Summary of Product characteristics

1. NAME OF THE MEDICINAL PRODUCT

BLENREP

The marketing of Blenrep is subject to a risk mangment plan (RMP) including Physician guides and Patient guides that emphasizes important safety information that physicians and patients should be aware of before and during treatment. Please explain to the patient the need to review the guides before starting treatment.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of powder contains 100 mg of belantamab mafodotin.

After reconstitution, the solution contains 50 mg belantamab mafodotin per mL.

Belantamab mafodotin is an antibody-drug conjugate that contains belantamab, an afucosylated humanised monoclonal IgG1k antibody specific for B cell maturation antigen (BCMA), produced using recombinant DNA technology in a mammalian cell line (Chinese Hamster Ovary) that is conjugated with maleimidocaproyl monomethyl auristatin F (mcMMAF).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for concentrate for solution for infusion (powder for concentrate).

Lyophilised white to yellow powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

4.2 Posology and method of administration

Treatment with BLENREP should be initiated and supervised by physicians experienced in the treatment of multiple myeloma.

Recommended supportive care

Patients should have an ophthalmic examination (including visual acuity and slit lamp examination) performed by an eye care professional at baseline, before the subsequent 3 treatment cycles, and as clinically indicated whilst on treatment (see section 4.4).

Physicians should 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 (see section 4.4).

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

Posology

The recommended dose is 2.5 mg/kg of BLENREP administered as an intravenous infusion once every 3 weeks.

It is recommended that treatment should be continued until disease progression or unacceptable toxicity (see section 4.4).

Dose modifications

Recommended dose modifications for corneal adverse reactions are provided in Table 1. Table 2 provides dose modifications recommended for other adverse reactions.

Management of corneal adverse reactions

Corneal adverse reactions may include findings upon eye examination and/or changes in visual acuity (see sections 4.4 and 4.8). The treating physician 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 (Table 1).

During the ophthalmic examination, the eye care professional should assess the following:

- The corneal examination finding(s) and the decline in best corrected visual acuity (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.

Table 1. Dose modifications for corneal adverse reactions

Category[a]	**Eye examination findings**	**Recommended dose modifications**
Mild	*Corneal examination finding(s)* Mild superficial keratopathy[b] *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[c] *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[d] Corneal epithelial defect[e] *Change in BCVA* Decline from baseline of more than 3 lines on Snellen Visual Acuity	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] The severity category is defined by the most severely affected eye as both eyes may not be affected to the same degree.
[b] Mild superficial keratopathy (documented worsening from baseline), with or without symptoms.
[c] Moderate superficial keratopathy – with or without patchy microcyst-like deposits, sub-epithelial haze (peripheral), or a new peripheral stromal opacity.
[d] Severe superficial keratopathy with or without diffuse microcyst-like deposits involving the central cornea, sub-epithelial haze (central), or a new central stromal opacity.
[e] A corneal defect may lead to corneal ulcers. These should be managed promptly and as clinically indicated by an eye care professional.

Table 2. Dose modifications for other adverse reactions

Adverse reaction	Severity	Recommended dose modifications
Thrombocytopenia *(see section 4.4)*	Grade 2-3: Platelet count 25,000 to less than 75,000/microlitres	Consider withholding BLENREP and/or reducing the dose of BLENREP to 1.9 mg/kg.
	Grade 4: Platelet count less than 25,000/microlitres	Withhold BLENREP until platelet count improves to Grade 3 or better. Consider resuming at a reduced dose of 1.9 mg/kg.
Infusion-related reactions *(see section 4.4)*	Grade 2 (moderate)	Interrupt infusion and provide supportive treatment. Once symptoms resolve, resume at lower infusion rate by at least 50%.
	Grade 3 or 4 (severe)	Interrupt infusion and provide supportive treatment. Once symptoms resolve, resume at lower infusion rate reduced by at least 50%. If anaphylactic or life-threatening infusion reaction, permanently discontinue the infusion and institute appropriate emergency care.

Adverse reactions were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE).

Special populations

Elderly
No dose adjustment is required for elderly patients (see section 5.2).

Renal impairment
No dose adjustment is required in patients with mild or moderate renal impairment (eGFR ≥30 mL/min). There are insufficient data in patients with severe renal impairment to support a dose recommendation (see section 5.2).

Hepatic impairment
No dose adjustment is required in patients with mild hepatic impairment (bilirubin greater than ULN to less than or equal to 1.5 × ULN or aspartate transaminase [AST] greater than ULN). There are insufficient data in patients with moderate hepatic impairment and no data in patients with severe hepatic impairment to support a dose recommendation (see section 5.2).

Body weight
BLENREP has not been studied in patients with body weight < 40 kg or > 130 kg (see section 5.2).

Paediatric population
The safety and efficacy of BLENREP in children and adolescents under the age of 18 years have not been established. No data are available.

Method of administration

BLENREP is for intravenous use.
BLENREP must be reconstituted and diluted by a healthcare professional prior to administration as an intravenous infusion. BLENREP should be infused over a minimum of 30 minutes (see section 6.6).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name of the administered product should be clearly recorded. It is recommended to record the batch number as well.

Corneal adverse reactions

Corneal adverse reactions have been reported with the use of BLENREP. The most commonly reported adverse reactions were keratopathy or microcyst-like epithelial 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. Changes in visual acuity may be associated with difficulty in driving or operating machinery (see section 4.7).

Ophthalmic examinations, including assessment of visual acuity and slit lamp examination, should be performed at baseline, before the subsequent 3 treatment cycles and during treatment as clinically indicated. Patients should be advised to administer preservative-free artificial tears at least 4 times a day during treatment (see section 4.2). Patients should avoid using contact lenses until the end of treatment.

Patients experiencing keratopathy with or without changes in visual acuity may require a dose modification (delay and/or reduction) or treatment discontinuation based on severity of findings (see Table 1).

Cases of corneal ulcer (ulcerative and infective keratitis) have been reported (see section 4.8). 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 (see Table 1).

Thrombocytopenia

Thrombocytopenic events (thrombocytopenia and platelet count decreased) were frequently reported in study 205678. Thrombocytopenia may lead to serious bleeding events, including gastrointestinal and intracranial bleeding.

Complete blood counts should be obtained at baseline and monitored during treatment, as clinically indicated. Patients experiencing Grade 3 or 4 thrombocytopenia or those on concomitant anticoagulant treatments may require more frequent monitoring and should be managed with a dose delay or dose reduction (see Table 2). Supportive therapy (*e.g.* platelet transfusions) should be provided according to standard medical practice.

Infusion-Related Reactions

Infusion-related reactions (IRR) have been reported with BLENREP. Most IRRs were Grade 1-2 and resolved within the same day (see section 4.8). If a grade 2 or higher infusion- related reaction occurs during administration, reduce the infusion rate or stop the infusion depending on the severity of the

symptoms. Institute appropriate medical treatment and restart infusion at a slower rate, if the patient's condition is stable. If Grade 2 or higher IRR occurs, administer premedication for subsequent infusions (see Table 2).

Pneumonitis

Cases of pneumonitis from spontaneous reports and named patient programs, including fatal events, have been observed with BLENREP. Evaluation of patients with new or worsening unexplained pulmonary symptoms (e.g. cough, dyspnea) should be performed to exclude possible pneumonitis. In case of suspected Grade 3 or higher pneumonitis, BLENREP should be withheld. If Grade 3 or higher pneumonitis is confirmed, appropriate treatment should be initiated. BLENREP should only be resumed after an evaluation of the benefit and risk.

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per 100 mg dose, that is to say essentially "sodium-free".

4.5 Interaction with other medicinal products and other forms of interaction

No formal drug interaction studies have been performed with belantamab mafodotin.
Based on available *in vitro* and clinical data, there is a low risk of pharmacokinetic or pharmacodynamic drug interactions for belantamab mafodotin (see section 5.2).

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential/Contraception in males and females

Women
The pregnancy status of child-bearing women should be verified prior to initiating therapy with BLENREP.

Women of child-bearing potential should use effective contraception during treatment with BLENREP and for 4 months after the last dose.

Men
Men with female partners of child-bearing potential should use effective contraception during treatment with BLENREP and for 6 months after the last dose.

Pregnancy

There are no data from the use of BLENREP in pregnant women.

Based on the mechanism of action of the cytotoxic component monomethyl auristatin F (MMAF), belantamab mafodotin can cause embryo-foetal harm when administered to a pregnant woman (see section 5.3). Human immunoglobulin G (IgG) is known to cross the placenta; therefore, belantamab mafodotin has the potential to be transmitted from the mother to the developing foetus (see section 5.3).

BLENREP should not be used during pregnancy unless the benefit to the mother outweighs the potential risks to the foetus. If a pregnant woman needs to be treated she should be clearly advised on the potential risk to the foetus.

Breast-feeding

It is not known whether belantamab mafodotin is excreted into human milk. Immunoglobulin G (IgG) is present in human milk in small amounts. Since belantamab mafodotin is a humanised IgG monoclonal antibody, and based on the mechanism of action, it may cause serious adverse reactions in breast-fed children. Women should be advised to discontinue breast-feeding prior to initiating treatment with BLENREP and for 3 months after the last dose.

Fertility

Based on findings in animals and the mechanism of action, belantamab mafodotin may impair fertility in females and males of reproductive potential (see section 5.3).

Therefore, women of childbearing potential who may desire children in the future should be counselled prior to therapy regarding the option of having eggs frozen before treatment. Men being treated with this medicine are advised to have sperm samples frozen and stored before treatment.

4.7 Effects on ability to drive and use machines

BLENREP has a moderate influence on the ability to drive or use machines (see sections 4.4 and 4.8). Patients should be advised to use caution when driving or operating machines as BLENREP may affect their vision.

4.8 Undesirable effects

Summary of the safety profile

The safety of BLENREP was evaluated in 95 patients who received BLENREP 2.5 mg/kg in study 205678. The most frequent adverse reactions (≥30%) were keratopathy (71%) and thrombocytopenia (38%). The most commonly reported serious adverse reactions were pneumonia (7%), pyrexia (7%) and IRRs (3%). Permanent discontinuation due to an adverse reaction occurred in 9% of patients who received BLENREP with 3% related to ocular adverse reactions.

Tabulated list of adverse reactions

Table 3 summarises adverse drug reactions that occurred in patients receiving the recommended dose of BLENREP 2.5 mg/kg once every 3 weeks.

Frequencies are defined as very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) , very rare (< 1/10,000) and not known (cannot be estimated from the available data). Within each frequency grouping, where relevant, adverse reactions are presented in order of decreasing seriousness.

Table 3. Adverse reactions reported in multiple myeloma patients treated with BLENREP

System Organ Class	Adverse reactions[a]	Frequency	Incidence (%)	
			Any Grade	Grade 3-4
Infections and infestations	Pneumonia[b]	Very common	11	7
	Upper respiratory tract infection	Common	9	0
Blood and lymphatic system disorders	Thrombocytopenia[c]	Very common	38	22
	Anaemia		27	21
	Lymphopenia[d]		20	17
	Leukopenia[e]		17	6
	Neutropenia[f]		15	11
Eye disorders	Keratopathy[g]	Very common	71	31

	Blurred vision events[h]		25	4
	Dry eye events[i]		15	1
	Photophobia	Common	4	0
	Eye irritation		3	0
	Ulcerative keratitis	Uncommon	1	1
	Infective keratitis		1	1
Respiratory, thoracic and mediastinal disorders	pneumonitis	Not known	NA	NA
Gastrointestinal disorders	Nausea	Very common	25	0
	Diarrhoea		13	1
	Vomiting	Common	7	2
Renal and urinary Disorders	Albuminuria[k]	Common	2	1
General disorders and administration site conditions	Pyrexia	Very common	23	4
	Fatigue		16	2
Investigations	Increased aspartate aminotransferase	Very common	21	2
	Increased gamma glutamyltransferase		11	3
	Increased creatine phosphokinase	Common	5	2
Injury, poisoning and procedural complications	Infusion-related reactions[j]	Very common	21	3

NA = not applicable
[a] Adverse reactions coded using MedDRA and graded for severity based 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, diarrhea, nausea, asthenia, hypertension, lethargy, tachycardia.
[k] Identified from patients across the BLENREP clinical program including study 205678. The frequency is based on the program-wide exposure.

Description of selected adverse reactions

Corneal adverse reactions

Corneal adverse reactions were assessed in Study 205678 from the safety population (n = 218) which included patients treated with 2.5 mg/kg (n=95). Eye disorder events occurred in 74% patients and the most common adverse reactions were keratopathy or microcyst-like epithelial changes in corneal epithelium [identified on eye exam, with or without symptoms] (71%), blurred vision (25%), and dry eye symptoms (15%). Decreased vision (Snellen Visual Acuity worse than 20/50) in the better eye was reported in 18% and severe vision loss (20/200 or worse) in the better seeing eye was reported in 1% of patients treated with belantamab mafodotin.
The median time to onset of Grade 2 or above corneal findings (best corrected visual acuity or keratopathy on eye examination) was 36 days (range: 19 to 143 days). The median time to resolution of these corneal findings was 91 days (range: 21 to 201 days).

Corneal findings (keratopathy) led to dose delays in 47% of patients, and dose reductions in 27% of patients. Three percent of patients discontinued treatment due to ocular events.

Infusion-related reactions

In clinical studies, the incidence of infusion-related reactions (IRR) with belantamab mafodotin 2.5 mg/kg was 21%, and most (90%) occurred during the first infusion. Most IRRs were reported as Grade 1 (6%) and Grade 2 (12%) while 3% experienced Grade 3 IRRs. Serious IRRs were reported by 4% of patients and included symptoms of pyrexia and lethargy. Median time to onset and the median duration of the first occurrence of an IRR was 1 day. One patient (1%) discontinued treatment due to IRRs, experiencing Grade 3 IRRs at first and second infusion. No Grade 4 or 5 IRRs were reported.

Thrombocytopenia

Thrombocytopenic events, (thrombocytopenia and platelet count decreased) occurred in 38% of patients treated with belantamab mafodotin 2.5 mg/kg. Grade 2 thrombocytopenic events occurred in 3% of patients, Grade 3 in 9%, and Grade 4 in 13%. Grade 3 bleeding events occurred in 2% of patients and no Grade 4 or 5 events were reported.

Infections

Upper respiratory tract infections were commonly reported across the belantamab mafodotin clinical programme and were mostly mild to moderate (Grade 1 to 3), occurring in 9% of patients treated with belantamab mafodotin 2.5 mg/kg. There were no SAEs of upper respiratory tract infections reported. Pneumonia was the most frequent infection reported in 11% of patients treated with belantamab mafodotin 2.5 mg/kg. Pneumonia was also the most frequent SAE, reported in 7% of patients. Infections with a fatal outcome were primarily due to pneumonia (1%).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

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).

4.9 Overdose

There has been no experience of overdosage in clinical studies.

There is no known specific antidote for belantamab mafodotin overdose. In the event of an overdose, the patient should be monitored for any signs or symptoms of adverse effects and appropriate supportive treatment should be instituted immediately.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antineoplastic agents, monoclonal antibodies, ATC code: L01XC39

Mechanism of action

Belantamab mafodotin is a humanised IgG1κ monoclonal antibody conjugated with a cytotoxic agent, maleimidocaproyl monomethyl auristatin F (mcMMAF). Belantamab mafodotin binds to cell surface

BCMA and is rapidly internalised. Once inside the tumour cell, the cytotoxic agent is released disrupting the microtubule network, leading to cell cycle arrest and apoptosis. The antibody enhances recruitment and activation of immune effector cells, killing tumour cells by antibody-dependent cellular cytotoxicity and phagocytosis. Apoptosis induced by belantamab mafodotin is accompanied by markers of immunogenic cell death, which may contribute to an adaptive immune response to tumour cells.

Pharmacodynamic effects

Cardiac Electrophysiology
Based on exposure-QT_c analysis, belantamab mafodotin had no meaningful QTc prolongation (>10 ms) at the recommended dose of 2.5 mg/kg once every 3 weeks.

Immunogenicity

In clinical studies in patients with multiple myeloma, <1% of patients (2/274) tested positive for anti-belantamab mafodotin antibodies after receiving belantamab mafodotin. One of the two patients tested positive for neutralising anti-belantamab mafodotin antibodies.

Clinical efficacy

Study 205678 was an open-label, two arm, Phase II, multicentre study which evaluated belantamab mafodotin as 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 included if they had undergone autologous stem cell transplant or were considered transplant ineligible and had measurable disease by International Myeloma Working Group (IMWG) criteria.

Patients were randomised to receive 2.5 mg/kg (N=97) or 3.4 mg/kg (N=99) belantamab mafodotin by intravenous infusion every 3 weeks until disease progression or unacceptable toxicity (see Table 4). The data presented below is from the 2.5 mg/kg cohort who received the recommended therapeutic dose based on overall benefit risk assessment (see section 4. 2).

Table 4: Baseline demographics and disease characteristics

Baseline Characteristics		**2.5 mg/kg (N=97)**
Age	Median (range) Interquartile range	65.0 (39-85) 60-70
Gender	Male Female	51 (53%) 46 (47%)
ECOG at baseline	0/1 2	33%, 50%, 17%
ISS stage at screening	II III	33 (34%) 42 (43%)
Cytogenetics risk	High risk*	26 (27%)
Number of prior lines	Median Range	7 (3-21)
Duration of exposure	Median Range	9 weeks (2-75)
Treatment cycles	Median Range	3 (1-17)

ECOG = Eastern Cooperative Oncology Group Performance Status
ISS= International Staging System

*High risk cytogenetic factors [positive for t (4;14), t (14;16), and 17p13del]

The primary endpoint was overall response rate as evaluated by an Independent Review Committee (IRC) based on the IMWG Uniform Response Criteria for Multiple Myeloma. Table 5 provides the results of study 205678.

Table 5. Efficacy of BLENREP in patients with multiple myeloma in study 205678

Clinical response	2.5 mg/kg (N = 97)
Overall response rate (ORR), % (97.5% CI)	32% (22, 44)
Stringent complete response (sCR), n (%)	2 (2%)
Complete response (CR), n (%)	5 (5%)
Very good partial response (VGPR), n (%)	11 (11%)
Partial response (PR), n (%)	13 (13%)
Clinical benefit rate (CBR)*, % (95% CI)	36% (26.6, 46.5)
Median duration of response in months (95% CI)	11 (4.2 to Not reached)
Probability of Maintaining Response at 12 Months (95% CI)	0.50 (0.29, 0.68)
Median time to response in months (95% CI)	1.5 (1.0, 2.1)
Median time to best response in months (95% CI)	2.2 (1.5, 3.6)
Median overall survival (OS) in months (95% CI)	13.7 (9.9 to Not reached)
Survival probability at 12 Months (95% CI)	0.57 (0.46, 0.66)

*CBR: sCR+CR+VGPR+PR+Minimal response

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with BLENREP in all subsets of the paediatric population in multiple myeloma (see section 4.2 for information on paediatric use).

This medicinal product has been authorised under a so-called 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited.

The European Medicines Agency will review new information on this medicinal product at least every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Absorption

Maximum concentration for belantamab mafodotin occurred at or shortly after the end of infusion while cys-mcMMAF concentrations peaked ~24 hours after dosing. Geometric mean belantamab mafodotin C_{max} and $AUC_{(0\text{-}tau)}$ concentrations were 43 mcg/mL and 4,666 mcg.h/mL, respectively. Geometric mean cys-mcMMAF C_{max} and $AUC_{(0\text{-}168h)}$ concentrations were 0.90 ng/mL and 84 ng.h/mL, respectively.

Distribution

The mean steady-state volume of distribution of belantamab mafodotin was 10.8 L.

Biotransformation

The monoclonal antibody portion of belantamab mafodotin is expected to undergo proteolysis to small peptides and individual amino acids by ubiquitous proteolytic enzymes. Cys-mcMMAF had limited metabolic clearance in human hepatic S9 fraction incubation studies.

Drug interactions

In vitro studies demonstrated that cys-mcMMAF is a substrate of organic anion transporting polypeptide (OATP)1B1 and OATP1B3, multidrug resistance-associated protein (MRP)1, MRP2, MRP3, bile salt export pump (BSEP), and a possible substrate of P-glycoprotein (P-gp).

Elimination

Belantamab mafodotin was cleared slowly with total plasma clearance of 0.92 L/day and a terminal phase half-life of 12 days. Over time, clearance was reduced by 28% to 0.67 L/day with an elimination half-life of 14 days. Predose cys-mcMMAF concentrations at each dose were typically below the limit of quantification (0.05 ng/mL).

In an animal study, approximately 83% of the radioactive dose of cys-mcMMAF was excreted in the faeces; urinary excretion (approximately 13%) was a minor route; intact cys-mcMMAF was detected in human urine, with no evidence of other MMAF-related metabolites.

Linearity/non-linearity

Belantamab mafodotin exhibits dose-proportional pharmacokinetics over the recommended dose range with a reduction in clearance over time.

Special populations

Elderly patients (≥65 years old)
No formal studies have been conducted in elderly patients. Age was not a significant covariate in population pharmacokinetic analyses.

Renal impairment
No formal studies have been conducted in patients with renal impairment. Renal function was not a significant covariate in population pharmacokinetic analyses that included patients with normal renal function and mild or moderate renal impairment.

Hepatic impairment
No formal studies have been conducted in patients with hepatic impairment. Hepatic function was not a significant covariate in population pharmacokinetic analyses that included patients with normal hepatic function or mild hepatic impairment.

Body weight
Body weight was a significant covariate in population pharmacokinetic analyses. Belantamab mafodotin C_{tau} was predicted to be +10% at a body weight of 100 kg (+20% for 130 kg) and -10% at a body weight of 55 kg (-20% for 40 kg) compared to the typical patient (75 kg).

5.3 Preclinical safety data

Animal toxicology and/or pharmacology

In non-clinical studies, the principal adverse findings (directly related to belantamab mafodotin) in the rat and monkey, at exposures ≥1.2 times of the recommended clinical dose of 2.5 mg/kg, were elevated liver enzymes sometimes associated with hepatocellular necrosis at ≥ 10 and ≥3 mg/kg, respectively, and increases in alveolar macrophages associated with eosinophilic material in the lungs at ≥3 mg/kg (rat only).Most findings in animals were related to the cytotoxic drug conjugate, the histopathological changes observed in the testes and lungs, were not reversible in rats.

Single cell necrosis in the corneal epithelium and/or increased mitoses of corneal epithelial cells was observed in rat and rabbit. Belantamab mafodotin was taken up into cells throughout the body by a mechanism unrelated to BCMA receptor expression on the cell membrane.

Carcinogenesis/mutagenesis

Belantamab mafodotin was genotoxic in an *in vitro* screening assay in human lymphocytes, consistent with the pharmacological effect of cys-mcMMAF-mediated disruption of microtubules causing aneuploidy.
No carcinogenicity or definitive genotoxicity studies have been conducted with belantamab mafodotin.

Reproductive Toxicology

No animal studies have been performed to evaluate the potential effects of belantamab mafodotin on reproduction or development. The mechanism of action is to kill rapidly dividing cells which would affect a developing embryo which has rapidly dividing cells. There is also a potential risk of heritable changes via aneuploidy in female germ cells.

Effects on male and female reproductive organs have been observed in animals at doses of ≥ 10 mg/kg, which is approximately 4 times the exposure of the clinical dose. Luteinized nonovulatory follicles were seen in the ovaries of rats after 3 weekly doses. Findings in male reproductive organs, that were adverse and progressed following repeat dosing in rat, included marked degeneration/atrophy of seminiferous tubules that generally did not reverse following dosing cessation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Trehalose dihydrate
Trisodium citrate dihydrate
Citric acid
Polysorbate 80
Disodium edetate dihydrate

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened vial

The expiry date of the product is indicated on the packaging materials.

Reconstituted solution

The reconstituted solution can be stored for up to 4 hours at room temperature (20ºC to 25ºC) or stored in a refrigerator (2°C to 8°C) for up to 4 hours. Do not freeze.

Diluted solution

From a microbiological point of view, the product should be used immediately. If not used immediately, the diluted solution can be stored in a refrigerator (2ºC to 8ºC) prior to administration for up to 24 hours. Do not freeze. If refrigerated, allow the diluted solution to equilibrate to room temperature prior to administration.

The diluted infusion solution may be kept at room temperature (20ºC to 25ºC) for a maximum of 6 hours (including infusion time).

6.4 Special precautions for storage

Store in a refrigerator (2ºC to 8ºC).

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Type 1 glass vial sealed with bromobutyl rubber stopper and aluminium overseal with a plastic removable cap containing 100 mg powder.

Pack size: 1 vial

6.6 Special precautions for disposal and other handling

Preparation of solution for infusion

BLENREP is a cytotoxic anticancer medicinal product. Proper handling procedures should be followed. Use aseptic technique for the reconstitution and dilution of the dosing solution.

The recommended dose of BLENREP is 2.5 mg/kg administered as an intravenous infusion once every 3 weeks.

Calculate the dose (mg), total volume (mL) of solution required and the number of vials needed based on the patient's actual body weight (kg).

Reconstitution

1. Remove the vial(s) of BLENREP from the refrigerator and allow to stand for approximately 10 minutes to reach room temperature.
2. Reconstitute each vial with 2 mL of water for injections to obtain a concentration of 50 mg/mL. Gently swirl the vial to aid dissolution. Do not shake.
3. Visually inspect the reconstituted solution for particulate matter and discoloration. The reconstituted solution should be a clear to opalescent, colourless to yellow to brown liquid. Discard the reconstituted vial if extraneous particulate matter other than translucent to white proteinaceous particles is observed.

Dilution Instructions for Intravenous Use

1. Withdraw the necessary volume for the calculated dose from each vial.
2. Add the necessary amount of BLENREP to the infusion bag containing 250 mL of sodium chloride 9 mg/mL (0.9%) solution for injection. Mix the diluted solution by gentle inversion. The final concentration of the diluted solution should be between 0.2 mg/mL to 2 mg/mL. DO NOT SHAKE.
3. Discard any unused reconstituted solution of BLENREP left in the vial.

If the diluted solution is not used immediately, it may be stored in a refrigerator (2ºC to 8ºC) for up to 24 hours prior to administration. If refrigerated, allow the diluted solution to equilibrate to room temperature prior to administration. The diluted solution may be kept at room temperature (20ºC to 25ºC) for a maximum of 6 hours (including infusion time).

Administration Instructions

1. Administer the diluted solution by intravenous infusion over a minimum of 30 minutes using an infusion set made of polyvinyl chloride or polyolefin.

2. Filtration of the diluted solution is not required. However, if the diluted solution is filtered, polyethersulfone (PES) based filter is recommended.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MANUFACTURER

GlaxoSmithKline Manufacturing SpA, Parma, Italy

8. LICENSE HOLDER

GlaxoSmithKline (Israel) Ltd., 25 Basel St., Petach Tikva

9. LICENSE NUMBER

168-62-36882-00

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Blenrep DR V3.0