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Important Information for Physicians: Management of Corneal Adverse Reactions for Your Patients Prescribed With BLENREP

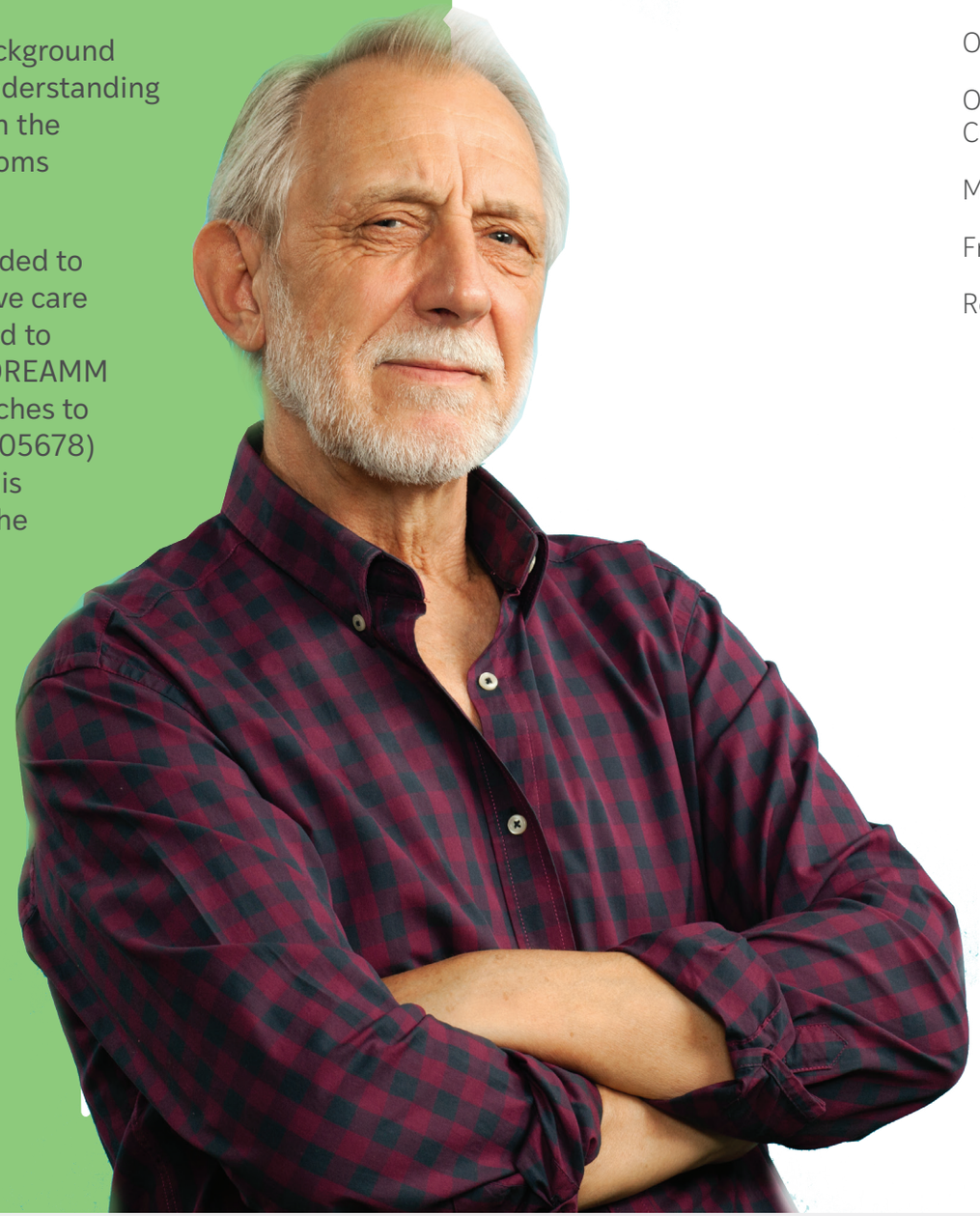
Adverse reactions (ARs) have been reported with BLENREP (belantamab mafodotin), including commonly reported ARs of keratopathy or microcyst-like epithelial changes (MECs) in the corneal epithelium.[1] This guide is intended to provide an overview of the corneal ARs that may occur with BLENREP.

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

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]

Please refer to the Singapore Package Insert for further information.



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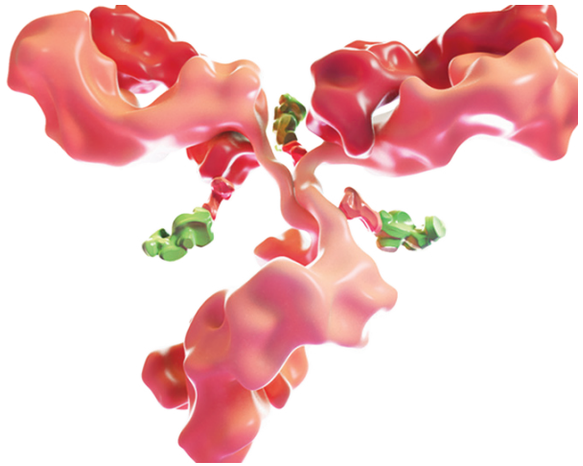
Overview of BLENREP

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

BLENREP is indicated as monotherapy for the treatment of multiple myeloma in adult patients, who have received at least four prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy.[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]



BLENREP 3D Molecule. Photo for illustration purposes only.

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

To help manage corneal ARs associated with BLENREP, remember the 3 Ms, detailed on pages 8-17:

MONITOR **MINIMISE** **MODIFY**

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ADC=antibody-drug conjugate; BCMA=B-cell maturation antigen; MMAF=monomethyl auristatin F.

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

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]

Keratopathy (or microcyst-like epithelial changes, 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]

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.

- 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 keratopathy on eye 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
Renal and urinary disorders	Albuminuria[k]	2	1

[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.
[k]Identified from patients across the BLENREP clinical program including study 205678. The frequency is based on the program-wide exposure.

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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/oncologists, 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]

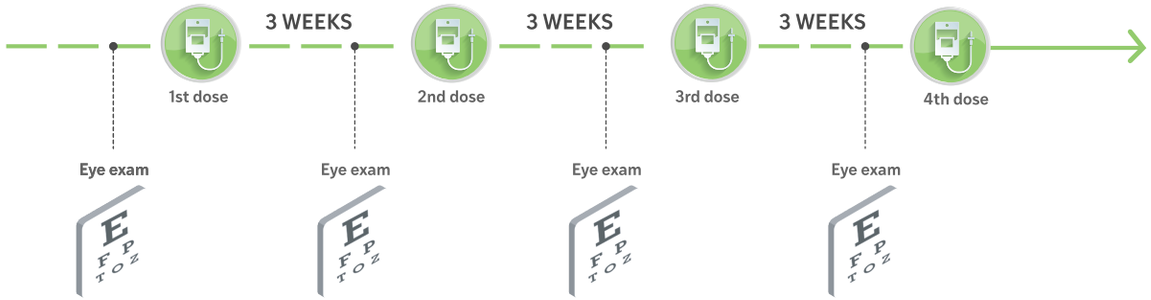
Advise patients to[1]:

- **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/oncologist if any symptoms occur. Dose modifications may be necessary, including discontinuation of therapy.

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

The eye care professional should provide the graded results of the eye exams to the haematologist/oncologist at baseline and prior to the first and subsequent doses of BLENREP using the Eye Care Evaluation Guide. 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 also recommended before the subsequent 3 treatment cycles, and as clinically indicated while on treatment.

*Eye care professional refers to an ophthalmologist who is able to provide comprehensive eye care to the patient, including routine eye-check-ups and treatment and management of visual diseases.

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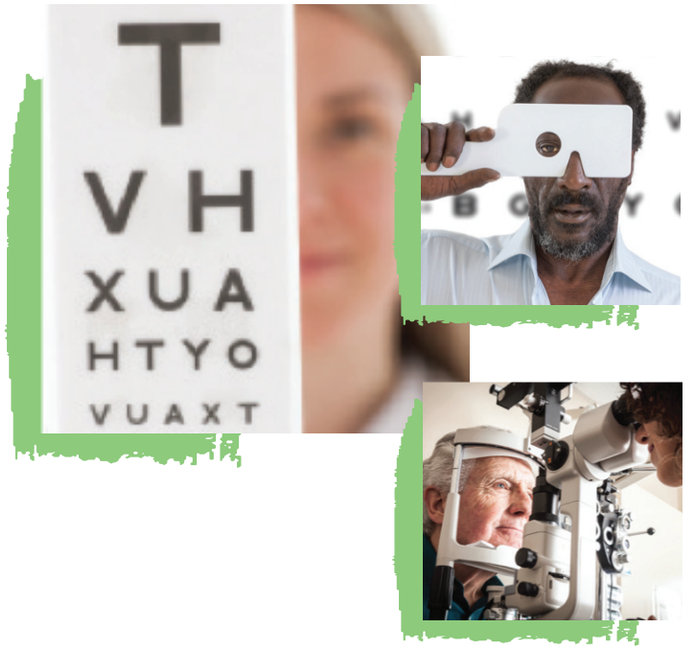
The 3 Ms of Corneal AR Management

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]

Instruct your patients being treated with BLENREP to bring the Eye Care Evaluation Guide to every eye care professional visit to facilitate communication between you and the eye care professional.



Changes in visual acuity as indicated in the grading scale on page 17 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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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 13.

Patients and caregivers should receive education on potential corneal ARs, and be provided with a copy of the Patient Guide ("Important Information on Understanding the Vision and Eye Changes That May Occur With BLENREP Treatment").

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]

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/ oncologist 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]

At every doctor visit, patients should be encouraged to share what medications they are taking as well as contact information for their haematologist/ oncologist, eye care professional, primary healthcare provider, and any other specialty healthcare provider.

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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 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: 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. Complete permanent vision loss was not reported in the DREAMM-2 trial.[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]

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 17[1]

Q: Whom should patients contact if the symptoms occur?

A: Patients should consult their haematologist/oncologist 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; MECs=microcyst-like epithelial changes; MMAF=monomethyl auristatin F.

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Notes

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Scan the QR code here to view BLENREP's full prescribing information:

This document has been approved by HSA as of 21-09-2022.

For Healthcare Professionals only.
Full prescribing information is available upon request.
Please read the full prescribing information prior to administration, available from GlaxoSmithKline Pte Ltd.
For reporting of adverse events please write to sg.drugsafety@gsk.com.
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