swissmedic

*Date:* 1 October 2025
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 19 May 2025

**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

| | |
|---|---|
| AE | Adverse event |
| ASCT | Autologous stem cell transplant |
| CI | Confidence interval |
| $C_{max}$ | Maximum observed plasma/serum concentration of drug |
| CR | Complete response |
| ERA | Environmental risk assessment |
| HR | Hazard ratio |
| $IC/EC_{50}$ | Half-maximal inhibitory/effective concentration |
| ICH | International Council for Harmonisation |
| Ig | Immunoglobulin |
| INN | International non-proprietary name |
| IKd | Isatuximab, carfilzomib, and dexamethasone |
| IMWG | International Myeloma Working Group |
| IPd | Isatuximab, pomalidomide, and dexamethasone |
| IRC | Independent review committee |
| IVRd | Isatuximab, bortezomib, lenalidomide, and dexamethasone |
| LoQ | List of Questions |
| MAH | Marketing Authorisation Holder |
| Max | Maximum |
| Min | Minimum |
| MM | Multiple myeloma |
| MRD | Minimal residual disease |
| NDMM | newly diagnosed multiple myeloma |
| NGS | Next generation sequencing |
| OS | Overall survival |
| PD | Pharmacodynamics |
| PFS | Progression-free survival |
| PK | Pharmacokinetics |
| PopPK | Population pharmacokinetics |
| R-ISS | Revised international staging system |
| RMP | Risk management plan |
| RRMM | Relapsed/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) |
| VGPR | Very good partial response |
| VRd | Bortezomib, lenalidomide and dexamethasone |



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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 4 paragraph 1 letter a$^{decies}$ no. 2 of the TPA.
Orphan drug status was granted on 12 July 2018.

**Work-sharing procedure**
The applicant requested a work-sharing procedure with Singapore's Health Sciences Authority (HSA).
The Access NAS (new active substance) work-sharing initiative is a collaboration between regulatory authorities – specifically Australia's Therapeutic Goods Administration (TGA), Health Canada (HC), Singapore's Health Sciences Authority (HSA), the UK Medicines & Healthcare products Regulatory Agency (MHRA) and Swissmedic - and the pharmaceutical industry.
The work-sharing initiative involves the coordinated assessment of NAS applications that have been filed in at least two jurisdictions.

**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 bortezomib, lenalidomide and dexamethasone, for the treatment of adult patients with newly diagnosed active multiple myeloma who are not eligible for autologous stem cell transplant (ASCT) or with no intent for ASCT as initial therapy.

### 2.2.2 Approved indication

SARCLISA is indicated in combination with bortezomib, lenalidomide and dexamethasone, for the treatment of adult patients with newly diagnosed multiple myeloma who are not eligible for autologous stem cell transplant (ASCT) (see "Clinical Efficacy").

### 2.2.3 Requested dosage

**Summary of the requested standard dosage:**

| Cycles | SARCLISA (isatuximab) 10 mg/kg body weight i.v. | Bortezomib 1.3 mg/m$^2$ s.c. | Lenalidomide 25 mg/day orally | Dexamethasone 20 mg/day i.v. / orally |
|---|---|---|---|---|
| Cycle 1 (42-day cycle) | D1, D8, D15, D22 and D29 (weekly) | D1, D4, D8, D11, D22, D25, D29 and D32 | D1 – D14 and D22 – D35 | D1, D2, D4, D5, D8, D9, D11, D12, D15, D22, D23, D25, D26, D29, D30, D32 and D33 |
| Cycles 2 to 4 (42-day cycles) | D1, D15 and D29 (once every two weeks) | D1, D4, D8, D11, D22, D25, D29 and D32 | D1 – D14 and D22 – D35 | D1, D2, D4, D5, D8, D9, D11, D12, D15, D22, D23, D25, D26, |



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| | | | | |
|---|---|---|---|---|
| | | | | D29, D30, D32 and D33 |
| Cycles 5 to 17 (28-day cycles) | D1 and D15 (once every two weeks) | - | D1 – D21 | D1, D8, D15, D22 (weekly) |
| Cycles 18 and subsequent cycles (28-day cycles) | D1 (once every four weeks) | - | D1 – D21 | D1, D8, D15, D22 (weekly) |

### 2.2.4 Approved dosage

(see appendix)

## 2.3 Regulatory history (milestones)

| | |
|---|---|
| Application | 30 September 2022 |
| Formal control completed | 27 June 2024 |
| List of Questions (LoQ) | 25 October 2024 |
| Response to LoQ | 22 December 2024 |
| Preliminary decision | 14 February 2025 |
| Response to preliminary decision | 3 March 2025 |
| Labelling corrections | 26 March 2025 |
| Response to labelling corrections | 16 April 2025 |
| Final decision | 19 May 2025 |
| Decision | approval |



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# 3 Medical context

Multiple myeloma (MM) is a plasma cell neoplasm that accounts for approximately 1 to 2% of all cancers and is the second most common haematological malignancy with an estimated incidence in Europe of approximately 5 to 6/100,000/year[1]. The incidence increases with age, and the median age at onset of MM is approximately 70 years, with approximately two thirds of patients aged older than 65 years. Since 2000, survival from the time of diagnosis of MM has improved. A recent long-term follow-up analysis of 1000 patients with newly diagnosed MM treated between 2007 and 2016 reported a median overall survival of approximately 10.5 years (median follow-up 67 months), while prior to the year 2000, median overall survival was closer to 2.5 years[2]. Despite therapeutic achievements, the disease recurs and remains incurable, thus warranting the need for novel therapeutic approaches[3].

Eligibility for autologous stem cell transplant (ASCT) is determined by several factors including age, performance status, and co-morbidities[4]. The reason for transplant ineligibility is an increased risk of treatment-related toxicities, caused by older age, high comorbid burden, or poor performance status[5]. International guidelines (e.g. ESMO, NCCN) recommend 3-drug and 4-drug regimens for those patients that are non-transplant candidates[6,1].

[1] Dimopoulos MA et al. Multiple myeloma: EHA-ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Annals of Oncology 2021;32:309-322 (including corrigendum 2022: https://doi.org/10.1016/j.annonc.2021.10.001).
[2] Cowan AJ et al. Diagnosis and Management of Multiple Myeloma – A Review. JAMA 2022;327:464-477.
[3] Rodriguez-Otero P, et al. International Myeloma Working Group. International Myeloma Working Group immunotherapy committee consensus guidelines and recommendations for optimal use of T-cell-engaging bispecific antibodies in multiple myeloma. Lancet Oncol. 2024 May;25(5):e205-e216. Erratum in: Lancet Oncol. 2024 Jul;25(7):e284.
[4] Goel U et al. Current approaches to management of newly diagnosed multiple myeloma. Am J Hematol. 2022 May;97 Suppl 1:S3-S25.
[5] Grant SJ, et al. Transplant-ineligible newly diagnosed multiple myeloma: Current and future approaches to clinical care: A Young International Society of Geriatric Oncology Review Paper. J Geriatr Oncol. 2021 May;12(4):499-507. doi: 10.1016/j.jgo.2020.12.001. Epub 2020 Dec 17
[6] NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®), Multiple Myeloma, version 1.2025, September 17, 2024.



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# 4 Nonclinical aspects

The applicant did not submit new nonclinical studies to support the requested new indication. This was considered acceptable since there are no changes with regard to dose and method of administration. According to ICH S9, toxicology studies investigating the safety of combinations of pharmaceuticals intended to treat patients with advanced cancer are not warranted, particularly if the human toxicity profile of the pharmaceuticals has been characterised. Thus, no additional nonclinical studies are required.
Since isatuximab is a protein consisting of naturally occurring amino acids, the extension of the indication will not be associated with a significant risk for the environment. The ERA is accepted.
From the nonclinical point of view, there are no objections to approval of the proposed indication.



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# 5 Clinical aspects

## 5.1 Clinical pharmacology

The pharmacokinetics (PK) of isatuximab in combination with bortezomib, lenalidomide, and dexamethasone (IVRd) in newly diagnosed multiple myeloma (NDMM) patients was investigated in the Phase 1 Study TCD13983 and the pivotal Phase 3 study EFC12522 (IMROZ). The clinical pharmacology package was supplemented with data from the Investigator-sponsored Phase 3 study IIT15403. Whereas rich PK samples were collected in study TCD13983, a sparse sampling strategy was applied in the Phase 3 studies.
The PK of isatuximab in NDMM patients was evaluated in multiple population PK analyses as PK data from the three studies became available. For the population PK analyses, the final model from previous submissions was used. This was a 2-compartment model with combined linear and non-linear elimination. The linear clearance was time-dependent and decreased over time. Ig MM type, β2-microglobulin, Weight, Sex and Asian Race were included in the final model. This model, with fixed parameters, was applied to the different NDMM patient datasets in order to obtain post hoc Bayesian isatuximab exposure estimates. Overall, the population PK model described the data reasonably well.
Using 3883 samples records from 281 NDMM patients enrolled in the pivotal Phase 3 study IMROZ, the PK of isatuximab as well as sources of variability were investigated. As compared to relapsed/refractory multiple myeloma (RRMM) patients enrolled in the ICARIA (pomalidomide and dexamethasone, IPd) and IKEMA (carfilzomib and dexamethasone, IKd) studies from previous submissions, the patients from the study IMROZ had a slightly more advanced disease state. Consistent with RRMM patients receiving IPd or IKd, isatuximab showed low linear clearance at steady state and a low volume of distribution in NDMM. As observed for the IKd population, the decrease in linear clearance was slightly delayed and more pronounced in NDMM patients receiving IVRd compared to IPd, resulting in higher exposures at steady state. The exposure differences after the first dose were mainly due to different assay methods.
In line with the previous analyses, Ig MM type, β2-microglobulin, and body weight were the covariates with the largest impact on isatuximab exposure. Overall, the magnitude of the covariate effects was comparable between the NDMM and RRMM populations. Lower exposure was observed in Asian patients compared to Caucasian patients in the pivotal Phase 3 study IMROZ. This effect was driven by the Chinese patients, in whom the slightly more advanced disease characteristics and the slightly lower body weight may have contributed to the effect.
Altogether, no isatuximab dose adjustments are required in the NDMM population for any of the investigated covariates, except for body weight, which is part of dosing regimen.

There were no mutual PK interactions between isatuximab, bortezomib, lenalidomide, and dexamethasone. Based on a comparison with published data, no impact of isatuximab on the PK of bortezomib and lenalidomide was observed. When compared to exposure data from previous submissions, isatuximab PK was not affected when co-administered in combination with bortezomib, lenalidomide, and dexamethasone.

## 5.2 Dose finding and dose recommendation

The dosage of isatuximab is the same as in the already approved indications: 10 mg/kg body weight weekly in cycles 1, and every 2 weeks (q2w) in cycle 2 and onwards. New is the reduction to every 4 weeks (q4w) starting in cycle 18 and onwards. This interval was implemented in phase 1 study TCD13983 (see below).

The combination partners lenalidomide combined with bortezomib and dexamethasone (VRd) are already approved in adult patients with NDMM, and the same doses as already approved were used in the pivotal study IMROZ. However, the rationale for reduced administered application of dexamethasone 20 mg on days 1, 4, 8, 11, 15, 22, 25, 29, and 32 in the older patient population was not provided.



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## 5.3 Efficacy

The applicant submitted two studies for the evaluation of efficacy and safety. The pivotal study was EFC12522 (IMROZ) and the supportive study TCD13983.

Study IMROZ is a randomised, open-label, phase III study that evaluates isatuximab in combination with bortezomib, lenalidomide and dexamethasone (IVRd) versus bortezomib, lenalidomide and dexamethasone (VRd) in participants with newly diagnosed multiple myeloma (NDMM) who are ineligible for ASCT. Participants were randomised in a 3:2 ratio of IVRd to VRd. Randomisation was stratified by country (Non-China versus China), age (<70 years versus ≥70 years) and revised international staging system (R-ISS) I or II versus III versus not classified.

For details regarding dosing, please refer to the attached Information for healthcare professionals.

Participants aged 18 to 80 years were eligible if they were diagnosed with multiple myeloma, as defined by the International Myeloma Working Group (IMWG) criteria and had evidence of measurable disease (serum M-protein/urine M-protein/serum free light chain) and were not considered for high-dose chemotherapy due to: age ≥ 65 years; or < 65 years with important comorbidities likely to have a negative impact on tolerability of high-dose chemotherapy with stem cell transplantation.

The primary endpoint was progression free survival (PFS) as per independent review committee (IRC). The key secondary endpoints were rate of complete response (CR), minimal residual disease (MRD) negativity rate in CR patients, rate of very good partial response (VGPR) or better and overall survival (OS).

With a median follow up of 59.7 months, 162 PFS events were reported. The addition of isatuximab to VRd led to a statistically significant (p-value=0,0009) improvement for the primary efficacy endpoint of PFS as per IRC, with a hazard ratio (HR) of 0.596 [98.5% CI: 0.406 to 0.876]. Median PFS was not reached for the IVRd group and was 54.3 months for the VRd group. A statistically significantly higher rate of CR was observed in the IVRd group compared to the VRd group (IVRd: 74.7%; VRd: 64.1% of participants; p-value=0,0160). With next generation sequencing (NGS) at $10^{-5}$, the MRD negativity rate in CR patients was statistically significantly higher in the IVRd group than in the VRd group at 55.5% versus 40.9%, p-value=0.0026. The depth of response, VGPR or better, was numerically, but not statistically significantly improved in the IVRd group compared to the VRd group (89.1% versus 82.9%). Therefore, the statistical testing hierarchy stopped. Consequently, the OS analysis is of descriptive nature. OS was immature at the time of data cutoff (26 September 2023) with a median follow-up of 59.7 months. The HR for OS was 0.776 (99.97% CI: 0.407 to 1.48) and the median OS was not reached in either group.

The supportive study TCD13983 was a Phase 1b, open-label, fixed-dose study of isatuximab administered in combination with bortezomib, lenalidomide, and dexamethasone in adult patients with NDMM not eligible for transplantation or with no intent for immediate transplantation.
The supportive efficacy results for PFS were in line with the phase III trial.

## 5.4 Safety

In study IMROZ, the most frequently reported treatment-emergent adverse events (TEAEs) in the IVRd arm (≥20%) by preferred term were peripheral sensory neuropathy (IVRd: 54.4%; VRd: 60.8%), diarrhoea (IVRd: 54.8%; VRd: 48.6%), constipation (IVRd: 35.7%; VRd: 40.9%), upper respiratory tract infection (IVRd: 34.2%; VRd: 33.7%), oedema peripheral (IVRd: 32.7%; VRd: 32.6%), fatigue (IVRd: 34.6%; VRd: 26.5%), cataract (IVRd: 38.0%; VRd: 25.4%), neutropenia (IVRd: 30.0%; VRd: 21.5%), pneumonia (IVRd: 30.0%; VRd: 19.3%), infusion related reaction (IVRd: 23.6%; VRd: 1.1%),



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Covid-19 (IVRd: 22.4%; VRd: 16.6%), insomnia (IVRd: 22.4%; VRd: 16.6%), back pain (IVRd: 22.1%; VRd: 17.1%), bronchitis (IVRd: 22.1%; VRd: 17.7%) and asthenia (IVRd: 21.7%; VRd: 24.3%).
More grade ≥3 TEAEs (91.6% vs. 84.0%) occurred in the IVRd arm. In particular, grade 5 TEAEs were higher in the IVRd arm (11.0% vs. 5.5%) compared to the VRd arm. TEAEs with a fatal outcome were driven in both groups by infections, several of which were related to COVID-19.
Serious adverse events (SAEs) (70.7% vs 67.4%) or TEAEs leading to definitive treatment discontinuation (22.8% vs 26.0%) were balanced.

The incidences of any grade 5 TEAEs and TEAEs leading to definitive treatment discontinuation were higher in patients aged 70 years or older compared to patients under 70 years of age in the IVRd group. Patients with impaired renal function (clearance: <60 mL/min) had higher incidences of SAEs and grade 5 TEAEs in both groups. These risks were included in the Information for healthcare professionals.

## 5.5 Final clinical benefit risk assessment

A statistically significant PFS benefit was shown in pivotal study IMROZ. The Kaplan Meier curves of OS are overlapping but start to separate from month 48 onwards.
Treatment with IVRd is associated with increased toxicity compared to VRd. However, the 4-drug regimen is manageable in the hands of experienced haematologists.

In conclusion, the final benefit-risk assessment is positive for an authorization without special condition.



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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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## 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).

### Indications/Uses

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.
- in combination with bortezomib, lenalidomide and dexamethasone, for the treatment of adult patients with newly diagnosed multiple myeloma who are not eligible for autologous stem cell transplant (ASCT) (see “Clinical Efficacy”).

### 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*

*Prevention of infusion reaction*

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.

*Prevention of infection*

Antibacterial and antiviral prophylaxis (such as herpes zoster prophylaxis) should be considered during treatment (see “Warnings and precautions”).

*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), or in combination with bortezomib, lenalidomide and dexamethasone (Isa-VRd) according to the schedules in Tables 1, 2 and 3:

*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.

*In combination with bortezomib, lenalidomide and dexamethasone*

*Table 3 – SARCLISA dosing schedule in combination with bortezomib, lenalidomide and dexamethasone*

| Cycles | SARCLISA (isatuximab) | Bortezomib | Lenalidomide | Dexamethasone |
|---|---|---|---|---|
| Cycle 1 (42-day cycle) | D1, D8, D15, D22 and D29 (weekly) | D1, D4, D8, D11, D22, D25, D29 and D32 | D1 – D14 and D22 – D35 | D1*, D2, D4*, D5, D8*, D9, D11*, D12, D15*, D22*, D23, D25*, D26, D29*, D30, D32* and D33 |

| Cycles | SARCLISA (isatuximab) | Bortezomib | Lenalidomide | Dexamethasone |
|---|---|---|---|---|
| Cycles 2 to 4 (42-day cycles) | D1, D15 and D29 (once every two weeks) | D1, D4, D8, D11, D22, D25, D29 and D32 | D1 – D14 and D22 – D35 | D1*, D2, D4*, D5, D8*, D9, D11*, D12, D15*, D22*, D23, D25*, D26, D29*, D30, D32* and D33 |
| Cycles 5 to 17 (28-day cycles) | D1 and D15 (once every two weeks) | - | D1 – D21 | D1, D8, D15, D22 (weekly) |
| Cycles 18 and subsequent cycles (28-day cycles) | D1 (once every four weeks) | - | D1 – D21 | D1, D8, D15, D22 (weekly) |

* for patients ≥75 years old

The dose of bortezomib is 1.3 mg/m$^2$. It is administered subcutaneously on days D1, D4, D8, D11, D22, D25, D29 and D32 in the cycles 1 to 4. Bortezomib is not administered from cycle 5.
The dose of lenalidomide is 25 mg/day. It is taken orally on days D1 until D14 and on days D22 until D35 in the cycles 1 to 4. From cycle 5 and subsequent it is taken on days D1 until D21.
The dose of dexamethasone is 20 mg/day. For patients < 75 years old it is given on days D1, D2, D4, D5, D8, D9, D11, D12, D15, D22, D23, D25, D26, D29, D30, D32 and D33 in the cycles 1 to 4. For patients ≥ 75 years old it is given on days D1, D4, D8, D11, D15, D22, D25, D29, and D32 in the cycles 1 to 4. From cycle 5 and subsequent it is given once weekly on days D1, D8, D15, and D22 of each cycle for both age groups. In all cycles dexamethasone is either administered intravenously on the days of SARCLISA infusions or taken orally on the other days.

Treatment is repeated until disease progression or unacceptable toxicity.
For the adaptation of pomalidomide, carfilzomib, bortezomib, lenalidomide 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 4 below. Incremental escalation of the infusion rate should be considered only in the absence of infusion reactions (IR).

*Table 4 – 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 4 (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*

Sarclisa is not authorised for use in the paediatric population. Outside its authorised indications, Sarclisa has been studied in children aged 1.4 to 17 years with relapsed or refractory acute

lymphoblastic or myeloid leukemia. The efficacy of Sarclisa in children aged 1.4 to 17 years has not been established. Currently available data are described in sections "Undesirable effects" and “Properties/Effects” but no recommendation on a posology can be made.

*Elderly patients*

Based on population pharmacokinetic analysis, no dose adjustment is recommended in elderly patients (see "Pharmacokinetics").
In elderly patients > 70 years of age, there was an increase in toxicity with isatuximab in combination with bortezomib, lenalidomide, and dexamethasone (see also section “Adverse effects - elderly patients”, “Warnings and precautions”, and “Properties/effects - clinical efficacy”).

*Patients with impaired renal function*

Based on population pharmacokinetic analysis and on clinical data, no dose adjustment is recommended in patients with mild to severe renal impairment including end-stage renal disease (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 36.0% of patients treated with SARCLISA (see "Undesirable effects"). Almost all IRs started during the first SARCLISA infusion (33.9%), 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.
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). This interference with the indirect Coombs test may persist for approximately 6 months after the last infusion of Sarclisa. 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 was observed as a laboratory abnormality in 94.7% of patients and reported 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 was observed as a laboratory abnormality in 54.8% of patients and reported 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”).

In patients treated with Isa-VRd, neutropenia was observed as a laboratory abnormality in 60.7% of patients and reported as an adverse reaction in 21,8% of patients, with grade 3-4 neutropenia reported as a laboratory abnormality in 30.3% of patients (with 20.2% grade 3 and 10.1% grade 4) and as an adverse reaction in 21,2% of patients. Neutropenic complications have been observed in 6.6% of patients, including 1.9% of febrile neutropenia and 1.0% of upper respiratory tract infection (see “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"). In IMROZ study, fatal infections were reported in 6.5% of patients in the Isa-VRd group. 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 at a median follow-up time of 52.44 months in 10 patients (6.6%) treated with Isa-Pd and in 3 patients (2%) treated with Pd. SPM were skin cancer in 6 patients treated with Isa-Pd and in 3 patients treated with Pd, solid tumours other than skin cancer in 3 patients treated with Isa-Pd (one patient also had a skin cancer), and haematological malignancy (myelodysplastic syndrome) in 1 patient treated with Isa- Pd. Patients continued treatment after resection of the new malignancy, except two patients treated with Isa-Pd. One patient developed metastatic melanoma and the other developed myelodysplastic syndrome. In IKEMA, at a median follow-up time of 56.61 months, SPMs were reported in 18 patients (10.2%) treated with Isa-Kd and in 10 patients (8.2%) treated with Kd. SPMs were skin cancers in 13 patients (7.3%) treated with Isa-Kd and in 4 patients (3.3%) treated with Kd, and were solid tumours other than skin cancer in 7 patients (4.0%) treated with Isa-Kd and in 6 patients (4.9%) treated with Kd, and was an hematological malignancy (acute myeloid leukemia) in 1 patient (0.8%) in the Kd group. For 1 patient (0.6%) in the Isa-Kd group, the etiology of the SPM was unknown. Two patients (1.1%) 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. In IMROZ study, at a median follow-up time of 59.73 months, SPMs were reported in 42 patients (16.0%) treated with Isa-VRd and in 16 patients (8.8%) treated with VRd. SPMs were skin cancers in 22 patients (8.4%)

treated with Isa-VRd, were solid tumours other than skin cancer in 17 patients (6.5%) treated with Isa-VRd, and haematological malignancy in 3 patients (1.1%) treated with Isa-VRd. Patients with SPM of skin cancer continued treatment after resection of the skin cancer, except one patient in each treatment group.
The overall incidence of SPMs in all the SARCLISA-exposed patients is 6.0% and included skin cancer in 3.5%, solid non tumors other than skin cancer in 2.4% and hematological malignancy in 0.3% 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.

*Tumor lysis syndrome*

Cases of tumor lysis syndrome (TLS) have been reported in patients who received regimens containing isatuximab. Patients should be monitored closely and appropriate precautions taken.

*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").

*Elderly patients*

An increased rate of serious adverse effects, Grade 5 adverse effects, and those leading to treatment discontinuation was observed in elderly patients (≥70 years) receiving isatuximab in combination with bortezomib, lenalidomide, and dexamethasone compared with patients < 70 years of age.
In addition, the hazard ration for overall survival (OS) in the ≥ 75-year population was 1.25 [95% CI: 0.68 to 2.3] for Isa-VRd compared to VRd (see also section “Dosage/administration”, “Undesirable effects”, and “Properties/effects - clinical efficacy”).

**Interactions**

SARCLISA has no impact on the pharmacokinetics of pomalidomide or carfilzomib, or bortezomib, or lenalidomide, 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 1787 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 with bortezomib, lenalidomide and dexamethasone (692 patients), isatuximab in combination therapies that are not currently authorized and as monotherapy (674 patients) pooled across clinical trials.
The most frequent adverse reactions (in ≥ 20% of patients) were infusion related reactions (35.9%), diarrhoea (29.7%), upper respiratory tract infection (24.5%), and fatigue (23,6%). The most frequent serious adverse reaction (in ≥ 5% of patients) was pneumonia (12.6%). Permanent discontinuation of treatment because of adverse reactions was reported in 193 patients (10.8%).

*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 1787 patients with multiple myeloma and treated with Isatuximab are presented below:

*Infections and infestations*

*Very common*: upper respiratory tract infection (all grades: 24.5%; grade 3: 1.7%; grade 4 < 0.1%), pneumonia [a] (all grades: 17.7%; grade 3: 11.1%; grade 4: 0.8%), bronchitis (all grades: 13.0%; grade 3: 1.9%; grade 4: 0%).
*Common*: herpes zoster (all grades: 2.5%; grade 3: 0.2%, 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, pneumonia staphylococcal, Covid-19 pneumonia, pneumonia klebsiella, pneumonia pseudomonal, pulmonary tuberculosis and tuberculosis.

*Blood and lymphatic system disorders*

Haematology laboratory abnormalities in patients receiving isatuximab treatment are presented below:
*Very common*: anaemia (all grades: 94.6%; grade 3: 18.8%; grade 4: 0%), lymphopenia (all grades: 82.1%; grade 3: 34.5%; grade 4: 11.5%), thrombocytopenia (all grades: 70.6%; grade 3: 11.5%; grade 4: 10.7%), 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%, for patients receiving Isa-VRd: all grades: 60.7%; grade 3: 20.2%; grade 4: 10.1%)
*Common*: 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%, for patients receiving Isa-VRd: all grades: 1.9%; grade 3: 1,6 %; grade 4: 0,1 %)
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: 9.2%; grade 3: 0.4%; grade 4: 0%), hypokalaemia (all grades: 2.5%; grade 3: 1.1%; grade 4: 0.1%), hyperglycaemia (all grades: 2.3%; grade 3: 1.0%; grade 4: 0.3%), hypercalcaemia (all grades: 2.1%; grade 3: 0.5%; grade 4: 0.8%), dehydration (all grades: 2.0%; grade 3: 0.4%; grade 4: < 0.1%),
*Uncommon:* hypomagnesaemia (all grades: 0.9%; grade 3: < 0.1%; grade 4: 0%), diabetes mellitus (all grades: 0.7%; grade 3: 0.2%; grade 4: 0.1%)

*Investigations*

*Common:* weight decrease (all grades: 5.4%; grade 3: 0.3%; grade 4: 0%), blood creatinine increased (all grades: 1.8%; grade 3: 0.3%; grade 4: < 0.1%), weight increased (all grades: 1.1%; grade 3: 0.1%; grade 4: 0%).

*Cardiac disorders*

*Common*: Atrial fibrillation (all grades: 3.6%; grade 3: 1.3%; grade 4: 0.2%), palpitations (all grades: 1.5%; grade 3: 0%; grade 4: 0%), angina pectoris (all grades: 1.0%; grade 3: 0.2%; grade 4: 0%).
*Uncommon:* sinus tachycardia (all grades: 0.8%; grade 3: 0%; grade 4: 0%), tachycardia (all grades: 0.8%; grade 3< 0.1%; grade 4: 0%)

*Vascular disorders*

*Common*: hypertension (all grades: 9.4%; grade 3: 4.9%; grade 4: < 0.1%).

*Respiratory, thoracic and mediastinal disorders*

*Very common*: cough (all grades: 13.7%; grade 3: 0%; grade 4: 0%), dyspnoea (all grades: 11.7%; grade 3: 1.8%; grade 4: 0%).

*Gastrointestinal disorders*

*Very common*: diarrhoea (all grades: 29.7%; grade 3: 3.2%; grade 4: 0.1%), constipation (all grades: 17.3%; grade 3: 0.9%; grade 4: 0%), nausea (all grades: 15.2%; grade 3: 0.3%; grade 4: 0%)
*Common:* vomiting (all grades: 9.6%; grade 3: 0.6%; grade 4: 0%).

*General disorders and administration site conditions*

*Very common: fatigue (all grades: 23.6%; grade 3: 3.4%; grade 4: 0%), oedema peripheral (all grades: 15.3%; grade 3: 0.4%; grade 4: 0%), pyrexia (all grades: 12.4%; grade 3: 1.0%; grade 4: 0.1%)*

*Injury, poisoning and procedural complications*

*Very common*: infusion reaction (all grades: 35.9%; grade 3: 1.3%; grade 4: 0.4%).

*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 643 patients (36.0%) treated with SARCLISA. Among the 1787 patients, 605 (33.9%) experienced IRs during the 1st infusion of SARCLISA, with 38 patients (2.1%) also having IRs at subsequent infusions. Grade 1 IRs were reported in 4.8%, grade 2 in 29.4%, grade 3 in 1.3%, and grade 4 in 0.4% of the patients. Signs and symptoms of grade 3 or 4 IRs included hypertension (1.4%) and dyspnoea (1.0%).
The incidence of patients with infusion interruptions because of infusion reactions was 26.8%. The median time to infusion interruption was 61 minutes. The median duration of SARCLISA infusion was 3.67 hours during the first infusion, 2.90 hours during the second infusion and 2.52 hours for the subsequent infusions. Isatuximab was discontinued in 1.7% 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. In the IMROZ clinical trial 1 patient (0.4%) experienced an anaphylactic reaction (Grade 4 infusion reaction) (see section “warnings and precautions”).

*Infections*

The incidence of grade 3 or higher infections was 30.3%. Pneumonia was the most commonly reported severe infection with grade 3 reported in 11.1% of patients, and grade 4 in 0.8% of patients. Discontinuations from treatment due to infection were reported in 4.0% of patients. Fatal infections were reported in 3.6% of patients.

*Immunogenicity*

As with all therapeutic proteins, there is a potential for immunogenicity to SARCLISA. The incidence of anti-drug antibodies (ADAs) is highly dependent on the sensitivity and specificity of the test. In addition, the observed incidence of antibody positivity (including neutralizing antibodies) in a test may be influenced by several factors, such as test methodology, sample handling, time of sample collection, concomitant medications, and underlying disease. Therefore, comparing the incidence of antibodies to isatuximab with the incidence of antibodies to other drugs can be misleading.
Overall, across 9 clinical studies in relapsed or refractory multiple myeloma (RRMM) with SARCLISA single agent and combination therapies including ICARIA-MM and IKEMA (N=1023), the incidence of treatment-emergent ADAs was <2% (19 patients with positive ADA response out of the 1023 patients).
In ICARIA-MM and IKEMA, no patients with RRMM tested positive for ADA. Therefore, the neutralizing ADA status was not determined. In RRMM, no effect of ADAs was observed on the pharmacokinetics, safety or efficacy of SARCLISA.
Across 3 clinical studies in newly diagnosed multiple myeloma (NDMM) with SARCLISA in combination therapy with bortezomib, lenalidomide, and dexamethasone, including IMROZ, ADA incidence ranged from 8.7% to 21.6%. In IMROZ, out of the 263 patients with NDMM treated with SARCLISA in combination with bortezomib, lenalidomide, and dexamethasone, 253 were evaluable for the presence of ADA, 22 patients (8.7%) tested positive for treatment-emergent ADAs, with 21 patients considered to have a transient ADA response and 1 considered to have an indeterminate ADA response. Among these 22 ADA-positive patients, 13 had neutralizing antibodies (incidence of neutralizing antibodies: 5.1%). In IMROZ, a trend to lower exposure was observed in ADA-positive patients. No meaningful impact of ADAs on efficacy of SARCLISA was observed. No conclusions can be drawn on safety due to the small subgroup of ADA positive patients.

*Elderly patients*

Of the total number of patients in clinical studies of SARCLISA, 57.3% (1024 patients) were 65 and over, while 14.1% (252 patients) were 75 and over. Differences in safety were observed between patients 65 and over and younger patients. Grade >3 TEAEs was reported in 64.6%, of patients less than 65 and in 78.8% of patients 65 and above, Grade 5 TEAEs was reported in 5.5% of patients less than 65 and in 8.7% of patients 65 and above; serious TEAEs were reported in 46.7% of patients less than 65 and in 59.3% of patients 65 and above, TEAEs leading to definitive treatment discontinuation were reported in 6.0% of patients less than 65 and in 14.4% of patients 65 and over.
Of the 263 multiple myeloma patients treated with SARCLISA in combination with bortezomib, lenalidomide, and dexamethasone in the IMROZ study, 69.6 % were 70 years and older and 25.9 % were 75 years and older.
In IMROZ study adverse events occurred at a higher frequency in the Isa-VRd group in elderly patients 70 years of age and older compared to younger patients (< 70 years).

In IMROZ study, elderly patients (≥ 70 years) in the Isa-VRd group experienced a higher rate of serious adverse effects (71.6 % versus 68.8 %), Grade 5 adverse effects (13.1 % versus 6.3 %) and those leading to definitive treatment discontinuation (24.6 % versus 18.8 %) compared with patients under 70 years of age.

*Patients with renal impairment*

In IMROZ study, serious adverse events were observed in the Isa-VRd group in 75.8 % of patients with eGFR < 60 mL/min/1.73 $m^2$ compared to 69.0 % in patients with eGFR ≥ 60 mL/min/1.73 $m^2$ and Grade 5 adverse events in 15.2 % of patients with eGFR < 60 mL/min/1.73 $m^2$ compared to 9.6 % in patients with eGFR ≥ 60 mL/min/1.73 $m^2$.

*Paediatric population*

In a phase 2 single-arm study conducted in 67 paediatric patients with relapsed or refractory acute lymphoblastic leukaemia or acute myeloid leukaemia, all evaluable for safety, Grade ≥3 TEAEs were reported in 79.1% of patients. The most common Grade ≥3 TEAEs occurring in >10% of patients included febrile neutropenia (41.8%), septic shock (11.9%), and stomatitis (10.4%). The addition of SARCLISA to standard chemotherapies did not modify the expected safety profile observed with standard chemotherapies in this paediatric population and was consistent with isatuximab safety profile for adults with multiple myeloma in ICARIA and IKEMA studies (see section “dosage/administration”).

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

**Overdose**

*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*

*Relapsed and/or refractory multiple myeloma*

*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 $m^2$) 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 Review 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 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. 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/1.73m$^2$) 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. Overall, 24.2% of patients had high-risk chromosomal abnormalities at study entry.

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 6:*

*Table 6 – 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 Review 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 Isa-Kd and Kd arms, respectively. At a median follow-up time of 56.61 months, median overall survival was not reached in the Isa-Kd group (95% CI: 52.172-NR) and was 50.60 months in Kd group (95% CI: 38.932-NR) (HR=0.855; 95% CI: 0.608-1.202). The median time to next anti-myeloma treatment was 43.99 months in the Isa-Kd group and 25.00 months in the Kd group (HR=0.583; 95% CI: 0.429-0.792).

*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").

*Newly diagnosed multiple myeloma*

*IMROZ (EFC12522)*

The efficacy and safety of SARCLISA in combination with bortezomib, lenalidomide, and dexamethasone were evaluated in IMROZ (EFC12522), a multicenter, international, randomized, open-label, 2-arm, phase III study in patients with newly diagnosed multiple myeloma who are not eligible for stem cell transplantation. Patients over the age of 80 years were excluded. Patients with NDMM aged 65 years or older or younger than 65 years with comorbidities that do not allow stem cell transplantation based on investigator’s medical assessment were included.

A total of 446 patients were randomized in a 3:2 ratio to receive either SARCLISA in combination with bortezomib, lenalidomide, and dexamethasone (Isa-VRd, 265 patients) or bortezomib, lenalidomide, and dexamethasone (VRd, 181 patients) administered in both groups during 4 cycles of 42-day for the induction period. After completion of cycle 4, patients entered the continuous treatment period starting

from cycle 5, 28-day cycles administered up to disease progression or unacceptable toxicity. During the continuous treatment period, patients of the Isa-VRd group received SARCLISA in combination with lenalidomide, and dexamethasone (Isa-Rd), and patients in the VRd group received lenalidomide, and dexamethasone (Rd).

During the induction period (cycle 1 to 4, 42-day cycles), SARCLISA 10 mg/kg was administered as an IV infusion on day 1, 8, 15, 22, and 29, in the first cycle and on day 1, 15, and 29, from cycle 2 to 4. Bortezomib was administered subcutaneously at the dose of 1.3 mg/m² on days 1, 4, 8, 11, 22, 25, 29, and 32 of each cycle. Lenalidomide was administered per os at the dose of 25 mg/day from day 1 to 14 and from day 22 to 35 of each cycle. Dexamethasone (IV on the days of isatuximab infusions, and PO on the other days) 20 mg/day was given on days 1, 2, 4, 5, 8, 9, 11, 12, 15, 22, 23, 25, 26, 29, 30, 32, and 33 of each cycle for patients < 75 years old, and on days 1, 4, 8, 11, 15, 22, 25, 29, and 32 of each cycle for patients ≥ 75 years old.

During the continuous treatment period (from cycle 5, 28-day cycles), SARCLISA 10 mg/kg was administered as an IV infusion on day 1 and 15 from cycle 5 to 17, and on day 1 from cycle 18. Lenalidomide was administered per os at the dose of 25 mg/day from day 1 to 21 of each cycle. Dexamethasone (IV on the days of isatuximab infusions, and PO on the other days) 20 mg/day was given on days 1, 8, 15, and 22 of each cycle.

Overall, demographic and disease characteristics at baseline were similar between the two treatment groups. The median patient age was 72 years (range 60-80), 26% of patients were ≥75 years. The proportion of patients with renal impairment (eGFR < 60 mL/min/1.73m$^2$) was 24.9% in the Isa-VRd group. The Revised International Staging System (R-ISS) stage at study entry was I in 24.9%, II in 61.5%, and III in 10.2% of patients. Overall, 15.1% of patients had high-risk chromosomal abnormalities at study entry; del(17p), t(4;14), and t(14;16) were present in 5.7%, 7.9% and 1.9% of patients, respectively. In addition, 1q21+ was present in 35.8% of patients.

The median duration of treatment was 53.2 months for the Isa-VRd group compared to 31.3 months for the VRd group.

Progression-free survival (PFS) was the primary efficacy endpoint of IMROZ.

With a median follow-up time of 59.73 months, the pre-planned second interim analysis of PFS showed a statistically significant improvement in PFS representing a 40.4% reduction in the risk of disease progression or death in patients treated with Isa-VRd compared to patients treated with VRd. *Efficacy results are presented in Table 7:*

*Table 7 – Efficacy of SARCLISA in combination with bortezomib, lenalidomide, and dexamethasone versus bortezomib, lenalidomide, and dexamethasone in the treatment of multiple myeloma (intent-to-treat analysis)*

| Endpoint | SARCLISA + bortezomib + lenalidomide + dexamethasone<br>N =265 | Bortezomib + lenalidomide + dexamethasone<br>N = 181 |
|---|---|---|
| Progression-Free Survival [a] | | |
| Median (months) | NR | 54.34 |
| [95% CI] | [NR-NR] | [45.21-NR] |
| Hazard ratio [b] [98.5% CI] | 0.596 [0.406-0.876] | |
| p-value (Stratified Log-Rank test)[b] | 0.0009 | |
| Overall Response Rate[c] | | |
| Responders (sCR+CR+VGPR+PR) | 91.3% | 92.3% |
| Stringent Complete Response (sCR) | 10.9% | 5.5% |
| Complete Response (CR) | 63.8% | 58.6% |
| Very Good Partial Response (VGPR) | 14.3% | 18.8% |
| Partial Response (PR) | 2.3% | 9.4% |
| CR or better (sCR and CR) | 74.7% | 64.1% |
| [95% CI][d] | [0.6904-0.7984] | [0.5664-0.7107] |
| p-value (Stratified Log-Rank test)[b] | 0.0160 | |
| Minimal Residual Disease negativity[e] and CR | 55.5% | 40.9% |
| [95% CI][d] | [0.4927-0.6155] | [0.3365-0.4842] |

[a] PFS results were assessed by an Independent Review Committee based on central laboratory data for M-protein and central radiologic imaging review using the International Myeloma Working Group (IMWG) criteria.

[b] Stratified by age (<70 years vs ≥70 years) and Revised International Staging System (R-ISS) stage (I or II vs. III or 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] Based on a sensitivity level of $10^{-5}$ by NGS in ITT population.

* Cut-off date of 26 September 2023. Median follow-up time=59.73 months.

NR: not reached.

Median overall survival was not reached for either treatment group. At a median follow-up time of 59.73 months, 26.0% of patients in the Isa-VRd group and 32.6% of patients in the VRd group had died (HR=0.776; 99.97% CI: 0.407 to 1.48). The hazard ratio for overall survival (OS) in patients 75 years of age and older was 1.25 [95% CI: 0.68 to 2.3].

*Pediatrics*

A phase 2, single-arm, study in 67 pediatric patients was conducted in 3 separate cohorts, patients with relapsed or refractory T-acute lymphoblastic leukemia (T-ALL, 25 patients), B-acute lymphoblastic leukemia (B-ALL, 11 patients), and acute myeloid leukemia (AML, 23 patients). The median age was 8 years (range 1.4 to 17). Patients were treated with Sarclisa in combination with standard chemotherapies (e.g., antimetabolites, anthracyclines, and alkylating agents).
At interim analysis, complete response rate (the primary efficacy endpoint, defined as complete response, CR, or complete response with incomplete peripheral recovery, CRi), did not meet the pre-specified statistical threshold. The study was stopped after the prespecified interim analysis.

**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 $C_{max}$ 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. In IMROZ, the mean (CV%) predicted maximum plasma concentration $C_{max}$ and $AUC_{2weeks}$ at steady state were 494 µg/ml (25.5%) and 119,000 µg.h/ml (31.8%), respectively. The difference in exposure with Isa-Kd and Isa-VRd 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 and Isa-VRd 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.
A pharmacokinetic analysis on 22 patients with End-Stage Renal Disease (ESRD) including patients on dialysis (eGFR <15 mL/min/1.73 m²) showed no clinically meaningful effects of ESRD on Sarclisa pharmacokinetics compared to those of normal renal function and mild, or moderate renal impairment. No dose adjustment of Sarclisa is needed in patients with mild, moderate, severe or end-stage renal impaired function.

*Children and adolescents*

Pharmacokinetics data reported in paediatric population with AML and ALL were consistent with those from adults with ALL and MM at the same isauximab dose.

**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.

*Instructions for 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.

**Authorisation number**

67525 (Swissmedic)

**Packs**

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

**Date of revision of the text**

February 2025