Date: 7 May 2020
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Sarclisa

International non-proprietary name: isatuximab
Pharmaceutical form: concentrate for solution for infusion
Dosage strength: 500 mg/25 mL and 100 mg/5 mL
Route(s) of administration: intravenous use
Marketing Authorisation Holder: Sanofi-Aventis (Suisse) SA
Marketing Authorisation No.: 67525
Decision and Decision date: approved on 18 March 2020

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
AE	Adverse events
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24 h	Area under the plasma concentration-time curve for the 24-hour dosing interval
CD38	Cluster of differentiation 38
CI	Confidence interval
Cmax	Maximum observed plasma/serum concentration of drug
CR	Complete response
CYP	Cytochrome P450
DDI	Drug-drug interaction
ECOG	Eastern Cooperative Oncology Group
ER	Exposure response
ERA	Environmental Risk Assessment
Fc	Fragment crystallisable
GLP	Good Laboratory Practice
HR	Hazard ratio
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International Nonproprietary Name
IPd	Isatuximab in combination with Pd
IRC	Independent review committee
IRR	Infusion-related reaction
ISS	International scoring system
Kd	Dissociation constant
LoQ	List of Questions
mAb	Monoclonal antibody
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MM	Multiple myeloma
N/A	Not applicable
NK	Natural killer
NO(A)EL	No Observed (Adverse) Effect Level
ORR	Objective response rate
OS	Overall survival
PBMCs	Peripheral blood mononuclear cells
Pd	Pomalidomide and lowdose dexamethasone
PD	Pharmacodynamics
PFS	progression-free survival
Ph. Eur.	Pharmacopoeia Europaea
PI	Proteasome inhibitor
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
Pop PK	Population PK
PR	Partial response
PSP	Pediatric Study Plan (US-FDA)
QW	once a week
Q2W	every 2 weeks

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R-ISS	Revised international scoring system
RMP	Risk Management Plan
RRMM	Relapsed and refractory multiple myeloma
SAE	Serious adverse events
sCR	Stringent complete response
SE-HPLC	Size-exclusion high-performance liquid chromatography
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment emergent adverse events
TMDD	Target-mediated drug disposition
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)
VGPR	Very good partial response

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance (INN) of the medicinal product mentioned above.

Fast-track authorisation procedure (FTP)
The applicant requested a fast-track authorisation procedure in accordance with Article 7 of the TPO.

Orphan drug status
The applicant requested Orphan Drug Status in accordance with Article 4 a^{decies} no. 2 of the TPA.
The Orphan Status was granted on 12 July 2018.

2.2 Indication and Dosage

2.2.1 Requested Indication

SARCLISA is indicated, in combination with pomalidomide and dexamethasone, for the treatment of patients with multiple myeloma (MM) who have received at least two prior therapies including lenalidomide and a proteasome inhibitor (PI).

2.2.2 Approved Indication

SARCLISA is indicated, in combination with pomalidomide and dexamethasone, for the treatment of adult patients with relapsed and refractory multiple myeloma (MM) who have received at least two prior lines of therapy including lenalidomide and a proteasome inhibitor (PI) and have demonstrated disease progression on the last therapy

2.2.3 Requested Dosage

The recommended dose of SARCLISA is 10 mg/kg body weight administered as an intravenous infusion (IV) in combination with pomalidomide and dexamethasone, according to the schedule in the following Table 1:

Table 1. SARCLISA dosing schedule in combination with pomalidomide and dexamethasone

Cycles	Dosing schedule
Cycle 1	Days 1, 8, 15 and 22 (weekly)
Cycle 2 and beyond	Days 1, 15 (every 2 weeks)

Each treatment cycle consists of a 28-day period. Treatment is repeated until disease progression or unacceptable toxicity.
For pomalidomide and dexamethasone dosage and administration, see local prescribing information.

2.2.4 Approved Dosage

(see appendix)

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2.3 Regulatory History (Milestones)

Application	21 August 2019
Formal control completed	22 August 2019
List of Questions (LoQ)	24 October 2019
Answers to LoQ	6 December 2019
Predecision	27 January 2020
Answers to Predecision	27 February 2020
Final Decision	18 March.2020
Decision	approval

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2.4 Medical Context

Multiple myeloma (MM) is a neoplastic proliferation of plasma cells. It remains an incurable and deadly disease. While the treatment landscape has rapidly changed over the past few years, options for patients with relapsed and refractory multiple myeloma (RRMM) are currently available but their long-term benefit, in particular survival of the patients, remains limited, with overall survival rates below 2 years. There is a clear medical need to improve patient outcome with well tolerated (combination) therapies for patients with RRMM.

3 Quality Aspects

3.1 Drug Substance

Isatuximab is an IgG1 monoclonal antibody that selectively binds to the CD38 protein expressed at a high level on the surface of multiple myeloma tumour cells. Isatuximab can also bind to normal immune cells expressing CD38 at various levels. It is produced from a mammalian cell line (Chinese Hamster Ovary, CHO) using a fed-batch production process in a production bioreactor. The cell broth is harvested as a single batch and is subsequently purified by several chromatographic steps. The drug substance is finally stored frozen.

Several changes were implemented during the development of the isatuximab drug substance process, including changes to production site, production scale, and drug substance concentration. However, all processes used the same cell line, and the analytical comparability studies, which included batch release data, extended characterisation, and stability data, demonstrated comparability between process changes.

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

The specifications for release include relevant tests and limits, e.g. for appearance, identity, pH, several purity tests (e.g. SE-HPLC, capillary gel electrophoresis), assay of protein, and a cell-based potency assay. Specifications are based on batch analysis data and are also based upon regulatory requirements, e.g. Ph. Eur. ‘Monoclonal antibodies for human use’ and ICH guidelines, e.g. ICH Q6B guideline on “Specifications: test procedures and acceptance criteria for biotechnological/biological products”.

Batch analysis data of non-clinical batches, clinical batches, and process performance qualification batches were provided. The non-compendial analytical methods are described and were fully validated.

During storage, no significant changes were observed under the proposed storage conditions. A shelf-life of 36 months has been accepted.

3.2 Drug Product

The isatuximab drug product is available as a sterile 20 mg/mL concentrate for solution for infusion in two single-use vial presentations: 500 mg/25 mL and 100 mg/5 mL. The isatuximab formulated drug substance formulation is identical to the formulation for isatuximab drug product. All excipients used comply with the European Pharmacopoeia.

The finished product manufacturing process consists of thawing of formulated drug substance, pooling and homogenisation, pre-filtration, sterile filtration, filling/stoppering, crimping and visual inspection.

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The validation was executed by manufacturing and testing three consecutive production scale batches of each presentation, i.e. 100 mg/5 mL and 500 mg/25 mL.

The release and stability specifications include relevant tests and limits, e.g. for appearance, identity, pH, extractable volume, purity tests (e.g. SE-HPLC, capillary gel electrophoresis), assay of protein, a cell-based potency assay, particulate matter, sterility, and bacterial endotoxins. All non-compendial methods were validated.

Batch analysis data of several batches (early development drug product batches and representative drug product batches) were provided. All batch release data comply with the drug product specifications, which were valid at the time of batch release.

The primary packaging container for isatuximab drug product consists of a colourless type I glass vial coated with a bromobutyl rubber closure:
- for the 100 mg presentation with a nominal volume of 6 mL
- for the 500 mg presentation with a nominal volume of 30 mL

The drug product is stored at 2 – 8°C. Purity decreases only slightly under the proposed storage conditions; the stability studies are ongoing. A shelf-life of 36 months for vials has been accepted.

3.3 Quality Conclusions

The manufacturing processes (drug substance and drug product) are well described and demonstrate a consistent quality of drug substance and drug product. The shelf-life of the drug substance and drug product are supported by data from recommended storage conditions, as well as accelerated and stress studies. Safety concerns with regard to viral and non-viral contaminants were satisfactorily addressed. The risk for adventitious agents is minimised.

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4 Nonclinical Aspects

The recommendations outlined in ICH guidelines M3(R2), S6(R1), and S9 were taken into consideration for the nonclinical testing strategy. The pivotal toxicology studies (including toxicokinetics) were performed in accordance with GLP regulations.

Pharmacology

Isatuximab bound to human CD38 (K_D of 0.12 nM) and inhibited CD38 enzymatic activity (cyclic GDP-ribose production was reduced to approximately 12% of control in the presence of ≥20 nM). *In vitro* studies in several CD38-expressing human tumour cell lines derived from multiple myeloma and other haematological malignancies demonstrated that isatuximab mediates complement-dependent cytotoxicity (CDC), antibody-dependent cell-mediated cytotoxicity (ADCC), and antibody-dependent cellular phagocytosis (ADCP). In addition to these Fc-mediated mechanisms, isatuximab also showed (direct) pro-apoptotic activity. The anti-tumour effect was also confirmed in fresh tumour samples of various haematological malignancies expressing CD38.

In vivo activity of isatuximab, alone or in combination with pomalidomide, was shown in xenograft mouse models implanted with tumour cell lines expressing CD38. Dose-dependent anti-tumour effect of isatuximab was observed in mice bearing SU-DHL-8 tumours (diffuse large B-cell lymphoma) at intravenous doses of 2.5-40 mg/kg twice weekly. In combination with pomalidomide, significant anti-tumour efficacy was observed in mice bearing human MOLP-8 tumours (multiple myeloma), while isatuximab alone was not efficacious. Previous *in vitro* investigations concluded that pomalidomide enhances the direct and indirect effects of isatuximab on multiple myeloma cells. Binding of isatuximab to CD38 on human immune cells resulted in immunomodulatory effects. These included the activation and increased lytic activity of natural killer (NK) cells, polarisation of monocytes/macrophages and restoration of T-cell immune function by blocking the immunosuppressive effect of regulatory T cells. Tissue cross-reactivity studies with human tissue revealed isatuximab-specific staining in lymphoid tissues, but also in some non-lymphoid tissues such as prostate, pituitary gland, lung and brain. Isatuximab bound to human peripheral B cells, T cells, NK cells, and monocytes. There was minimal binding to granulocytes. In contrast, isatuximab did not specifically bind to platelets or red blood cells. CD38 was only expressed at low levels in normal human peripheral blood mononuclear cells (PBMCs), with highest levels in NK cells and monocytes, followed by T cells, and lowest levels in B cells. CD38 expression was much higher in human tumour cell lines, with multiple myeloma cell lines showing the highest expression.

Isatuximab did not induce any significant cytokine release, cellular activation or proliferation of human PBMCs. Isatuximab only elicited very minor depletion (<10%) of T cells, B cells, NK cells, and monocytes. It showed no effect on the percentage of apoptotic T cells, B cells or monocytes, but induced an increased percentage of apoptotic NK cells.

Despite a high amino acid sequence identity (93%), isatuximab did not bind to a representative population of cynomolgus monkey PBMCs. A tissue cross-reactivity study showed that, except for the chimpanzee, none of the tested animal species (including mouse, rat, hamster, rabbit, dog, cynomolgus monkey, and minipig) was suitable for safety assessment of isatuximab. As the chimpanzee is not a common species for toxicology studies, the applicant evaluated two potential surrogate anti-CD38 antibodies, but their biological properties did not match those of isatuximab (lack of pro-apoptotic activity and different tissue cross-reactivity pattern).

Even in the absence of a pharmacologically relevant animal species, safety pharmacology endpoints were included in the repeated-dose toxicity study in the cynomolgus monkey. Isatuximab did not show any effects on electrocardiograms, blood pressure, gross behaviour, body temperature or respiratory rate at up to approximately 12-15 times human C_{max} at recommended clinical dose. However, the data are considered of limited value.

Pharmacokinetics

Isatuximab pharmacokinetics were characterised in mice and cynomolgus monkeys. In both species, isatuximab showed the typical pharmacokinetic profile of an IgG1 monoclonal antibody, with a long half-life (14 days), a low clearance, and a volume of distribution corresponding to blood volume.

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Isatuximab plasma exposure increased proportionally to dose in the monkey and greater than dose proportionally in tumour-bearing mice. Accumulation was observed in both mice and monkeys after repeated administration. There were no gender differences.
The presence of ADAs resulted in slightly lower exposure to isatuximab.
The applicant did not conduct any distribution, metabolism or excretion studies with isatuximab, which is acceptable for a monoclonal antibody, i.e. in line with ICH S6(R1).

Toxicology
The overall nonclinical safety assessment of isatuximab was limited as no relevant animal species exists, and no suitable surrogate antibody or adequate transgenic mouse model was available at the time of nonclinical development. Nevertheless, a repeated-dose toxicity study was conducted in the cynomolgus monkey with isatuximab administered on days 1, 8 and 15 intravenously, in line with the intended clinical route of administration. The clinical formulation was used. There were no isatuximab-related findings, and the NOAEL was considered to be 100 mg/kg/week (exposure at least 3-8 times human AUC).
The applicant did not conduct genotoxicity or carcinogenicity studies, which is in line with ICH S6(R1) and ICH S9. Nor did it conduct any developmental or reproductive toxicity studies. According to ICH S9, embryo-foetal development studies would have been required but, in the absence of a pharmacologically relevant animal species, this is acceptable. The lack of information on reproductive toxicity is adequately reflected in the information for professionals; use of Sarclisa during pregnancy and lactation is not recommended.
No local effects of isatuximab were observed in the rabbit or monkey after intravenous injection. Isatuximab did not induce haemolysis of human whole blood cells and showed compatibility with human plasma.
The potential targets of isatuximab identified in the tissue cross-reactivity studies, i.e. prostate, pituitary gland and lung were followed up clinically, with no relevant laboratory or clinical abnormalities that would suggest an adverse effect of isatuximab on these organs.
The applicant provided a satisfactory ERA. The nonclinical study requested in the PIP was completed. The RMP addresses all key safety findings from nonclinical studies and, in particular, the missing information due to the absence of a pharmacologically relevant animal species for safety assessment.

Conclusion
The submitted nonclinical documentation is considered sufficient to support the approval of Sarclisa (isatuximab) for the proposed indication. The pharmacological data provided an adequate “proof of concept” for the treatment of multiple myeloma. Toxicology data are limited. However, considering the lack of relevant animal species, additional preclinical studies are considered not useful and will not be requested.

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5 Clinical and Clinical Pharmacology Aspects

5.1 Clinical Pharmacology

Isatuximab (SAR650984, hu38SB19) is an immunoglobulin G1 (IgG1) monoclonal antibody (mAb) that binds to a specific extracellular epitope of cluster of differentiation 38 (CD38) receptor and triggers several mechanisms leading to the death of CD38 expressing tumour cells.

ADME
The pharmacokinetic profiles of isatuximab were evaluated in a number of phase 1 and 2 studies. The studies were conducted only in the target indication and evaluated multiple QW and/or Q2W doses between 0.0001 mg/kg and 20 mg/kg, either as single agent or as combination therapy. The pharmacokinetic characterisation of isatuximab was primarily based on population PK analyses using data from the phase 1/2 studies as well as from the pivotal phase 3 study.

Dose Proportionality
Isatuximab binds to a cellular target and exhibits target-mediated drug disposition (TMDD), i.e. its pharmacokinetics are nonlinear. However, at doses between 5 mg/kg and 20 mg/kg QW or Q2W, there was an approximately dose-proportional increase of isatuximab exposure.

Pharmacokinetics after multiple Dosing
Based on pop PK simulations, the overall median accumulation ratios of Ctrough and Cmax at steady state versus first dose were 3.1 and 1.8, respectively. After the proposed therapeutic dosing schedule, the median time to reach 90% of steady state was estimated to be 8 weeks (2 cycles).

Distribution
The isatuximab central volume of distribution for a typical patient was 5.13 L.

Metabolism
Monoclonal antibodies are not metabolised via the liver and are subject to catabolic degradation.

Elimination
As mentioned above, isatuximab exhibits TMDD. Its pharmacokinetics were best described by a two-compartment model with combined linear and nonlinear elimination. Furthermore, the linear clearance showed some time dependency. In a typical patient, linear clearance was found to decrease by about 50% between treatment start and steady state. The linear clearance was also affected by the myeloma type (IgG or non-IgG, see “Special Populations”). The time needed to reach a 50% decrease in linear clearance was about 6 weeks and about 2.5 weeks in IgG and non-IgG patients, respectively.

Linear clearance at steady state accounted for about 90% of the total clearance after 10 mg/kg QW4 then Q2W.

The typical isatuximab half-life based on the linear elimination at steady state was 28 days.

Special Populations
A number of factors associated with treatment, demography, renal or hepatic function and the disease to be treated were investigated as covariates for their potential impact on isatuximab PK. The pop PK dataset used for this analysis included 476 patients. The range of the continuous covariates was sufficiently wide and, for most categorical covariates, the number of patients per category was sufficient to detect potential covariate relationships.

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However, the dataset included only one patient with moderate hepatic impairment and no patients with severe hepatic impairment.

The final pop PK model included body weight, beta-2 microglobulin, (the number of) bone marrow plasma cells and the main immunoglobulin type (of MM) as statistically significant covariates of several clearance components, as well as body weight, formulation, sex and Asian race as statistically significant covariates of volume of distribution.

The covariate with the largest impact on isatuximab PK/exposure was the IgG type, followed by beta-2 microglobulin and body weight. Formulation, race and gender had only a small effect on isatuximab exposure. The (unbound) isatuximab exposure at steady state was about 2-fold higher in non-IgG patients compared to IgG patients. A mechanistic explanation for this finding would be a higher number of binding sites in IgG patients.

The impact of all available covariates (i.e. not just those that reached statistical significance in the formal covariate analysis) on isatuximab exposure was evaluated by simulations with the final pop PK model. As expected, the impact of the disease-related covariates became more pronounced with increasing treatment duration.

Age, gender, renal impairment of all degrees and mild hepatic impairment had no major impact on isatuximab exposure. As mentioned above, the dataset included only one patient with moderate and no patients with severe hepatic impairment, so no conclusions can be drawn for these groups. Despite the body weight-based dosing, the isatuximab troughs were considerably lower in patients < 50 kg compared to the reference value. The impact of low body weight on AUC was less than on Ctrough.

ADAs also had no major impact on isatuximab PK.

Interactions
Since monoclonal antibodies are not metabolised via the liver, the interaction potential is expected to be low, and no dedicated DDI studies were conducted.

Mutual pharmacokinetic interactions between isatuximab and pomalidomide or lenalidomide (both plus dexamethasone) were investigated in two pop PK analyses. The assessment of the potential impact of isatuximab on pomalidomide or lenalidomide PK was based on a comparison with published data for the two compounds.

Pomalidomide had no major impact on isatuximab PK. The pomalidomide PK parameters estimated after co-administration with isatuximab were comparable to published data.

Lenalidomide had no major impact on isatuximab PK. The lenalidomide PK parameters estimated after co-administration with isatuximab were comparable to published data.

Pharmacodynamics
An exposure response (ER) analysis to evaluate the potential impact of isatuximab on QTcF was done on the data from cycle 1 of part 1 of study TED10893. In the concentration range available for this analysis, isatuximab caused no QTcF prolongation. However, the analysis had several flaws:

- The isatuximab concentrations available for the ER analysis did not fully cover the expected steady-state concentration range after therapeutic dosing.

- Since isatuximab had a considerable impact on heart rate, QTcF did not provide a full correction of the QT interval.

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- Some degree of hysteresis was observed, as expected for non-steady-state data.

In summary, the ER analysis is not sufficient to conclude that isatuximab has no impact on QTc.

Immunogenicity
Overall, the ADA incidence was 13/564 patients (2.3%).

5.2 Dose Finding and Dose Recommendation

The TCD14079 study included 45 patients in a dose-escalation and dose-expansion cohort looking at the combination of isatuximab with pomalidomide and dexamethasone. At a median overall follow-up duration of 8.61 months, the objective response rate (ORR) was 62.2**%** (28 out of 45 patients), including two patients with complete response (CR) or stringent CR (sCR), very good partial response (VGPR) in 10 patients, and partial response (PR) in 16 patients. The 10 mg/kg dose level had an ORR of 64.5%. Duration of response was 18.7 months, and median PFS was 17.6 months.

5.3 Efficacy

ICARIA-MM is a multinational open-label, parallel group phase 3 study conducted in 24 countries and 102 sites in North America, Europe and Asia. Between 10 Jan 2017 and 01 Feb 2018, the study randomised 307 patients with RRMM who had received at least two prior lines of anti-myeloma therapy, including at least two consecutive cycles of lenalidomide and a proteasome inhibitor (PI). Patients were randomised in a 1:1 fashion to receive either pomalidomide and low-dose dexamethasone (Pd) or isatuximab in combination with Pd (IPd). Patients were stratified according to age (<75 years versus ≥75 years) and number of prior lines of therapy (two or three versus more than three). Primary endpoint was progression-free survival (PFS), as determined by an independent review committee (IRC). Key secondary endpoints were objective response rate (ORR) and overall survival (OS).

In both arms, pomalidomide was administered at the registered dose of 4 mg/d by mouth on days 1 to 21 of 28-day cycles. Dexamethasone was dosed at 40 mg on days 1, 8, 15 and 22. In the IPd arm, the patients additionally received isatuximab 10 mg/kg intravenously as a weekly infusion during the first cycle, and then every two weeks starting at cycle 2. Study treatment was administered until progression or until unacceptable toxicity or withdrawal of consent. Patients were eligible if they had received at least two prior lines of treatment and were refractory (defined as progressing on treatment or within 60 days of end of treatment) to lenalidomide and a proteasome inhibitor (bortezomib, carfilzomib or ixazomib) as well as to their last line of treatment.

The comparator of pomalidomide and dexamethasone is an approved regimen in this 3+ line setting. The only other registered drug in Switzerland in this setting is daratumumab as monotherapy. Elotuzumab in combination with pomalidomide and low-dose dexamethasone was recently approved but was not available when the ICARIA-MM study was initiated. Furthermore, panobinostat is registered as a third-line therapy, but only in patients who are not refractory to bortezomib, and this population was specifically excluded from the ICARIA-MM study. Therefore, the comparator arm is valid. PFS was the primary endpoint of the study, which has been validated in the past as an acceptable endpoint in this disease. Key secondary endpoints were ORR and OS.

ICARIA-MM is an open-label study. To avoid bias by investigator, response assessment was performed centrally as defined by IMWG (International Myeloma Working Group) criteria by an independent, blinded, review committee (IRC). This is an appropriate measure in this open-label design that seems unavoidable given the intravenous administration of the add-on isatuximab. Nevertheless, the open design of the study may have influenced safety reporting regarding the triplet combination.

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Assessments were mostly based on M-protein measurement by a central laboratory in serum and urine at day 1 of each cycle. If M protein was not detectable in urine, measurement was performed every 12 weeks. Bone was evaluated at baseline and once a year if no lesions were identified or if clinically indicated. If extramedullary disease was present (including in bone), assessment was to be performed every 12 weeks.

Statistically, no interim analysis was planned for PFS. Therefore, the data presented by the applicant corresponds to the final analysis for PFS. Additionally an interim analysis for OS was presented with the final PFS analysis, and a final OS analysis will be performed when 220 deaths have occurred. This approach seems adequate and appropriate.

Overall, 307 patients were randomised and 301 patients received study treatment. From the patient disposition at data cut-off for primary PFS analysis, one can observe that nearly twice as many patients in the IPd arm (42.2%) than in the Pd arm (22.9%) are still on treatment. More patients in the Pd arm discontinued study treatment due to progressive disease, but also due to AEs. More patients are alive at data cut-off in the IPd arm versus the Pd arm with 72.1% versus 63.4% respectively.

Regarding baseline characteristics, median age is 67 years and balanced between the treatment arms. Most patients are white (86%), and ethnicity is not reported in some cases (10%). There are some differences in baseline characteristics between the two arms. In particular, while about 20% of patients are older than 75 years of age in both arms (stratification factor), there are more patients older than 65 years in the IPd arm (65% versus 55% in the IPd versus Pd arms, respectively). In addition, there are more male patients in the IPd arm than the Pd arm (58% versus 46%, respectively). There are also more patients in the IPd arm with an ECOG (Eastern Cooperative Oncology Group) performance status of 1 (54% versus 44%, respectively). Finally, there are fewer patients from Western countries in the IPd arm with 50% compared to 63% in the Pd arm. Overall, the differences in baseline characteristics are rather to the disadvantage of the IPd arm with higher age and higher ECOG. With respect to disease characteristics, there were some imbalances to the disadvantage of the Pd arm with higher R-ISS (revised international scoring system) stage at baseline. There were also more cytogenetic high-risk patients in the Pd arm versus the IPd arm (23.5% versus 15.6%, respectively). Slightly more than one third of patients had renal impairment, with a creatinine clearance of 30 to 60 mL/min at inclusion, representing an important population in MM patients.

At the time of data cut-off, the median follow-up is 11.6 months. The primary endpoint PFS shows an advantage for the IPd arm over the control Pd arm with 11.53 (95% CI: 8.936-13.897) versus 6.47 (95% CI: 4.468-8.279) months. This difference is statistically significant despite the fact that the control arm showed a longer PFS than was postulated to calculate sample size (where it was estimated at 4 months).

Four appropriate sensitivity analyses were performed, and the results were consistent with the primary analysis. Subgroup analyses are consistent in all cases with the main PFS analysis. Benefit of IPd over Pd is observed in all subgroups including ISS and R-ISS stage III patients, ECOG performance status 2, patients older than 65, as well as in patients with impaired renal function. The benefit is also observed independently of region of the world and independently of gender.

Regarding the secondary endpoints, ORR (sCR, CR, VGPR and PR) is superior in the IPd arm with 60.4% compared to the Pd arm with 35.3%. This observation is consistent in all analysed subgroups. After a median follow-up of 11.6 months, OS shows a trend in favour of IPd versus Pd with a hazard ratio of 0.69 (95% CI: 0.46 to 1.02). The OS data are immature, and the efficacy boundaries for OS based on the O'Brien-Fleming α spending function according to the actual number of deaths observed at the time of the interim analysis of OS were not reached. The estimated median OS for the Pd control arm is 13.9 months and lies within the assumption of 13 months median OS, which formed the basis for the sample size calculation.

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5.4 Safety

When comparing all patients treated with the IPd combination (in studies ICARIA-MM and TCD14079) with Pd treated patients (in study ICARIA-MM), all-grade treatment emergent adverse events (TEAEs) were similar between the Pd and the IPd treated patients. However, there were more ≥ grade 3 TEAEs in the IPd treated group (87% versus 71%), more treatment-related TEAEs (93% versus 80%), more adverse events of special interest (AESIs) (16% versus 1%; mostly infusion-related reactions [IRRs]), as well as more serious treatment-related TEAEs (34% versus 16%).

There were not more fatal TEAEs (8.1% versus 8.7% in IPd and Pd arm, respectively), and fewer patients discontinued treatment due to TEAEs in the IPd treatment arm (7% versus 13%). Therefore, while IPd is more toxic overall than Pd, the toxicity is not prohibitive.

The most frequently observed all-grade TEAEs in the IPd treatment group were clinically relevant neutropenia (47%; while laboratory neutrophil count was decreased in 94.7%), IRR (37%), upper respiratory tract infection (28%), diarrhoea (26%), bronchitis (24%), pneumonia (20%), fatigue (17%), back pain (16%), constipation 16%), nausea (15%), dyspnoea (15%), asthenia (15%), thrombocytopenia (13%) and febrile neutropenia (12%). Except for IRR, bronchitis, nausea and dyspnoea, all of these TEAEs were also observed in the control Pd treatment arm, although neutropenia, upper respiratory tract infection, diarrhoea and pneumonia occurred to a lesser extent. There was a higher incidence of cardiac disorders in the IPd arm compared to the Pd arm (14.5% versus 4.0%). This was mostly due to arrhythmias (11.2% versus 2%). The cardiac TEAEs were mostly of grade 1-2 with only 3.3% of grade 3 or more. The most frequent cardiac arrhythmia was atrial fibrillation, affecting seven patients (4.6%) in the IPd arm versus three (2%) in the Pd arm.

Grade 3 and higher toxicities observed in the IPd treatment arm were neutropenia, pneumonia, thrombocytopenia, febrile neutropenia and disease progression. Compared to the Pd control arm, there was a notable difference in febrile neutropenia, which occurred in 11.8% of IPd treated patients.

Deaths
The incidence of death during the treatment period was similar between the two arms IPd and Pd, and the cause of death was mostly disease progression, AEs in three (2%, IPd arm) and six (4%, Pd arm) patients and other causes in two patients in each arm. Deaths during the post-treatment period were lower in the IPd treated patients compared to the Pd treated patients, mostly due to less disease progression. There was also no difference between the arms regarding deaths within 60 days from first dose. In study EFC14335, fatal TEAEs were considered treatment-related in two (1.3%) patients in the Pd arm (pneumonia and urinary tract infection), and in one (0.7%) patient in the IPd arm (sepsis).

Serious AEs (SAEs)
SAEs were more frequent in the IPd treated patients compared to the Pd treated patients and mostly involved neutropenia and its complications. However, as stated above, there were no more fatal SAEs in the IPd arm than the Pd arm. SAEs in the isatuximab single agent treated population were also mostly infectious complications such as pneumonia and sepsis. However, disease progression also figured among the SAEs in both populations.

Infusion-related reactions
About one third of all isatuximab treated patients experienced an infusion reaction. The vast majority of IRRs occurred during the first infusion. Only one patient experienced an IRR at infusion 18. Most IRRs resolved within the same day and, overall, only 3.3% of patients discontinued isatuximab due to IRRs.

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5.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

In Switzerland, there were approximately 560 new cases of multiple myeloma per year between 2009 and 2013. Multiple myeloma is a disease of older adults with a median age at diagnosis of 71 years. The age-adjusted incidence appears to be stable and is slightly higher in men than in women, with a ratio of approximately 1.4:1. While much progress has been made in recent years in the treatment of multiple myeloma, it remains incurable, and patients will eventually succumb to the disease. According to the stage of the disease at diagnosis, median OS can range from 43 months (R-ISS stage III) to 83 months (for R-ISS stage II) and more (median OS not reached for R-ISS stage I; 82% of patients alive at 5 years). Multiple myeloma still accounts for >300 deaths in Switzerland per year. Clearly, there is a medical need for improved treatment, particularly in patients who have relapsed after initial therapy.

Isatuximab shows the typical pharmacokinetics of an antibody binding to a cellular target, i.e. nonlinear pharmacokinetics due to target-mediated drug disposition (TMDD). At the proposed therapeutic dose of 10 mg/kg QW for one month followed by 10 mg/kg Q2W, the isatuximab exposure was mostly in the linear range. No dose adjustments based on age, renal impairment of all degrees or mild hepatic impairment are required. The weight dependency of isatuximab PK is accounted for by weight-based dosing.
There were no mutual pharmacokinetic interactions between isatuximab and pomalidomide/dexamethasone or isatuximab and lenalidomide/dexamethasone.

The addition of isatuximab to the currently approved third line therapy of pomalidomide and dexamethasone (IPd) has shown a significant improvement in PFS compared to pomalidomide and dexamethasone (Pd) from 6.5 to 11.5 months with a hazard ratio (HR) of 0.596 (p=0.0010). This benefit was observed in all analysed subgroups. Due to some imbalances in baseline characteristics between the treatment arms, a propensity-weighted analysis of PFS was performed and still demonstrated a statistically significant benefit for the triple combination of IPd versus Pd with an HR of 0.651 (p=0.0073). The combination of IPd also improved the objective response rate (ORR) over Pd from 35% to 60%.
After a median follow-up of 11.6 months, OS shows a trend in favour of IPd versus Pd with a hazard ratio of 0.69 (0.46 to 1.02). Estimated OS at 12 months was 72% for IPd and 63% for Pd. However, the OS data are immature, and the efficacy boundaries for OS based on the O'Brien-Fleming α spending function according to the actual number of deaths observed at the time of the interim analysis of OS were not reached. The final OS analysis will be performed when the predefined number of 220 events is reached, which is projected to occur in the first quarter of 2021.

Isatuximab appears to have a considerable impact on heart rate. The predicted increase at 10 mg/kg was 9.71 beats per minute.
The addition of isatuximab to pomalidomide and dexamethasone increases the occurrence of AEs, and most particularly the occurrence of neutropenia and its complications. However, there was no excess mortality in the ICARIA-MM study linked to this safety observation.

Given that isatuximab is a monoclonal antibody, anti-drug antibodies (ADAs) can arise. In the submitted studies, the frequency of these ADAs is low, at 2.3%, and there are no data on their impact on safety or efficacy. However, given the low incidence this does not pose a major concern.

The applicant is applying for a fixed infusion volume studied in 47 patients. The safety is consistent with what was observed in the pivotal ICARIA-MM trial. The primary endpoint of this study was to show that a fixed infusion volume would not increase the rate of infusion reactions, and this is the case. The fixed infusion volume has the advantage of reducing the risk of errors in infusion rates because it will be the same for all patients.

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Apart from the potential effect on QTc and heart rate, the isatuximab clinical pharmacology data do not raise any specific concerns.
Given the increase in PFS of 5 months using IPd versus Pd in this heavily pre-treated patient population with a trend towards longer OS and a manageable safety profile, the benefit-risk assessment is favourable.

5.6 Approved Indication and Dosage

See Information for healthcare professionals in the Appendix.

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6 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order 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. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. 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 occurring in populations or indications not included in the Swiss authorisations.

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7 Appendix

7.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Sarclisa, concentrate for solution for infusion 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 reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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

NAME OF THE MEDICINAL PRODUCT

SARCLISA 20 mg/mL, concentrate for solution for infusion.

Composition

Active substances

Isatuximab (produced from genetically modified Chinese hamster ovary cells).

Excipients

Sucrose, L-histidine monohydrochloride monohydrate, L-histidine, polysorbate 80, water for injection.

Pharmaceutical form and active substance quantity per unit

Concentrate for solution for infusion (intravenous administration).
The concentrate for solution for infusion is a colourless to slightly yellow solution, essentially free of visible particulates.
Each mL of Sarclisa solution contains 20 mg of isatuximab:

- 100 mg/5 mL dose in a 6 mL single-use vial. Each single-use vial of Sarclisa solution contains 100 mg of isatuximab (20 mg/mL).
- 500 mg/25 mL dose in a 30 mL single-use vial. Each single-use vial of Sarclisa solution contains 500 mg of isatuximab (20 mg/mL).

Therapeutic indications

SARCLISA is indicated, in combination with pomalidomide and dexamethasone, for the treatment of adult patients with relapsed and refractory multiple myeloma (MM) who have received at least two prior lines of therapy including lenalidomide and a proteasome inhibitor (PI) and have demonstrated disease progression on the last therapy.

Dosage/Administration

SARCLISA should be administered by a healthcare professional, in an environment where resuscitation facilities are available.

In order to ensure the traceability of biological medicinal products, the trade name and the batch number of the administered product should be recorded.

Premedication

Premedication with the following medications should be used prior to SARCLISA infusion to reduce the risk and severity of infusion reactions (IRs):

- Dexamethasone 40 mg PO or IV (or 20 mg PO or IV for patients ≥75 years of age).
- Paracetamol 650 mg to 1000 mg PO (or equivalent).
- H2 antagonists (ranitidine 50 mg IV or equivalent [e.g. cimetidine]), or a proton pump inhibitor (e.g. omeprazole, esomeprazole).
- Diphenhydramine 25 to 50 mg IV or PO (or equivalent [e.g. cetirizine or equivalent]). The intravenous route is preferred for at least the first 4 infusions.

The above recommended dose of dexamethasone (PO or IV) corresponds to the total dose to be administered once only before the infusion, as part of the premedication and the backbone treatment, before isatuximab and pomalidomide administration.

The recommended premedication agents should be administered 15-60 minutes prior to starting a SARCLISA infusion. Patients who do not experience an IR upon their first 4 administrations of SARCLISA may have their need for subsequent premedication reconsidered.

Usual dosage

The recommended dose of SARCLISA is 10 mg/kg body weight administered as an intravenous infusion (IV) in combination with pomalidomide and dexamethasone, according to the schedule in Table 1:

The recommended starting dose of pomalidomide is 4 mg orally once daily. The recommended dose of dexamethasone is 40 mg (or 20 mg for patients over the age of 75 years) once weekly.

Table 1 - SARCLISA, pomalidomide and dexamethasone dosing schedule

Cycles	SARCLISA (isatuximab)	Pomalidomide	Dexamethasone
Cycle 1	D1, D8, D15 and D22 (weekly)	D1 to D21	D1, D8, D15 and D22 (weekly)
Cycle 2 and subsequent cycles	D1, D15 (once every two weeks)	D1 to D21	D1, D8, D15 and D22 (weekly)

Each treatment cycle consists of a 28-day period. Treatment is repeated until disease progression or unacceptable toxicity.
For the adaptation of pomalidomide and dexamethasone doses, refer to the respective current summary of product characteristics.
The administration schedule must be carefully followed. If a planned dose of SARCLISA is missed, administer the dose as soon as possible and adjust the treatment schedule accordingly, maintaining the treatment interval.

Mode of administration

SARCLISA is for intravenous use. For instructions on dilution of the medicinal product before administration, see the section "Special precautions for handling".

Infusion rates

Following dilution, the SARCLISA infusion should be administered intravenously at the infusion rate presented in Table 2 below. Incremental escalation of the infusion rate should be considered only in the absence of infusion reactions (IR).

Table 2 – Infusion rates of SARCLISA administration:

	Dilution volume	Initial rate	Absence of IR	Rate increment	Maximum rate
First infusion	250 mL	25 mL/hour	For 60 minutes	25 mL/hour every 30 minutes	150 mL/hour
Second infusion	250 mL	50 mL/hour	For 30 minutes	50 mL/hour for 30 minutes then increase by 100 mL/h every 30 minutes	200 mL/h
Subsequent infusions	250 mL	200 mL/h	___	___	200 mL/h

Dosage adjustment

No dose reduction of SARCLISA is recommended.
Administration adjustments should be made if patients experience the following adverse reactions:

Infusion reactions (IRs)

- In patients who experience an IR, a temporary interruption of the infusion should be considered and additional symptomatic medication can be administered. After improvement, SARCLISA infusion may be resumed at half of the initial infusion rate under close monitoring and subject to supportive care, as needed. If symptoms do not recur after 30 minutes, the infusion rate may be increased to the initial rate, and then increased incrementally, as shown in Table 2 (see "Warnings and precautions").
- If symptoms do not resolve rapidly or improve after interruption of SARCLISA infusion, recur after initial improvement with appropriate medications, or require hospitalisation or are life-threatening, treatment with SARCLISA should be permanently discontinued and additional supportive therapy should be administered.

Neutropenia

In the event of grade 4 neutropenia, SARCLISA administration should be delayed until neutrophil count improves to at least 1.0 x 10^9/L. The use of colony-stimulating factors (e.g. G-CSF) should be considered, according to local guidelines (see "Warnings and precautions").

For other medicinal products that are administered with SARCLISA, refer to the respective current summary of product characteristics.

Special dosage instructions

Children and adolescents

The safety and efficacy of SARCLISA in children below 18 years of age have not been established.

Elderly patients

Based on population pharmacokinetic analysis, no dose adjustment is recommended in elderly patients (see "Pharmacokinetics").

Patients with impaired renal function

Based on population pharmacokinetic analysis and on clinical safety, no dose adjustment is recommended in patients with mild to severe renal impairment (see "Pharmacokinetics").

Patients with impaired hepatic function

Based on population pharmacokinetic analysis, no dose adjustment is recommended in patients with mild hepatic impairment (see "Pharmacokinetics"). Limited data are available on patients with moderate hepatic impairment, and no data are available on patients with severe hepatic impairment (see "Pharmacokinetics").

Contraindications

Hypersensitivity to the active substance or to any of its excipients listed in the section "Composition".

Warnings and precautions

Infusion reactions

Infusion reactions (IRs), mostly mild or moderate, have been observed in 38.7% of patients treated with SARCLISA (see "Undesirable effects"). All IRs started during the first SARCLISA infusion, and resolved on the same day in most patients. The most common symptoms of an IR included dyspnoea, cough, chills and nausea. The most common severe signs and symptoms included hypertension and dyspnoea (see "Undesirable effects").
To decrease the risk and severity of IRs, patients should be pre-medicated prior to SARCLISA infusion with paracetamol, H2 antagonists or proton pump inhibitors, diphenhydramine or equivalent; dexamethasone is to be used as both premedication and anti-myeloma treatment (see "Dosage/Administration”). Vital signs should be frequently monitored during the entire SARCLISA infusion. If required, interrupt SARCLISA infusion and provide appropriate medical and supportive measures (see "Dosage/Administration"). In case symptoms do not improve after interruption of SARCLISA infusion, recur after initial improvement with appropriate medications, require hospitalisation or are life-threatening, permanently discontinue SARCLISA and institute appropriate management.

Interference with serological testing (indirect antiglobulin test)

SARCLISA binds to CD38 on red blood cells (RBCs) and may result in a false positive indirect antiglobulin test (indirect Coombs test). In ICARIA-MM, the indirect antiglobulin test was positive during Isa-Pd treatment in 67.7% of the tested patients. In patients with a positive indirect antiglobulin test, blood transfusions were administered without evidence of haemolysis. ABO/RhD typing was not affected by SARCLISA treatment (see "Interactions"). To avoid potential problems with RBC transfusion, patients being treated with SARCLISA should be subjected to blood type and screen tests prior to the first SARCLISA infusion. Phenotyping may be considered prior to starting SARCLISA treatment as per local practice. If treatment with SARCLISA has already started, the blood bank

should be informed that the patient is receiving SARCLISA and that SARCLISA interference with blood compatibility testing can be resolved using dithiothreitol (DTT)-treated RBCs. If an emergency transfusion is required, non–cross-matched ABO/RhD-compatible red blood cells can be given as per local blood bank practices (see "Interactions").

Neutropenia

Grade 3-4 neutropenia (46.5%) and neutropenic complications (all grades: 23.9%) have been observed in patients treated with SARCLISA (see "Undesirable effects").
Monitor complete blood cell counts periodically during treatment. Antibiotic, antifungal and antiviral prophylaxis may be considered during treatment. Monitor patients with neutropenia for signs of infection. No dose reductions of SARCLISA are recommended. SARCLISA dose delays and the use of colony-stimulating factors (e.g. G-CSF) may be required to allow improvement of neutrophil count (see “Dosage/administration”).

Interference with response assessment

SARCLISA is an IgG kappa monoclonal antibody that can be incidentally detected on both serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein (see "Interactions"). This interference can impact the accuracy of the determination of complete response in some patients with IgG kappa myeloma protein. Twenty-two patients in the Isa-Pd arm who met VGPR criteria with only residual immunofixation-positivity were tested for interference. Serum samples taken from these patients were tested by mass spectrometry to separate the SARCLISA signal from the myeloma M-protein signal. In 11 out of 22 patients, there was no residual myeloma M protein detectable at the sensitivity level of the immunofixation test (25 mg/dl); 10 of the 11 patients had IgG subtype myeloma at baseline, showing SARCLISA interference with the immunofixation assay (see "Interactions").

Interactions

SARCLISA has no impact on the pharmacokinetics of pomalidomide (see "Pharmacokinetics").

Interference with serological testing

Because CD38 protein is expressed on the surface of red blood cells, SARCLISA, an anti-CD38 antibody, may interfere with blood bank serologic tests with potential false positive reactions in indirect antiglobulin tests (indirect Coombs tests), antibody detection (screening) tests, antibody identification panels, and antihuman globulin (AHG) crossmatches in patients treated with SARCLISA (see "Warnings and precautions").

Interference with serum protein electrophoresis and immunofixation tests

SARCLISA may be incidentally detected by serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the monitoring of M-protein and could interfere with accurate response classification based on International Myeloma Working Group (IMWG) criteria (see "Warnings and precautions").

Pregnancy, lactation

Pregnancy

There are no available data on SARCLISA use in pregnant women. Animal reproduction toxicity studies have not been conducted with SARCLISA. No conclusions can be drawn regarding whether or not SARCLISA is safe for use during pregnancy.

Immunoglobulin G1 monoclonal antibodies are known to cross the placenta. SARCLISA must not be used during pregnancy, except if the potential benefit for the mother is considered greater than the potential risk to the foetus. If a woman becomes pregnant on treatment with SARCLISA, she should be informed of the potential risks for the foetus. Women of childbearing potential treated with SARCLISA should use effective contraception during treatment and for at least 5 months after the last infusion.

For other medicinal products that are administered with SARCLISA, refer to the respective current summary of product characteristics.

Lactation

There are no available data on the presence of SARCLISA in human milk, milk production, or the effects on the breast-fed infant. However, human immunoglobulin G is known to be present in human milk. Antibodies can be secreted in human milk. No conclusions can be drawn regarding whether or not SARCLISA is safe for use during breastfeeding The use of SARCLISA is not recommended during breastfeeding.

Fertility

No human or animal data are available to determine potential effects of SARCLISA on fertility in males and females (see "Preclinical data").

Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. On the basis of reported adverse reactions, SARCLISA is not expected to influence the ability to drive and use machines (see "Dosage/Administration" and "Undesirable effects"). Fatigue and dizziness, however, have been reported in patients taking SARCLISA; this should be taken into account when driving or using machines.
For other medicinal products that are administered with SARCLISA, refer to the respective current summary of product characteristics.

Undesirable effects

Summary of the safety profile

The adverse reactions considered to be possibly or probably related to the administration of SARCLISA have been observed in:

- 230 patients who received SARCLISA 10 mg/kg in combination with pomalidomide and low-dose dexamethasone

Adverse reactions are described using the NCI Common Toxicity Criteria, the Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART) and the MedDRA terms. Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from available data). Within each frequency grouping, the adverse reactions in question are presented in order of decreasing seriousness.

The safety data described in this section are based on the pooled safety data with isatuximab 10 mg/kg administered in combination with pomalidomide and dexamethasone, and are obtained from ICARIA-MM study (a randomised, open-label clinical trial in patients with previously treated multiple myeloma, see "Properties/Effects"), the TCD14079 Part B study (isatuximab 10 mg/kg administered in combination with pomalidomide and dexamethasone) and the TCD14079 Part A study (isatuximab 5 mg/kg, 10 mg/kg and 20 mg/kg in combination with pomalidomide and dexamethasone).
The most frequent adverse reactions (in ≥ 20% of patients on Isa-Pd) were neutropenia (47.4%), infusion reactions (38.7%), upper respiratory tract infection (31.7%), fatigue (30.4%), diarrhoea (27.4%), pneumonia (27.0%), constipation (20.4%). The most frequent serious adverse reaction (in ≥ 5% of patients) was pneumonia (14.3%). Permanent discontinuation of treatment because of adverse reactions was reported in 17 patients (7.4%) treated with SARCLISA 10 mg/kg in combination with pomalidomide and low-dose dexamethasone (Isa-Pd).

The adverse reactions observed during the treatment period in 230 patients with multiple myeloma and treated with Sarclisa 10 mg/kg in combination with pomalidomide and low-dose dexamethasone (Isa-Pd), and reported in the ICARIA-MM study (see "Properties/Effects") and the TCD 14079 study part A and part B, are presented below:

Infections and infestations

Very common: upper respiratory tract infection (all grades: 31.7%; grade 3: 2.6%; grade 4: 0.4%), pneumonia [a] (all grades: 27.0%; grade 3: 18.3%; grade 4: 2.6%), bronchitis (all grades: 17.8%; grade 3: 2.2%; grade 4: 0%).

[a] The term "pneumonia" is a grouping of the following terms: atypical pneumonia, bronchopulmonary aspergillosis, pneumonia, pneumonia haemophilus, pneumonia influenza, pneumonia pneumococcal, pneumonia streptococcal, pneumonia viral, candida pneumonia, pneumonia bacterial, haemophilus infection, lung infection, pneumonia fungal and pneumocystis jirovecii pneumonia.

Blood and lymphatic system disorders

Very common: neutropenia (all grades: 47.4%; grade 3: 15.7%; grade 4: 30.9%), thrombocytopenia (all grades: 11.7%; grade 3: 1.7%; grade 4: 9.1%.

Common: febrile neutropenia (all grades: 8.3%; grade 3: 7.4%; grade 4: 0.9%), anaemia (all grades: 4.8%; grade 3: 3.0%; grade 4: 0%).

Haematology laboratory abnormalities in patients receiving Isa-Pd treatment are presented below:

Very common: anaemia (all grades: 99.1%; grade 3: 25.9%; grade 4: 0%), neutropenia (all grades: 94.7%; grade 3: 26.8%; grade 4: 54.8%), lymphopenia (all grades: 94.3%; grade 3: 46.1%; grade 4: 12.7%), thrombocytopenia (all grades: 83.3%; grade 3: 15.4%; grade 4: 14.9%).

The denominator used for the percentage calculation is the number of patients with at least 1 evaluation of the laboratory test during the considered observation period.

Metabolism and nutrition disorders

Common: decreased appetite (all grades: 8.7%; grade 3: 1.3%; grade 4: 0%).

Cardiac disorders

Common: Atrial fibrillation (all grades: 4.3%; grade 3: 1.7%; grade 4: 0.4%).

Respiratory, thoracic and mediastinal disorders

Very common: dyspnoea (all grades: 18.7%; grade 3: 3.0%; grade 4: 0%).

Gastrointestinal disorders

Very common: diarrhoea (all grades: 27.4%; grade 3: 2.2%; grade 4: 0%), nausea (all grades: 17.4%; grade 3: 0%; grade 4: 0%), vomiting (all grades: 11.7%; grade 3: 0.9%; grade 4: 0%).

Investigations

Common: weight decrease (all grades: 4.3%; grade 3: 0%; grade 4: 0%).

Injury, poisoning and procedural complications

Very common: infusion reaction (all grades: 38.7%; grade 3: 1.3%; grade 4: 0.9%).

Description of selected adverse reactions in the treatment of multiple myeloma for isatuximab 10 mg/mL in combination with pomalidomide and low-dose dexamethasone.

Infusion reactions

In the pooled safety data from the ICARIA-MM and TCD 14079 parts B and A studies with isatuximab 10 mg/kg administered in combination with pomalidomide and dexamethasone, infusion reactions (IRs, defined as adverse reactions associated with the SARCLISA infusions, with an onset typically within 24 hours from the start of the infusion) were reported in 89 patients (38.7%) treated with SARCLISA.. All patients who experienced IRs experienced them during the 1st infusion of SARCLISA, with 5 patients (2.2%) also having IRs at subsequent infusions. Grade 1 IRs were reported in 2.6%, grade 2 in 34.8%, grade 3 in 1.3%, and grade 4 in 0.9% of the patients. Signs and symptoms of Grade 3 or higher IRs included dyspnoea, hypertension and bronchospasm.
In the ICARIA-MM and TCD14079 Part A studies, the incidence of infusion interruptions because of infusion reactions was 30.6%. The median time to infusion interruption was 55 minutes. The median duration of SARCLISA infusion was 3.3 hours during the first infusion and 2.8 hours for the subsequent infusions. In the TCD14079 Part B study, the incidence of infusion interruptions because of infusion reactions was 38.3%, and the median time to infusion interruption was 80 minutes. The median duration of infusion was 3.7 hours for the first infusion, 1.85 hours for the second infusion, and 1.25 hours from the third infusion onwards.

Infections

In the pooled safety data from the ICARIA-MM and TCD14079 Part B and Part A studies with isatuximab 10 mg/kg administered in combination with pomalidomide and dexamethasone, the incidence of grade 3 or higher infections was 35.7%. Pneumonia was the most commonly reported severe infection with grade 3 reported in 18.3% of patients, and grade 4 in 2.6% of patients.

Discontinuations from treatment due to infection were reported in 2.6% of patients. Fatal infections were reported in 3.0% of patients.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity to SARCLISA.
In ICARIA-MM, no patients tested positive for anti-drug antibodies (ADA). Therefore, the neutralising ADA status was not determined. Overall, across 6 multiple myeloma (MM) clinical studies with SARCLISA single agent and combination therapies including ICARIA-MM, the incidence of treatment-emergent ADAs was 2.3% (13 patients with positive ADA response out of the 564 patients) No effect of ADAs was observed on the pharmacokinetics, safety or efficacy of SARCLISA.

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are required to report any suspected new or severe side-effect using the ElViS (Electronic Vigilance System) online portal. You will find information in this respect at www.swissmedic.ch.

Overdose

Signs and symptoms

There has been no experience of overdosage in clinical studies. Doses of intravenous SARCLISA up to 20 mg/kg have been administered in clinical studies.

Management

There is no known specific antidote for SARCLISA overdose. In the event of overdose, monitor the patient for any signs or symptoms of undesirable effects and take all appropriate measures immediately.

Properties/Effects

ATC code

L01XC

Mechanism of action

Isatuximab is an IgG1-derived monoclonal antibody that binds to a specific extracellular epitope of the CD38 receptor and triggers several mechanisms leading to the death of CD38-expressing tumour cells.

CD38 is a transmembrane glycoprotein with ectoenzymatic activity, expressed in haematological malignancies, and is highly and uniformly expressed on multiple myeloma cells .
Isatuximab acts through IgG Fc-dependent mechanisms including: antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP) and complement-dependent cytotoxicity (CDC). Isatuximab can also trigger tumour cell death by inducing apoptosis via an Fc-independent mechanism.
In human peripheral blood mononuclear cells (PBMCs), natural killer (NK) cells express the highest CD38 levels. In vitro, isatuximab can activate NK cells in the absence of CD38-positive target tumour cells through a mechanism which is dependent on the Fc portion of isatuximab. Also, isatuximab inhibits Tregs which express higher levels of CD38 in MM patients compared to healthy individuals.
Isatuximab blocks the enzymatic activity of CD38 which catalyses the synthesis and hydrolysis of cyclic ADP-ribose, a calcium mobilising agent, and this may contribute to immunoregulatory functions. Isatuximab inhibits cADPR production from extracellular NAD in multiple myeloma cells.
The combination of isatuximab and pomalidomide in vitro enhances cell lysis of CD38-expressing multiple myeloma cells by effector cells (ADCC) and by direct tumour cell killing, compared to the activity of isatuximab alone. In vivo experiments using a human multiple myeloma xenograft model demonstrated that the combination of isatuximab and pomalidomide results in enhanced antitumour activity compared to the activity of isatuximab or pomalidomide alone.

Pharmacodynamics

The pharmacodynamic properties of isatuximab have been characterised in monotherapy. A decrease in absolute counts of total NK cells (including inflammatory $CD16^{+\ low}$ $CD56^{+\ bright}$ and cytotoxic $CD16^{+\ bright}$ $CD56^{+\ dim}$NK cells), $CD19^{+}$ B-cells, $CD4^{+}$ T cells and TREG ($CD3^{+}$, $CD4^{+}$, $CD25^{+}$, $CD127^{-}$) was observed in peripheral blood. The decrease in the TREG was higher in responder patients than in non-responder patients.
T-cell receptor (TCR) DNA sequencing was used to quantify expansion of individual T-cell clones, each of them having a unique TCR conferring antigen specificity. In multiple myeloma patients, SARCLISA monotherapy induced clonal expansion of the T-cell receptor repertoire.
Two multiple myeloma patients who had a clinical response under SARCLISA treatment developed T-cell responses against CD38 and tumour-associated antigens. In the same monotherapy study, two patients who were unresponsive to SARCLISA did not develop such T-cell response.

In multiple myeloma patients treated with SARCLISA combined with pomalidomide and dexamethasone, a decrease in absolute counts of total NK cells (including inflammatory $CD16^{+}$ low $CD56^{+}$ bright and cytotoxic $CD16^{+\ bright}$ $CD56^{+\ dim}$) NK cells and $CD19^{+}$ B-cells was observed in peripheral blood. An increase in $CD4^{+}$ T cells and TREG ($CD3^{+}$, $CD4^{+}$, $CD25^{+}$, $CD127^{-}$) was observed in all the treated populations and non-responder patients.

The pharmacodynamic effects of SARCLISA in multiple myeloma patients support its immunomodulatory mechanism of action. In addition to its effector functions, SARCLISA induced T-cell response indicating an adaptive immune response.

Clinical efficacy

ICARIA-MM (EFC14335)

The efficacy and safety of SARCLISA in combination with pomalidomide and low-dose dexamethasone were evaluated in ICARIA-MM (EFC14335), a multicentre, multinational, randomised, open-label, 2-arm, phase III study in patients with relapsed and refractory multiple myeloma. Patients had received at least two prior therapies including lenalidomide and a proteasome inhibitor, but had failed to respond to the lenalidomide and/or the proteasome inhibitor, experiencing disease progression during the previous therapy or within 60 days following the end of treatment. Patients with primary refractory disease were excluded.

A total of 307 patients were randomised in a 1:1 ratio to receive either SARCLISA in combination with pomalidomide and low-dose dexamethasone (Isa-Pd, 154 patients) or pomalidomide and low-dose dexamethasone (Pd, 153 patients). Treatment was administered in both groups in 28-day cycles until disease progression or unacceptable toxicity. SARCLISA 10 mg/kg was administered as an IV infusion weekly in the first cycle and every two weeks thereafter. Pomalidomide 4 mg was taken orally once daily from day 1 to day 21 of each 28-day cycle. Low-dose dexamethasone (PO/IV) 40 mg (20 mg for patients ≥75 years of age) was given on days 1, 8, 15 and 22 for each 28-day cycle.

Overall, demographic and disease characteristics at baseline were similar in the two treatment groups. The median patient age was 67 years (range 36-86); 19.9% of patients were ≥75 years, 10.4% of patients entered the study with a history of COPD or asthma, and 38.6% versus 33.3% of patients with renal impairment (creatinine clearance [MDRD formula] between 30-60 mL/min/1.73 m²) were included in Isa-Pd versus Pd groups, respectively. The International Staging System (ISS) stage at initial diagnosis was I in 25.1%, II in 31.6% and III in 28.0% of patients. Overall, 19.5% of patients had high-risk chromosomal abnormalities at study entry; del(17p), t(4;14) and t(14;16) were present in 12.1%, 8.5% and 1.6% of patients, respectively.

The median number of prior lines of therapy was 3 (range 2-11). All patients received a prior proteasome inhibitor, all patients received prior lenalidomide, and 56.4% of patients received prior stem cell transplantation. The majority of patients (92.5%) were refractory to lenalidomide, 75.9% to a

proteasome inhibitor, and 72.6% to both an immunomodulatory and a proteasome inhibitor, and 59% of patients were refractory to lenalidomide at last line of therapy.

The median duration of treatment was 41.0 weeks for the Isa-Pd group compared to 24.0 weeks for the Pd group.

Progression-free survival (PFS) was the primary efficacy endpoint of ICARIA-MM. PFS was significantly prolonged in the Isa-Pd group compared with the Pd group. The median PFS was 11.53 months (95% CI: 8.936-13.897) in the Isa-Pd group versus 6.47 months (95% CI: 4.468-8.279) in Pd group (hazard ratio [HR]=0.596; 95% CI: 0.436-0.814, p=0.0010), representing a 40.4% reduction in the risk of disease progression or death in patients treated with Isa-Pd. PFS results were assessed by an Independent Response Committee based on central laboratory data for M-protein and central radiologic imaging review using the International Myeloma Working Group (IMWG) criteria.

Efficacy results are presented in Table 5:

Table 5 - Efficacy of SARCLISA in combination with pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in the treatment of multiple myeloma (intent-to-treat analysis)

Endpoint	**SARCLISA + pomalidomide + low-dose dexamethasone N = 154**	**Pomalidomide + low-dose dexamethasone N = 153**
Overall Response Rate[a] Responders (RCs+RC+RPTB+RP), n(%) [95% CI][b]	93 (60.4) [0.5220-0.6817]	54 (35.3) [0.2775-0.4342]
p-value (stratified Cochran-Mantel-Haenszel)[c]	< 0.0001	
Stringent Complete Response (sCR) + Complete Response (CR) n(%)	7 (4.5)	3 (2.0)
Very Good Partial Response (VGPR) n(%)	42 (27.3)	10 (6.5)
Partial Response (PR) n (%)	44 (28.6)	41 (26.8)
VGPR or better n (%) [95% CI][b]	49 (31.8) [0.2455-0.3980]	13 (8.5) [0.0460-0.1409]
p-value (stratified Cochran-Mantel Haenszel)[c]	< 0.0001	

Endpoint	SARCLISA + pomalidomide + low-dose dexamethasone N = 154	Pomalidomide + low-dose dexamethasone N = 153
Minimal Residual Disease negative rate[d] (%)	5.2	0

[a] sCR, CR, VGPR and PR were evaluated by the IRC using the IMWG response criteria.

[b] Estimated using Clopper-Pearson method.

[c] Stratified on age (<75 years versus >75 years) and number of previous lines of therapy (2 or 3 versus >3) according to IRT.

[d] based on a sensitivity level of 10^{-5} by NGS

The benefit of Isa-Pd treatment compared to Pd treatment was observed in the PFS analyses for pre-specified subgroups (high-risk cytogenetics, renal impairment, patients older than 75 years, ISS stage III at study entry, > 3 prior lines of therapy, refractory to prior therapy with lenalidomide or to a proteasome inhibitor, refractory to lenalidomide at the last line prior to study entry).

The median time to first response in responders was 35 days in the Isa-Pd group versus 58 days in the Pd group. Median overall survival was not reached for either treatment group. At a median follow-up time of 11.6 months, 43 (27.9%) patients on Isa-Pd and 56 (36.6%) patients on Pd had died. The hazard ratio for OS was 0.687 (95% CI: 0.461-1.023, p = 0.0631).

Among patients with creatinine clearance <50 mL/min/1.73m^2 at baseline, complete renal response (≥60 mL/min/1.73m2 at ≥1 postbaseline assessment) was observed for 71.9% of patients in the Isa-Pd versus and 38.1% in the Pd group. Sustained complete renal response (>60 days) occurred in 31.3% of patients in the Isa-Pd group and in 19.0% in the Pd group (see "Dosage/Administration").

TCD14079

In a multi-centre, 2-part, open-label, non-comparative Phase Ib study (TCD14079 Part A and B), SARCLISA 10 mg/kg was administered in combination with pomalidomide and low-dose dexamethasone (Isa-Pd) to patients with relapsed/refractory multiple myeloma (same treatment regimen and similar patient population and characteristics as in ICARIA-MM). The median duration of treatment was 41.0 weeks. Of the 31 patients evaluable for efficacy in Part A, the overall response rate (ORR) was 64.5% and the median PFS was 17.58 months (95% CI: 6.538 to not reached) with a median duration of follow-up of 8.6 months. Efficacy results were consistent with the ICARIA-MM results. Part B of the study investigated a fixed infusion volume (see "Undesirable effects").

Pharmacokinetics

The pharmacokinetics of isatuximab were assessed in 476 patients with multiple myeloma treated with isatuximab intravenous infusion as a single agent or in combination with pomalidomide/dexamethasone, at doses ranging from 1 to 20 mg/kg, administered either once weekly; every 2 weeks; or every 2 weeks for 8 weeks followed by every 4 weeks; or every week for 4 weeks followed by every 2 weeks.
Isatuximab displays nonlinear pharmacokinetics with target-mediated drug disposition due to its binding to the CD38 receptor.
Isatuximab exposure (area under the plasma concentration-time curve over the dosing interval AUC) increases in a greater than dose-proportional manner from 1 to 20 mg/kg following an every-2-weeks schedule, while no deviation from the dose proportionality is observed between 5 and 20 mg/kg following a weekly schedule for 4 weeks, followed by an every-2-weeks schedule. After isatuximab 10 mg/kg administration every week for 4 weeks followed by every 2 weeks, the median time to reach steady state was 8 weeks with a 3.1-fold accumulation. The mean (CV%) predicted maximum plasma concentration Cmax and AUC at steady state were 351 µg/mL (36.0%) and 72,600 µg.h/mL (51.7%), respectively.

Absorption

Isatuximab is administered intravenously, therefore there is no absorption.

Distribution

The estimated total volume of distribution of isatuximab is 8.75 L.

Metabolism

As a large protein, isatuximab is expected to be metabolised by non-saturable proteolytic catabolism processes.

Elimination

Isatuximab is eliminated by two parallel pathways: a nonlinear target-mediated pathway predominating at low concentrations, and a nonspecific linear pathway predominating at higher concentrations. In the therapeutic plasma concentrations range, the linear pathway is predominant and decreases over time by 50% to a steady-state value of 0.00955 L/h (0.229 L/day). This is associated with a terminal half-life of 28 days.

Drug interactions

The pharmacokinetics of isatuximab and pomalidomide were not influenced by their co-administration.

Kinetics in specific patient groups

Age, gender and race

The population pharmacokinetic analyses of 476 patients aged 36 to 85 years showed comparable exposure to isatuximab in patients < 75 years old versus > 75 years old (n=70). Gender and race had no clinically meaningful effect on isatuximab pharmacokinetics.

Weight

Isatuximab exposure (AUC) at steady state decreased with increasing body weight.

Hepatic impairment

No formal studies of isatuximab in patients with hepatic impairment have been conducted. Out of the 476 patients included in the population pharmacokinetic analyses, 65 patients presented with mild hepatic impairment [total bilirubin 1 to 1.5 times upper limit of normal (ULN) or aspartate amino transferase (AST) > ULN] and 1 patient had moderate hepatic impairment (total bilirubin> 1.5 to 3 times ULN and any AST). Mild hepatic impairment had no clinically meaningful effect on the pharmacokinetics of isatuximab. The effect of moderate (total bilirubin >1.5 times to 3 times ULN and any AST) and severe hepatic impairment (total bilirubin >3 times ULN and any AST) on isatuximab pharmacokinetics is unknown.

Renal Impairment

No formal studies of isatuximab in patients with renal impairment have been conducted. The population pharmacokinetic analyses on 476 patients included 192 patients with mild renal impairment (60 mL/min/1.73 m2 ≤ estimated glomerular filtration rate (e-GFR) <90 mL/min/1.73 m2), 163 patients with moderate renal impairment (30 mL/min/1.73 m2≤ e-GFR < 60 mL/min/1.73 m2) and 12 patients with severe renal impairment (e-GFR <30 mL/min/1.73 m2). Analyses suggested no clinically meaningful effect of mild to severe renal impairment on isatuximab pharmacokinetics compared to normal renal function.

Children and adolescents

SARCLISA was not evaluated in patients under 18 years of age.

Preclinical data

Carcinogenicity and genotoxicity

No carcinogenicity or genotoxicity studies have been conducted with SARCLISA..

Reproductive toxicity

No toxicity studies relating to reproduction, embryo-foetal development or fertility have been carried out.

Other information

Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in the section "Instructions for handling".

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the container.

Shelf life after opening

Microbiological, chemical and physical in-use stability of SARCLISA infusion solution has been demonstrated for 48 hours at 2–8°C, followed by 8 hours (including the infusion time) at room temperature. No protection from light is required for storage in the infusion bag.

Special precautions for storage

Keep refrigerated (2–8°C).
Do not freeze.
Keep in original packaging, away from light.
Do not shake.
Keep out of the reach of children.

Special precautions for disposal and other handling

Preparation for the intravenous administration
The infusion solution must be prepared under aseptic conditions.

- The dose (mg) of required SARCLISA concentrate should be calculated based on patient weight (measured prior to each cycle so that the administered dose adjusted accordingly (see

"Dosage/Administration"). More than one SARCLISA concentrate vial may be necessary to obtain the required dose for the patient.

- Vials of SARCLISA concentrate should be visually inspected before dilution to ensure they do not contain any particles and are not discolored.
- The appropriate volume of SARCLISA concentrate should be withdrawn and diluted in an infusion bag with 250 mL of 9 mg/mL (0.9%) of sodium chloride or dextrose 5% solution to achieve the appropriate SARCLISA concentration for infusion.
- The infusion bag must be made of polyolefins (PO), polyethylene (PE), polypropylene (PP), polyvinyl chloride (PVC) with di (2-ethylhexyl) phthalate (DEHP) or ethyl vinyl acetate (EVA).
- Gently homogenise the diluted solution by inverting the bag. Do not shake.

Administration

- The infusion solution must be administered by intravenous infusion using an IV tubing infusion set (in PE, PVC with or without DEHP, polybutadiene (PBD) or polyurethane (PU)) with an in-line filter (polyethersulfone (PES), polysulfone or nylon).
- The infusion solution should be administered for a period of time that will depend on the infusion rate (see "Dosage/Administration").
- Prepared SARCLISA infusion solution should be used within 48 hours when stored at 2–8°C, followed by 8 hours (including the infusion time) at room temperature.
- No protection from light is required for the prepared infusion bag in a standard artificial light environment.
- Do not infuse SARCLISA solution concomitantly in the same intravenous line with other agents.

Disposal

Dispose of any unused medicinal product or waste material in accordance with local requirements.

Marketing authorisation number

67525 (Swissmedic)

Nature and contents of container

SARCLISA 100 mg/5mL, concentrate for solution for infusion in a glass vial: each carton contains 1 or 3 single-use vial(s) (A)
SARCLISA 500 mg/25mL, concentrate for solution for infusion in a glass vial: each carton contains 1 single-use vial (A)

Marketing authorisation holder

sanofi-aventis (switzerland) sa, 1214 Vernier / GE

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