyes were more prone to develop changes in the corneal epithelium[1]
- Decreased vision (Snellen Visual Acuity worse than 20/50) in the better eye was reported in 18% of patients and severe vision loss (20/200 or worse) in the better-seeing eye was reported in 1% of patients[1]
- The median time to onset of moderate to severe corneal findings (BCVA or slit lamp examination) was 36 days (range: 19 to 143 days), and the median time to resolution of these corneal findings was 91 days (range: 21 to 201 days)[1]
- Corneal findings (keratopathy) led to dose delays in 47% of patients and dose reductions in 27% of patients. 3% of patients discontinued treatment due to ocular ARs[1]
- Cases of corneal ulcer (ulcerative and infective keratitis) have been reported. These should be managed promptly and as clinically indicated by an eye care professional. Treatment with BLENREP should be interrupted until the corneal ulcer has healed[1]

Adverse reactions (ARs)

ARs (Any Grade) Reported in DREAMM-2; (N=95)[a,1]

System Organ Class	Adverse Reactions	Any Grade (%)	Grade 3/4 (%)
Eye disorders	Keratopathy[b]	71	31
	Blurred vision events[c]	25	4
	Dry eye events[d]	15	1
	Photophobia	4	0
	Eye irritation	3	0
	Ulcerative keratitis	1	1
	Infective keratitis	1	1
Infections and infestations	Pneumonia[e]	11	7
	Upper respiratory tract infection	9	0
Blood and lymphatic system disorders	Thrombocytopenia[f]	38	22
	Anaemia	27	21
	Lymphopenia[g]	20	17
	Leukopenia[h]	17	6
	Neutropenia[i]	15	11
Gastrointestinal disorders	Nausea	25	0
	Diarrhoea	13	1
	Vomiting	7	2
General disorders and administration site conditions	Pyrexia	23	4
	Fatigue	16	2
Investigations	Increased aspartate aminotransferase	21	2
	Increased gamma glutamyltransferase	11	3
	Increased creatine phosphokinase	5	2
Injury, poisoning, and procedural complications	Infusion-related reactions[j]	21	3

[a]Adverse reactions coded using MedDRA and graded for severity based on Common Terminology Criteria for Adverse Events (CTCAE v4.03).

[b]Based on eye examination, characterised as corneal epithelium changes with or without symptoms.

[c]Includes diplopia, vision blurred, visual acuity reduced, and visual impairment.

[d]Includes dry eye, ocular discomfort, and eye pruritus.

[e]Includes pneumonia and herpes simplex pneumonia.

[f]Includes thrombocytopenia and decreased platelet count.

[g]Includes lymphopenia and decreased lymphocyte count.

[h]Includes leukopenia and decreased leukocyte count.

[i]Includes neutropenia and decreased neutrophil count.

[j]Includes events determined by investigators to be related to infusion. Infusion reactions may include, but are not limited to, pyrexia, chills, diarrhoea, nausea, asthenia, hypertension, lethargy, and tachycardia.

These are not all the possible ARs of BLENREP.

If your patient experiences any ARs while taking BLENREP, please tell your patient to contact the haematologist.

BLENREP
belantamab mafodotin

MONITOR, MINIMISE, MODIFY:

The 3 Ms of Corneal AR Management

In order to provide optimal care for your patients being treated with BLENREP, follow these 3 management approaches. Monitor their vision, looking for changes in the cornea. Minimise any ARs they may have. Consult with the haematologyst, who may need to modify treatment when necessary with dose adjustments.

The recommended dose of BLENREP is 2.5 mg/kg administered as an intravenous infusion once every 3 WEEKS until disease progression or unacceptable toxicity.[1]

Advise patients to[1]:

Administer preservative-free artificial tear drops at least 4 times a day beginning on the first day of infusion and continuing until completion of treatment, as this may reduce corneal symptoms

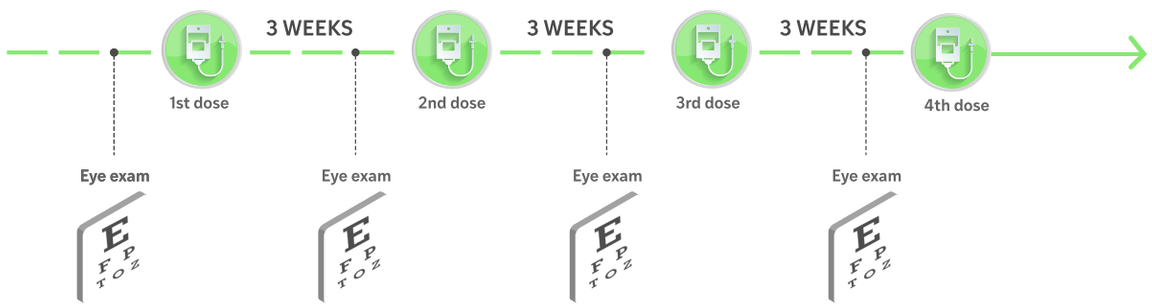
For patients with dry eye symptoms, additional therapies may be considered as recommended by their eye care professional

Avoid contact lenses until the end of treatment

Use caution when driving or operating machines

Continue monitoring for corneal adverse reactions after treatment and contact haematologist/oncologist if any symptoms occur. Dose modifications may be necessary, including discontinuation of therapy (see dose modifications on page 18)

Treatment every 3 WEEKS until disease progression or unacceptable toxicity[1]



Ophthalmic exams and observations for potential ophthalmic symptoms, until symptom resolution[1]

Ophthalmic exams are recommended at baseline, before the subsequent 3 treatment cycles, and as clinically indicated while on treatment.

BLENREP
belantamab
mafodotin

Clinician-patient interactions[1]

Assessment of possible corneal ARs before initiating and during treatment with BLENREP can help identify patients who need additional monitoring and/or management by an eye care professional.[1]

Visual acuity and slit lamp examination should be performed at baseline, before the subsequent 3 treatment cycles, and as clinically indicated while on treatment[1]

Advise patients to administer preservative-free artificial tears at least 4 times a day beginning on the first day of infusion and continuing until completion of treatment[1]

Questions to help identify symptoms are included on page 15

You will receive the Eye Care Evaluation Report to facilitate communication with your patient's haematologyst

Patient-reported symptom communications

Educating patients on possible symptoms associated with the corneal ARs observed in the clinical study will help them monitor, identify, and report potential symptoms that may occur outside the clinical setting.

Patient-identified symptoms reported to you should be conveyed to the haematologyst immediatley.

You can evaluate possible patient-reported corneal ARs with questions targeting the signs and symptoms of corneal ARs, such as[1]:

- Have you noticed any changes in your vision?
- Do you have a history of eye problems?
- Have you noticed any redness, dryness, itching, burning sensation, or sandy or gritty sensation in your eyes?
- Do you feel any sensitivity to light?
- Do you ever feel that your vision is blurry?
- Do you feel any discomfort or pain in your eyes?
- Have you noticed if your eyes are watery or irritated?
- Have you noticed if your vision has changed at all since your last checkup? Gotten worse, better, or stayed the same?
- Have you been using preservative-free artificial tears eye drops as directed?

BLENREP
belantamab
mafodotin

Patients and caregivers should receive education on potential corneal ARs, and patients should complete initial ophthalmological exams prior to initiating the first infusion with BLENREP. During the treatment and in subsequent follow-ups with the clinician, patients may report signs and symptoms indicative of corneal ARs[1]:

My vision is blurry.

My eyes are watery and feel irritated.

My eyes feel dry and itchy.

My eyes hurt.

I cannot see very clearly.

I am always squinting or shielding my eyes away from light.

MINIMISE

Supportive care

Advise patients that corneal ARs may occur during treatment with BLENREP and that they will have ophthalmic exams performed at baseline, before the subsequent 3 treatment cycles, and as clinically indicated while on treatment.[1]

Advise patients to administer preservative-free artificial tears at least 4 times a day beginning on the first day of infusion and continuing until completion of treatment as this may reduce corneal symptoms.[1]

Advise patients to avoid contact lenses until the end of treatment.[1]

Advise patients to use caution when driving or operating machines as BLENREP may affect their vision.[1]

For patients with dry eye symptoms, you may recommend additional therapies.[1]

BLENREP
belantamab mafodotin

Dose Modifications for Corneal ARs

MODIFY

The recommended dose modifications for corneal ARs are summarised in the table on the facing page.

Modification of BLENREP dosing may be necessary to manage corneal ARs[1]

Corneal adverse reactions may include findings upon eye examination and/or changes in visual acuity. The haematologyst team should review the patient's ophthalmic examination report before dosing and should determine the dose of BLENREP based on the highest category from the report in the most severely affected eye, as both eyes may not be affected to the same degree. During the ophthalmic examination, assess[1]:

- The corneal examination finding(s) and the decline in BCVA
- If there is a decline in BCVA, the relationship of corneal examination findings to BLENREP should be determined
- The highest category grading for these examination findings and BCVA should be reported to the treating physician

Category[a,b]	Eye examination findings	Recommended dose modifications
Mild	Corneal examination finding(s) Mild superficial keratopathy[c] Change in BCVA Decline from baseline of 1 line on Snellen Visual Acuity	• Continue treatment at current dose
Moderate	Corneal examination finding(s) Moderate superficial keratopathy[d] Change in BCVA Decline from baseline of 2 or 3 lines (and Snellen Visual Acuity not worse than 20/200)	• Withhold treatment until improvement in examination findings and BCVA to mild severity or better • Consider resuming treatment at a reduced dose of 1.9 mg/kg
Severe	Corneal examination finding(s) Severe superficial keratopathy[e] Corneal epithelial defect[f] Change in BCVA Decline from baseline of more than 3 lines	• Withhold until improvement in examination findings and BCVA to mild severity or better • For worsening symptoms that are unresponsive to appropriate management, consider discontinuation

[a]Note: This guide does not cover all potential ARs and recommended dose modifications.
[b]The severity category is defined by the most severely affected eye, as both eyes may not be affected to the same degree.
[c]Mild superficial keratopathy (documented worsening from baseline), with or without symptoms.
[d]Moderate superficial keratopathy—with or without patchy microcyst-like deposits, subepithelial haze (peripheral), or a new peripheral stromal opacity.
[e]Severe superficial keratopathy with or without diffuse microcyst-like deposits involving the central cornea, subepithelial haze (central), or a new central stromal opacity.
[f]A corneal defect may lead to corneal ulcers. These should be managed promptly and as clinically indicated by an eye care professional.

BLENREP
belantamab
mafodotin

Frequently Asked Questions

You can use these FAQs as a tool during your management of BLENREP patients. They highlight the core material that we have outlined throughout this guide.

Q: What type of eye exams will patients need before starting BLENREP, and when will these exams be conducted?
A: Ophthalmic examination, including visual acuity and slit lamp exam, should be performed by an eye care professional at baseline, before the subsequent 3 treatment cycles, and as clinically indicated while on treatment.[1]

Q: Are there materials to document symptoms of corneal events?
A: You will receive the Eye Care Evaluation Report to facilitate communication with your patient's haematologist regarding corneal ARs.

Q: Were patients in DREAMM-2 (Study 205678) eligible to participate in the study if they had pre-existing eye conditions?
A: Patients with current corneal epithelial disease (except for mild punctate keratopathy) were excluded from the study.[13]

Q: What types of effects on the eyes may occur during and after treatment with BLENREP?
A: Corneal ARs have been reported with the use of BLENREP. Eye disorders (any grade) reported in ≥3% of patients in the clinical trial were keratopathy (71%), blurred vision events (25%), dry eye events (15%), photophobia (4%), and eye irritation (3%). Keratopathy or microcyst-like epithelial changes were characterised as changes in corneal epithelium (as seen on eye examination) with or without changes in visual acuity, blurred vision, and dry eye symptoms. Patients with a history of dry eyes were more prone to develop changes in the corneal epithelium. Decreased vision (Snellen Visual Acuity worse than 20/50) in the better eye were reported in 18% of patients and severe vision loss (20/200 or worse) in the better-seeing eye was reported in 1% of patients. Cases of corneal ulcer (ulcerative and infective keratitis) have been reported.[1]

Q: When did corneal symptoms begin in patients treated with BLENREP?
A: In the DREAMM-2 study, the median time to onset of moderate to severe corneal findings (BCVA or corneal examination) was 36 days (range: 19 to 143 days).[1]

Q: How long did corneal symptoms last in patients treated with BLENREP?
A: In the DREAMM-2 study, the median time to resolution of these corneal findings was 91 days (range: 21 to 201 days).[1]

Q: Whom should patients contact if symptoms occur?
A: Patients should contact you and their haematologyst if corneal ARs occur.[1]

Q: Can patients use contact lenses during treatment with BLENREP?
A: Advise patients to avoid contact lenses unless directed by an eye care professional.[1]

Q: Are there any restrictions on certain daily activities involving vision after initiating treatment with BLENREP?
A: Advise patients to use caution when driving or operating machines, as BLENREP may affect their vision.[1]

Q: Why does BLENREP affect the eyes?
A: In nonclinical studies, BLENREP was taken up into cells throughout the body, including corneal epithelial cells, by a mechanism unrelated to BCMA receptor expression on the cell membrane.[12]

BLENREP
belantamab
mafodotin

Frequently Asked Questions (continued)

Q: How can the ARs be managed?
A: Remember the 3 Ms: Monitor, Minimise, and Modify.

To monitor corneal ARs, ophthalmic examination, including visual acuity and slit lamp exam, should be performed by an eye care professional at baseline, before the subsequent 3 treatment cycles, and as clinically indicated while on treatment.[1]

To minimise corneal symptoms, preservative-free artificial tears need to be administered at least 4 times a day beginning on the first day of infusion and continuing until completion of treatment. For patients with dry eye symptoms, additional therapies may be considered as recommended by their eye care professional.[1]

Modification of BLENREP dosing by the haematologist, including discontinuation, may be necessary to manage corneal ARs.[1]

Q: What type of eye drops should my patient use?
A: Preservative-free artificial tears, an over-the-counter medicine, should be used at least 4 times a day beginning on the first day of infusion and continuing until completion of treatment with BLENREP, as they may minimise corneal symptoms. For patients with dry eye symptoms, additional therapies may be considered.[1]

Abbreviations: ADC=antibody-drug conjugate; AR=adverse reaction; BCMA=B-cell maturation agonist; BCVA=best corrected visual acuity; ICVM=in vitro confocal microscopy; mAbs=monoclonal antibodies; MECs=microcyst-like epithelial changes; MMAF=monomethyl auristatin F; PI=proteasome inhibitor.

References

1. BLENREP (belantamab mafodotin) Summary of Product Characteristics.
2. Deulofeu M, et al. Sci Rep. 2019;9(1):7975.
3. Bray F, et al. CA Cancer J Clin. 2018;68(6):394-424.
4. Moreau P, et al. Ann Oncol. 2017;28(suppl 4):iv52-iv61.
5. Cowan AJ, et al. JAMA Oncol. 2018;4(9):1221-1227.
6. Sonneveld P. Hematology Am Soc Hematol Educ Program. 2017;2017(1):508-517.
7. Palumbo A, et al. N Engl J Med. 2011;364(11):1046-1060.
8. Kurtin SE. J Adv Pract Oncol. 2013;4(suppl 1):5-14.
9. Richardson PG, et al. J Blood Med. 2017;8:107-121.
10. Yong K, et al. Br J Hematol. 2016;175(2):252-264.
11. Cho S-F, et al. Front Immunol. 2018;9:1921.
12. Farooq AV, et al. Opthalmol Ther. 2020;9:889-911.
13. Lonial S, et al. Blood Cancer J. 2021;11:1-11.

BLENREP
belantamab
mafodotin

BLENREP
belantamab
mafodotin

NX-IL-BLM-BROC-210006 October 2021
Produced in Israel

For full information on the medicine, read the MOH approved physician insert, located in the drug database on the Ministry of Health website:
https://www.gov.il/he/service/israeli-drug-index

Requests for medical information should be addressed to il.medinfo@gsk.com.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il
Additionally, you should also report to GSK Israel (il.safety@gsk.com)

This booklet and its contents were approved by the Ministry of Health on FEB 2022