swissmedic

Date: 6 September 2023
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report
Extension of therapeutic indication

Sarclisa

International non-proprietary name: isatuximab

Pharmaceutical form: concentrate for solution for infusion

Dosage strength(s): 100 mg/5 mL, 500 mg/25 mL

Route(s) of administration: intravenous

Marketing authorisation holder: Sanofi-Aventis (Suisse) SA

Marketing authorisation no.: 67525

Decision and decision date: extension of therapeutic indication approved on 12.06.2023

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.

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1 Terms, Definitions, Abbreviations

1L	First-line
2L	Second-line
ADA	Anti-drug antibody
ADCC	Antibody-dependent cell-mediated cytotoxicity
ADCP	Antibody-dependent cellular phagocytosis
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ASCT	Autologous stem cell transplantation
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
CDC	Complement-dependent cytotoxicity
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CR	Complete response
CT4W	C_{trough} at week 4
CYP	Cytochrome P450
DDI	Drug-drug interaction
DOR	Duration of response
ECOG	Eastern Cooperative Oncology Group
EMA	European Medicines Agency
ER	Exposure-response
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
HR	Hazard ratio
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
IKd	Isatuximab + carfilzomib + dexamethasone
IMWG	International Myeloma Working Group
INN	International non-proprietary name
IPd	Isatuximab + pomalidomide + dexamethasone
ITT	Intention-to-treat
Kd	Carfilzomib + dexamethasone
LoQ	List of Questions
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
NCCN	National Comprehensive Cancer Network
NO(A)EL	No observed (adverse) effect level
ORR	Overall response rate
OS	Overall survival

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PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PFS	Progression-free survival
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
RRMM	Relapsed and/or refractory multiple myeloma
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
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)
Vc	Volume of central distribution
VGPR	Very good partial response

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2 Background information on the procedure

2.1 Applicant's request(s)

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

Extension(s) of the therapeutic indication(s)
The applicant requested the addition of a new therapeutic indication or modification of an approved one in accordance with Article 23 TPO.

2.2 Indication and dosage

2.2.1 Requested indication

Sarclisa is indicated in combination with carfilzomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior line of therapy.

2.2.2 Approved indication

Sarclisa is indicated in combination with carfilzomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received 1 to 3 prior lines of therapy.

2.2.3 Requested dosage

Summary of the requested standard dosage:
The recommended dose of Sarclisa is 10 mg/kg body weight as intravenous infusion in combination with carfilzomib and dexamethasone, according to the schedule in the following table:

Cycles	**SARCLISA (isatuximab)**	**Carfilzomib**	**Dexamethasone**
Cycle 1	Days 1, 8, 15 and 22 (weekly)	Days 1, 2, 8, 9, 15 and 16	Days 1, 2, 8, 9, 15, 16, 22 and 23
Cycle 2 and beyond	Days 1, 15 (every 2 weeks)	Days 1, 2, 8, 9, 15 and 16	Days 1, 2, 8, 9, 15, 16, 22 and 23

The initial recommended dose of carfilzomib is 20 mg/m^2 on days 1 and 2 of cycle 1, and then 56 mg/m^2 for the following infusions.

Dexamethasone (intravenously on the days of isatuximab and/or carfilzomib infusions, and orally on the other days) 20 mg is given on days 1, 2, 8, 9, 15, 16, 22, and 23 for each 28-day cycle.

On the days when both Sarclisa and carfilzomib are administered, dexamethasone is to be administered first, followed by Sarclisa infusion, then by carfilzomib infusion.

Each treatment cycle consists of a 28-day period. Treatment is repeated until disease progression or unacceptable toxicity.

2.2.4 Approved dosage

(see appendix)

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2.3 Regulatory history (milestones)

Application	30 September 2022
Formal control completed	4 October 2022
Preliminary decision	19 January 2023
Response to preliminary decision	19 March 2023
Labelling corrections	21 April 2023
Response to labelling corrections	21 May 2023
Final decision	12 June 2023
Decision	approval

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3 Medical context

3.1 Information on the condition being treated

Multiple Myeloma (MM) is a malignancy involving clonal expansion of plasma cells in the bone marrow and associated with the production of excessive amounts of a monoclonal immunoglobulin (usually IgG or IgA or urinary light chain). This is known as paraprotein, M-protein, or M-component. MM is considered incurable and has seen improvements in treatment in recent years with the development of more effective agents such as immunomodulators (thalidomide, lenalidomide, and pomalidomide), proteasome inhibitors (bortezomib, carfilzomib, and ixazomib), and anti-CD38 antibodies (which includes the current agent under consideration isatuximab and also daratumumab). These agents have significantly improved overall survival of myeloma patients from approximately 3 to 6 years (Röllig et al. 2015).

3.2 Current treatment options

First-line treatment often involves induction followed by maintenance therapy. This includes thalidomide, bortezomib, and/or lenalidomide. For younger and fit patients autologous stem cell transplantation (ASCT) is part of the first-line consolidation therapy. In patients not eligible for high-dose therapy and ASCT, conventional therapy with immunomodulatory agents, proteasome inhibitors, monoclonal antibodies, and conventional cytotoxic agents is used. The majority of patients will progress or relapse and need further lines of therapy.

3.3 Clinical rationale

Isatuximab (SAR650984) is an IgG1-derived monoclonal antibody that selectively binds to a unique epitope of CD38 and triggers several mechanisms leading to the death of CD38-expressing tumour cells. CD38 is a transmembrane glycoprotein with ectoenzymatic activity and is expressed in haematological malignancies and overexpressed in MM cells, with >98% of MM patients being positive for CD38 (Goldmacher et al., 1994; Lin et al., 2004).

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4 Nonclinical aspects

This is an authorisation application for the extension of the indication for Sarclisa with isatuximab as the active ingredient. The company has not submitted any preclinical documentation. The lack of an environmental risk assessment can be accepted, since no additional risks or an increase in environmental pollution can be expected. As the dose strength, route of administration, and dosing recommendation remain unchanged, the lack of preclinical documentation is acceptable. Efficacy for the proposed indication is to be clinically assessed.

From the nonclinical review perspective, there were no open questions based on the documentation submitted.

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5 Clinical aspects

5.1 Clinical pharmacology

Special Populations

The pharmacokinetics of isatuximab in the study EFC15246 (IKEMA) patient population was investigated in a PopPK analysis. The dataset included 172 patients with multiple myeloma (MM) treated with isatuximab plus carfilzomib and dexamethasone. The overall age range of the patients was 37 to 86 years. Fifteen (8.72%) of the patients were older than 75 years, and 73 (42.44%) were between 65 and 75 years old. The overall weight range was 44 to 123 kg. The majority of the patients (73.26%) were Caucasians. As expected from the age distribution, 52.33% of the patients had mild renal impairment. The dataset included only 5 (2.91%) patients with severe renal impairment. The majority of the patients (90.12%) had normal hepatic function. The dataset included only 2 (1.16%) patients with moderate hepatic impairment and no patients with severe hepatic impairment.

The majority of the patients had serum albumin levels < 35 g/L (74.42%), Ig MM type with serum M protein (90.7%), and Ig type IgG.

Compared to the patient population of the previous isatuximab PopPK analysis, the current patient population had a slightly less advanced disease state.

The final previous PopPK model was a 2-compartment model with combined linear and non-linear elimination. The linear clearance was time-dependent and decreased over time. This decrease is deemed to be associated with disease improvement. It included body weight as a covariate of volume and linear clearance terms, Asian race and gender as covariates of Vc, and IgG type and beta-2 microglobulin as covariates of clearance. This model (with fixed parameters) was applied to the EFC15246 (IKEMA) dataset in order to obtain post hoc Bayesian isatuximab exposure estimates. The model described the EFC15246 (IKEMA) data reasonably well. As in the previous analysis, Ig MM type was the covariate with the largest impact on isatuximab exposure.

Compared to MM patients treated with isatuximab + pomalidomide + dexamethasone (IPd), the mean isatuximab C_{max} and AUC_{1week} in the current patient population (isatuximab + carfilzomib + dexamethasone (IKd)) after the first administration were approximately 1.35- and 1.42-fold higher, respectively. At steady state (Cycle 6), C_{max}, and AUC_{2weeks} were approximately 1.87- to 2.19-fold higher. The higher isatuximab exposures in IKd patients were most likely caused by a combination of better health status and different bioanalytical methods.

Interactions

There were no mutual pharmacokinetic interactions between isatuximab and carfilzomib.

Pharmacodynamics

Relationship between Plasma Concentration and Effect

The relationship between efficacy and safety endpoints and isatuximab exposures was investigated in Study EFC15246 (IKEMA). The dataset included 294 patients, of whom 122 were randomised to carfilzomib + dexamethasone (Kd) and 172 were randomised to isatuximab + carfilzomib + dexamethasone (IKd). The patients in the first isatuximab exposure quartile were more severely ill than the patients in the higher exposure quartiles. Considering the target-mediated disposition of isatuximab PK, this finding is not unexpected.

Efficacy

Consistent with the previous exposure-response (ER) analyses, isatuximab C_{trough} at Week 4 (CT4W) was the best predictor of isatuximab efficacy.

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As the overall response rate (ORR) was similar in the IKd and Kd arms of study EFC15246, only descriptive ER analyses were done. The isatuximab exposures were higher in responders than in non-responders. The analyses by CT4W quartiles showed a lower response rate in the first quartile. The response rates in the higher quartiles were similar and higher compared to Q1 and Kd.

In summary, there was an ER relationship for all efficacy endpoints. However, it appeared to be mainly driven by the differences between the first and the other exposure quartiles. The assessment of efficacy in Q1 is confounded by the relationship between isatuximab exposure and disease severity due to target-mediated disposition. Nevertheless, compared to Kd, even the patients in Q1 appeared to benefit from IKd.

Safety
The incidence of the safety endpoints investigated was generally higher in the IKd group than in the Kd group of Study EFC15246, but there was no trend of increasing adverse event (AE) incidence with increasing isatuximab exposures.

5.2 Dose finding and dose recommendation

No new dose finding studies have been submitted. The proposed dose of 10 mg/kg isatuximab on days 1, 8, 15, and 22 in cycle 1 and on days 1 and 15 in cycle 2 and following cycles corresponds to the currently authorised dose.

5.3 Efficacy

The pivotal Study EFC15246 (IKEMA) was a randomised, open-label multicentre study assessing isatuximab with carfilzomib and dexamethasone (IKd) vs. carfilzomib with dexamethasone (Kd) in patients with relapsed and/or refractory multiple myeloma (RRMM) patients previously treated with 1-3 lines of therapy. This involved 69 study centres in 16 countries. The first patient was enrolled on 25 October 2017 and the last patient on 7 February 2020.

In this prospective, multicentre, multinational, randomised, open-label, parallel-group, 2-arm study, patients were treated with isatuximab 10mg/kg body weight weekly in the first cycle (4 weeks) and every 2 weeks when combined with carfilzomib twice per week 3 out of 4 weeks and dexamethasone twice weekly (IKd arm). The comparator arm was carfilzomib twice per week 3 out of 4 weeks and dexamethasone twice weekly without isatuximab (Kd arm). Patients were randomly assigned in a 3:2 ratio to the IKd:Kd arm.

The primary objective of the study was to demonstrate the benefits of IKd in the prolongation of progression-free survival (PFS) using the International Myeloma Working Group (IMWG) criteria.

Key secondary efficacy objectives were to evaluate the overall response rate (ORR), the rate of very good partial response (VGPR) or better, the rate of VGPR or better with minimal residual disease (MRD) negativity, complete response (CR) rate in both arms (IMWG criteria), and the overall survival (OS) in both arms.

The applicant provided the final PFS analysis of study EFC15246 (cut-off: 14.01.2022) with a median follow-up of 44 months. The primary endpoint of the study was met, and the addition of isatuximab to Kd led to a statistically significant improvement in PFS (Independent Review Committee [IRC] assessment) compared to Kd, with a hazard ratio (HR) of 0.576 (95% CI: 0.418-0.792). The median PFS was 35.65 months in the IKd arm compared to 19.15 in the Kd arm and the one-sided p-value was 0.0002. The ORR was similar in both arms 86.6% in IKd and 82.9% in Kd, respectively. The depth of response was deeper with IKd vs. Kd, with 72.6% and 56.1% of patients with VGPR or better. Also, the proportion of patients with MRD negativity (next generation sequencing (NGS) level: 10(-5)) was improved by 14% (29.6% vs. 13%). OS was not mature and is planned to be analysed 3 years after the primary end point (PFS) is met. In the pre-planned analysis of OS at the date of the final PFS analysis, 35.8% of patients in the IKd arm and 43.9% of patients in the KD arm have died,

with an HR of 0.78 (95% CI: 0.542–1.123). The curves start to separate after 33 months in favour of patients in the IKd arm, and no detrimental effect is observed.

5.4 Safety

The pivotal study EFC15246 (IKEMA), which assessed addition of isatuximab to carfilzomib and dexamethasone in RRMM, revealed more grade 3/4 events (82.5% vs. 72.1%) and a higher rate of SAEs (70.1 vs. 59.8%) with the 3-drug regimen (Data cut-off: 20.07.2022). Grade 5 adverse events were similar between the IKd and Kd arms (5.6% vs. 4.9%, respectively).
Focussing on SAEs, infections (including higher grade and grade 5 events) occurred more frequently in the 3-drug regimen (44.6% vs. 31.1%, respectively). Similarly, cardiac disorders occurred more frequently in patients treated in the IKd arm (10.2%) as compared to the Kd arm (6.6%). The exposure-adjusted analysis revealed that the event rate per patient year remained higher for infections in the 3-drug regimen, while the event rate for cardiac disorders was similar between the 3- and 2-drug regimens.

5.5 Final clinical benefit risk assessment

Beneficial Effects and Associated Uncertainties
The previous PopPK model described the EFC15246 data after IKd treatment reasonably well. The isatuximab exposures were up to 2-fold higher in the EFC15246 patient population compared to the previous EFC14335 (IPd) patient population. This increase is most likely due to different bioanalytical methods and different disease severity.

There were no mutual pharmacokinetic interactions between isatuximab and carfilzomib.
There was an ER relationship for all efficacy endpoints, which appeared to be mainly driven by the difference between exposure quartile 1 and the higher quartiles. The differences between Q2 to Q4 were negligible. The assessment of the Q1 data is confounded by the relationship between isatuximab exposure and disease severity. Nevertheless, the ER analyses indicated a benefit regarding PFS after IKd compared to Kd even for the Q1 patients.
There was no ER relationship for safety endpoints.

Conclusion Clinical Pharmacology
From a mechanistic point of view, the isatuximab PK is consistent between the prior and the current patient population. The ER analyses support the proposed dosing regimen.

Conclusion Clinical Assessment
Based on the final PFS analysis and the updated OS data which - although still immature - show a separation in favour of the experimental arm and an acceptable safety profile in the hands of experienced oncologists, the risk benefit is considered positive.

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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 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.

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7 Appendix

Approved information for healthcare professionals

Please be aware that the following version of the information for healthcare professionals for Sarclisa 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.

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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.

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 who have received at least two prior lines of therapy including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy.
- in combination with carfilzomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received 1 to 3 prior lines of 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:

- Dexamethasone 40 mg PO or IV (or 20 mg PO or IV for patients ≥75 years of age) D1, D8, D15, D22 (weekly) for each 28-day cycle: when administered in combination with SARCLISA and pomalidomide (please refer to below table 1 for dosing schedule).
- Dexamethasone 20 mg (IV on the days of SARCLISA and/or carfilzomib infusions, and PO on the other days) D1, D2, D8, D9, D15, D16, D22 and D23 for each 28-day cycle: when administered in combination with SARCLISA and carfilzomib (please refer to below table 2 for dosing schedule).
- Paracetamol 650 mg to 1000 mg PO (or equivalent).
- 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 and before isatuxumab and carfilzomib 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 (Isa-Pd) or in combination with carfilzomib and dexamethasone (Isa-Kd), according to the schedules in Tables 1 and 2:

In combination with pomalidomide and dexamethasone

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

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)

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.

In combination with carfilzomib and dexamethasone

Table 2 - SARCLISA dosing schedule in combination with carfilzomib and dexamethasone

Cycles	SARCLISA (isatuximab)	Carfilzomib	Dexamethasone
Cycle 1	D1, D8, D15 and D22 (weekly)	D1, D2, D8, D9, D15 and D16	D1, D2, D8, D9, D15, D16, D22 and D23
Cycle 2 and subsequent cycles	D1, D15 (once every two weeks)	D1, D2, D8, D9, D15 and D16	D1, D2, D8, D9, D15, D16, D22 and D23

The starting dose for carfilzomib is 20 mg/m² on D1 and D2 of cycle 1 and then 56 mg/m² for further infusions. The dose of dexamethasone is 20 mg on days D1, D2, D8, D9, D15, D16, D22 and D23. Dexamethasone is administered intravenously on the days of SARCLISA and/or carfilzomib infusions, orally on day 22 in cycle 2 and beyond, and orally on day 23 in all cycles.
On the days where both SARCLISA and carfilzomib were administered, dexamethasone was administered first, followed by SARCLISA infusion, then followed by carfilzomib infusion.
Each treatment cycle consists of a 28-day period. Treatment is repeated until disease progression or unacceptable toxicity.
For the adaptation of pomalidomide, carfilzomib and dexamethasone doses, see section “Clinical efficacy” and the respective current Information for Healthcare Professionals.
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 3 below. Incremental escalation of the infusion rate should be considered only in the absence of infusion reactions (IR).

Table 3 – 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/hour	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 requiring an intervention (grade 2, moderate IR), a temporary interruption of the infusion should be considered, and additional symptomatic medication can be administered. After symptom improvement to grade ≤1 (mild), 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 3 (see "Warnings and precautions").
- If symptoms do not resolve rapidly or do not improve to grade ≤1 after interruption of SARCLISA infusion, persist or worsen despite appropriate medications, or require hospitalisation or are life-threatening, treatment with SARCLISA should be permanently discontinued and additional supportive therapy should be administered (see "Warnings and precautions").

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 Information for Healthcare Professionals.

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 44.3% of patients treated with SARCLISA (see "Undesirable effects"). Almost all IRs started during the first SARCLISA infusion (42.8%), and resolved on the same day in most patients. The most common symptoms of an IR included dyspnoea, cough, chills, nausea, and nasal congestion. The most common severe signs and symptoms included hypertension,dyspnoea and bronchospasm.
SARCLISA may cause serious infusion reactions including anaphylactic reactions (see “Dosage/administration” and "Undesirable effects").
To decrease the risk and severity of IRs, patients should be pre-medicated prior to SARCLISA infusion with paracetamol, 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 to grade ≤1 after interruption of SARCLISA infusion, persist or worsen despite 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). The indirect antiglobulin test was positive during isatuximab treatment in 64.2% 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").

Cardiac failure

In IKEMA, cardiac failure (including cardiac failure, cardiac failure congestive, cardiac failure acute, cardiac failure chronic, left ventricular failure and pulmonary edema) was reported in 7.3% of patients with the Isa-Kd group (4.0% of grade ≥3) and in 6.6% of patients with the Kd group (4.1% of grade ≥3). Serious cardiac failure was observed in 4.0% of patients in the Isa-Kd group and in 3.3% of patients in the Kd group (see the current carfilzomib’s Information for Healthcare Professionals).

Neutropenia

In patients treated with Isa-Pd, neutropenia occurred as a laboratory abnormality in 94.7% of patients and as an adverse reaction in 47.4% of patients, with grade 3-4 neutropenia reported as a laboratory abnormality in 81.6% of patients and as an adverse reactions in 46.5% of patients. Neutropenic complications (all grades) have been observed in 23.9% of patients, including 8.3% of febrile neutropenia and 20.0% of neutropenic infections(see "Undesirable effects").
In patients treated with Isa-Kd, neutropenia occurred as a laboratory abnormality in 54.8% of patients and as an adverse reaction in 4.5% of patients, with grade 3-4 neutropenia reported as a laboratory abnormality in 19.2% of patients (with 17.5% grade 3 and 1.7% grade 4) and as an adverse reaction in 4.0% of patients. Neutropenic complications have been observed in 2.8% of patients, including 1.1% of febrile neutropenia and 1.7% of neutropenic infections (see section “Undesirable effects”). Monitor complete blood cell counts periodically during treatment. Antibacterial 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”).

Infections

A higher incidence of infections, including grade ≥ 3 infections, mainly pneumonia, upper respiratory tract infection and bronchitis, occurred with SARCLISA (see "Undesirable effects"). Patients receiving SARCLISA should be closely monitored for signs of infection and appropriate standard therapy instituted.

Second primary malignancies

In ICARIA-MM, second primary malignancies (SPMs) were reported in 6 patients (3.9%) treated with Isa-Pd and in 1 patient (0.7%) treated with Pd, and included skin cancer in 4 patients treated with Isa-Pd and in 1 patient treated with Pd. Patients continued treatment after resection of the skin cancer. In IKEMA, SPMs were reported in 13 patients (7.3%) treated with Isa-Kd and in 6 patients (4.9%) treated with Kd. SPMs were skin cancers in 9 patients (5.1%) treated with Isa-Kd and in 3 patients (2.5%) treated with Kd, and were solid tumours other than skin cancer in 5 patients (2.8%) treated with Isa-Kd and in 4 patients (3.3%) treated with Kd. One patient (0.6%) in the Isa-Kd group and one patient (0.8%) in the Kd group had both skin cancer and solid tumours other than skin cancer. Patients with skin cancer continued treatment after resection of the skin cancer. Solid tumours other than skin cancer were diagnosed within 3 months after treatment initiation in 3 patients (1.7%) treated with Isa-Kd and in 2 patients (1.6%) treated with Kd. The overall incidence of SPMs in all the SARCLISA-exposed patients is 3.6% and included skin cancer in 2.1%, solid non skin cancer in 1.5% and hematological malignancy in 0.2% of patients treated with isatuximab. Physicians should carefully evaluate patients before and during treatment as per IMWG guidelines for occurrence of SPM and initiate treatment as indicated.

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. Interference between Isatuximab and the myeloma M-protein was shown by mass spectrometry in ICARIA and IKEMA clinical trials. (see "Interactions").

Interactions

SARCLISA has no impact on the pharmacokinetics of pomalidomide or carfilzomib, or vice versa (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"). In patients with persistent very good partial response (VGPR), in whom isatuximab interference is suspected, consideration should be given to the use of a validated isatuximab-specific IFE assay to differentiate isatuximab from endogenous M protein that may remain in the patient's serum to facilitate determination of complete response (CR) (see "Clinical Studies").

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 "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

The safety data of isatuximab have been assessed from a total of 1047 patients with multiple myeloma treated with isatuximab in combination with pomalidomide and dexamethasone (244 patients), isatuximab in combination with carfilzomib and dexamethasone (177 patients), isatuximab in combination therapies that are not currently authorized and as monotherapy (626 patients) pooled across clinical trials.
The most frequent adverse reactions (in ≥ 20% of patients) were infusion reactions (44.3%), fatigue (27.7%), diarrhoea (26.9%) and upper respiratory tract infection (25.8%). The most frequent serious adverse reaction (in ≥ 5% of patients) was pneumonia (14.2%). Permanent discontinuation of treatment because of adverse reactions was reported in 84 patients (8.0%).

Summary of the safety profile

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 category, the adverse reactions in question are presented in order of decreasing seriousness.
The adverse reactions observed during the treatment period in 1047 patients with multiple myeloma and treated with Isatuximab are presented below:

Infections and infestations

Very common: upper respiratory tract infection (all grades: 25.8%; grade 3: 1.9%; grade 4< 0.14%), pneumonia [a] (all grades: 18.6%; grade 3: 12.2%; grade 4: 1.5%), bronchitis (all grades: 12.7%; grade 3: 1.6%; grade 4: 0%).
Common: herpes zoster (all grades: 2.6%; grade 3: 0.4%, grade 4: 0%).
[a] The term "pneumonia" is a grouping of the following terms: pneumonia, pneumonia viral, pneumocystis jirovecii pneumonia, atypical pneumonia, pneumonia bacterial, pulmonary sepsis, pneumonia influenzal, pneumonia haemophilus, pneumonia pneumococcal, pneumonia streptococcal, bronchopulmonary aspergillosis, haemophilus infection, pneumonia fungal, pneumonia legionella,

pneumomia mycoplasmal, pneumonia parainfluenzae viral, pneumonia respiratory syncytial viral and pneumonia staphylococcal.

Blood and lymphatic system disorders

Haematology laboratory abnormalities in patients receiving isatuximab treatment are presented below:
Very common: anaemia (all grades: 97.4%; grade 3: 23.4%; grade 4: 0%), lymphopenia (all grades: 85.1%; grade 3: 36.4%; grade 4: 12.1%), thrombocytopenia (all grades: 76.4%; grade 3: 12.5%; grade 4: 11.1%), neutropenia (for patients receiving Isa-Pd: all grades: 95.0%; grade 3: 26.9%; grade 4: 55.4%, for patients receiving Isa-Kd: all grades: 54.8%; grade 3: 17.5%; grade 4: 1.7%), febrile neutropenia (for patients receiving Isa-Pd all grades: 8.3%; grade 3: 7.4%; grade 4: 0.9%, for patients receiving Isa-Kd: all grades: 1.1%; grade 3: 1.1%; grade 4: 0%)
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: 9.6%; grade 3: 0.5%; grade 4: 0%), hypokalaemia (all grades: 2.9%; grade 3: 0.9%; grade 4: 0%), dehydration (all grades: 2.7%; grade 3: 0.6%; grade 4: 0%), hyperglycaemia (all grades: 2.7%; grade 3: 1.2%; grade 4: 0.4%), hypercalcaemia (all grades: 2.3%; grade 3: 0.5%; grade 4: 1.0%), diabetes mellitus (all grades: 1.1%; grade 3: 0.4%; grade 4: 0.2%), hypomagnesaemia (all grades: 1.0%; grade 3: 0%; grade 4: 0%), weight decrease (all grades: 4.8%; grade 3< 0.1%; grade 4: 0%), weight increased (all grades: 1.1%; grade 3< 0.1%; grade 4: 0%).

Cardiac disorders

Common: Atrial fibrillation (all grades: 2.5%; grade 3: 1.0%; grade 4< 0.1%), palpitations (all grades: 1.5%; grade 3: 0%; grade 4: 0%), sinus tachycardia (all grades: 1.1%; grade 3: 0%; grade 4: 0%), tachycardia (all grades: 1.1%; grade 3< 0.1%; grade 4: 0%), angina pectoris (all grades: 1.0%; grade 3: 0%; grade 4: 0%).

Vascular disorders

Very common: hypertension (all grades: 10.8%; grade 3: 5.2%; grade 4: 0).

Respiratory, thoracic and mediastinal disorders

Very common: cough (all grades: 16.0%; grade 3: 0%; grade 4: 0%), dyspnoea (all grades: 14.1%; grade 3: 2.3%; grade 4: 0%).

Gastrointestinal disorders

Very common: diarrhoea (all grades: 26.9%; grade 3: 2.0%; grade 4: 0%), nausea (all grades: 18.5%; grade 3: 0.2%; grade 4: 0%), constipation (all grades: 12.4%; grade 3: 0.3%; grade 4: 0%), vomiting (all grades: 12.3%; grade 3: 0.7%; grade 4: 0%).

General disorders and administration site conditions

Very common: fatigue (all grades: 27.7%; grade 3: 2.7%; grade 4: 0%), pyrexia (all grades: 12.5%; grade 3: 1.0%; grade 4: 0%), oedema peripheral (all grades: 10.9%; grade 3: 0.4%; grade 4: 0%).

Renal and urinary disorders

Common: blood creatinine increased (all grades: 2.0%; grade 3: 0.4%; grade 4: 0%),

Injury, poisoning and procedural complications

Very common: infusion reaction (all grades: 44.3%; grade 3: 1.6%; grade 4: 0.6%).

Description of specific adverse reactions and further information.

Infusion reactions

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 464 patients (44.3%) treated with SARCLISA.. Among the 1047 patients, 448 (42.8%) experienced IRs during the 1st infusion of SARCLISA, with 16 patients (1.5%) also having IRs at subsequent infusions. Grade 1 IRs were reported in 6.9%, grade 2 in 35.2%, grade 3 in 1.6%, and grade 4 in 0.6% of the patients. Signs and symptoms of grade 3 or 4 IRs included hypertension (1.3%) dyspnoea (1.1%)and bronchospasm (1.1%).
The incidence of patients with infusion interruptions because of infusion reactions was 32.6%. The median time to infusion interruption was 60 minutes. The median duration of SARCLISA infusion was 3.9 hours during the first infusion and 2.83 hours for the subsequent infusions. Isatuximab was discontinued in 2.3% of patients due to infusion reactions.
In multiple myeloma clinical trials, anaphylactic reactions have been reported in association with infusion reactions in 0.3% of patients. Signs and symptoms of anaphylactic reactions included bronchospasm, dyspnea, angioedema, and swelling.

Infections

The incidence of grade 3 or higher infections was 27.5%. Pneumonia was the most commonly reported severe infection with grade 3 reported in 12.2% of patients, and grade 4 in 1.5% of patients. Discontinuations from treatment due to infection were reported in 2.4% of patients. Fatal infections were reported in 1.9% of patients.

Immunogenicity

As with all therapeutic proteins, there is a potential for immunogenicity to SARCLISA.
In ICARIA-MM and IKEMA studies, no patients tested positive for anti-drug antibodies (ADA). Therefore, the neutralising ADA status was not determined. Overall, across 9 multiple myeloma (MM) clinical studies with SARCLISA single agent and combination therapies including ICARIA-MM and IKEMA (N=1018), the incidence of treatment-emergent ADAs was 1.9% (19 patients with positive ADA response out of the 1018 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 of isatuximab 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

L01FC02

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 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 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. 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 were refractory to lenalidomide (92.5%), to a proteasome inhibitor (75.9%), to both an immunomodulatory and a proteasome inhibitor (72.6%), and to lenalidomide at last line of therapy (59%).

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 4:

Table 4 - Efficacy of SARCLISA in combination with pomalidomide and dexamethasone versus pomalidomide and dexamethasone in the treatment of multiple myeloma (intent-to-treat analysis)

Endpoint	SARCLISA + pomalidomide + dexamethasone N = 154	Pomalidomide + dexamethasone N = 153
Overall Response Rate[a] Responders (sCR+CR+VGPR+PR), 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	
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 52.44 months, final median overall survival was 24.57 months in the Isa-Pd group and 17.71 months in Pd group (HR=0.776; 95% CI: 0.594 to 1.015).
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").

IKEMA (EFC15246)

The efficacy and safety of SARCLISA in combination with carfilzomib and dexamethasone were evaluated in IKEMA (EFC15246), a multicenter, multinational, randomized, open-label, 2-arm, phase III study in patients with relapsed and/or refractory multiple myeloma. Patients had received one to three prior lines of therapies. Patients with primary refractory disease, who had previously been treated with carfilzomib, or who were refractory to previous anti-CD38 monoclonal antibody treatment or who had acute cardiac events within 4 to 6 months prior to treatment or with left ventricular ejection fraction (LVEF) < 40% were excluded.

A total of 302 patients were randomized in a 3:2 ratio to receive either SARCLISA in combination with carfilzomib and dexamethasone (Isa-Kd, 179 patients) or carfilzomib and dexamethasone (Kd, 123 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.

Overall, demographic and disease characteristics at baseline were similar between the two treatment groups. The median patient age was 64 years (range 33-90), 8.9% of patients were ≥75 years. The proportion of patients with renal impairment (eGFR<60 ml/min/1.73m2) was 24.0% in the Isa-Kd group versus 14.6% in the Kd group. The International Staging System (ISS) stage at study entry was I in 53.0%, II in 31.1%, and III in 15.2% of patients.

The median number of prior lines of therapy was 2 (range 1-4) with 44.4% of patients who received 1 prior line of therapy. Overall, 89.7% of patients received prior proteasome inhibitors, 78.1% received prior immunomodulators (including 43.4% who received prior lenalidomide), and 61.3% received prior stem cell transplantation. Overall, 33.1% of patients were refractory to prior proteasome inhibitors, 45.0% were refractory to prior immunomodulators (including 32.8% refractory to lenalidomide), and 20.5% were refractory to both a proteasome inhibitor and an immunomodulator.

The median duration of treatment was 80.0 weeks for the Isa-Kd group compared to 61.4 weeks for the Kd group.

Progression-free survival (PFS) was the primary efficacy endpoint of IKEMA. With a median follow-up time of 20.73 months, the primary analysis of PFS showed a statistically significant improvement in PFS represented by a 46.9% reduction in the risk of disease progression or death in patients treated with Isa-Kd compared to patients treated with Kd.

Efficacy results are presented in Table 5:

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

Endpoint	*SARCLISA + carfilzomib + dexamethasone N = 179*	*Carfilzomib + dexamethasone N = 123*
Progression-Free Survival[a,]*		
Median (months)	NR	19.15
[95% CI]	[NR-NR]	[15.77-NR]
Hazard ratio[b] [99% CI]	0.531 [0.318-0.889]	
p-value (Stratified Log-Rank test)[b]	0.0013	
Final Progression-Free Survival[**]		
Median (months)	35.65	19.15
[95% CI]	(25.758 to 43.959)	(15.770 to 25.035)
Hazard ratio[b] [95% CI]	0.576 [0.418 - 0.792]	
Nomimal p-value (Stratified Log-Rank test)[b]	0.0002	
*Overall Response Rate[c, *]*		
Responders (sCR+CR+VGPR+PR)	86.6%	82.9%
[95% CI][d]	[0.8071-0.9122]	[0.7509-0.8911]
p-value (stratified Cochran-Mantel-Haenszel)[b]	0.3859	
Complete Response (CR)	39.7%	27.6%
VGPR or better (sCR+CR+VGPR) [*]	72.6%	56.1%
[95% CI][d]	[0.6547-0.7901]	[0.4687 -0.6503]
Nominal p-value (stratified Cochran-Mantel-Haenszel) [b]	0.0021	
CR[e]	39.7%	27.6%
[95% CI][d]	[0.3244-0.4723]	[0.1996 to 0.3643]
*Minimal Residual Disease negative Rate[f, *]*	29.6%	13.0%
[95% CI][d]	[0.2303-0.3688]	[0.0762-0.2026]
Nominal p-value (stratified Cochran-Mantel-Haenszel)b	0.0008	

[a] 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.
[b] Stratified on number of previous lines of therapy (1 versus >1) and R-ISS (I or II versus III versus not classified) according to IRT.
[c] sCR, CR, VGPR, and PR were evaluated by the IRC using the IMWG response criteria.
[d] Estimated using Clopper-Pearson method.
[e] CR to be tested with final analysis.

[f] Based on a sensitivity level of 10-5 by NGS in ITT population.
[*] Cut-off date of 7 February 2020. Median follow-up time=20.73 months. HR<1 favors Isa-Kd arm.
NR: not reached.
[**] Final median PFS at a median follow-up time of 43.96 months.

At the time of the final PFS analysis with a median follow-up time of 43.96 months, the final complete response, determined using a validated isatuximab-specific IFE assay (Sebia Hydrashift) (see section “Interactions”), was 44.1% in Isa-Kd group compared to 28.5% in Kd group, with odds ratio 2.094 (95% CI: 1.259 to 3.482, descriptive p=0.0021).

With a median follow-up time of 20.73 months, 17.3% patients in the Isa-Kd arm and 20.3% patients in the Kd arm had died. With a median follow-up time of 43.96 months, 64 (35.8%) and 54 (43.9%) patients had death events in the IKd and Kd arms, respectively.

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 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. Part B of the study investigated a fixed infusion volume. Efficacy and safety results were consistent with the ICARIA-MM results (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 18 weeks with a 3.1-fold accumulation. In ICARIA-MM, 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. In IKEMA, the mean (CV%) predicted maximum plasma concentration C_{max} and AUC at steady state were 637 µg/ml (30.9%) and 152,000 µg.h/ml (37.8%), respectively.The difference in exposure with Isa-Kd compared to Isa-Pd is mainly due to change in the assay method for concentration determination and in a higher treatment effect in patients treated with Isa-Kd which presented with less advanced myeloma disease compared to those treated with isa-Pd.

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.

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

The clearance of satuximab increased with increasing body weight, supporting a weight-based dosing.

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. However, since isatuximab is a monoclonal antibody, it is not expected to be cleared via hepatic enzyme-mediated metabolism and as such, variation in hepatic function is not expected to affect the elimination of isatuximab (see section “Special dosage instructions”).

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 volume of diluent equal to the required volume of SARCLISA concentrate should be removed from a 250 ml sodium chloride 9 mg/ml (0.9%) solution for injection or glucose 5% solution diluent bag.
- The appropriate volume of SARCLISA concentrate should be withdrawn from the SARCLISA vial and diluted in an infusion bag with 250 ml of 9 mg/ml (0.9%) of sodium chloride or dextrose 5% solution.
- 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 a 0.22 micron 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 (between 15°C – 25°C).
- 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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