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Support in the Management of Corneal Adverse Reactions for Your Patients Prescribed BLENREP

NX-IL-BLM-BROC-210005

Adverse reactions (ARs) have been reported with BLENREP (belantamab mafodotin).[1] This guide is intended to provide an overview of the corneal ARs that may occur with BLENREP.

This guide will provide the background information to support the understanding of the corneal ARs observed in the clinical study, how symptoms may present, and anatomy of the cornea that may be affected.

In addition, this guide is intended to provide direction on supportive care and dose modifications related to corneal ARs observed in the DREAMM (Driving Excellence in Approaches to Multiple Myeloma)-2 (Study 205678) clinical study.[1] In this guide, this information is referred to as the **3 Ms of corneal AR management: Monitor, Minimise, and Modify**.[1]

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

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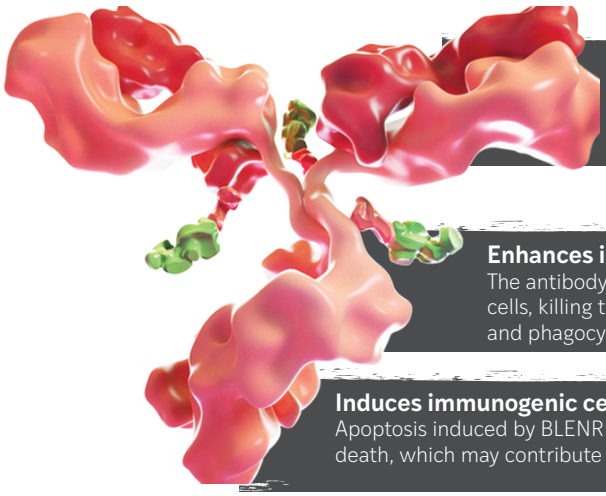
Overview of BLENREP MOA

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

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.[1]

BLENREP specifically binds to BCMA, a cell-surface protein expressed on myeloma cells, late-stage B cells, and plasma cells. BLENREP binds to cell surface BCMA and is rapidly internalised.[1,2]

Multiple mechanisms of action[1]



Delivers cytotoxic payload
The free cytotoxic agent (cys-mcMMAF) 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]

BLENREP may have an effect on healthy cells.[2]

BLENREP is an MMAF-containing ADC linking a monoclonal antibody with mafodotin, a toxic payload with known corneal ARs[1,3]

In nonclinical studies, BLENREP was taken up into cells throughout the body, including human corneal epithelial cells, by a mechanism unrelated to BCMA receptor expression on the cell membrane.[1]

MECs are commonly reported with similar ADCs.[3]

- Rates of ocular events range from **31% to 92%**
- **Grade 3/4 events occurred in up to 35%** of patients with ADCs

To help manage corneal ARs associated with BLENREP, remember the 3 Ms, detailed on pages 12-21:


MONITOR


MINIMISE


MODIFY

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ADC=antibody-drug conjugate; BCMA=B-cell maturation antigen; MECs=microcyst-like epithelial changes; MMAF=monomethyl auristatin F.

Overview of the DREAMM-2 (Study 205678) Clinical Trial[1]

DREAMM-2 study design overview

DREAMM-2 was an open-label, 2-arm, phase 2, multicentre study, which evaluated BLENREP as monotherapy in heavily pretreated patients with multiple myeloma.[1]

Study Population[1,4]

- Relapsed/refractory multiple myeloma patients, N=97
- ≥3 prior lines of therapy[a] and who were refractory to an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 antibody alone or in combination
- Had undergone autologous HSCT or were considered ineligible
- Patients with pre-existing eye conditions, including mild punctate keratopathy, were not excluded from the study, with the exception of patients with current corneal epithelial disease

Dosing[1]

- 2.5 mg/kg BLENREP as a single agent by intravenous infusion
- Administered over at least 30 minutes, every 3 weeks
- Treatment continued until disease progression or unacceptable toxicity
- Dose was modified or discontinued in some cases of ARs

Primary Endpoint[1,5]

- Overall response rate

Secondary Endpoints[5]

- Duration of response
- Time to first response
- Progression-free survival
- Overall survival
- Safety

[a]The BLENREP indication requires at least 4 prior therapies.[1]

HSCT=haematopoietic stem cell transplantation.

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

Keratopathy (or MECs), the most commonly reported AR, was 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 (best corrected visual acuity [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 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 (Study 205678); (N=95)[a1]

System Organ Class	Adverse Reactions	Any Grade (%)	Grade 3/4 (%)
Infections and infestations	Pneumonia[b]	11	7
	Upper respiratory tract infection	9	0
Blood and lymphatic system disorders	Thrombocytopenia[c]	38	22
	Anaemia	27	21
	Lymphopenia[d]	20	17
	Leukopenia[e]	17	6
	Neutropenia[f]	15	11
Eye disorders	Keratopathy[g]	71	31
	Blurred vision events[h]	25	4
	Dry eye events[i]	15	1
	Photophobia	4	0
	Eye irritation	3	0
	Ulcerative keratitis	1	1
	Infective keratitis	1	1
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]Includes pneumonia and herpes simplex pneumonia.

[c]Includes thrombocytopenia and decreased platelet count.

[d]Includes lymphopenia and decreased lymphocyte count.

[e]Includes leukopenia and decreased leukocyte count.

[f]Includes neutropenia and decreased neutrophil count.

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

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

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

[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.

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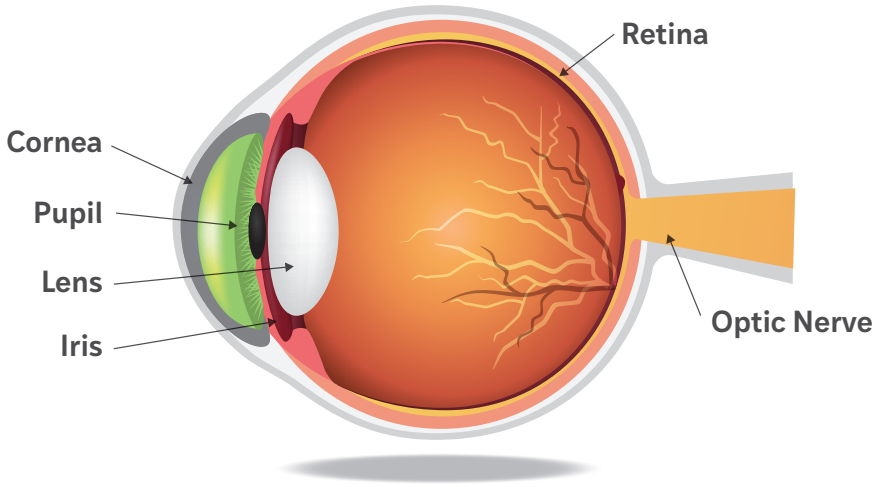
Understanding the Anatomy and Physiology of the Eye

An overview of the eye helps provide an understanding of ARs.[6]



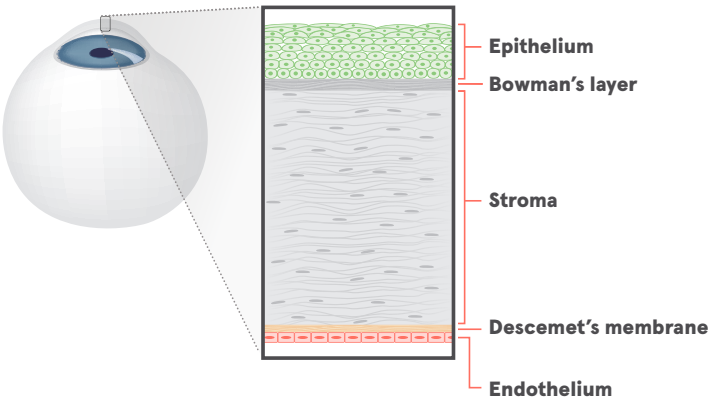
The eye is a complex organ composed of many structures that work together to enable vision[6]

Cornea	Covers the iris and the pupil[6] Responsive for focusing most of the light that enters the eye[6] The cornea is where ARs from BLENREP may occur[1]
Pupil	Is at the center of the iris[6] Allows light to strike the retina[6]
Iris	Forms the colored portion of the eye[6] Controls the size of the pupil, which in turn controls the amount of light that enters the eye[6]
Lens	Is a transparent structure in the eye[6] Works in concert with the cornea to help refract light and focus it on the retina[6]
Retina	Is the innermost layer of the eye that contains light-responsive cells[6] Transmits electrochemical signals to the brain via the optic nerve[6]
Optic nerve	Consists of nerve fibers that carry visual information from the retina to the brain[6]

Corneal ARs have been associated with the use of BLENREP[1]

Cornea

There are 5 layers of the cornea—epithelium, Bowman's layer, stroma, Descemet's membrane, and endothelium[6]



The cellular layers of the corneal epithelium regenerate, allowing for repair after trauma, typically without scarring[6]

Keratopathy (or MECs), the most common AR reported with BLENREP, was characterised as changes in the corneal epithelium (as seen on eye examination) with or without changes in visual acuity, blurred vision, and dry eye symptoms.[1]

MECs represent an off-target effect of BLENREP in the cornea leading to apoptosis of epithelial cells. These epithelial cells are then replaced with new ones, allowing for **resolution of MECs and symptoms after completion of treatment**.[3]

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MONITOR, MINIMISE, MODIFY:
The 3 Ms of Corneal AR Management

A multidisciplinary approach, involving close collaboration between eye care professionals and haematologists, is needed to determine appropriate diagnosis and management of these patients[3]

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. **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

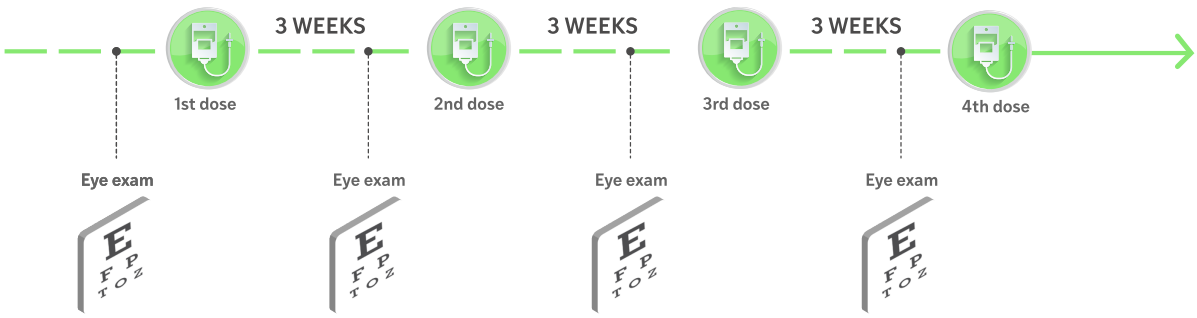
Use caution when driving or operating machines

Continue monitoring for corneal adverse reactions after treatment and contact haematologist if any symptoms occur. Dose modifications may be necessary, including discontinuation of therapy
(see dose modifications on page 21)

Effective communication between the eye care professional and the haematologist throughout treatment is critical

The eye care professional should provide the graded results of the eye exams to the haematologist at baseline and prior to the first and subsequent doses of BLENREP using the Eye Care Evaluation Report. The graded results provide the information you need to make a clinical decision regarding dosing of BLENREP.

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.

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The 3 Ms of Corneal AR Management

MONITOR

Ophthalmic exam

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]

The eye care professional will receive the Eye Care Evaluation Report to facilitate communication with you.

Changes in visual acuity as indicated in the grading scale on page 21 can determine if dose modifications are clinically warranted during treatment with BLENREP

Visual acuity assessment

Visual acuity, a "vital sign" of ocular function, provides a measure of the ability of the visual system to discern fine distinctions in the visual environment.[7]

BCVA refers to the visual acuity achieved with correction (such as glasses), as measured on the standard Snellen eye chart.[8]

What is measured?

- A patient's visual function is measured by assessing their ability to distinguish fine details with and without corrective lenses, monocularly and binocularly[9]

How is it measured?

- Patient reads the smallest letters that they can identify on a chart (typically a Snellen eye chart) located 20 feet away, or if the chart cannot be set at 20 feet, the height of the letters is calibrated to the appropriate size[9-11]

What do the measurements mean?

- "Normal" vision, a visual acuity score of 20/20 or better, indicates proper refraction, clarity of ocular media, proper functioning of the retina, and generally unimpaired optic nerve and visual cortex[7,9,10]
- A visual acuity score lower than 20/20 may need to be corrected with new or updated prescription glasses, or it may indicate the presence of an eye condition, such as eye infection, injury, or disorder[11,12]

Slit lamp exam

Slit lamp exams provide detailed information on the anatomical structures in the eye. They can help detect a range of conditions, including dry eye events.[13,14]

Examination of the surface of the eye is assessed using the slit lamp and can help identify superficial punctate epithelial erosions or superficially damaged cells.[14,15]

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MONITOR, MINIMISE, MODIFY:
The 3 Ms of Corneal AR Management

MONITOR

Advise patients that corneal ARs are commonly reported during treatment with BLENREP, and are manageable with dose modifications and supportive care.[1,3]

Advise patients that they will have ophthalmic examinations performed at baseline, before the subsequent 3 treatment cycles, and as clinically indicated while on treatment.[1]

Clinician-patient interactions

Assessment of possible corneal ARs before initiation and during treatment with BLENREP can help identify patients who need additional monitoring and/or management by an eye care professional.[1] Questions to help identify symptoms are included on page 17.

Patients and caregivers should receive education on potential corneal ARs.

Corneal ARs can be assessed with questions targeting signs and symptoms, such as[1]:

- Are you experiencing 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?
- Is it taking longer for your eyes to adjust to light?
- Do you ever feel that your vision is blurred?
- Do you feel any 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?

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The 3 Ms of Corneal AR Management

Patients who report corneal symptoms should be referred to an eye care professional[1]

My eyes feel dry and itchy.

My eyes hurt.

I cannot see very clearly. Everything seems blurry.

My eyes are watery and feel irritated.

My daughter says I'm squinting a lot.

Everything seems so bright. I wear my sunglasses more.

MINIMISE

- Counsel patients on the importance of using **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]
- Patients should be advised to **avoid contact lenses** until the end of treatment.[1]
- Patients should also be advised to **use caution when driving or operating machines, as BLENREP may affect their vision**.[1]
- Patients need to be reminded to **contact their haematologist immediately if they experience any vision/eye symptoms**.[1]
- For patients with dry eye symptoms, additional therapies may be considered as recommended by their eye care professional.[1]

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The 3 Ms of Corneal AR Management

MODIFY

The recommended dose modifications for corneal ARs are summarised in the table on the next page.[1]

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

Corneal ARs may include findings upon eye examination and/or changes in visual acuity. You and your 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, the eye care professional should assess the following:

- 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 you, as the treating physician

AR[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.

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Frequently Asked Questions

Q: What type of eye exams will my patient 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: What type of eye drops should my patient use?

A: Preservative-free artificial tears, available over the counter, should be used at least 4 times a day beginning on the first day of infusion and continuing until completion of treatment with BLENREP to help reduce corneal symptoms. For patients with dry eye symptoms, additional therapies may be considered as recommended by their eye care professional.[1]

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 was 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 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. Cases of corneal ulcer (ulcerative and infective keratitis) have also been reported.[1]

Q: What is keratopathy (or MECs)?

A: Keratopathy (or MECs) was characterised as changes in corneal epithelium (as seen on eye examination) with or without changes in visual acuity, blurred vision, and dry eyes. MECs are typically seen early in treatment, are manageable with dose modifications, and tend to resolve after completing treatment.[1,3]

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.[4]

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: Did all patients experience eye-related ARs with BLENREP?

A: Keratopathy was reported in 71% of the patients in the DREAMM-2 study. Corneal exam findings did not always correspond to symptoms reported by patients.[1,16]

Q: Can patients use contact lenses during treatment with BLENREP?

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

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Frequently Asked Questions *(continued)*

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: Keratopathy represents an off-target effect of BLENREP in the cornea leading to apoptosis of epithelial cells. These epithelial cells are then replaced with new ones, allowing for resolution of MECs and symptoms after completion of treatment.[3]

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, including discontinuation, may be necessary to manage corneal ARs. Please see recommended dose modifications on page 21[1]

Q: Whom should patients contact if the symptoms occur?

A: Patients should consult their haematologist as well as their eye care professional if corneal ARs occur.[1]

Abbreviations: ADC=antibody-drug conjugate; AR=adverse reaction; BCMA=B-cell maturation antigen; HSCT=haematopoietic stem cell transplantation; MECs=microcyst-like epithelial changes; MMAF=monomethyl auristatin F.

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Support in the Management of Corneal Adverse Reactions (ARs) for Your Patients Prescribed BLENREP

An overview of the corneal ARs that may occur with BLENREP, including:

- Corneal ARs observed in the DREAMM-2 (Study 205678) clinical trial
- How symptoms may present
- Anatomy of the cornea that may be affected
- The 3 Ms of corneal AR management: Monitor, Minimise, and Modify
- Frequently asked questions

NX-IL-BLM-BROC-210005 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)

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

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