swissmedic

Date: 24 January 2024
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Elrexfio

International non-proprietary name: elranatamab

Pharmaceutical form: solution for injection

Dosage strength(s): 44 mg, 76 mg

Route(s) of administration: subcutaneous

Marketing authorisation holder: Pfizer AG

Marketing authorisation no.: 68646

Decision and decision date: temporary authorisation in accordance with Art. 9a TPA approved on 5 September 2023

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

1 Terms, Definitions, Abbreviations

1L	First-line
2L	Second-line
Ab	Antibody
ADA	Anti-drug antibody
ADC	Antibody-drug conjugate
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ASCT	Allogeneic stem cell transplant
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
BCMA	B-cell maturation antigen
BICR	Blinded independent central review
CAR	Chimeric antigen receptor
CD	Cluster of differentiation
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CR	Complete response
CRS	Cytokine release syndrome
CxDy	Day x of treatment cycle y
CYP	Cytochrome P450
DCO	Data cut-off
DDI	Drug-drug interaction
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
EMD	Extramedullary disease
ER	Exposure-response
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
FLC	Free light chain
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
ICANS	Immune effector cell-associated neurotoxicity syndrome
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
IFN	Interferon
Ig	Immunoglobulin
IL	Interleukin
IMiD	Immunomodulatory drug
IMWG	International Myeloma Working Group
INN	International non-proprietary name
IR	Information request
ITT	Intention-to-treat
IV	Intravenous
JP	Japanese Pharmacopeia
LDH	Lactate dehydrogenase
LoQ	List of Questions

LOT	Line(s) of therapy
mAb	Monoclonal antibody
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MM	Multiple myeloma
MRD	Minimal residual disease
MRHD	Maximum recommended human dose
MTD	Maximum tolerated dose
N/A	Not applicable
NAB	Neutralizing antibody
NCCN	National Comprehensive Cancer Network
NE	Not evaluable, not estimable
NO(A)EL	No observed (adverse) effect level
OR	Objective response
ORR	Objective response rate
OS	Overall survival
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PFS	Progression-free survival
pI	Isoelectric point
PI	Proteasome inhibitor
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PR	Partial response
PS	Performance status
PSP	Pediatric study plan (US FDA)
QW	Once a week
Q2W	Every other week
R-ISS	Revised International Staging System
RRMM	Relapsed or refractory multiple myeloma
RMP	Risk management plan
SAE	Serious adverse event
sBCMA	Soluble B-cell maturation antigen
SC	Subcutanous
sCR	Suspected complete response
SPEP	Serum protein electrophoresis
SwissPAR	Swiss Public Assessment Report
TCRMM	Triple-class refractory disease
TEAE	Treatment-emergent adverse event
TNF	Tumour necrosis factor
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
ULN	Upper limit of normal
UPEP	Urine protein electrophoresis
USP	United States Pharmacopeia
VGPR	Very good partial response

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for elranatamab in the above-mentioned medicinal product.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 a^{decies} no. 1 of the TPA. Orphan drug status was granted on 9 September 2021.

Temporary authorisation for human medicinal products
The applicant requested a temporary authorisation in accordance with Article 9a TPA.

Project Orbis
The applicant requested a marketing authorisation procedure within the framework of Project Orbis. Project Orbis is a programme for the assessment of promising cancer treatments coordinated by the FDA. It provides a framework for concurrent submission and review of oncology products among international partners.

2.2 Indication and dosage

2.2.1 Requested indication

Elrexfio is indicated as monotherapy for the treatment of adult patients with relapsed or refractory multiple myeloma, who have received at least three prior therapies, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody, and have demonstrated disease progression on the last therapy.

2.2.2 Approved indication

Elrexfio is indicated as monotherapy for the treatment of relapsed or refractory multiple myeloma in adult patients whose multiple myeloma is refractory to at least one immunomodulatory agent, one proteasome inhibitor, and one anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy (see «Clinical efficacy»).

The medicinal product Elrexfio has been granted temporary authorisation as the clinical data was incomplete at the time the authorisation application was assessed (Art. 9a TPA). The temporary authorisation is contingent on the timely fulfilment of conditions. After these have been met, the temporary authorisation can be transformed into an ordinary authorisation.

2.2.3 Requested dosage

Summary of the requested standard dosage:

76 mg subcutaneous (SC) once a week (QW), with a 2 step-up priming dose regimen (12 mg on Day 1 and 32 mg on Day 4), reduced to 76 mg SC once every two weeks (Q2W) after at least 24 weeks for patients who have achieved a response.

Premedications (paracetamol, diphenhydramine, and dexamethasone) should be administered before the two priming doses and the first full dose.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	19 January 2023
Formal control completed	20 January 2023
Preliminary decision	15 May 2023
Response to preliminary decision	16 July 2023
Labelling corrections	3 August 2023
Response to labelling corrections	22 August 2023
Final decision	5 September 2023
Decision	approval (temporary authorisation in accordance with Art. 9a TPA)

3 Medical context

Multiple myeloma (MM) is a plasma cell neoplasm that accounts for approximately 1 to 2% of all cancers. It is the second most common haematological malignancy, with an estimated incidence in Europe of approximately 5 to 6/100,000/year. The incidence increases with age, and the median age at onset of MM is approximately 70 years, with approximately two thirds of patients aged older than 65 years. Although survival from the time of diagnosis of MM has improved since 2000, the prognosis for patients with relapsed or refractory MM (RRMM) that relapses following prior exposure to all 3 MM drug classes is poor, and the remaining therapeutic options are limited (Dimopoulos et al. 2021; Cowan et al. 2022). The majority of these patients has triple-class refractory disease (TCRMM), and many have been exposed to all 5 drugs that have demonstrated single-agent effectiveness against MM (so-called penta-exposed patients). Historically this patient population achieved an objective response rate (ORR) of approximately 30%, median PFS of approximately 3 to 6 months, and median OS of approximately 6 to 12 months (Gandhi et al. 2019).

References

- Dimopoulos MA et al. Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 2021; 32:309-322 (including corrigendum 2022: https://doi.org/10.1016/j.annonc.2021.10.001).
- Cowan AJ et al. Diagnosis and Management of Multiple Myeloma – A Review. JAMA 2022; 327:464-477.
- Gandhi UH et al. Outcomes of patients with multiple myeloma refractory to CD38-targeted monoclonal antibody therapy. Leukemia 2019; 33:2266–2275.

4 Quality aspects

4.1 Drug substance

Elranatamab is a bispecific IgG2 kappa antibody that is directed against cluster of differentiation 3 (CD3) and against the B-cell maturation antigen (BCMA). Elranatamab is derived from two monoclonal antibodies (mAbs), the anti-BCMA mAb and the anti-CD3 mAb. Each of these mAbs contributes one distinct heavy (H) chain and one distinct light (L) chain to the bispecific elranatamab antibody (Ab). The resulting 4-chain bispecific antibody is covalently linked via five inter-chain disulfide bonds.
Elranatamab is a glycoprotein (molecular weight approx. 148.5 kDa, depending on the glycoform) with an experimental pI of approximately 8.8 and a specific absorption coefficient at 280 nm of 1.44 $(mg/mL)^{-1}cm^{-1}$.

Both parts of the elranatamab bispecific Ab (anti-BCMA mAb and anti-CD3 mAb) are produced in CHO K1 Chinese hamster ovary cells. For each of the antibodies, a two-tiered cell banking system of Master Cell Bank and Working Cell Bank (WCB) is in place. After the WCB vial has been thawed, the cells are grown in suspension culture using chemically defined, animal-derived component-free media. Cells are grown in a series of seed train bioreactors to generate sufficient cell mass to seed the production bioreactor. The anti-BCMA mAb and anti-CD3 mAb production fed-batch bioreactor cultures are harvested separately, then clarified by centrifugation and depth filtration to remove cells and debris. This is followed by a viral inactivation step via detergent addition. The anti-BCMA and anti-CD3 mAbs are processed separately through Protein A affinity chromatography. Through reduction and subsequent oxidation, the disulfide bonds reform preferentially between one half of anti-BCMA mAb and one half of anti-CD3 mAb, forming the elranatamab bispecific Ab. The elranatamab Ab is then further concentrated and purified through different chromatography and filtration steps, including a virus filtration step. After addition of excipients, final filtration and filling, the elranatamab drug substance is frozen for storage.

The cell culture and purification processes for elranatamab drug substance are both validated with several consecutive batches, and the data demonstrated consistent production and efficient removal of impurities.

Several changes were implemented during development of the manufacturing process for the drug substance, including changes to the manufacturing site and production scale. However, comparability studies, including batch release data, extended characterisation data, and stability data, demonstrated comparability between the different processes.

The characterisation of the physicochemical and biological properties of the elranatamab drug substance and its impurities was performed using state-of-the-art methods.

The specifications for release and stability of the drug substance include relevant tests and acceptance criteria, e.g. for identity, purity and impurities, quantity, and potency. Specifications are based on published limits, stability data, clinical experience and batch analysis data and are in conformance with current compendial or regulatory guidelines.

Batch analysis data for development, clinical, and process validation batches of elranatamab Ab drug substance were provided. All specific analytical methods are described and have been validated.

No significant changes were observed during storage of elranatamab Ab drug substance under the proposed storage conditions.

4.2 Drug product

The elranatamab drug product is supplied as a clear to slightly opalescent, and colourless to pale brownish liquid solution. The 44 mg/1.1 mL (40 mg/mL) and 76 mg/1.9 mL (40 mg/mL) strength drug product presentations are provided as a solution for injection in a single-dose vial. The drug product is supplied in a 5 mL glass vial, sealed with a stopper and an aluminium seal with flip-off plastic cap. The drug product contains no preservative and is for single dose only. To ensure that a 1.1 mL

nominal volume can be withdrawn from the 44 mg vial, there is an overfill of approximately 0.3 mL. To ensure that a 1.9 mL nominal volume can be withdrawn from the 76 mg vial, there is an overfill of approximately 0.3 mL.

All excipients (L-histidine, L-histidine hydrochloride monohydrate, edetate disodium dihydrate, polysorbate 80, sucrose and water for injection), are of compendial grade and commonly used for the formulation of biopharmaceuticals. None of the excipients are of animal or human origin.

Several drug product dosage strengths, formulations, presentations, and filling facilities were used during clinical development. However, comparability studies, which included batch release data, extended characterisation data, and stress stability data, demonstrated comparability of the relevant quality attributes between the different processes.

Compatibility studies were conducted to establish in-use stability with the intended materials and conditions of use.

The drug product manufacturing process consists of drug substance thawing, dilution with formulation buffer, bioburden-reducing filtration of the formulated drug substance, sterile filtration and aseptic filling, crimping, visual inspection, labelling, and secondary packaging.

The drug product manufacturing process was validated with several consecutive batches. The data demonstrated consistent production.

The specifications for drug product release and stability include relevant tests and acceptance criteria, e.g. for identity, purity and impurities, quantity, potency, appearance, pH, osmolality, visible and subvisible particles, bacterial endotoxins, and sterility. The drug product specifications comply with current compendial or regulatory guidelines.

Batch analysis data for several batches of the drug product, including development batches, clinical batches, and process validation batches were provided. All batch release data comply with the drug product specifications that were valid at the time of batch release. All specific analytical methods are validated.

The primary packaging components and materials of construction for the container closure system consist of a Type I borosilicate glass vial and chlorobutyl rubber vial stopper. The vial meets USP <660>, Ph. Eur. 3.2.1, and JP 7.01 requirements for Type I glass containers. The vial stopper has a fluoropolymer film (ethylene tetrafluoroethylene (ETFE)) laminate coating on the product contact surface of the stopper and meets the USP <381>, Ph. Eur. 3.2.9, and JP 7.03 requirements. Filled and labelled drug product vials are packed in cartons with lids and with a package insert.

The data currently available provide the rationale and justification for the current elranatamab drug product shelf life of 18 months when stored at the recommended temperature of 5 +/-3 °C for the 76 mg/1.9 mL presentation and the 44 mg/1.1 mL presentation.

4.3 Quality conclusions

Satisfactory and consistent drug substance and drug product quality has been demonstrated.

Safety of the product with regard to viral and non-viral contaminants is adequately addressed.

5 Nonclinical aspects

5.1 Pharmacology

Elranatamab bound to the B-cell maturation antigen (BCMA) of mice, rats, cynomolgus monkeys and humans (K_D values approximately 1.5 nM, 5.4 nM, 57 pM, and 38 pM respectively), and to CD3δε of cynomolgus monkeys and humans (K_D values approximately 14 nM and 17 nM respectively). However, it did not bind to mouse or rat CD3. Elranatamab blocked the interaction of BCMA with human B-cell activating factor (BAFF) and A proliferation-inducing ligand (APRIL).

In the presence of T cells, elranatamab mediated lysis of BCMA-expressing cells in various myeloma cell lines (EC_{50} values 2.1 to 748.2 pM) as well as in primary tumour cells from myeloma patients (EC_{50} values 20.8 to 276.3 pM). Elranatamab-mediated myeloma cell line killing was associated with upregulation of the T-cell activation markers CD69 and CD25 as well as a concomitant induction of cytokine release (TNF-α, IFN-γ, IL-2, IL-6, IL-8, and IL-10).

In vivo activity was shown in mouse xenograft models using multiple myeloma cell lines that express varying levels of BCMA. Since elranatamab does not bind to mouse CD3, mice were also implanted with human T cells. The anti-tumour effect of elranatamab observed at single IV doses of 10 to 300 µg/kg overall correlated with the level of BCMA expression. Improved anti-tumour activity was achieved in combination with lenalidomide or with the gamma secretase inhibitor nirogacestat. The expected pharmacology of elranatamab *in vivo* was further confirmed in the toxicity studies.

In conclusion, the pharmacology of elranatamab as a bispecific antibody against BCMA and CD3 for the treatment of BCMA-expressing tumour cells has been sufficiently characterised from a nonclinical perspective.

Elranatamab bound to the cynomolgus monkey and human neonatal Fc receptor (FcRn). However, the modified IgG2 antibody domain of elranatamab showed only weak or no binding to human Fcγ receptors. Furthermore, elranatamab showed no binding to complement component 1q.

Elranatamab was not found to have any effect on electrocardiograms and there were no clinical observations indicating any direct effect on the central nervous or respiratory system at doses up to 0.3 mg/kg IV or 6 mg/kg SC (C_{max} >6 times human C_{max} at clinical dose).

5.2 Pharmacokinetics

Elimination half-life ($t_{1/2}$) of elranatamab in the cynomolgus monkey ranged from approximately 4 to 6 days. The low volume of distribution (approximately 0.1 L/kg) is consistent with the limited distribution expected for an IgG antibody. The estimated bioavailability after SC administration was approximately 50%.

After repeat SC doses of 0.3 to 6 mg/kg/week, serum exposure to elranatamab increased in an approximately dose-proportional manner. Accumulation (up to 7-fold after 12 weeks) occurred after repeated weekly administration. There were no clear sex-related differences in exposure.

Formation of ADAs reduced exposure in some of the animals during the repeat-dose toxicity studies at lower doses (≤ 0.3 mg/kg/week). However, this did not impair the overall interpretation of the studies. In the 3-month study, the 2 animals with ADAs showed a (partial) return of the depleted B cells and/or plasma cells at the end of the study.

The applicant did not conduct any distribution, metabolism, excretion or pharmacokinetic drug interaction studies with elranatamab; however, this is acceptable for an antibody, i.e. in line with ICH S6(R1).

5.3 Toxicology

The toxicology programme was conducted in the cynomolgus monkey, a pharmacologically relevant animal species. Elranatamab was administered SC, in line with the intended clinical route of administration. Sufficient exposure was achieved with once-weekly dosing. The duration of the

repeat-dose toxicity studies (up to 3 months) is appropriate for a product intended for the treatment of advanced cancer.

Elranatamab did not show any severe acute toxicity after single SC doses up to 15 mg/kg. Key findings in the repeat-dose toxicity studies were consistent with the expected pharmacology of elranatamab, and included increases in the percentage of circulating activated T cells, transient decreases in total circulating T cells, decreases in circulating BCMA-expressing cells (plasma cells and B cells) resulting in decreases in circulating immunoglobulins, as well as increases in cytokines (IL-2, IL-6, IL-10 and IFN-γ). In the 3-month study, exposures below the clinical exposure resulted in immunosuppression with secondary infections that ultimately led to moribundity. Although the increases in cytokines were not associated with adverse clinical signs in the monkey, they remain a risk for cytokine release syndrome (CRS) in patients. The risk and management of infections and CRS are included in the information for healthcare professionals and the RMP lists serious infections as important identified risks.

The applicant did not conduct any genotoxicity studies with elranatamab; however, this is acceptable for an antibody, i.e. in line with ICH S6(R1).

No carcinogenicity studies were conducted with elranatamab; this is in line with ICH S9 and ICH S6(R1).

In line with ICH S9, no fertility and early embryonic development or pre- and postnatal development studies were conducted. Repeat-dose toxicity studies in sexually mature cynomolgus monkeys lasting up to 3 months and involving exposures up to 6.5 times human AUC at clinical dose did not reveal any potential effects on male or female fertility based on an assessment of reproductive organs. No embryofetal development studies were conducted either, the justification for this being the identified risk of fetal harm due to B-cell lymphocytopenia and the potential impact of CRS on pregnancy. Use of elranatamab during pregnancy is not recommended.

All relevant nonclinical safety findings are included in the nonclinical part of the safety specification of the RMP. There is no risk for the environment due to the protein nature of elranatamab.

5.4 Nonclinical conclusions

The submitted nonclinical documentation is considered adequate to support the approval of elranatamab in the proposed indication. All safety-relevant nonclinical data are included in the information for healthcare professionals.

6 Clinical aspects

6.1 Clinical pharmacology

ADME

Absorption
The median tmax of total and free elranatamab serum concentrations was about 7 days after s.c. administration.
The absolute bioavailability of elranatamab after s.c. administration was estimated to be 56.2%. The impact of the injection site on elranatamab absorption after s.c. administration was not formally evaluated. However, the available raw data indicated no major differences in total and free elranatamab concentrations after injection into the abdomen or the thigh.

Dose proportionality
There was a dose-proportional increase in total elranatamab Cmax and AUCtau after administration of single i.v. doses of between 0.1 to 50 µg/kg and single s.c. doses of between 80 to 1000 µg/kg. The free elranatamab exposures appeared to increase slightly less than dose proportionally after s.c. administration.

These findings were confirmed by simulations using the final pop PK model over an s.c. dosing range of 6 mg to 76 mg after single dosing and at steady state. There was a more than dose-proportional increase in free elranatamab AUC at steady state in patients with high baseline soluble B-cell maturation antigen (sBCMA) (> 90th percentile).

As elranatamab exhibits target-mediated drug disposition, it can be concluded that saturation was reached at the doses investigated.

Pharmacokinetics after multiple dosing
The median accumulation ratio of elranatamab total and free Cmax after 76 mg QW was 4.8 and 6.6 for total and free concentrations respectively. The corresponding values for AUCtau were 8.0 (total) and 11.2 (free). If the recommended dosing regimen of 12/32/76 mg QW is followed, >95% of steady-state for total elranatamab and >90% of steady-state for free elranatamab is reached by 168 days (6 cycles).

Distribution
The volume of distribution for elranatamab was 4.78 L for the central compartment and 2.83 L for the peripheral compartment.

Metabolism
No *in vitro* or clinical studies of metabolism were conducted. This is acceptable given the biological nature of the molecule.

Elimination
The typical value for elranatamab clearance was 0.324 L/d. The median terminal half-life of free elranatamab, total elranatamab serum concentrations and the elranatamab - sBCMA complex was 23.5, 24.5, and 34.4 days, respectively.

The median time to 50% exposure reduction from Cmax – i.e. time to half maximal concentration after 6 cycles of 76 mg QW dosing of elranatamab – in the analysis population was approximately 24, 27 and 25 days after tmax for free or total elranatamab serum concentration and the concentrations of the elranatamab -sBCMA complex respectively. The median time to 97% reduction of Cmax is expected to occur after 115, 126, and 94 days after tmax for free, total elranatamab serum concentrations and the elranatamab -sBCMA complex respectively.

Special populations

Elranatamab PK in patients with multiple myeloma and the impact of covariates including age, immunogenicity, sex, race, body weight, soluble B-cell maturation antigen (sBCMA), and markers for hepatic, and renal function were investigated in a pop PK analysis that included the data from Studies 1001, 1002, 1003 and 1009.

The dataset included 321 patients. The majority of the patients received s.c. treatment (93%) with the 40 mg/mL strength (78%). Most of the patients (60%) were white. Forty (12%) patients were ADA positive at baseline, and 28 (9%) developed treatment-induced or -boosted ADA. The mean age of the patients was 66 years (range: 36 to 89 years). The majority of patients (56.8%) were ≥ 65 years old. Their mean body weight was 71.5 kg (range: 36.5 to 159.6 kg).

The dataset included 128 (39.9%) patients with normal renal function, 123 (38.3%) patients with mild renal impairment, 70 (21.8%) patients with moderate renal impairment, and 3 (0.93%) patients with severe renal impairment. The majority of the patients (278, 86.6%) had normal hepatic function, 45 (12%) had mild hepatic impairment, nobody had moderate hepatic impairment, and 1 patient had severe hepatic impairment.

The final pop PK model was a semi-mechanistic target-binding model describing the concentration-time profiles of free and total elranatamab that also incorporated elranatamab binding to sBCMA. The final model included the following relationships:

- Age on ka
- Sex on CL
- Body weight on Vc

Baseline or treatment-induced ADA had no statistically significant or clinically relevant impact on elranatamab PK.

The impact of age, gender, body weight, and hepatic and renal function on total and free elranatamab exposures was small. No dose adjustments for these covariates is required from a pharmacokinetic point of view.

Total elranatamab exposures tended to decrease with increasing body weight, i.e. patients with a low body weight had the highest total elranatamab exposures. This trend was not observed for free elranatamab exposures and may be at least partially due to higher baseline sBCMA levels in patients with a low body weight.

Interactions

No *in vitro* or clinical interaction studies were conducted.

Impact of other drugs on elranatamab
The co-administration of lenalidomide or pomalidomide appeared to have no major impact on total and free elranatamab exposures. However, the number of patients in the different dose groups was small, and no formal statistical comparison was performed.

Impact of elranatamab on other drugs
Elranatamab produced a temporary increase in cytokine serum levels that can be attenuated, but not completely eliminated, by pre-medication. This may lead to a reduction in CYP activity resulting in clinically relevant interactions with sensitive CYP substrates.

Pharmacodynamics

Secondary pharmacology (safety)
Instead of a tQT study, an exposure-response (ER) analysis that included matched PK/ECG data pairs covering Cmax from Studies 1001, 1002, 1003 and 1009 was conducted to assess the impact of total and free elranatamab serum concentrations on QTcF.

The dataset for the total elranatamab concentrations included 302 patients with total elranatamab concentrations ranging between 0 and 117000.0 ng/mL.

The dataset for the free elranatamab concentrations included 295 patients with free elranatamab concentrations ranging between 0 and 101000.0 ng/mL.

In addition to the total and free elranatamab serum concentrations, age, sex and race were investigated as covariates.

Neither total nor free elranatamab serum concentrations had an impact on heart rate, and QTcF was an appropriate correction of the QT interval in both datasets. There was also no apparent hysteresis.

There was no clinically relevant relationship between total and free elranatamab serum concentrations and QTcF for the available exposure range, and none of the covariates investigated reached statistical significance in the final models.

The final models for total and free elranatamab serum concentrations slightly under-predicted the observed QTcF data, but QTcF did not tend to increase with increasing elranatamab concentrations.

The simulated 97.5th percentile of ΔQTcF at the mean free and total elranatamab Cmax was 0.454 msec and -0.178 msec respectively.

The dataset covered total and free elranatamab concentrations up to 117000.0 ng/mL and 101000.0 ng/mL, respectively. Compared to the total and free elranatamab Cmax after 6 cycles of 76 mg QW derived from the final pop PK model, these concentrations were 4.5- fold and 6.3-fold higher, respectively.

Exposure efficacy/safety relationship

Efficacy

There was a statistically significant relationship between total and free elranatamab exposures and the probability of achieving OR. Free elranatamab exposures were the better predictor. Additional covariates associated with a higher probability of OR were lower baseline sBCMA levels, a lower number of prior therapy lines, and the absence of extramedullary disease. For these patients, a maintenance dose of 44 mg QW might be sufficient. ADA or NAB status had no impact on the probability of achieving OR.

There was no statistically significant relationship between elranatamab exposures and DOR.

Safety - CRS

There were statistically significant relationships between total and free elranatamab exposures and the probability to experiencing CRS. As with efficacy, free elranatamab exposures were the stronger predictor. Lower baseline sBCMA levels were also associated with a higher probability of experiencing CRS. This finding correlates with the results of the ER analyses efficacy, indicating that a maintenance dose of 44 mg QW may be sufficient for patients with low baseline sBCMA levels. ADA status had no impact on the probability to experience CRS.

CRS occurred mainly after the first priming dose of 12 mg. The incidence decreased after the second priming dose of 32 mg. A further decrease was observed after the maintenance dose of 76 mg. A statistically significant relationship between free or total elranatamab exposures was identified for elranatamab Ctrough on Day 4 following the first step-up priming dose only, but not for the second step-up priming dose or the maintenance dose. The only covariate identified was baseline LDH (lower probability of experiencing CRS with higher baseline LDH values).

The incidence of CRS was similar across body weight quartiles. It decreased with increasing total or free sBCMA levels, i.e. patients with low sBCMA levels had the highest incidence of CRS.

The CRS grade increased with increasing cytokine serum concentrations in patients receiving the 2-dose step-up priming dose regimen. These results were confounded by the administration of tocilizumab for the treatment of CRS, which increased the cytokine levels. However, after the first step-up priming dose of 12 mg, the CRS grade increased with increasing cytokine concentrations if the samples prior to tocilizumab administration only were considered.

The results of the ER analyses for CRS raised concerns regarding the recommendations for restarting elranatamab treatment after dosage delay that had been originally proposed; these started with the second step-up priming dose of 32 mg in all cases. The applicant proposed more granular recommendations based on PK simulations.

From a pharmacometric point of view, the updated recommendations for treatment re-start are reasonable and were finally adopted.

Other safety endpoints

There were no total elranatamab exposure trends for peripheral neuropathy, neutropenia and infection. The free elranatamab exposures tended to be higher in patients who experienced these AEs, but there was no statistical significance.

There was a statistically significant relationship between both total and free elranatamab Cmax,event (Cmax in the time up to the first event) and the probability to experiencing TEAEs leading to dose interruption. The final model for total Cmax also included baseline albumin as a covariate (probability ↑ with increasing albumin levels).
There was a statistically significant relationship between both total and free elranatamab Cmax,event and the probability to experience TEAEs leading to dose modifications. Both final models also included baseline albumin as a covariate (probability ↑ with increasing albumin levels).
There was a statistically significant relationship between both total and free elranatamab Cmax,event and the probability to experiencing TEAEs leading to dose reductions. However, after backwards elimination from the full models, including all covariates (p 0.01), statistical significance was not achieved for either free or total elranatamab Cmax,event; only baseline albumin remained within the model (=> no elranatamab exposure measures).

There was no statistically significant relationship between total and free Cmax,event and total and free Cave,event and the probability to experiencing TEAEs leading to dose discontinuation.

The elranatamab exposures were lower or similar in patients experiencing or not experiencing nervous system or psychiatric disorder events, nervous system disorder events, psychiatric disorder events, headache events, motor dysfunction events and encephalopathy events.

The elranatamab exposures were higher in patients experiencing sensory neuropathy events compared to patients not experiencing these events.

The elranatamab exposures were lower or similar in patients experiencing or not experiencing ALT or AST 3 x ULN, ALT or AST 5 x ULN.

6.2 Dose finding and dose recommendation

Based on the results of the dose-escalation part of the first-in-human study – C1071001 – a dosage of 1000 µg/kg once weekly (QW) subcutaneously (SC) was selected. This was the highest dose level tested and was selected to maximise the potential for clinical activity while no dose-limiting toxicity had been observed. SC dosing was selected over intravenous (IV) dosing as it appeared to be associated with a lower rate of Grade 2 cytokine release syndrome (CRS). Because population PK analysis indicated that body weight is not a clinically relevant covariate of elranatamab exposure, a fixed dose regimen was finally selected and used in the subsequent registration study, C1071003.

Maximum CRS severity was consistently observed after the first dose, while logistic regression analysis showed an association between elranatamab Cmax within 24 hours post first dose and the likelihood of CRS. Thus, a 2 step-up priming dosing approach was selected for registration study C1071003 (plus prior anti-CRS premedication), starting with a low dose of 12 mg on Day 1 of treatment cycle 1 (C1D1), followed by a half maximal second step-up dose of 32 mg on C1D4, before the first full elranatamab dose of 76 mg on C1D8. Logistic regression analysis indicated that after a starting dose of 12 mg on C1D1, the predicted probabilities of All Grades and Grade ≥2 CRS would be in an acceptable range (55% (95% CI: 29% to 78%) and 14% (95% CI: 5% to 31%) respectively). Furthermore, increases in the levels of several cytokines suggested that the 12 mg dose would be

able to stimulate the immune system such that any CRS events with the second step-up dose of 32 mg would be less frequent and of lower grade.

Dose finding based on studies C1071001 and C1071003 was further supported by exposure-response (E-R) analyses for efficacy and safety parameters. While there was a statistically significant relationship between elranatamab exposure and the probability of achieving objective response, E-R analyses for safety did not suggest that selection of a lower dose would meaningfully mitigate the risk for the investigated AEs. In fact, the recommendation is to manage elranatamab-related toxicities by dose interruptions rather than dose reductions.

While these data support the proposed maintenance dose of 76 mg at population level, at patient level the 76 mg maintenance dose may be too high and 44 mg might be better suited for patients who have low soluble BCMA.

The proposed switch from QW dosing to dosing every other week (Q2W) after at least 6 cycles of QW treatment and a treatment response of PR or better persisting for at least 2 months was sufficiently backed by clinical study data and exposure-response analyses, and further supported by simulations.

Overall, dose finding and selection were found to be acceptable.

6.3 Efficacy

- Registration study

The registration study for the application was **C1071003** (**MagnetisMM-3**), an open-label, multicentre, non-randomised, Phase 2 study to evaluate the efficacy and safety of elranatamab in patients with RRMM who have measurable disease and are refractory to at least 1 PI, 1 IMiD, and 1 anti-CD38 antibody, and have MM that was relapsed or refractory to the last anti-MM regimen. To determine the effects of prior BCMA-directed therapy on the response to elranatamab monotherapy, the study enrolled 2 independent and parallel cohorts:

- Cohort A: patients who were naïve to BCMA-directed therapies (BCMA-naïve).
- Cohort B: patients who have been previously exposed to BCMA-directed antibody-drug conjugate (ADC) and/or CAR T-cell therapies (BCMA-exposed).

Disease assessments including blood and urine laboratory assessments for evaluation of disease response according to International Myeloma Working Group (IMWG) criteria were to be performed locally at 28-day intervals. Imaging was to be performed at screening, at suspected (stringent) complete response (CR/sCR), at suspected progressive disease from extramedullary disease (EMD), and annually if not done within the past 12 months. Bone marrow assessments were to be conducted at screening, suspected CR and then after 6 months, 12 months, and yearly after achieving CR (provided CR was maintained clinically).

76 mg elranatamab was to be administered QW as SC injections (on Days 1, 8, 15, and 22 of each 28-day cycle) starting from C1D8, following a 2 step-up priming regimen of 12 mg SC on C1D1, and 32 mg SC on C1D4 during the first week of treatment. The priming dose(s) and first full dose (76 mg) required premedication for CRS with paracetamol, diphenhydramine, and dexamethasone. Other concomitant treatment considered necessary for the patient's wellbeing was given at the investigator's discretion. This included the administration of antibacterial, antifungal, and/or antiviral agents for infection prophylaxis in patients at increased risk of infection. Additional anticancer therapy was not permitted while patients were receiving the study intervention.

Patients were required to be hospitalised and monitored for CRS / immune-effector cell-associated neurotoxicity syndrome (ICANS) for at least 2 days (approx. 48 hours) beginning on C1D1, and for 1 day (approx. 24 hours) on C1D4. There was also the option of hospitalising patients for up to 5 days between C1D1 to C1D5 inclusive.

If a patient had received QW dosing for at least 6 cycles and had achieved an IMWG response category of partial response (PR) or better persisting for at least 2 months, the dose interval was to be changed from QW to Q2W.

Each patient was to receive the study intervention until confirmed disease progression, unacceptable toxicity, withdrawal of consent, or study termination. If the study intervention was definitively discontinued, the patient was to remain in the study to be evaluated for safety, disease assessments, subsequent anticancer therapies, and survival.

Efficacy data was to undergo blinded independent central review (BICR) using IMWG response criteria. With the exception of stable disease, all response categories required confirmation by 2 consecutive assessments. ORR by BICR was the primary endpoint and included confirmed sCR, CR, very good partial response (VGPR), and PR. Secondary endpoints included ORR by BICR baseline EMD status in Cohort A, ORR by investigator, duration of response (DOR), progression-free-survival (PFS), overall survival (OS), and minimal residual disease (MRD) negativity rate.Overall, eligibility criteria were adequate. However, according to IMWG consensus criteria, measurable disease in terms of serum M protein is defined as serum M protein ≥1 g/dL. A baseline M spike of ≥0.5 g/dL, as used for eligibility in Study C1071003, would only be acceptable if VGPR or higher was the response endpoint to be measured, and in situations where PFS or time to progression were the endpoints of interest (Kumar et al. 2016). However, neither was the case in Study C1071003, where ORR, defined as PR or better, was the response endpoint to be measured and the primary endpoint of interest. In response to a pertinent information request (IR), the applicant clarified that there were 9 patients in Cohort A (7 patients in the primary analysis of ORR), and 6 patients in Cohort B who were enrolled with serum M protein (SPEP) <1 g/dL, but for whom MM was not measurable by urine M protein (UPEP) and free light chain (FLC). Because of the low numbers of patients and the similar overall results in the requested sensitivity analyses of ORR, PFS and OS, this issue was considered to have been resolved.

A total of 187 patients (123 in Cohort A and 64 in Cohort B) were assigned to and received at least one dose of study treatment.

A high incidence of important protocol deviations in approximately 80% of all patients in registration Study C1071003 was observed. Of particular focus were the rates of visits and/or disease assessments not done / not completely done, which ranged between 22% and 33% across cohorts. In response to a pertinent information request (IR), the applicant provided supplementary analyses, which suggested a limited impact on ORR, PFS, and OS results.

The applicant provided ORR data as of data cut-off (DCO) on 14 October 2022 for the primary analysis. However, because the pre-specified boundary for efficacy in Cohort A had already been crossed during the interim analysis of DCO on 23 March 2022, the latter was considered the relevant analysis set for the primary analysis of Cohort A. Cohort B also crossed the pre-specified boundary for efficacy earlier, i.e., during the final analysis as of DCO on 17 June 2022, and was considered the relevant analysis set for the primary analysis of Cohort B. The results of the primary analysis were used to label the ORR results, while the results of subsequent ORR analyses, which were consistent with the primary analysis, were considered to be supportive only.

At the time of the primary analysis of Cohort A, approximately 45% of the 94 patients who formed the primary population of this cohort had discontinued treatment. The most frequent reason for discontinuation of treatment was progressive disease (31%), followed by adverse events (AEs) (7%), and withdrawal by subject (3%).

At the time of the primary analysis of Cohort B, approximately 67% of the 64 patients who formed the primary population of this cohort had discontinued treatment. The most frequent reason for discontinuation of treatment was progressive disease (39%), followed by death (11%), AEs (8%), and withdrawal by subject (8%).

By the time of the DCO as of January 2023, approximately 66% of all 123 patients in Cohort A had discontinued treatment, with the most frequent reason for discontinuation being progressive disease (39%), followed by AEs (14%), death (7%), and withdrawal by subject (3%).

At this time, approximately 78% of all 64 patients in Cohort B had discontinued treatment, with the most frequent reason for discontinuation being progressive disease (44%), followed by death (14%), AEs (11%), and withdrawal by subject (6%).

A total of 28% of patients in the overall population received follow-up anticancer therapy; 26% in Cohort A, and 33% in Cohort B. The most frequently reported follow-up anticancer medications were dexamethasone (overall 21%; 21% and 20% respectively), cyclophosphamide (overall 11%; 12% and 9% respectively), carfilzomib (overall 10%; 9% and 11% respectively), bortezomib (overall 7%; 8% and 6% respectively), and pomalidomide (overall 7%; 6% and 7% respectively). Two patients (1.1%), one in each cohort, had a transplant, and no patients received follow-up radiation therapy.

The median (range) age of patients in the overall population was 68 (36, 89) years, with 81% aged below 75 years. This is younger than one would expect from an unselected MM population (median age at onset of approximately 70 years), especially considering an overall median time from first diagnosis of 6.7 years (see below). Nevertheless, the population in registration Study C1071003 is older than in the registration studies of other recently approved therapies for late-stage RRMM, where median age ranged from 61 to 65 years.

The majority of patients (52%) in the overall population were male (55% and 47% in Cohort A and B respectively) and white (overall 82%; 80% and 90% respectively), and approximately half of patients (51%) in the overall population were from North America (47% and 58% respectively), followed by 38% from Europe (37% and 41% respectively).

In the overall population, the median (range) time since first diagnosis of MM was 80 months (16, 228) corresponding to 6.7 years, and was longer in Cohort B than in Cohort A (103 months = 8.6 years vs. 73 months = 6.1 years). This is in line with the more heavily pre-treated population in Cohort B (see below). The median time since onset of current relapse was slightly more than 1 month (overall 1.2 months; 1.3 and 1.1 months in Cohort A and B respectively).

The performance status (PS) in the overall population was approximately 35% ECOG 0, 59% ECOG 1, and 6% ECOG 2, and similar across cohorts.

As expected, IgG was the most common type of MM in approximately 57% of all patients (59% and 47% in Cohort A and Cohort B respectively), followed by light chain MM (overall 18%; 20% and 16% respectively), and non-IgM myeloma (overall 16%; 17% and 13% respectively), which was almost always of IG A type.

EMD, as assessed by BICR at baseline, was present in 41% of all patients, but was lower in Cohort A vs. Cohort B (32% and 58% respectively). High-risk cytogenetics [any of the following: t(4;14), t(14;16), and/or del (17P)], was detected in 24% of all patients (25% and 20% respectively). Approximately 20% of all patients had 50% or more plasma cells in their bone marrow (21% and 17% respectively). Revised ISS (R-ISS) staging was Stage I in 21% (23% vs. 17% respectively), Stage II in 56% (53% vs. 56% respectively), and Stage III in 18% (15% vs. 23% respectively). Overall, 69% of all patients had at least one poor prognosis feature at baseline, i.e. EMD (per BICR), high-risk cytogenetics, bone marrow plasma cell involvement ≥50%, R-ISS Stage III, or ECOG PS 2 (66% and 75% respectively).

Approximately one third (35%) of the patients had impaired renal function (creatinine clearance ≤60 mL/min) at baseline, with similar fractions in both cohorts.

All patients had received prior anticancer medications. The median (range) number of prior MM therapy lines was 5 (2, 22) in the overall population, 97% of patients had received at least 3 prior lines of therapy (LOT) and 86% had received at least 4 prior LOT.

Overall, all patients were triple-class exposed, and 97% had TCRMM. A total of 75% were penta-drug exposed, and 46% were penta-drug refractory. The majority (93%) were also refractory to their last line of anti-myeloma therapy.

The most frequently reported (≥50%) prior anticancer medications by PT were dexamethasone, bortezomib, lenalidomide, daratumumab, pomalidomide, carfilzomib, cyclophosphamide, and

melphalan (most commonly used as part of stem cell transplant (SCT) conditioning regimen). A total of 140 patients (75%) had prior SCT, primarily (73%) autologous.

In Cohort A, the median (range) of prior anticancer therapy lines was 5 (2, 22); 96% received 3 or more prior anticancer therapy lines, and 79% received 4 or more prior anticancer therapy lines. 97% had TCRMM and 42% were penta-drug refractory.

All patients in Cohort B received prior BCMA-targeted therapy (ADC [72%] and/or CAR T-cells [33%]), patients in Cohort B were more heavily pre-treated, with a median (range) of 7.5 (3, 19) prior LOT compared to 5 (2, 22) in Cohort A; a higher proportion of patients in Cohort B (77%) had more than 5 prior LOT compared to Cohort A (34%). A higher proportion of patients in Cohort B were penta-drug exposed (84% versus 71%) and penta-drug refractory (52% vs 42%) than in Cohort A.

As expected, patients in Cohort B were more heavily pre-treated than in Cohort A. Besides this difference, the notably higher fraction of EMD at baseline in Cohort B is also suspected to have contributed to less favourable efficacy outcomes in Cohort B (see below).

Results

ORR by BICR – Primary analysis

Cohort A
At the time of the primary analysis of Cohort A (DCO 23 March 2022), the median duration of treatment for the 94 patients was 17.4 weeks (0.1 to 58.1), corresponding to 4 months.

Because the primary analysis for Cohort A as of DCO 23 March 2022 included 3 patients who had not had a response assessment by the DCO and for whom a later DCO (13 April 2022) had instead been used, an additional analysis was requested in which all patients who had not had a response assessment by the DCO were to be categorised as “not evaluable”. Based on the corrected primary analysis results, **ORR per BICR** for Cohort A was **57.4%** (95% confidence interval (CI) 46.8−67.6), including 11 (11.7%) patients with CR or sCR. VGPR and PR were achieved in 28 (29.8%) and 15 (16.0%) patients respectively. Progressive disease was reported in 18 patients (19.1%), while objective response was not evaluable in 4 patients (4.3%).

Cohort B
At the time of the primary analysis of Cohort B (DCO 17 June 2022), the median duration of treatment was 12.4 weeks (0.1 to 36.4), corresponding to 2.8 months.

Because the primary analysis for Cohort B as of DCO 17 June 2022 included an unspecified number of patients who had not had a response assessment by the time of the DCO, an additional analysis was also requested for this cohort. Based on the corrected primary analysis results, **ORR per BICR** was **29.7%** (95% CI 18.9−42.4) for Cohort B, including 3 (4.7%) patients with CR or sCR (no patient had sCR). VGPR and PR were achieved in 13 (20.3%) and 3 (4.7%) patients respectively. Progressive disease was reported in 17 patients (26.6%), while (10.9%) objective response was not evaluable in 7 patients.

Study C1071003 met its primary endpoint of demonstrating a statistically significant BICR-assessed ORR improvement above the prespecified minimum thresholds of 30% and 15% used for the null hypotheses in BCMA-naïve (Cohort A) and BCMA-exposed (Cohort B) patients respectively.

Overall, subgroup results for ORR by BICR were consistent with the main analysis. However, in both cohorts, patients with EMD at baseline fared worse in terms of ORR than patients without EMD. Given that EMD is a known negative prognostic factor, a difference of this type is to be expected (see also *ORR by BICR baseline EMD in Cohort A* below). Moreover, ORR by BICR was lower in patients with R-ISS stage 3 as well as in patients with penta-refractory RRMM, which is again to be expected, given the known negative prognostic value of both factors.

Secondary endpoints

ORR by BICR baseline EMD in Cohort A
In Cohort A, 39 patients (32%) had EMD at baseline by BICR. ORR by BICR by baseline EMD status for Cohort A was 71.4% (95% CI: 60.5, 80.8) for patients without baseline EMD as compared to 38.5% (95% CI: 23.4, 55.4) for patients with baseline EMD.

Patients in Cohort A with EMD at baseline fared worse in terms of ORR than patients without EMD. Although patient and event numbers are relatively low in these subgroups, a difference of this type is to be expected and its extent is plausible. In addition, this finding is supported by the exposure-response analyses. Therefore, although the results of the endpoint ORR by BICR baseline EMD Cohort A are not considered to be confirmatory in nature, a request was made to include information that ORR was lower in patients with EMD at baseline in the information for healthcare professionals. This also included patients who had received prior anti-BCMA therapy in Cohort B (an ORR by BICR had been reported in 7 of 37 patients with EMD in Cohort B, with a lower limit of the 95% CI of 8%).

ORR by investigator
Investigator-assessed ORR was consistent with the BICR-assessed results: Confirmed ORR by investigator was 57.7% (95% CI: 48.5, 66.6) in Cohort A, and 40.6% (95% CI: 28.5, 53.6) in Cohort B.

While the focus of clinical assessment for ORR was on the primary analyses, efficacy updates as of later DCOs were primarily used to assess (DCO January 2023) and label (DCO April 2023) time-to-event endpoints, which were mostly immature at earlier DCOs. At the latest available DCO (April 2023), the median duration of treatment was 5.6 months (0.03 to 25.8) in Cohort A, 2.8 months (0.03 to 17.1) in Cohort B, and 4.4 months (0.03 to 25.8) in the total population of registration Study C1071003.

DOR by BICR
As of DCO April 2023, the median duration of follow-up from initial response to DOR was 15.2 months (2.4 to 24.2) in Cohort A and 13.4 months (2.4 to 17.0) in Cohort B.

In Cohort A (N=75), median DOR had still not been reached at a maturity of 27% (95% CI NE−NE), and DOR at 9 and 12 months was 80.7% (95% CI 69.5−88.1) and 74.3% (95% CI 62.3−83.0) respectively.

In Cohort B (N=22), median DOR had still not been reached at a maturity of 27% (95% CI 11.8−NE) and DOR at 9 and 12 months was 85.9% (95% CI 62.4−95.2) and 67.5% (95% CI 40.9−84.1) respectively.

Even when considering updated results as of the latest available DCO in April 2023, DOR was still immature, and the number of patients in Cohort B was low, as is reflected by the wide CIs.

PFS by BICR
As of DCO April 2023, the median duration of follow-up for PFS was 9.3 months in Cohort A (0.03 to 25.8) and 2.6 months in Cohort B (0.03 to 17.8).

In Cohort A, median PFS had still not been reached at a maturity of 44% (95% CI 9.8−NE), and PFS at 6, 9, 12, and 15 months was 63.6% (95% CI 53.9−71.8), 61.7% (95% CI 52.0−70.0), 55.7% (95% CI 45.8−64.5), and 50.2% (95% CI 40.2−59.3) respectively.

In Cohort B, median PFS was 3.5 months (95% CI 1.9-6.6) at a maturity of 66%. PFS at 3, 6, and 12 months was 51.4% (95% CI 38.1−63.2), 38.6% (95% CI 26.2−50.9), and 31.1% (95% CI 19.5−43.3) respectively.

PFS in Cohort A was still immature.

OS
As at DCO April 2023, the median duration of follow-up was 15.9 months in Cohort A (0.23 to 26.2) and 9.9 months in Cohort B (0.33 to 18.4).

In Cohort A, median OS had still not been reached at a maturity of 46% (95% CI 13.4−NE), and OS at 9, 12, and 15 months was 69.7% (95% CI 60.7−77.0), 62.2% (95% CI 53.0−70.2), and 56.3% (95% CI 47.0−64.6), respectively.

In Cohort B, median OS was 11.3 months at a maturity of 56% (95% CI 6.5-NE), and OS at 9 and 12 months was 58.9% (95% CI 45.7−69.8), and 47.1% (95% CI 34.3−58.9) respectively.

OS in Cohort A was still immature and median OS in this cohort could not be estimated.

Calibration failure rates for MRD negativity were high, so that MRD results were not considered robust.

- Supportive studies

Two additional studies were submitted in support of the present application.

Study C1071001 (MagnetisMM-1) was a Phase 1 open-label, multidose, multicentre, dose escalation, safety, PK and PD study of elranatamab as monotherapy and in combination with lenalidomide, pomalidomide or dexamethasone in adult patients with advanced MM who had relapsed from or were refractory to standard therapy. At the time of submission, the study had completed enrolment but was still ongoing.

Eligible patients had to have measurable RRMM by IMWG criteria, with progression on or intolerance to established therapies known to provide clinical benefit in MM, including PI, an IMiD, and an anti-CD38 antibody. Patients had to have adequate organ function and ECOG PS of 0-2, except in one cohort (Part 2A), where maximum ECOG PS was 1.

Different IV and SC dosing regimen were investigated. Assessment focused on the pooled data of 55 patients from 4 cohorts who received elranatamab monotherapy SC at effective dosages as of DCO 22 June 2022.

The median (range) time since first diagnosis of MM was 6.4 years (0.5, 16.8) among the 55 patients exposed to effective dosages (6.1 years in the other cohorts).

The median (range) number of prior MM treatment regimens was 5 (2, 14) among the 55 patients exposed to effective dosages, ranging from 5 to 5.5 across the 4 cohorts. All patients except one were triple-class exposed, and 91% had TCRMM, ranging from 80-91% across the 4 cohorts. Approximately, 78% were penta-drug exposed (78-93%), and 58% were penta-drug refractory (58-73%). The majority (89%) were also refractory to their last line of anti-myeloma therapy (86-93%).

The median duration of treatment (range) among the 55 patients exposed to effective dosages was 7.9 months (0-29), ranging from 2.2 to 7.9 months across the 4 cohorts, with the lowest exposure duration in Part 2A. The median duration of follow-up (range) was 12 months (0.3, 29), ranging from 10.6 to 12.1 months across the 4 cohorts.

The primary efficacy endpoint **ORR** by investigator (95% CI) was 64% (50, 75) for the 55 patients exposed to effective dosages, ranging from 60 to 64% across the 4 cohorts. Of the 55 patients exposed to effective dosages, 13 had received prior anti-BCMA therapy. Of these, 7 (54%) achieved an objective response, with ORR ranging between 0% and 54% in this subgroup across the 4 cohorts.

For **DOR** by investigator, maturity was 46% among the 35 responders (out of 55 patients) exposed to effective dosages, ranging from 33 to 50% across the 4 cohorts. Estimated median DOR was 17.1 months (95% CI 10.6−NE), ranging from 9.2 to 17.1 months across the 4 cohorts.

For **PFS** by investigator, maturity was 56% among the 55 patients exposed to effective dosages, ranging from 56 to 61% across the 4 cohorts. Estimated median PFS was 11.8 months (95% CI 6.0, 19.1), ranging from 8.0 to 11.8 months across the 4 cohorts. PFS at 6, 9, and 12 months was 66.4% (95% CI 51.6−77.6), ranging from 51.9 to 65.5% across the 4 cohorts; 54.9% (95% CI 39.8−67.7), ranging from 41.5 to 54.9% across cohorts; and 47.4% (95% CI 32.5−61.0), ranging from 31.1 to 47.4% across cohorts respectively.

At a maturity of 44% among the 55 patients exposed to effective dosages, estimated median **OS** was 19.1 months (95% CI 10.9, NE), ranging from 12.1 to 19.1 months across the 4 cohorts. OS at 9 and 12 months was 73.5% (95% CI 58.7−83.7), ranging from 69.8 to 73.5% across the 4 cohorts, and 64.8% (95% CI 49.6−76.5), ranging from 53.3 to 64.8% across cohorts respectively.

Study C1071009 (MagnetisMM-9) is a Phase 1/2, open-label, multicentre, non-randomised study to evaluate a dosing regimen that involved premedication and 2 step-up priming doses as well as higher doses with longer dosing intervals of elranatamab monotherapy administered SC to patients with RRMM who are refractory to at least 1 PI, 1 IMiD, and 1 anti-CD38 antibody.

Eligible patients had to have measurable RRMM by IMWG criteria that was refractory to at least 1 PI, 1 IMiD, and 1 anti-CD38 antibody, and relapsed or refractory to their last anti-MM regimen. Patients had to have adequate organ function, serum calcium ≤3.5 mmol/L, and ECOG PS of 0-1.

The study was ongoing at the time of submission. As of DCO 29 July 2022, a total of 46 patients had been enrolled in Part 1 [N=34, of whom 33 treated] and Part 2A dose level (DL) 1 [N=12] only. These had started therapy with elranatamab 4 mg on C1D1 and 20 mg on C1D4 (2 priming doses), followed by 76 mg QW.

In Part 1 (N=33), the majority of patients was female (58%) and Asian (58%), and median age (range) was 63 years (36,79). In Part 2A DL1 (N=12), the majority of patients was male (67%) and white (50%), and median age (range) was 66 years (49, 78).

Performance status in Part 1 / Part 2A DL1 was 58% / 42% ECOG 0, and 42% / 58% ECOG 1. R-ISS was 33% / 0% Stage I, 36% / 75% Stage II, and 21% / 17% Stage III. High cytogenetic risk (T(4;14), T(14;16) or DEL(17P)) was present in 30% / 50%, and 39% / 50% had EMD at baseline. Approximately 15% / 8% had 50% or more plasma cells in their bone marrow, and about 27% / 16% had impaired renal function (creatinine clearance >60 mL/min) at baseline.

Median (range) time since first diagnosis of MM was 79 months (13, 326) and 69 months (15, 119), i.e. 6.6 years and 5.7 years, in Part 1 and Part 2A DL1 respectively.

The median (range) number of prior therapy lines in Part 1 / Part 2A DL1 was 5 (3, 11) / 4.5 (2, 12). All patients were triple-class exposed, and 88% / 83% had TCRMM. Approximately 94% / 92% were penta-drug exposed, 39% / 25% were penta-drug refractory, and 85% / 92% were refractory to last therapy).

The median duration of treatment (range) was 4.5 months (0.5-7.9) and 1.6 (0.1, 3.3) in Part 1 and Part 2A DL1, respectively. As of DCO, 19 out of 33 patients in Part 1, 7 out of 12 patients in Part 2 2DL1 were still on treatment.

Results of the primary efficacy endpoint **ORR** by investigator (95% CI) in all 33 treated patients of Part 1 were consistent with the results of registration study C1071003.

Compared to the other 2 studies, Study C1071009 had shorter durations of exposure and follow-up and more favourable prognostic baseline characteristics. In addition, no PFS and OS results were provided for Study C1071009.

Besides the inherent limitations of cross-study comparisons of studies, and despite differences across the studies, the extent of similarity between studies C1071001 and C1071009 and registration study C1071003 was considered sufficient overall to accept these studies as supportive evidence for the proposed indication.

- Other relevant efficacy data

Study C1071005 (MagnetisMM-5) is an ongoing randomised, controlled Phase 3 study intended to support subsequent conversion from temporary to regular approval, as has been requested with the present application. The study started in October 2021 and at the time temporary authorisation was granted was scheduled to complete by the end of 2025. The objective is to compare the efficacy of elranatamab monotherapy and elranatamab + daratumumab vs. daratumumab + pomalidomide + dexamethasone (DPd), as measured by BICR-assessed PFS (primary endpoint) and OS (key

secondary endpoint) in patients with measurable RRMM by IMWG criteria who have received 1 to 3 prior lines of anti-MM therapy.

6.4 Safety

In the 6 clinical studies that provided safety data for this application, a total of 372 patients with RRMM had been exposed to at least 1 dose of elranatamab. Pooled safety data were presented for 265 of these patients, who had been assigned to receive a therapeutic dose of 1000 µg/kg or fixed dose equivalent of 76 mg, including all 187 patients from registration study C1071003.

As of DCO January 2023, the median duration of treatment in the safety pool was 4.8 months (0.03 to 30.4), 5.6 months in Cohort A (0.03 to 23.0) and 2.8 months in Cohort B (0.03 to 14.8).

All patients in the safety pool experienced at least 1 treatment-emergent AE (TEAE), and these were judged to be drug-related in more than 90% of patients. The most frequently reported all-cause, all-grade TEAEs (≥ 20%) were CRS, anaemia, neutropenia, fatigue / asthenia, injection site reaction, diarrhoea, pneumonia, upper respiratory tract infection, thrombocytopenia, decreased appetite, lymphopenia, pyrexia, arthralgia, rash, nausea, hypokalaemia, and dry skin.

Grade 3/4 TEAEs were observed in more than 90% of patients in the safety pool, and were judged to be drug-related in approximately 70%. The most frequently reported all-cause, grade 3/4 TEAEs (≥ 5%) were cytopenia, infections (mainly pneumonia, including COVID-19 pneumonia), hypokalaemia, hypophosphatemia, and increased transaminases.

Serious TEAEs were reported in approximately 73% of patients in the safety pool, and were judged to be drug-related in almost 40%. The most frequently reported all-cause, serious TEAEs were infections (mainly pneumonia, including COVID-19 pneumonia).

Overall mortality was 42%, and the majority of deaths (28%) occurred within 90 days of the last elranatamab dose. Approximately 3% died within the first month of treatment. Of the 112 deaths, the majority – approximately 65% (73/112) – were primarily due to the disease under study (28% of all pooled patients).

Grade 5 (fatal) TEAEs occurred in approximately 20% of patients in the safety pool, and were judged to be drug-related in 3-4% of patients across safety pools. The fatal events most commonly reported as grade 5 TEAEs were related to the underlying disease in approximately 10% of all pooled patients and represented almost half of all fatal TEAEs. These were coded under different system organ classes (SOCs) and preferred terms (PTs), such as disease progression and plasma cell myeloma (refractory) in 6% and 3% of cases respectively. Besides the fatal TEAEs related to the underlying disease, fatal infections were the most prevalent grade 5 TEAEs in approximately 7% of patients, with sepsis, COVID-19, and adenovirus infection being the most common infections leading to death in 2 or more patients. In total, there were 3 patients with fatal adenoviral infections related to the liver. Other reported grade 5 TEAEs were unspecific and/or reported in single instances only.

TEAEs leading to discontinuation of the study drug were observed in almost 20% of patients in the safety pool. Overall, approximately 75% of patients experienced AE leading to any dose modifications, with infections and cytopenias, mainly neutropenia, being the most frequent. Nervous system disorders, namely ICANS (immune effector cell-associated neurotoxicity syndrome) and neuropathy, also played a role in AE leading to treatment discontinuation.

AEs of special interest (AESIs) included CRS, which was reported in 64% of patients in the safety pool, and in 58% of patients who had received pre-medications and step-up dosing per protocol. The majority of the latter had Grade 1 (44%) or Grade 2 (14%) CRS; 1 patient (0.5%) had a Grade 3 CRS, but no CRS events were Grade 4 or Grade 5, while 13% of patients had CRS that was reported as serious. The majority of CRS events occurred after the first (overall 43%; 75% of the patients with CRS) or the second (19%; 33%) step-up dose; 7% (12%) of patients had CRS after the third dose and 1.6% (2.8%) after a later dose. More than 1 CRS event was reported in 13% of patients. Only 1 patient (0.5%) discontinued elranatamab due to CRS, but this patient also had concurrent ICANS. Other CRS-related dose modifications were reported in 5% of patients. The median (range) time to

onset of CRS of any grade relative to the most recent dose of elranatamab was 2 days (1, 9), with maximum time to onset of 4 days and 5 days after first dose and second dose respectively. All CRS events resolved and the median (range) time to resolution was 2 days (1, 19), with maximum time to resolution of 8 days and 19 days after the first and second dose respectively. The most common preferred term associated with CRS was fever (99%), while hypotension occurred in 21% of patients, and 11% had hypoxia.

ICANS was reported in 6% of patients in the safety pool and in 3.3% of patients who had received pre-medications and step-up dosing per protocol. Of the latter 6 patients, 1 (0.5%) had a Grade 1 event, 3 (1.6%) had Grade 2 events and 2 (1.1%) had Grade 3 events, but no ICANS were Grade 4 or 5 according to ASTCT criteria (2019), while 2 (1.1%) patients had ICANS that were reported as serious. The majority of ICANS events occurred after the first (5 of the 6 patients with ICANS) step-up dose. Only single occurrences were reported after later doses. All 6 patients with ICANS had concurrent CRS (concurrent with the first ICANS event in the 2 patients with more than 1 event). Three of 6 patients with ICANS underwent dose modifications, with both patients who had Grade 3 severity permanently discontinuing elranatamab treatment due to ICANS. The median (range) time to ICANS onset relative to the most recent dose of elranatamab was 3 days (1, 4). All ICANS events resolved, and the median (range) time to resolution was 2 days (1,18). Clinical manifestations of ICANS included changes in consciousness level in 5 of 6 patients (2 awakened only to tactile stimulus, 2 to voice and 1 spontaneously), and an ICE (immune effector cell-associated encephalopathy) score below 10 (no impairment) in 4 of 6 patients. No patient had seizures, motor findings or elevated intracranial pressure/cerebral oedema.

According to protocol, patients had to be hospitalised and monitored for CRS/ICANS for at least 2 days (approx. 48 hours) beginning on C1D1, and for 1 day (approx. 24 hours) for C1D4. There was also the option of hospitalising patients for up to 5 days between C1D1 and C1D5 inclusive. However, almost all patients were hospitalised continuously for both step-up doses, and the actual median duration of hospitalisation of 7 days was longer than the recommended maximum of 5 days. Similarly, even for the limited numbers of patients who were not hospitalised continuously, the actual median duration of hospitalisation was longer than recommended, i.e. 4 days actual vs. 2 days recommended for the first priming dose, and 2 days vs. 1 day for the second priming dose. This indicates that continuous hospitalisation was considered to be necessary in most patients, while the evidence for shorter inpatient or even outpatient safety monitoring is limited. In addition, it is anticipated that the real-world population treated with elranatamab following approval will be older and less healthy than the eligibility-restricted study population, which could lead to higher incidences and severity of CRS and/or ICANS, in particular if medical intervention is delayed. For instance, ICANS was more frequent in patients ≥65 years or with impaired renal or hepatic function. Clinical Assessment therefore requested hospitalisation and safety monitoring of a duration that adequately reflects the evidence provided, the onset dynamics of CRS and ICANS, and the fact that the real-world population is expected to be at greater risk.

Overall, nervous system disorders were observed in 54% of patients in the safety pool and in the majority of patients with Grade 1 or 2 events, while 7.9% exhibited neurotoxicity of Grade 3 or higher. A dedicated evaluation of peripheral neuropathy showed that 22% of patients suffered from this form of neurotoxicity. In addition to the 1 case of Grade 3 Guillain-Barré syndrome (GBS) reported in the registration study, a second case of GBS occurred in clinical studies of elranatamab. In response to a pertinent IR, the applicant provided information on 2 additional events of possible GBS that had been reported to the applicant's safety database as of 1 March 2023.

Opportunistic infections were reported in 12.8% of patients in the safety pool, with cytomegalovirus infection reactivation (5.7%) and pneumocystis jirovecii pneumonia being the most common (3.8%). Opportunistic infections of Grade 3 or higher occurred in 5.3% of patients, a comparable proportion of which were serious. 2 of the total 3 fatal hepatic adenoviral infections (see below) were reported as opportunistic as of January 2023. In addition, 1 case of progressive multifocal leukoencephalopathy (PML) for which there is at least a reasonable possibility of a link to elranatamab by virtue of its mode of action was reported across the elranatamab development programme. When interpreting the incidence of opportunistic infections, it is important to consider that these occurred despite a

considerable proportion of patients exposed to elranatamab having received prophylactic therapies. For instance, in registration study C1071003, the majority of patients received prophylactic therapies, including anti-viral (87%), anti-pneumocystis jirovecii pneumonia (48%), anti-fungal (9%), and anti-bacterial (5%) agents.

Hepatotoxicity is a risk associated with elranatamab, and appears to be secondary to immunological reactions such as CRS and/or infections, including reactivation of latent (viral) infections. Fatal outcomes have been reported for hepatic adenoviral infections (see above). Approximately 18% of patients exposed to elranatamab had increased transaminases, with approximately 7% of patients experiencing Grade 3/4 increases. Seven (2.7%) patients in the safety pool met the criteria of Hy's law (ALT or AST ≥ 3x ULN and total bilirubin ≥2x ULN). In response to a pertinent IR the applicant pointed out that 6 of the 7 patients had alternative aetiologies for the LFT increases. The patient without a clear alternative etiology experienced a full recovery after a short course of corticosteroids and continued treatment without reoccurrence.

Of the 240 anti-drug antibody (ADA) patients who were evaluable for immunogenicity, 20 patients (8.3%) developed an ADA response following administration of elranatamab, including 10 patients (4.2%) with neutralising ADA (NAb). The median onset for ADA and NAb was 57 and 53 days, respectively. ADA and NAb-positivity appeared be transient and median titre over time generally low. ADA had no statistically significant or clinically relevant impact on the pharmacokinetics of elranatamab. Taken together, and given the low incidence, low titres, transient nature, and minimal impact on elranatamab exposures, the applicant's conclusion that ADA are not expected to have a clinically relevant effect on elranatamab safety or efficacy was accepted.

6.5 Final clinical benefit risk assessment

In the present application, the applicant proposed elranatamab for the treatment of patients with TCRMM and applied for a temporary approval, fulfilment of the prerequisites for which had been confirmed with the approval of the temporary authorisation pathway in September 2022. Historically this patient population has a poor prognosis, as reflected in an ORR of approximately 30%, median PFS of approximately 3 to 6 months, and median OS of approximately 6 to 12 months.

Beneficial effects and respective uncertainties

In heavily pre-treated TCRMM (median of 5 lines of prior therapy) without prior anti-BCMA therapy (CAR T-cell or antibody-drug conjugate), elranatamab achieved an ORR of almost 60%. Compared with historical results for this patient population (excluding anti-BCMA CAR T-cell and bispecific antibody therapy), ORR was approximately doubled. Even in patients with RRMM who had additionally received prior anti-BCMA therapy including CAR T-cells (median of 7.5 lines of prior therapy), a population for whom almost no alternative therapies exist, elranatamab still achieved ORR of 30%. ORR results were supported by 2 supportive studies in RRMM.

Whereas PFS and OS results are promising, time-to-event endpoints were still immature due to short durations of treatment and follow-up, while the primary endpoint ORR is not considered an established surrogate parameter for OS (Kumar and Rajkumar 2019).

Moreover, the absence of comparator data is a relevant weakness of the submitted clinical study data, including registration study C1071003, and a major uncertainty in the interpretation of the efficacy and safety of elranatamab, in particular for the initial application of a new molecular entity.

Elranatamab bioavailability after SC injection was in the usual range for therapeutic antibodies. However, the impact of the injection site on elranatamab absorption was not formally investigated. Some elranatamab serum concentrations after injection into the thigh were available and not substantially different from the concentrations after injection into the abdomen though.
Total and free elranatamab exposures increased in approximate proportion to dose after SC doses of between 80 µg/kg to 1000 µg/kg or 6 mg to 76 mg – i.e., target saturation was reached in the

therapeutic dose range. Volume of distribution and clearance were in the expected range for therapeutic antibodies.
Elranatamab had no effect on heart rate and QTcF at therapeutic and supra-therapeutic exposures.
There was a statistically significant relationship between total and free elranatamab exposures, where the probability of achieving OR with free exposures was the better predictor. For patients with low baseline sBCMA levels, a maintenance dose of 44 mg QW might be sufficient.
There was no statistically significant relationship between elranatamab exposures and the probability to experiencing peripheral neuropathy, neutropenia, and infections.

Unfavourable effects and respective uncertainties

The most relevant risks associated with elranatamab therapy are infections (including fatal infections), CRS, cytopenia, and neurotoxicity. All these AEs were observed in substantial proportions of patients treated with elranatamab. Nevertheless, the safety profile was as expected for this mode of action, and is manageable by suitable medical institutions. Pertinent safety-related information and recommendations in the information for healthcare professionals, including duration of hospitalisation and safety monitoring, will support the safe use of the elranatamab following marketing authorisation.

The lack of any comparator data in the safety pool was a major uncertainty that hampered the interpretation of safety data, especially as the underlying disease might have affected AEs such as cytopenia and infections. The limited duration of exposure and follow-up further reduced the interpretability of the safety results. In addition, the safety database for this new molecular entity is small; 372 patients with RRMM were exposed to at least 1 dose of elranatamab, of whom only 265 patients received dosages in the therapeutic range (i.e., 1000 µg/kg or fixed dose of 76 mg).

Elranatamab causes a temporary cytokine release, which may lead to pharmacokinetic interactions due to the modulation of CYP activity. No *in vitro* or clinical data are available to quantify the possible effect of elranatamab on sensitive CYP substrates, but the issue is addressed in the information for healthcare professionals.
There was a statistically significant relationship between elranatamab exposures, particularly between free concentrations and the probability to experiencing CRS. An additional risk factor was low baseline sBCMA concentrations, indicating that a maintenance dose of 76 mg QW might be too high for these patients.

Taken together, while the basis of evidence has limitations, it has been found to be sufficient to grant the requested temporary authorisation considering the promising efficacy results and manageable safety profile. However, temporary authorization has been made contingent on an adequate description of the safety profile in the information for healthcare professionals (including safety monitoring requirements), and the modification of the proposed indication. The latter did not reflect the eligibility of Study C1071003, which did not specify a minimum number of prior lines of therapy (LOT), but restricted the target population to patients with TCRMM. The proposed indication deviated from this eligibility in that the applicant requested an indication for “at least 3 prior therapies” without considering that patients had to have triple-class refractory disease.

In addition, final/updated efficacy and safety results from registration study C1071003 and the 2 supporting studies C1071001 and C1071009, as well as meaningful efficacy and safety results from the ongoing Phase 3 randomised, controlled Study C1071005 need to be submitted to obtain conversion into a regular authorisation. Results from confirmatory Study C1071005 will allow for a comparative assessment of the efficacy and in particular the safety of elranatamab-based therapy (as monotherapy and combined with daratumumab) versus the standard DPd (daratumumab + pomalidomide + dexamethasone) triplet therapy for RRMM. Although the indication targeted by Study C1071005 (patients with RRMM who have previously received 1 to 3 prior line(s) of therapy including a PI and lenalidomide) differs from the proposed new indication based on pivotal study C1071003, these study data are considered acceptable as evidence for a conversion.

References

- Kumar S et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. Lancet Oncol 2016; 17: e328-46.
- Kumar S and Rajkumar SV. Surrogate endpoints in randomised controlled trials: a reality check. The Lancet 2019; 394:281-283.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Elrexfio was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the «Undesirable effects» section for advice on the reporting of adverse reactions.

Elrexfio is temporarily authorised – see «Indications/Uses».

Elrexfio®

Composition

Active substances

Elranatamabum (produced using recombinant Chinese Hamster Ovary (CHO) cell lines).

Excipients

L-histidinum, L-histidini hydrochloridum monohydricum, dinatrii edetas dihydricus, polysorbatum 80, saccharum, aqua ad iniectabile.

Sodium content: 0.006 mg per ml.

Pharmaceutical form and active substance quantity per unit

Solution for injection for subcutaneous use.

Elrexfio 44 mg: 1 vial of 1.1 ml contains 44 mg of elranatamab, corresponding to 40 mg/ml.

Elrexfio 76 mg: 1 vial of 1.9 ml contains 76 mg of elranatamab, corresponding to 40 mg/ml.

Clear to slightly opalescent, colourless to pale brownish liquid solution with a pH of 5.8 and osmolarity of approximately 301 mOsm/l.

Indications/Uses

Elrexfio is indicated as monotherapy for the treatment of relapsed or refractory multiple myeloma in adult patients whose multiple myeloma is refractory to at least one immunomodulatory agent, one proteasome inhibitor, and one anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy (see «Clinical efficacy»).

The medicinal product Elrexfio has been granted temporary authorisation as the clinical data was incomplete at the time the authorisation application was assessed (Art. 9a TPA). The temporary

authorisation is contingent on the timely fulfilment of conditions. After they have been met, the temporary authorisation can be transformed into an ordinary authorisation.

Dosage/Administration

Treatment with Elrexfio should be initiated and supervised by physicians experienced in the treatment of multiple myeloma as well as of cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS).

Elrexfio should be administered by a healthcare provider with adequately trained medical personnel and appropriate medical equipment to manage severe undesirable effects, including CRS and ICANS (see «Warnings and precautions»).

To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

Pre-medication

The following pre-treatment medicinal products should be administered approximately 1 hour prior to the first three doses of Elrexfio in the dosing schedule, which includes titration dose 1, titration dose 2, and the first full treatment dose as described in Table 1 to reduce the risk of CRS (see «Warnings and precautions»):

- paracetamol 500 mg orally (or equivalent)
- dexamethasone 20 mg orally or intravenously (or equivalent)
- diphenhydramine 25 mg orally (or equivalent)

Usual dosage

The recommended doses of Elrexfio subcutaneous (s.c.) injection are titration doses of 12 mg on Day 1 and 32 mg on Day 4 followed by a full treatment dose of 76 mg weekly, from week 2 to week 24, see recommended dosing schedule in Table 1.

For patients who have received at least 24 weeks of treatment with Elrexfio and have achieved a response [partial response (PR) or better] and maintained this response for at least 2 months, the dosing interval should transition to an every-two-week schedule.

Treatment with Elrexfio should be continued until disease progression or unacceptable toxicity.

Elrexfio should be administered subcutaneously according to the titration dosing schedule in Table 1 to reduce the incidence and severity of CRS and ICANS. Due to the risk of CRS and ICANS, patients

should be monitored after administration of each of the titration doses according to the Elrexfio dosing schedule according to the instructions in the following section «Monitoring» (see also «Warnings and precautions»).

Table 1 – Elrexfio dosing schedule

Dosing schedule	*Week/day*	*Dose (s.c.)*	
Titration doses[a,b]	Week 1: Day 1	Titration dose 1	12 mg
	Week 1: Day 4	Titration dose 2	32 mg
Weekly dosing[a,c,d]	Week 2-24: Day 1	Full treatment dose	76 mg once weekly
Every 2 weeks dosing[d,e]	Week 25 onward: Day 1	Full treatment dose	76 mg once every two weeks

Abbreviations: s.c.=subcutaneous
a. Pre-treatment medicinal products should be administered prior to the first three doses of Elrexfio.
b. A minimum of 2 days should be maintained between titration dose 1 (12 mg) and titration dose 2 (32 mg).
c. A minimum of 3 days should be maintained between titration dose 2 (32 mg) and the first full treatment (76 mg) dose.
d. A minimum of 6 days should be maintained between doses.
e. For patients who have achieved a response [partial response (PR) or better] and maintained this response for at least 2 months].
Note: See Table 2 for recommendations on restarting Elrexfio after dose delays.

Monitoring

After Elrexfio titration doses 1 and 2, inpatient monitoring should be carried out for at least 48 hours in appropriately equipped centres with multidisciplinary teams with sufficient experience to treat even the most severe complications in intensive care. In addition, patients should be monitored daily for signs and symptoms of CRS, as well as neurological and other toxicities, for up to 7 days after administration of Elrexfio titration doses 1 and 2. In addition, patients should be instructed to stay in the vicinity of a treatment centre during this period. Any further monitoring is at the discretion of the doctor.

Restarting Elrexfio after dose delay

If a dose of Elrexfio is delayed, therapy should be restarted based on the recommendations listed in Table 2, and Elrexfio should be resumed according to the dosing schedule (see Table 1). Pre-treatment medicinal products (see above) should be administered as indicated in Table 2.

Table 2 – Recommendations for restarting therapy with Elrexfio after dose delay

Last administered dose	*Duration of delay from the last administered dose*	*Action for next dose*
Titration dose 1 (12 mg)	≤2 weeks (≤14 days)	Restart Elrexfio at titration dose 2 (32 mg).[a] If tolerated, increase to 76 mg 4 days later.

	>2 weeks (>14 days)	Restart Elrexfio titration dosing schedule at titration dose 1 (12 mg).[a]
Titration dose 2 (32 mg)	≤2 weeks (≤14 days)	Restart Elrexfio at 76 mg
	>2 weeks to ≤4 weeks (>14 days and ≤28 days)	Restart Elrexfio at titration dose 2 (32 mg).[a] If tolerated, increase to 76 mg 1 week later.
	>4 weeks (>28 days)	Restart Elrexfio titration dosing schedule at titration dose 1 (12 mg).[a]
Any full treatment dose (76 mg)	≤6 weeks (≤42 days)	Restart Elrexfio at 76 mg.
	>6 weeks to ≤12 weeks (>42 days ≤84 days)[b]	Restart Elrexfio at titration dose 2 (32 mg).[a] If tolerated, increase to 76 mg 1 week later.
	>12 weeks (>84 days)[b]	Restart Elrexfio titration dosing schedule at titration dose 1 (12 mg).[a]
a. Pre-treatment medicinal products should be administered prior to the Elrexfio dose (see «Pre-medication»). b. Consider benefit-risk of restarting Elrexfio in patients who require a dose delay of more than 42 days due to an adverse reaction.		

Dose adjustment following undesirable effects/interactions

Dose reductions of Elrexfio are not recommended.

Dose delays may be required to manage toxicities related to Elrexfio (see «Warnings and precautions»). Recommendations on restarting Elrexfio after a dose delay are provided in Table 2.

See Tables 3, 4 and 5 for recommended actions for adverse reactions of CRS, ICANS and neurologic toxicity excluding ICANS, respectively, whereby current consensus-based guidelines for treatment should also be considered.

See Table 6 for recommended actions for other adverse reactions following administration of Elrexfio.

Table 3 – Recommendations for management of CRS

Grade[a]	*Presenting symptoms*	*Actions*
Grade 1	Temperature ≥38 °C[b]	• Withhold Elrexfio until CRS resolves.[c]
Grade 2	Temperature ≥38 °C with either: • Hypotension responsive to fluid and not requiring vasopressors, and/or • Oxygen requirement of low-flow nasal cannula[d] or blow-by	• Withhold Elrexfio until CRS resolves.[c] • Monitor patient daily for 48 hours following the next dose of Elrexfio. Instruct patients to remain within proximity of a healthcare facility.
Grade 3 (first occurrence)	Temperature ≥38 °C with either: • Hypotension requiring one vasopressor with or without vasopressin, and/or	• Withhold Elrexfio until CRS resolves.[c] • Provide supportive therapy, which may include intensive care. • Monitor patient daily for 48 hours following the next dose of Elrexfio.

	• Oxygen requirement of high-flow nasal cannula[d], facemask, non-rebreather mask, or Venturi mask	Instruct patients to remain within proximity of a healthcare facility.
Grade 3 (recurrent)	Temperature ≥38 °C with either: • Hypotension requiring one vasopressor with or without vasopressin, and/or • Oxygen requirement of high-flow nasal cannula[d], facemask, non-rebreather mask, or Venturi mask	• Permanently discontinue therapy with Elrexfio. • Provide supportive therapy, which may include intensive care.
Grade 4	Temperature ≥38 °C with either: • Hypotension requiring multiple vasopressors (excluding vasopressin), and/or • Oxygen requirement of positive pressure (e.g., continuous positive airway pressure [CPAP], bilevel positive airway pressure [BiPAP], intubation, and mechanical ventilation)	• Permanently discontinue therapy with Elrexfio. • Provide supportive therapy, which may include intensive care.

a. Based on American Society for Transplantation and Cellular Therapy (ASTCT) 2019 grading for CRS.
b. Attributed to CRS. Fever may not always be present concurrently with hypotension or hypoxia as it may be masked by interventions such as antipyretics or anti-cytokine therapy.
c. See Table 2 for recommendations on restarting Elrexfio after dose delays.
d. Low-flow nasal cannula is ≤6 l/min, and high-flow nasal cannula is >6 l/min.

Table 4 – Recommendations for management of ICANS

Grade[a]	*Presenting symptoms[b]*	*Actions*
Grade 1	ICE score 7-9[c] OR Depressed level of consciousness[d]: awakens spontaneously.	• Withhold Elrexfio until ICANS resolves.[e] • Monitor neurologic symptoms and consider consultation with a neurologist and other specialists for further evaluation and management. • Consider non-sedating, anti-seizure medicinal products for seizure prophylaxis.
Grade 2	ICE score 3-6[c] OR Depressed level of consciousness[d]: awakens to voice.	• Withhold Elrexfio until ICANS resolves.[e] • Administer dexamethasone[f] 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to ≤Grade 1, then taper. • Monitor neurologic symptoms and consider consultation with a neurologist and other specialists for further evaluation and management. • Consider non-sedating, anti-seizure medicinal products for seizure prophylaxis. • Monitor patient daily for 48 hours following the next dose of Elrexfio. Instruct patients to remain within proximity of a healthcare facility.

Grade 3 (first occurrence)	ICE score 0-2[c] OR Depressed level of consciousness[d]: awakens only to tactile stimulus, OR Seizures[d], either: • any clinical seizure, focal or generalised, that resolves rapidly, or • non-convulsive seizures on electroencephalogram (EEG) that resolve with intervention, OR Raised intracranial pressure: focal/local oedema on neuroimaging.[d]	• Withhold Elrexfio until ICANS resolves.[e] • Administer dexamethasone[f] 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to ≤Grade 1, then taper. • Monitor neurologic symptoms and consider consultation with a neurologist and other specialists for further evaluation and management. • Consider non-sedating, anti-seizure medicinal products for seizure prophylaxis. • Provide supportive therapy, which may include intensive care. • Monitor patient daily for 48 hours following the next dose of Elrexfio. Instruct patients to remain within proximity of a healthcare facility.
Grade 3 (recurrent)	ICE score 0-2[c] OR Depressed level of consciousness[d]: awakens only to tactile stimulus, OR Seizures[d], either: • any clinical seizure, focal or generalised, that resolves rapidly, or • non-convulsive seizures on electroencephalogram (EEG) that resolve with intervention, OR Raised intracranial pressure: focal/local oedema on neuroimaging.[d]	• Permanently discontinue Elrexfio. • Administer dexamethasone[f] 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to ≤Grade 1, then taper. • Monitor neurologic symptoms and consider consultation with a neurologist and other specialists for further evaluation and management. • Consider non-sedating, anti-seizure medicinal products for seizure prophylaxis. • Provide supportive therapy, which may include intensive care.
Grade 4	ICE score 0[c] OR Depressed level of consciousness[d] either: • patient is unarousable or requires vigorous or repetitive tactile stimuli to arouse, or • stupor or coma, OR Seizures[d], either:	• Permanently discontinue Elrexfio. • Administer dexamethasone[f] 10 mg intravenously every 6 hours. Continue dexamethasone use until resolution to ≤Grade 1, then taper. • Alternatively, consider administration of methylprednisolone 1’000 mg per day intravenously for 3 days. • Monitor neurologic symptoms and consider consultation with a neurologist and other specialists for further evaluation and management.

	• life-threatening prolonged seizure (>5 minutes), or • repetitive clinical or electrical seizures without return to baseline in between, OR Motor findings[d]: • deep focal motor weakness such as hemiparesis or paraparesis, Or Raised intracranial pressure / cerebral oedema[d], with signs/symptoms such as: • diffuse cerebral oedema on neuroimaging, or • decerebrate or decorticate posturing, or • cranial nerve VI palsy, or • papilloedema, or • Cushing's triad.	• Consider non-sedating, anti-seizure medicinal products for seizure prophylaxis. • Provide supportive therapy, which may include intensive care.

a. Based on American Society for Transplantation and Cellular Therapy (ASTCT) 2019 grading for ICANS.
b. Management is determined by the most severe event, not attributable to any other cause.
c. If patient is arousable and able to perform Immune Effector Cell-Associated Encephalopathy (ICE) Assessment, assess: Orientation (oriented to year, month, city, hospital=4 points); Naming (name 3 objects, e.g., point to clock, pen, button=3 points); Following Commands (e.g., «show me 2 fingers» or «close your eyes and stick out your tongue»=1 point); Writing (ability to write a standard sentence=1 point; and Attention (count backwards from 100 by ten=1 point). If patient is unarousable and unable to perform ICE Assessment (Grade 4 ICANS)=0 points.
d. Not attributable to any other cause.
e. See Table 2 for recommendations on restarting Elrexfio after dose delays.
f. All references to dexamethasone administration are dexamethasone or equivalent medicinal products.

Table 5 – Recommendations for management of Neurologic Toxicity, Excluding ICANS

Undesirable effect	*Severity*	*Actions*
Neurologic Toxicity (excluding ICANS)	*Grade 1*	• Withhold Elrexfio until neurologic toxicity symptoms resolve or stabilize.
	Grade 2 *Grade 3 (first occurrence)*	• Withhold Elrexfio until neurologic toxicity symptoms improve to Grade 1 or less. • Provide supportive therapy.
	Grade 3 (recurrent) *Grade 4*	• Permanently discontinue Elrexfio. • Provide supportive therapy, which may include intensive care.

Table 6 – Recommended dose modifications for other undesirable effects

Undesirable effects	*Severity*	*Actions*

Haematologic (see «Undesirable effects»)	Absolute neutrophil count <1.0 x 10^9/l	• Withhold Elrexfio until absolute neutrophil count is ≥1.0 x 10^9/l.[b]
	Febrile neutropenia	• Withhold Elrexfio until absolute neutrophil count is ≥1 x 10^9/l and fever resolves.[b]
	Haemoglobin <8 g/dl	• Withhold Elrexfio until haemoglobin is ≥8 g/dl.[b]
	Platelet count <25'000/μl Platelet count between 25'000/μl and 50'000/μl with bleeding	• Withhold Elrexfio until platelet count is ≥25'000/μl and no evidence of bleeding.[b]
Non-haematological[a] (see «Undesirable effects»)	Grade 3 or 4	• Withhold Elrexfio until recovery to ≤Grade 1 or baseline.[b] • Permanently discontinue if recovery does not occur.

a. Based on National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 5.0.
b. See Table 2 for recommendations on restarting Elrexfio after dose delays.

Special dosage instructions

Patients with hepatic disorders

No dose adjustments are required for mild hepatic impairment. The effects of moderate to severe hepatic impairment on the pharmacokinetics of elranatamab have not been studied (see «Pharmacokinetics»).

Patients with renal disorders

No dose adjustment is recommended in patients with mild to moderate renal impairment. Elranatamab has not been studied in patients with severe renal impairment (see «Pharmacokinetics»).

Elderly patients

No dose adjustment is necessary (see «Properties/Effects» and «Pharmacokinetics»).

Paediatric population

Elrexfio is not authorised for use in the paediatric population.

Mode of administration

Elrexfio is for subcutaneous injection only.

For instructions on handling of the medicinal product before administration, see «Oher information».

Contraindications

Hypersensitivity to elranatamab or to any of the excipients (see «Composition»).

Warnings and precautions

Cytokine release syndrome (CRS)

CRS, including life-threatening or fatal reactions, may occur in patients receiving Elrexfio. Clinical signs and symptoms of CRS may include, but are not limited to, fever, hypoxia, chills, hypotension, tachycardia, headache, and elevated liver enzymes (see «Undesirable effects – Cytokine release syndrome»).

Therapy should be initiated according to Elrexfio titration dose schedule to reduce risk of CRS (see «Dosage/Administration – Table 1» and patients should be monitored following administration of Elrexfio accordingly (see «Dosage/Administration – Monitoring»). Pre-treatment medicinal products should be administered prior to the first three doses of Elrexfio in the dosing schedule to reduce risk of CRS (see «Dosage/Administration – Pre-medication»). After dose delay consider the recommendations for restarting therapy with Elrexfio (see «Dosage/Administration – Table 2»).Patients should be counselled to seek medical attention should signs or symptoms of CRS occur.

Management of CRS:

CRS should be identified based on clinical presentation. Patients should be evaluated and treated for other causes of fever, hypoxia, and hypotension.

At the first sign of CRS, Elrexfio should be withheld, and patients should be immediately evaluated for hospitalisation. CRS should be managed according to the recommendations in Table 3 (see «Dosage/Administration») and further management should be considered per local institutional guidelines. Supportive therapy for CRS (including but not limited to anti-pyretic agents, intravenous fluid support, vasopressors, supplemental oxygen, etc.) should be administered as appropriate. Laboratory testing to monitor for disseminated intravascular coagulation (DIC), haematology parameters, as well as pulmonary, cardiac, renal, and hepatic function should be considered.

Neurologic toxicities, including ICANS

Serious or life-threatening neurologic toxicities, including ICANS, may occur following treatment with Elrexfio (see «Undesirable effects – Neurologic toxicities, including ICANS»). Patients should be

monitored for signs and symptoms of neurologic toxicities during treatment with Elrexfio (see «Dosage/Administration – Monitoring»). After dose delay consider the recommendations for restarting therapy with Elrexfio (see «Dosage/Administration – Table 2»). Patients should be counselled to seek medical attention should signs or symptoms of neurologic toxicity occur.

Due to the potential for ICANS, patients should be advised not to drive or operate heavy or potentially dangerous machinery during the Elrexfio titration dosing schedule and in the event of onset of any neurological symptoms (see «Dosage/Administration» and «Effects on ability to drive and use machines»).

Management of neurologic toxicities:

At the first sign of neurologic toxicity, including ICANS, Elrexfio should be withheld, and neurology evaluation should take place. Other causes of neurologic symptoms should be ruled out. Patients should be immediately evaluated and treated based on severity. Supportive therapy, which may include intensive care, for severe or life-threatening neurologic toxicities, should be provided. General recommendations for management for neurologic toxicity are summarised in Table 4 and 5 (see «Dosage/Administration»). Patients who experience ≥Grade 2 ICANS with the previous dose of Elrexfio should be instructed to remain within proximity of a healthcare facility and be monitored for signs and symptoms daily for 48 hours following the next dose.

Infections

Severe, life-threatening, or fatal infections have been reported in patients receiving Elrexfio, including opportunistic infections and new or reactivated viral infections (see «Undesirable effects – Infections»).

Fatal hepatotoxicity has been observed in association with hepatic adenovirus infection and a case of hepatitis B virus (HBV) reactivation occurred during therapy with Elrexfio. Due to possible fulminant progression, patients who have been diagnosed with positive HBV serology should be monitored for clinical signs and laboratory values that may be signs of HBV reactivation during treatment with Elrexfio and for at least six months after its cessation.

Treatment with Elrexfio should not be initiated in patients with active infections. Patients should be monitored for signs and symptoms of infection prior to and during treatment with Elrexfio and treated appropriately. Elrexfio should be withheld based on severity as indicated in Table 6 (see «Posology/Administration»). Prophylactic antimicrobials and anti-virals should be administered according to local institutional guidelines. Treatment with subcutaneous or intravenous immunoglobulin (IVIG) should be considered, as appropriate.

Hepatotoxicity

Elrexfio may cause liver enzyme elevations (see «Undesirable effects»). Liver enzyme elevation can occur with or without concurrent CRS. Hepatotoxicity has been observed in association with hepatic adenovirus infection and HBV reactivation (see «Infections»).

Liver enzymes and bilirubin should be monitored at baseline and during treatment as clinically indicated. Elrexfio should be suspended based on severity as indicated in Table 6 (see «Dosage/Administration»). Treatment should be carried out in accordance with the local guidelines of the facility.

Neutropenia

Neutropenia and febrile neutropenia have been reported in patients receiving Elrexfio (see «Undesirable effects»). Complete blood cell counts should be monitored at baseline and periodically during treatment with Elrexfio. Supportive therapy should be provided according to local institutional guidelines. Patients with neutropenia should be monitored for signs of infection. Treatment with Elrexfio should be withheld as indicated in Table 6 (see «Dosage/Administration»).

Hypogammaglobulinaemia

Hypogammaglobulinemia has been reported in patients receiving Elrexfio (see «Undesirable effects»). Immunoglobulin levels should be monitored during treatment with Elrexfio. Subcutaneous or intravenous immunoglobulin (IVIG) therapy should be considered if IgG levels fall below 400 mg/dl and patients should be treated according to local institutional guidelines, including infection precautions and antimicrobial prophylaxis.

Concomitant use of live viral vaccines

The safety of immunisation with live viral vaccines during or following treatment with Elrexfio has not been studied. Vaccination with live virus vaccines is not recommended within the 4 weeks prior to the first dose of Elrexfio and during treatment with Elrexfio.

Patient populations not studied in clinical trials

The following patient groups were excluded from the MagnetisMM-3 study: Patients with ECOG performance status >2; stem cell transplant within 12 weeks prior to enrolment or active GVHD; impaired cardiovascular function (including LVEF <40%) or clinically significant cardiovascular disease, including prolonged QT syndrome; inadequate hepatic function (transaminases >2.5 x ULN,

total bilirubin >2 x ULN); inadequate renal function (estimated creatinine clearance <30 ml/min); inadequate bone marrow function (absolute neutrophil count [ANC] <1.0 x 10^9/l, platelets <25 x 10^9/l, haemoglobin <8 g/dl); history of peripheral sensory or motor neuropathy, including Guillain-Barré syndrome; active infections; live vaccine.

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. it is almost «sodium-free».

Interactions

No interaction studies have been performed with Elrexfio.

The initial release of cytokines associated with the start of Elrexfio treatment may suppress cytochrome P450 (CYP) enzymes. The highest risk of interaction is expected to occur during the titration dosing schedule for Elrexfio and up to 7 days after CRS. During this time period, toxicity or medicinal product concentrations (e.g., cyclosporine) should be monitored in patients who are receiving concomitant sensitive CYP substrates with a narrow therapeutic index. The dose of the concomitant medicinal product should be adjusted as needed.

Pregnancy, lactation

Women of child-bearing potential

The pregnancy status of women of child-bearing potential should be verified prior to initiating treatment with Elrexfio.

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

Pregnancy

There are no human or animal data to assess the risk of elranatamab use during pregnancy. Human immunoglobulin (IgG) is known to cross the placenta after the first trimester of pregnancy. Based on the mechanism of action, elranatamab may cause foetal harm when administered to a pregnant woman; Elrexfio should not be used during pregnancy unless the clinical condition of the woman requires treatment with elranatamab.

Elrexfio is associated with hypogammaglobulinaemia, therefore, assessment of immunoglobulin levels in newborns of mothers treated with Elrexfio should be considered.

Lactation

It is not known whether elranatamab is excreted in human or animal milk, affects breastfed infants or affects milk production. Human IgGs are known to be excreted in breast milk. A risk to the breastfed child cannot be excluded and therefore breast-feeding is not recommended during treatment with Elrexfio and for 4 months after the last dose.

Fertility

There are no data on the effect of elranatamab on human fertility. Effects of elranatamab on male and female fertility have not been evaluated in animal studies.

Effects on ability to drive and use machines

Elrexfio may have a major influence on the ability to drive and use machines.

Due to the potential for ICANS, patients receiving Elrexfio are at risk of depressed level of consciousness and other neurological symptoms (see «Undesirable effects»). Patients should be instructed to refrain from driving or operating heavy or potentially dangerous machinery during the Elrexfio titration dosing schedule and in the event of new onset of neurologic toxicity until resolution of any neurological symptoms (see «Dosage/Administration» and «Warnings and precautions»).

Undesirable effects

Summary of the safety profile

The overall safety profile of Elrexfio is based on pooled data from 265 patients who received Elrexfio as monotherapy, including 183 adult patients with multiple myeloma who received the recommended dosing regimen of Elrexfio in study MagnetisMM-3 (see «Properties/Effects – Clinical efficacy»). The median duration of Elrexfio treatment was 4.8 months (range: 0.03 to 30.42 months).

The most frequent undesirable effect of any grade in patients were CRS (64.2%), anaemia (53.2%), neutropenia (51.7%), fatigue (46.0%), injection site reaction (42.6%), diarrhoea (39.2%), pneumonia (35.1%), upper respiratory tract infection (34.7%), thrombocytopenia (34.0%), decreased appetite (30.2%), lymphopenia (27.9%), pyrexia (27.9%), arthralgia (26.0%), rash (24.5%), nausea (23.4%), hypokalaemia (22.6%), and dry skin (22.3%).

Serious undesirable effects were reported in 72.5% of patients who received Elrexfio, including pneumonia (24.2%), CRS (15.8%), sepsis (12.1%), upper respiratory tract infection (4.2%), anaemia (3.8%), febrile neutropenia (3.4%), pyrexia (3.4%), urinary tract infection (3.0%), acute kidney injury (2.6%), diarrhoea (2.6%), fatigue (2.3%) and hypoxia (2.3%).

List of adverse reactions

The adverse reactions should be arranged according to MedDRA system organ classes and the conventional frequencies as follows: «very common» (≥1/10), «common» (≥1/100, <1/10), «uncommon» (≥1/1'000, <1/100), «rare» (≥1/10,000, <1/1'000), «very rare» (<1/10'000), «not known» (frequency cannot be estimated from the available data).

Infections and infestations

Very common: Pneumonia (35.1% [Grade 3/4: 20.0%]; includes preferred terms [PTs] pneumonia, COVID-19 pneumonia, bronchopulmonary aspergillosis, lower respiratory tract infection, pneumocystis jirovecii pneumonia, pneumonia adenoviral, pneumonia bacterial, pneumonia cytomegaloviral, pneumonia fungal, pneumonia influenzal, pneumonia pseudomonal, pneumonia viral, atypical pneumonia, coronavirus pneumonia, pneumonia haemophilus, pneumonia respiratory syncytial viral, lower respiratory tract infection viral), sepsis (13.6% [Grade 3/4: 9.4%]; includes PTs sepsis, bacteraemia, device related bacteraemia, device related sepsis, escherichia bacteraemia, escherichia sepsis, klebsiella sepsis, pseudomonal sepsis, septic shock, staphylococcal bacteraemia, staphylococcal sepsis, streptococcal sepsis, urosepsis), upper respiratory tract infection (34.7% [Grade 3/4: 4.5%]; includes PTs upper respiratory tract infection, sinusitis, acute sinusitis, pharyngitis, rhinitis, rhinovirus infection, viral upper respiratory tract infection, bronchitis viral, chronic sinusitis, nasopharyngitis, sinusitis bacterial, bronchitis, respiratory tract infection viral, bronchitis bacterial, respiratory tract infection), urinary tract infection (11.7% [Grade 3/4: 4.2%]; includes PTs urinary tract infection, cystitis, urinary tract infection bacterial, escherichia urinary tract infection, urinary tract infection enterococcal).

Uncommon: Progressive multifocal leukoencephalopathy.

Blood and lymphatic system disorders

Very common: Neutropenia (51.7% [Grade 3/4: 49.8%]; includes PTs neutropenia, neutrophil count decreased, neutrophil percentage decreased, cyclic neutropenia, agranulocytosis, granulocytopenia, granulocyte count decreased), anaemia (53.2% [Grade 3/4: 41.5%]; includes PTs anaemia, haemoglobin decreased, red blood cell count decreased, haematocrit decreased, normochromic

anaemia, normocytic anaemia, normochromic normocytic anaemia, aplasia pure red cell), thrombocytopenia (34.0% [Grade 3/4: 24.9%]; includes PTs thrombocytopenia, platelet count decreased), lymphopenia (27.9% [Grade 3/4: 26.0%]; includes PTs lymphopenia, lymphocyte count decreased, lymphocyte percentage decreased, CD4 lymphocytes decreased, CD4 lymphocyte percentage decreased, CD8 lymphocytes decreased, CD8 lymphocyte percentage decreased), leukopenia (19.2% [Grade 3/4: 14.0%]; includes PTs leukopenia, white blood cell count decreased).

Common: Febrile neutropenia.

Immune system disorders

Very common: Cytokine release syndrome (CSR) (64.2% [Grade 3/4: 0.8%]), hypogammaglobulinaemia (17.7% [Grade 3/4: 2.6%]; includes participants with blood immunoglobulin G decreased, hypogammaglobulinaemia, and immunoglobulins decreased).

Metabolism and nutrition disorders

Very common: Decreased appetite (30.2% [Grade 3/4: 1.1%]), hypokalaemia (22.6% [Grade 3/4: 9.8%]), hypomagnesaemia (12.5% [Grade 3/4: 0%)]), hypophosphataemia (11.3% [Grade 3/4: 4.5%]), hyponatraemia (10.6% [Grad 3/4: 2.6%]).

Nervous system disorders

Very common: Headache (21.1% [Grade 3/4: 0.4%]), encephalopathy (13.6%, [Grade 3/4: 2.3%]; includes PTs agitation, confusional state, delirium, depressed level of consciousness, disorientation, hallucination, lethargy, memory impairment, mental status changes, somnolence), motor dysfunction (13.6%, [Grade 3/4: 0.4%]; includes PTs dysphonia, gait disturbance, motor dysfunction, muscle spasms, muscular weakness, peroneal nerve palsy, tremor, VIth nerve paralysis).

Common: Immune effector cell-associated neurotoxicity syndrome (ICANS), sensory neuropathy (includes PTs neuralgia, peripheral sensory neuropathy, sciatica).

Uncommon: Guillain-Barré syndrome.

Respiratory, thoracic and mediastinal disorders

Very common: Dyspnoea (18.1%, [Grade 3/4: 4.2%]; includes PTs dyspnoea, dyspnoea exertional, respiratory distress).

Gastrointestinal disorders

Very common: Diarrhoea (39.2% [Grade 3/4: 2.6%]), nausea (23.4% [Grade 3/4: 1.1%]).

Hepatobiliary disorders

Very common: Transaminases increased (18.1% [Grade 3/4: 6.8%]; includes PTs alanine aminotransferase increased, aspartate aminotransferase increased).

Renal and urinary disorders

Common: Acute kidney injury, blood creatine increased.

Uncommon: Creatinine renal clearance decreased.

Skin and subcutaneous tissue disorders

Very common: Rash (24.5% [Grade 3/4: 0.8%]; includes PTs dermatitis exfoliative, dermatitis exfoliative generalised, erythema, palmar-plantar erythrodysaesthesia syndrome, rash, rash erythematous, rash macular, rash maculo-papular, rash pustular, rash follicular, rash pruritic, symmetrical drug-related intertriginous and flexural exanthema, epidermolysis), dry skin (22.3% [Grade 3/4: 0%]; includes PTs dry skin, skin exfoliation).

Musculoskeletal and connective tissue disorders

Very common: Arthralgia (26.0% [Grade 3/4: 1.5%]; includes PTs arthralgia, pain in extremity).

General disorders and administration site conditions

Very common: Injection site reaction (42.6% [Grade 3/4: 0.4%]; includes PTs injection site reaction, injection site erythema, injection site pruritus, injection site rash, injection site induration, injection site pain, injection site urticaria, injection site dryness, injection site haemorrhage, injection site inflammation), pyrexia (27.9% [Grade 3/4: 2.6%]), fatigue (46.0% [Grade 3/4: 6.4%]; includes PTs fatigue, asthenia, malaise).

Description of specific adverse reactions and additional information

Cytokine release syndrome (CRS)

CRS occurred in 64.2% of patients (N=265) following treatment with Elrexfio. CRS occurred in 57.9% of patients who received Elrexfio at the recommended dosing schedule using the 2 titration doses (see «Dosage/Administration»), with Grade 1 CRS in 43.7% of patients, Grade 2 CRS in 13.7% of patients and Grade 3 CRS in 0.5% of patients. Most patients experienced CRS after the first titration dose (43.2%) or the second titration dose (19.1%), with 7.1% of patients having CRS after the first full treatment dose and 1.6% of patients after a subsequent dose. Recurrent CRS occurred in 13.1% of patients. The median time to onset of CRS was 2 days (range: 1 to 9 days) after the most recent dose, with a median duration of 2 days (range: 1 to 19 days).

Among patients who developed CRS, associated symptoms included fever (99.0%), hypoxia (11.4%), and hypotension (21.0%).

Neurological toxicities, including Immune effector cell-associated neurotoxicity syndrome (ICANS)

Neurological toxicities occurred in 54.0% of patients treated with Elrexfio at the recommended dosing regimen. The majority of neurological toxicity events were of Grade 1 or 2, with 7.9% of events being Grade 3 or higher. The most frequently reported neurological toxicities were headache (21.1%), encephalopathy (13.6%), motor dysfunction (13.6%) and sensory neuropathy (7.5%). In clinical trials, cases of Guillain-Barré syndrome have been reported in association with treatment with Elrexfio.

ICANS occurred in 6.0% of patients (N=265) following treatment with Elrexfio. ICANS occurred in 3.3% of patients following treatment with Elrexfio at the recommended dosing schedule (see «Dosage/Administration»). The majority of patients had ICANS after the first titration dose (2.7%), 1 patient (0.5%) had ICANS after the second titration dose and 1 patient (0.5%) had ICANS after a subsequent dose. Recurrent ICANS occurred in 1.1% of patients. The median time to onset was 3 days (range: 1 to 4 days) after the most recent dose with a median duration of 2 days (range: 1 to 18 days).

The onset of ICANS can be concurrent with CRS, following resolution of CRS, or in the absence of CRS. The most frequent symptoms of ICANS included a depressed level of consciousness and Grade 1 or Grade 2 Immune Effector Cell-Associated Encephalopathy (ICE) scores.

Infections

Opportunistic infections occurred in 12.8% of patients treated with Elrexfio, with 5.3% of infections being Grade 3 or higher. The most common opportunistic infections were reactivation of cytomegalovirus infection (5.7%) and pneumocystis jirovecii pneumonia (3.8%). Other new or reactivated viral infections that occurred with Elrexfio were adenovirus (1.1%) and hepatitis B virus (HBV, 0.4%).

Three fatal cases of adenovirus infection leading to death in the 3 affected patients under the clinical picture of acute hepatitis and liver failure, respectively, were reported.

In the MagnetisMM-3 study, one case of progressive multifocal leukoencephalopathy (PML) was observed.

COVID-19 events occurred in 21.9% of patients (Grade 3/4: 10.2%, Grade 5: 2.3%), COVID-19 pneumonia occurred in 10.2% of patients (Grade 3/4: 7.5%, Grade 5: 1.5%), with fatal outcome reported in 2.2% of patients.

Immunogenicity

During treatment in the pooled safety data (up to 24 months), 20 out of 240 participants (8.3%) evaluable for immunogenicity treated with Elrexfio at the recommended dose developed anti-elranatamab antibodies (ADAs). Among the 20 participants who tested positive for ADAs, 50% (10/20) tested positive for neutralising antibodies against elranatamab. There was no identified clinically significant effect of ADAs on pharmacokinetics, safety, or effectiveness of elranatamab.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

No participant reported an elranatamab overdose in the clinical trial program and the maximum tolerated dose has not been determined. In clinical studies, the doses up to 76 mg once weekly have been administered.

Treatment

In the event of an overdose, the patient should be monitored for any signs or symptoms of adverse reactions and appropriate supportive treatment should be instituted immediately.

Properties/Effects

ATC code

L01F

Mechanism of action

Elrexfio is a bispecific B-cell maturation antigen (BCMA)-directed T-cell engaging antibody that binds on plasma cells, plasmablasts and multiple myeloma cells and CD3-epsilon on T-cells leading to selective cytolysis of the BCMA-expressing cells. The anticancer activity of Elrexfio involves selective therapeutic targeting and activation of T-cells re-directed against BCMA-expressing malignant plasma cells. Elrexfio activated T-cells, caused proinflammatory cytokine release, and resulted in multiple myeloma cell lysis.

Pharmacodynamics

Exposure-response relationships

Serum concentrations of cytokines (IL-2, IL-6, IL-8, IL-10, TNF-α, and IFN-γ) were measured before and after administration of titration dose 1, titration dose 2, and the first three full treatment doses of Elrexfio. Time of the maximum cytokine concentration generally occurred during the titration dosing and concentrations continue to decrease over the course of the first month of treatment.

Clinical efficacy

Relapsed or refractory multiple myeloma (MagnetisMM-3)

The efficacy of Elrexfio monotherapy was evaluated in patients with relapsed or refractory multiple myeloma in an open-label, non-randomised, multi-centre, Phase 2 study (MagnetisMM-3). The study included patients who were refractory to at least one proteasome inhibitor (PI), one immunomodulatory agent (IMiD), and one anti-CD38 monoclonal antibody. The study included 123 patients naïve to prior BCMA-directed therapy (pivotal Cohort A) and 64 patients with prior BCMA-directed antibody-drug conjugate (ADC) or chimeric antigen receptor (CAR) T-cell therapy (supportive Cohort B). Patients had measurable disease by International Myeloma Working Group (IMWG) criteria at enrolment. The study included patients with an ECOG score of ≤2, adequate baseline bone marrow (absolute neutrophil count ≥1.0x 10^9/l, platelet count ≥25x 10^9/l, haemoglobin level ≥8 g/dl), renal (CrCL ≥30 ml/min), and hepatic (AST and ALT ≤2.5 x ULN, total bilirubin ≤2 x ULN) function, and left ventricular ejection fraction ≥40%. Patients with a stem cell transplant within 12 weeks prior to enrolment and active infections were excluded from the study.

Eligible patients received subcutaneous administration of Elrexfio at titration doses of 12 mg on Day 1 and 32 mg on Day 4 of treatment, followed by the first full treatment dose of Elrexfio (76 mg) on Day 8 of treatment. Thereafter, patients received 76 mg once weekly. After 24 weeks, in patients who achieved an IMWG response category of partial response (PR) or better with responses persisting for

at least 2 months, the dosing interval was changed from every week to every 2 weeks (see «Dosage/Administration»).

Among the 123 patients treated in Cohort A, the median age was 68 years (range: 36 to 89) with 19.5% of patients ≥75 years of age. 44.7% were female; 58.5% were White, 13.0% were Asian, 8.9% were Hispanic/Latino, and 7.3% were Black. Disease stage (R-ISS) at study entry was 22.8% in Stage I, 55.3% in Stage II and 15.4% in Stage III. The median time since initial diagnosis of multiple myeloma to enrolment was 72.9 months (range: 16 to 228). Patients had received a median of 5 prior lines of therapy (range: 2 to 22) with 96.0% who received ≥3 prior lines of therapy. 96.7% were triple-class refractory and 95.9% refractory to their last line of therapy. 68.3% received prior autologous stem cell transplantation, and 5.7% received prior allogenic stem cell transplantation. High-risk cytogenetics [t(4;14), t(14;16), or del(17p)] were present in 25.2% of patients. 31.7% of patients had extramedullary disease (presence of any plasmacytoma [extramedullary and/or paramedullary] with a soft-tissue component) at baseline by Blinded Independent Central Review (BICR).

Efficacy results were based on response rate (ORR) as assessed by BICR based on the IMWG criteria. The predefined analysis of Cohort A was based on the initial 94 patients dosed at least 4 months prior to the data cutoff. These efficacy results from Cohort A are shown in Table 7. Patients with extramedullary disease showed lower response rates.

At an updated data cutoff date, the results of the time-dependent endpoints in the 123 patients of Cohort A were as follows (median duration of treatment 5.6 months [range: 0.03, 25.7 months]): The median time to first response (TTR) was 1.2 months (range: 0.9, 7.4 months). The duration of response (DOR) was immature after a median follow-up for DOR of 15.2 months from first response (range: 2.4, 24.1 months). The estimated median progression-free survival (PFS) was not reached after a median follow-up for PFS of 9.3 months (range: 0.03, 25.8 months) (95% CI: 9.8, NE) and the rate at 15 months was 50.2% (95% CI: 40.2, 59.3). Overall survival (OS) was immature after a total follow-up of 15.9 months (range: 0.2, 26.2 months) and the median was not yet estimable (95% CI: 13.4, NE), the rate at 15 months was 56.3% (95% CI: 47.0, 64.6).

Table 7 – Efficacy results for MagnetisMM-3 in Cohort A

	BCMA-directed therapy naïve patients (Cohort A)
	All treated (N=94)
Objective Response Rate (ORR: sCR+CR+VGPR+PR), n (%) (95% CI)	54 (57.4%) (46.8, 67.6)
Stringent complete response (sCR)	5 (5.3%)
Complete response (CR)	6 (6.4%)
Very good partial response (VGPR)	28 (29.8%)
Partial response (PR)	15 (16.0%)
Complete Response Rate (sCR+CR), n (%)	11 (11.7%)

(95% CI)	(6.0, 20.0)

Among the 64 patients treated in Cohort B (BCMA-exposed patients: BCMA-directed ADC and/or CAR T-cell therapy), the median age was 67 years (range: 41 to 84 years) with 18.8% of patients ≥75 years of age. 53.1% were female; 68.8% were White, 10.9% were Hispanic/Latino; 3.1% were Black and 1.6% were Asian. Disease stage (R-ISS) at study entry was 17.2% in Stage I, 56.3% in Stage II and 23.4% in Stage III. The median time since initial diagnosis of multiple myeloma to enrolment was 102.6 months (range: 23 to 219 months). Patients had received a median of 7.5 prior lines of therapy (range: 3 to 19); 96.9% were triple-class refractory and 51.6% were penta-drug refractory (refractory to at least 2 PIs, 2 IMiDs, and 1 anti-CD38 antibody); 87.5% were refractory to their last line of therapy. 71.9% and 32.8% received prior ADC and CAR T-cell therapy, respectively. 82.8% received prior autologous stem cell transplantation, and 3.1% received prior allogenic stem cell transplantation. High-risk cytogenetics [t(4;14), t(14;16),or del(17p)] were present in 20.3% of patients. 57.8% of patients had extramedullary disease at baseline by BICR.

Efficacy results in Cohort B (N=64) based on a data cutoff approximately 5 months after the last patient initial dose include confirmed ORR by BICR of 29.7% (95% CI: 18.9, 42.4); 4.7% of patients achieved CR or better, and 25.0% achieved VGPR or better. Patients with extramedullary disease showed lower response rates.

At an updated data cutoff date, the results of the time-dependent endpoints in the 64 patients of Cohort B were as follows (median duration of treatment 2.8 months [range: 0.03, 17.1 months]). The median TTR was 1.9 months (range: 0.9, 6.7 months). DOR was immature after a median follow-up of 13.4 months from first response (range: 2.4, 17.0 months). The estimated median PFS was 3.5 months (95% CI: 1.9, 6.6) after a median follow-up for PFS of 2.6 months (range: 0.03, 17.8 months). The estimated median OS was 11.3 months (95% CI: 6.5, NE) after a total follow-up of 9.9 months (range: 0.3, 18.4 months).

Pharmacokinetics

The average C_{max} and AUC_{tau} of elranatamab after the first subcutaneous dose increased in a dose proportional manner over the evaluated dose range via SC administration (~ 6 to 76 mg). The median accumulation ratio after 24 weeks of weekly dosing relative to the first subcutaneous dose of elranatamab 76 mg for C_{max} and AUC_{tau} was 6.6-fold and 11.2-fold, respectively. The C_{max}, C_{trough}, and AUC_{tau} of elranatamab are presented in Table 8.

Table 8 – Pharmacokinetic parameters of elranatamab at the end of the weekly dosing (week 24) following the recommended dosage

Pharmacokinetic parameter	*Geometric mean (CV%)*
C_{max} (mcg/ml)	33.6 (48%)
C_{trough} (mcg/ml)	31.2 (50%)
AUC_{tau} (mcg*d/ml)	229 (49%)

Absorption

The mean bioavailability of elranatamab was 56.2% when administered subcutaneously. The median T_{max} after elranatamab s.c. administration across all dose levels ranged from 3 to 7 days.

Distribution

The mean (coefficient of variation [CV]%) central volume of distribution of elranatamab was 4.78 l (69%).

Metabolism

No information.

Elimination

The mean (CV%) of elranatamab clearance was 0.324 l/day (100%). Patients who discontinue elranatamab after Week 24 are expected to have a 50% reduction from C_{max} at a median (5^{th} to 95^{th} percentile) time of 24 days (8 to 61 days) after T_{max} and a 97% reduction from C_{max} at a median (5^{th} to 95^{th} percentile) time of 115 days (33 to 283 days) after T_{max}.

Kinetics in specific patient groups

No clinically relevant differences in the pharmacokinetics of elranatamab were observed based on age (36 to 89 years), sex (167 male, 154 female), race (193 White, 49 Asian, 29 Black), and body weight (37 to 160 kg).

Hepatic impairment

No formal studies of Elrexfio in patients with hepatic impairment have been conducted. Results of population pharmacokinetic analyses indicate that mild hepatic impairment (total bilirubin >1 to 1.5 times upper limit of normal (ULN) and any aspartate aminotransferase (AST), or total bilirubin ≤ULN and AST>ULN) did not significantly influence the pharmacokinetics of elranatamab. No data are

available in patients with moderate (total bilirubin >1.5 to 3.0x ULN and any AST) or severe (total bilirubin >3.0x ULN and any AST) hepatic impairment.

Renal impairment

No formal studies of Elrexfio in patients with renal impairment have been conducted. Results of population pharmacokinetic analyses indicate that mild renal impairment (60 ml/min/1.73 m^2 ≤ estimated glomerular filtration rate (eGFR) <90 ml/min/1.73 m^2) or moderate renal impairment (30 ml/min/1.73 m^2 ≤ eGFR <60 ml/min/1.73 m^2) did not significantly influence the pharmacokinetics of elranatamab. Limited data are available from patients with severe renal impairment (eGFR less than 30 ml/min/1.73 m^2).

Preclinical data

Genotoxicity

No studies have been performed to assess the genotoxic potential of elranatamab.

Carcinogenicity

No studies have been performed to assess the carcinogenic potential of elranatamab.

Reproductive toxicity

No animal studies have been performed to evaluate the effects of elranatamab on fertility or reproduction. In a 13-week repeat-dose toxicity study in sexually mature cynomolgus monkeys, there were no adverse effects on male and female reproductive organs following subcutaneous doses up to 6 mg/kg/week (approximately 6.5 times the maximum recommended human dose, based on AUC exposure).

Other information

Incompatibilities

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

Shelf life

Do not use this medicine after the expiry date («EXP») stated on the pack.

Shelf life after opening

The single-dose preparation does not contain a preservative. Chemical and physical in-use stability has been demonstrated for 24 hours at 2-30 °C. For microbiological reasons, the punctured vial and dosing syringe should be used immediately. Discard after 24 hours if not used. Any solution remaining in the vial should be discarded after single withdrawal.

Special precautions for storage

Store in the refrigerator (2-8°C).

Do not freeze. Do not shake.

Keep the container in the outer carton in order to protect the contents from light.

Keep out of the reach of children.

Instructions for handling

Preparation

Elrexfio vials are supplied as ready-to-use solution that do not need dilution prior to administration. Elrexfio single-dose preparation does not contain a preservative. Aseptic technique should be used to prepare and administer Elrexfio.

Elrexfio is a clear to slightly opalescent, and colourless to pale brown liquid solution. Elrexfio should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The solution should not be administered if it is discoloured or contains particulate matter.

Elrexfio should be prepared following the instructions below (see Table 9) depending on the required dose. It is suggested to use a 44 mg/1.1 ml single dose vial for titration dose 1 or titration dose 2.

Table 9 – Preparation instructions for Elrexfio

Required dose	*Dose volume*
12 mg (titration dose 1)	0.3 ml
32 mg (titration dose 2)	0.8 ml
76 mg (full treatment dose)	1.9 ml

Administration

Elrexfio is intended for subcutaneous use by a healthcare provider only.

The required dose of Elrexfio should be injected preferably into the subcutaneous tissue of the abdomen. Alternatively, Elrexfio may be injected into the subcutaneous tissues at the thigh. Injections into the subcutaneous tissue of other sites (e.g. the upper arm) is not allowed.

Disposal

The vial and any remaining contents after withdrawal of a single dose should be discarded. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Authorisation number

68646 (Swissmedic)

Packs

Elrexfio 44 mg/1.1 ml: 1 vial [A].

Elrexfio 76 mg/1.9 ml: 1 vial [A].

Marketing authorisation holder

Pfizer AG, Zürich.

Date of revision of the text

May 2023.