# Summary Report of Benefit-Risk Assessment

## SARCLISA CONCENTRATE FOR SOLUTION FOR INFUSION 20MG/ML
## NEW DRUG APPLICATION

| | |
|---|---|
| **Active Ingredient(s)** | Isatuximab |
| **Product Registrant** | Sanofi-Aventis Singapore Pte. Ltd |
| **Product Registration Number** | SIN16630P |
| **Application Route** | Abridged evaluation |
| **Date of Approval** | 13 October 2022 |

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## A INTRODUCTION

SARCLISA concentrate for solution for infusion 20mg/ml 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 therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy; and in combination with carfilzomib and dexamethasone, for the treatment of adult patients with relapsed or refractory multiple myeloma who have received one to three prior therapies.

The active substance, isatuximab, is a humanised anti-CD38 IgG1-derived monoclonal antibody that binds to a specific extracellular epitope of CD38 which is highly expressed on multiple myeloma cells.

SARCLISA is available as concentrate for solution for infusion containing 100 mg and 500 mg of isatuximab in 5 ml and 25 ml of concentrate respectively. Other ingredients include sucrose, histidine hydrochloride monohydrate, histidine, polysorbate 80.

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## B ASSESSMENT OF PRODUCT QUALITY

The drug substance, Isatuximab, is manufactured at Sanofi Chimie, Vitry Sur Seine Cedex, France. The drug product, Sarclisa, is manufactured at Sanofi-Aventis Deutschland GmbH, Frankfurt, Germany.

Drug substance:

Adequate controls have been presented for the raw materials, reagents and cell banks. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate. The drug substance manufacturer is compliant with Good Manufacturing Practice (GMP). Process validation has been conducted on four consecutive production-scale batches.

The characterisation of the drug substance and its impurities are appropriately performed. Potential and actual impurities are adequately controlled in manufacturing process.

The drug substance specifications are established in accordance with ICH Q6B and the impurity limits are considered appropriately qualified. The analytical methods used are adequately described and non-compendial methods have been validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data presented is adequate to support the approved storage condition and shelf life. The packaging is a 20L polycarbonate bottle with silicone-lined polypropylene screw cap. The drug substance is approved for storage at -30°C±5°C with a shelf life of 36 months.

Drug product:

The manufacturing process involves pooling and homogenisation of the formulated drug substance, followed by prefiltration, sterile filtration and aseptic filling. This is considered to be a standard manufacturing process.

The manufacturing site involved is compliant with GMP. Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6B and impurity limits are considered adequately qualified. The analytical methods used are adequately described and non-compendial methods have been validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data submitted was adequate to support the approved shelf-life of 36 months when stored at 2 - 8°C. The in-use period after dilution is 48 hours at 2 - 8°C followed by 8 hours at room temperature (15°C-25°C) and is supported with appropriate data. The container closure system is a Type I glass vial closed with ETFE (copolymer of ethylene and tetrafluoroethylene)-coated Type I bromobutyl stoppers and crimped with an aluminium seal with a flip-off button.

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## C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of isatuximab in the treatment of relapsed and refractory multiple myeloma (RRMM) in combination with pomalidomide and dexamethasone was supported by STUDY ICARIA (EFC14335), and its use in combination with carfilzomib and dexamethasone was supported by Study IKEMA (EFC15246).

**Isatuximab in combination with pomalidomide/dexamethasone in RRMM with at least two prior lines of therapy:**

Study ICARIA (EFC14335) is a Phase 3, multicentre, multinational, randomised (1:1), open-label study which compared isatuximab in combination with pomalidomide and low-dose dexamethasone (IPd) versus pomalidomide and low-dose dexamethasone (Pd) in patients with RRMM.

The main inclusion criteria were patients 18 years and above, with a documented diagnosis of MM (measurable disease with serum M-protein ≥0.5 g/dL and/or urine M-protein ≥200 mg/24 hours) who had received at least two prior therapies which included at least 2 consecutive cycles of lenalidomide and a proteasome inhibitor (bortezomib, carfilzomib or ixazomib) alone or in combination, with disease progression on or within 60 days after the end of the previous therapy. An induction treatment followed by autologous stem cell transplant (ASCT) and consolidation/maintenance was considered as one line of treatment. Patients with primary refractory disease, free light chain measurable disease only, prior anti-CD38 monoclonal antibody treatment with progression on or within 60 days, or failure to achieve at least minimal response (MR) to treatment (i.e., refractory to anti-CD38), prior pomalidomide therapy were excluded. Patients were stratified by number of previous treatment lines (2-3 vs >3) and age (<75 vs ≥75 years).

In the IPd group, intravenous isatuximab 10 mg/kg was administered on days 1, 8, 15, and 22 of the first 4-week cycle, and then on days 1 and 15 of subsequent cycles. Both groups received oral pomalidomide 4 mg on days 1-21 of each cycle, and weekly oral or intravenous dexamethasone 40 mg (20 mg if aged ≥75 years) on days 1, 8, 15, and 22 of each cycle. Treatment was continued until disease progression, unacceptable toxicity, or withdrawal of consent.

Primary efficacy endpoint was progression free survival (PFS) determined by an independent review committee (IRC) based on International Myeloma Working Group (IMWG) criteria. The key secondary endpoints included objective response rate (ORR) by IRC using the IMWG criteria and overall survival (OS). The other secondary endpoints were clinical benefit rate (MR or better), very good partial response (VGPR) rate (VGPR or better), best overall response (BOR) by IRC (which included stringent complete response [sCR], complete response [CR], VGPR and partial response [PR]), time to progression (TTP), time to first response.

A total of 162 PFS events were needed to achieve a 90% power for the primary endpoint of PFS. OS objective was also supported by the sample size calculation and 220 death events were needed to achieve 80% power for the OS endpoint. An interim analysis for OS was planned at the time of analysis of PFS, which was estimated to occur when about 36% of the OS events were observed. An O'Brien and Fleming α-spending function was used to obtain the nominal significance levels for the interim and final analyses of survival.

A total of 307 patients were randomly assigned to either isatuximab (n=154) or the control group (n=153). The demographic and disease characteristics at baseline were similar between the two treatment groups, with some minor imbalances. The median patient age was 67 years (range 36 to 86 years) with 19.9% of patients ≥75 years. Majority had an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 (40.4%) or 1 (49.2%). The International Staging System (ISS) stage at study entry was I in 37.5% (41.6% in the isatuximab group and 33.3% in the comparator group), II in 35.5% (34.4% in the isatuximab group and 36.6% in the comparator group) and III in 25.1% (22.1% in the isatuximab group and 28.1% in the comparator group) of patients. Renal impairment was present in 36.2% and all these patients had creatinine clearance between 30-60 mL/min/1.73m$^2$ except one patient in IPd group who had creatinine clearance levels <30mL/min/1.73m$^2$. A total of 19.5% of patients had high-risk chromosomal abnormalities at study entry.

The number of prior lines and class of therapies were well-balanced between the treatment groups with a median of 3 (range 2-11). A total of 107 (34.9%) patients received 4 or more prior lines of treatment. All patients received a prior proteasome inhibitor, prior lenalidomide, and 56.4% of patients received prior stem cell transplantation. The majority of patients (92.5%) were refractory to lenalidomide (91.2% were refractory to lenalidomide at last line of therapy), 75.9% to a proteasome inhibitor, and 72.6% to both an immunomodulatory and a proteasome inhibitor. The median duration of last regimen was 7.87 months in the IPd group, and 6.64 months in the Pd group. The study population was representative of RRMM subjects with the heavily pre-treated patients, and all were relapsed/refractory to their last regimen.

There were some imbalances noted with lesser patients in the IPd group than in the Pd group for those with high risk cytogenetics (15.6% versus 23.5%), ECOG PS 0 (35.7% versus 45.1%), and more patients in the IPd group versus Pd group for patients ≥65 years (64.9% versus 54.2%), ECOG PS 1 (53.9% versus 44.4%), ISS stage I (41.6% versus 33.3%) and renal function impairment, i.e., creatinine clearance <60 mL/min/1.73m2 (38.7% versus 33.8%). Overall, the imbalances in prognostic factors did not seem to impact efficacy results based on the pre-defined subgroup analyses which demonstrated consistent efficacy.

Study ICARIA demonstrated superiority of IPd regimen compared to Pd regimen for the primary efficacy endpoint of PFS with a statistically significant reduction of 40.4% in risk of progression or death (HR: 0.596; 95% CI of 0.436, 0.814; p=0.001). The median PFS was 11.53 months in IPd group compared to 6.47 months in Pd group. The observed improvement in PFS, as determined by IRC was supported by multiple PFS sensitivity analyses as well as

multivariate analysis adjusted for baseline and demographic characteristics. Subgroup analyses for prespecified patient subgroups including poor prognosis subgroups such as the elderly, patients with renal function impairment, heavily pre-treated patients (>3 prior lines), and relapsed/refractory patients showed a consistent improvement of PFS in all subgroups favouring IPd regimen compared to Pd only.

The key secondary endpoint of ORR based on IRC assessment was 60.4% in IPd group compared to 35.3% in Pd group demonstrating a significant difference (p<0.0001) in favour of IPd group. The median time to first response was shorter in the IPd group (1.94 months; 95% CI: 1.31 to 2.00) than in the Pd group (3.02 months: 95% CI: 2.83 to 5.06). In the subgroup of patients who had achieved a response, a higher incidence of deeper response (VGPR or better, 31.8% versus 8.5%) and clinical benefit rate (66.9% versus 46.5%) were observed in IPd group compared to Pd group respectively. The median duration of response was numerically longer in the IPd group (13.27 months compared to PD groups (11.07 months). Median time to first response was faster in IPd group (1.94 months) compared to Pd group (3.02 months). Median TTP based on IRC assessment was longer in the IPd arm (12.71 months; 95% CI: 11.203 to 15.211) than in the Pd arm (7.75 months; 95% CI: 5.027 to 9.758) supporting the PFS. Duration of responses were also numerically longer in IPd group (13.27 months) compared to Pd group (11.07 months). The median time to next anti-myeloma treatment was not reached in the IPd group and was 9.10 months in the Pd group (HR 0.538), with fewer patients in the IPd group receiving subsequent therapy (39.0% versus 54.2%).

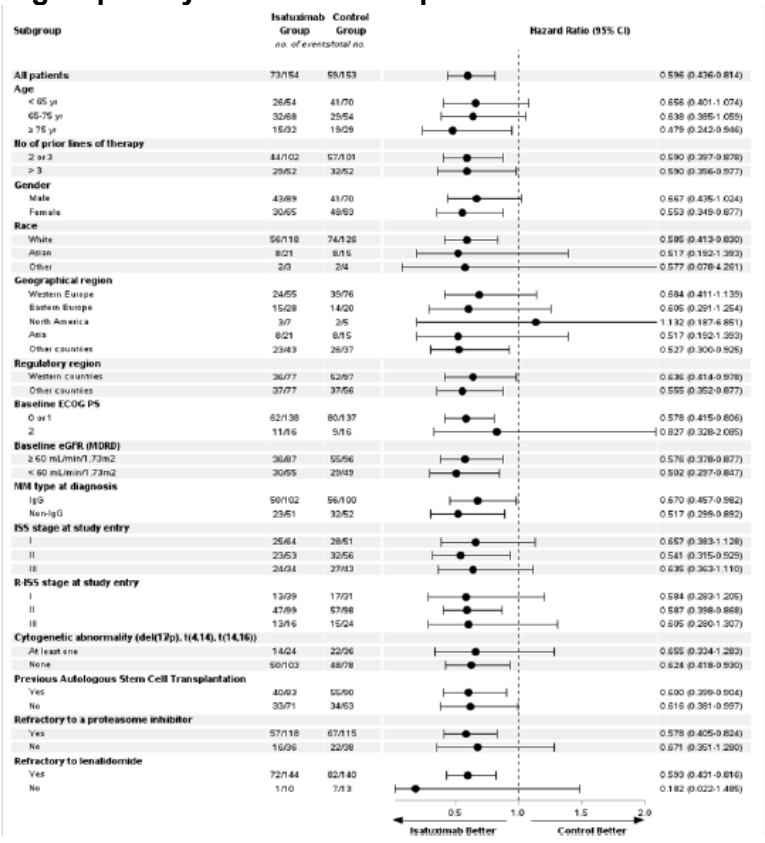
Median OS was not reached for both treatment groups based on median duration of follow-up of 11.56 months in the IPd group and 11.73 months in the Pd group. Although OS was not mature and not statistically significant, a trend favouring IPd group (HR: 0.687; 95% CI: 0.461,1.023; p-value=0.0631) was observed with 43 deaths (27.9%) in IPd group versus 56 deaths (36.6%) in Pd group.

**Summary of efficacy results from Study ICARIA (ITT)**

| | **Pd (N=153)** | **IPd (N=154)** |
|---|---|---|
| **Primary efficacy endpoint (PFS by IRC)** | | |
| Number (%) of events | 89 (58.2) | 73 (47.4) |
| Number (%) of patients censored | 64 (41.8) | 81 (52.6) |
| Median (months) (95% CI) | 6.47 (4.468 to 8.279) | 11.53 (8.936 to 13.897) |
| Stratified HR (95% CI) | - | 0.596 (0.436 to 0.814) |
| Stratified Log-Rank test p-value | - | 0.0010 |
| **Key Secondary efficacy endpoints** | | |
| ORR by IRC (%) | 35.3% | 60.4% (p<0.0001) |
| OS (interim analysis) | | |
| Number (%) of events | | |
| Median (months) (95% CI) | NR | NR |
| HR (95% CI) | - | 0.687 (0.461, 1.023) |
| p-value | - | 0.0631 |
| **Other Secondary endpoints** | | |
| VGFR or better by IRC | 8.5% (p<0.0001) | 31.8% |
| CR or better by IRC | 2.0% | 4.5% |
| MR or better by IRC | 46.4% | 66.9% |

| | | |
|---|---|---|
| ORR by investigator<br>VGPR by investigator | 32%<br>7.2% | 63%<br>33.8% |
| TTP (IRC) median (months)<br>95%CI | 7.75<br>5.027 to 9.758 | 12.71<br>11.203 to 15.211 |
| High risk cytogenetic subgroup<br>PFS event<br>Median PFS (months)<br>95%CI<br>HR (95%CI)<br>ORR | 22/36 (61.1%)<br>3.745<br>2.793, 7.885<br>-<br>16.7% | 14/24 (58.3%)<br>7.491<br>2.628, NR<br>0.655 (0.334 to 1.283)<br>50.0% |
| Median duration of response (months)<br>95%CI<br>HR (95%CI) | 11.07<br>8.542 to NC<br>- | 13.27<br>10.612 to NC<br>0.828 (0.464 to 1.474) |
| Time to first response<br>Median (month)<br>95%CI | 3.02<br>2.825 to 5.060 | 1.94<br>1.314 to 2.004 |

**Subgroup analyses for PFS endpoint:**




Study ICARIA demonstrated statistically significant reduction in the risk of progression or death by 40% based on the PFS analysis as per IRC assessment with the addition of isatuximab to the pomalidomide-dexamethasone regimen for RRMM patient with at least two prior therapies. The PFS was also consistent in subgroups including patients with high-risk chromosomal

abnormalities. The time to first response was numerically shorter and the median duration of response was numerically longer in IPd group compared to Pd group. Although OS was not mature, a trend favouring IPd regimen compared to Pd only was observed which was reassuring.

Overall, the efficacy data was adequate to support the use of isatuximab in combination with pomalidomide and dexamethasone in the treatment of RRMM with at least two prior therapies. The final results of the study will be required to confirm the survival benefit of isatuximab in this patient population.

**Isatuximab in combination with carfilzomib and dexamethasone in RRMM patients with at least one prior line of therapy:**

Study IKEMA (EFC15246) was a Phase 3, multicentre, multinational, randomised, open-label study which compared isatuximab in combination with carfilzomib and dexamethasone (IKd) versus carfilzomib and dexamethasone (Kd) in patients with RRMM.

The main inclusion criteria were patients 18 years and above, with documented diagnosis of MM and had received at least one prior therapy and not more than 3 prior lines of therapies. Patients with primary refractory disease, prior treatment with carfilzomib, prior anti-CD38 monoclonal antibody treatment with progression on or within 60 days or those refractory to previous anti-CD38 monoclonal antibody treatment were excluded.

In the IKd group, intravenous isatuximab 10 mg/kg once weekly for 1st cycle of 28 days, followed by once every 2 weeks in subsequent cycles. Both groups received carfilzomib 56 $mg/m^2$ twice per week 3 out of 4 weeks and dexamethasone 20 mg twice weekly. Treatment was continued until disease progression, unacceptable toxicity, or withdrawal of consent.

Primary efficacy endpoint was PFS determined by an IRC according to IMWG criteria in the ITT population. The key secondary endpoints included ORR, rate of VGPR or better, minimal residual disease (MRD) negativity rate in those with VGPR or better, CR rate and OS. The other secondary endpoints were DOR, TTP, PFS2 by investigator (time from the date of randomization to the date of first documentation of PD after initiation of further anti-myeloma treatment or death from any cause, whichever happens first).

A total of 159 PFS events were needed to achieve a 90% power for the study. A planned interim analysis for PFS was conducted when 65% of the PFS events had been observed; an interim analysis was planned to be done when 103 PFS events occurred as per IRC. In case of positive interim PFS analysis, key secondary endpoints were tested sequentially until the null hypothesis failed to be rejected for a key secondary endpoint. The group-sequential testing for PFS and hierarchically testing the other endpoints protected the type I error. OS was tested only at end-of-study.

A total of 302 patients were randomised in a 3:2 ratio to receive either IKd regimen (n=179) or Kd regimen (n=123). Overall, demographic and disease characteristics at baseline were similar between the two treatment groups. The median age was 64 years (range 33 to 90) with 8.9% of patients ≥75 years. ECOG PS was 0 in 53.1% of patients in the IKd group and 59.3% in the Kd group, 1 in 40.8% in the IKd group and 36.6% in the Kd group, and 2 in 5.6% in the IKd group and 4.1% in the Kd group, and 3 in 0.6% in the IKd group and 0% in the Kd group. The proportion of patients with renal impairment (eGFR<60 mL/min/1.73 m2) was 24.0% in the IKd group versus 14.6% in the Kd group. The ISS stage at study entry was I in 53.0%, II in 31.1%, and III in 15.2% of patients.

There was 24.2% of patients who had high -risk chromosomal abnormalities at study entry. The median number of prior lines of therapy was 2 (range 1 to 4) with 44.4% of patients who received 1 prior line of therapy. Overall, 89.7% of patients had received prior proteasome inhibitors, 78.1% had prior immunomodulators (including 43.4% who received prior lenalidomide), and 61.3 % had prior stem cell transplantation. A total of 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 IKd group compared to 61.4 weeks for the Kd group. The study population was representative of RRMM subjects with one to three prior lines of therapy, and all were relapsed/refractory to their last regimen.

Study IKEMA demonstrated statistical superiority for the interim PFS with a 47% reduction in the risk of progression or death in the IKd group compared to Kd group (HR:0.531; 95% CI: 0.318,0.889). An improvement in median PFS was shown with IKd regimen compared to Kd regimen at a median follow up of 20.7 months based on 103 events (median PFS in IKd has not been reached compared to a median PFS of 19.15 months in the Kd group). The PFS analysis was supported by the sensitivity analyses and the subgroup analysis which consistently favoured the IKd group.

The key secondary endpoint of ORR in the IKd and Kd groups was 86.6% and 82.9% respectively and the difference was not statistically significant (p=0.1930). Therefore, the subsequent endpoints were not tested for statistical significance. The other secondary endpoints of rate of VGPR or better (72.6% in the IKd group versus 56.1% in the Kd group), CR rate (39.7% in the IKd group versus 27.6% in the Kd group), MRD negativity rate in those with VGPR or better (29.6% in the IKd group and 13.0% in the Kd group) demonstrated consistent benefit in favour of IKd group. The median time to first response was comparable in IKd and Kd groups (1.08 months versus 1.12 months respectively). Duration of responses was not reached in either arm. The median TTP based on IRC assessment was not reached in the IKd arm and was 20.27 months (95% CI: 16.986 and upper limit not estimable) in the Kd arm supporting the PFS results. There was a lower proportion of patients initiated further anti-myeloma treatment in IKd group (26.3%) compared to Kd group (43.1%). Median PFS2 was not reached, but the proportion of patients with PFS2 were lower in IKd group (21.8%) compared to Kd group (28.5%).

OS was not tested as it was not planned at interim analysis. At a median duration of follow-up of 20.73 months, 17.3% of patients in the IKd group and 20.3% in the Kd group had died with a trend favouring IKd arm. The study is still ongoing and as pre-specified in the protocol, OS will be tested 3 years after positive PFS analysis (with positive interim PFS analysis in 2020 this OS analysis is planned in 2023).

**Summary of efficacy results from Study IKEMA (ITT)**

| | **Kd (N=123)** | **IKd (N=179)** |
|---|---|---|
| **Primary efficacy endpoint (Interim PFS by IRC)** | | |
| Number (%) of events | 55 (44.7) | 48 (26.8) |
| Median (months) (95% CI) | 19.15 (15.770 to NC) | NC (NC to NC) |
| Stratified HR (95% CI) | - | 0.531 (0.318 to 0.889) |
| Stratified Log-Rank test p-value | - | 0.0007 |

| Key secondary efficacy endpoints | | |
|---|---|---|
| ORR by IRC<br>VGFR or better by IRC<br>CR by IRC<br>MRD negativity rate by IRC | 82.9%<br>56.1%<br>27.6%<br>13.0% | 86.6%<br>72.6%<br>39.7%<br>29.6% |
| TTP (IRC) median (months) | 20.27 months | Not reached |
| Median duration of response (months) | Not reached | Not reached |
| Time to first response Median (month) | 1.12 | 1.08 |

Study IKEMA demonstrated statistically significant reduction in the risk of progression or death by 47% based on the interim PFS analysis with the addition of isatuximab to carfilzomib and dexamethasone regimen for RRMM patients with prior one to three lines of therapy. This was supported by higher ORR along with greater improvements in the depth of response as assessed by response rate of VGPR or better, CR and MRD negativity rate. Although median duration of response and median PFS2 were not reached at the cut-off date in either treatment groups, the lower proportion of subjects with PFS2 events in the IKd group was reassuring. OS was not assessed at the interim analysis.

Overall, the efficacy was demonstrated for use of isatuximab in combination with carfilzomib and dexamethasone in RRMM patients with one to three prior lines of therapy. The final results of the study will be required to confirm the final PFS and the survival benefit of isatuximab in this patient population.

## D ASSESSMENT OF CLINICAL SAFETY

The safety population included 152 patients in the IPd group and 149 patients in the Pd group from Study ICARIA, as well as 177 patients in the IKd group and 122 patients in the Kd group from Study IKEMA.

The extent of overall treatment exposure was greater in the IPd group compared to the Pd group in terms of the median number of cycles started (median: 10 versus 6, respectively) and the median duration of exposure (41 versus 24 weeks respectively). Similarly, the extent of overall treatment exposure was greater in the IKd group compared to the Kd group, in terms of median number of cycles (19.0 versus 14.5 respectively) and median duration of exposure (80.0 weeks versus 61.4 weeks respectively).

**Overview of safety profile (Study ICARIA)**

| Treatment emergent adverse event (TEAE) | Pd (N=149) | IPd (N=152) |
|---|---|---|
| Any TEAE (any grade) | 146 (98.0%) | 151 (99.3%) |
| Treatment-related TEAE | 119 (79.9%) | 138 (90.8%) |
| Patients with any TEAE of grade ≥ 3 | 105 (70.5%) | 132 (86.8%) |
| Serious TEAE | 80 (53.7%) | 94 (61.8%) |
| Treatment-related serious TEAE | 24 (16.1%) | 54 (35.5%) |

| | | |
|---|---|---|
| Discontinuations due to TEAE | 19 (12.8%) | 11 (7.2%) |
| Deaths due to TEAE | 13 (8.7%) | 11 (7.2%) |
| Deaths due to treatment related TEAE | 2 (1.3%) | 1 (0.7%) |

**Overview of safety profile (Study IKEMA)**

| TEAE | Kd (N=122) | IKd (N=177) |
|---|---|---|
| Any TEAE (any grade) | 117 (95.9%) | 172 (97.2%) |
| Treatment-related TEAE | 98 (80.3%) | 153 (86.4%) |
| Patients with any TEAE of grade ≥ 3 | 82 (67.2%) | 136 (76.8%) |
| Serious TEAE | 70 (57.4%) | 105 (59.3%) |
| Treatment-related serious TEAE | 31 (25.4%) | 44 (24.9%) |
| Discontinuations due to TEAE | 17 (13.9%) | 15 (8.5%) |
| Deaths due to TEAE | 4 (3.3%) | 6 (3.4%) |

**Study ICARIA:**

The incidence of treatment related TEAEs was higher in IPd group compared to Pd group (90.8% versus 79.9%, respectively). The most frequent TEAEs (reported in ≥15%) all Grades regardless of relationship with ≥5% higher incidence in IPd group compared to the Pd group were neutropenia (46.7% versus 33.6%), infusion related reactions (IRR) (36.8% versus 1.3%), upper respiratory tract infection (28.3% versus 17.4%), diarrhoea (25.7% versus 19.5%), bronchitis (23.7% versus 8.7%), dyspnoea (15.1% versus 10.1%), and nausea (15.1% versus 9.4%).

The Grade ≥ 3 TEAEs that occurred with an incidence ≥5% in IPd group compared to Pd group were neutropenia (46.1% versus 32.2%) and febrile neutropenia (11.8% versus 2.0%). The serious TEAEs reported in ≥3% of patients in the IPd group were pneumonia, febrile neutropenia, disease progression, infusion related reaction, urinary tract infection, neutropenia, acute kidney injury, and pathological fracture (in 3.3% to 15.1% of patients). The incidences of TEAEs leading to treatment discontinuation of all study treatments in IPd and Pd was 7.2% and 12.8%, respectively. In the IPd group, the only TEAE leading to premature discontinuation of isatuximab was a Grade ≥3 infusion related reaction, which was reported in 2.6% of patients. In the Pd arm, these included thrombocytopenia, pneumonia, neutropenia, and septic shock.

The incidence of deaths during the treatment period was similar between the two groups (7.2% in IPd group versus 8.7% in Pd group). The incidence of fatal TEAEs other than disease progression was similar across the two groups (5.3% versus 6.7% respectively). Overall, there was a higher incidence of deaths due to infections in both groups (1.3% versus 3.4% respectively) compared to other system organ classes.

**Study IKEMA:**

The incidence of treatment related TEAEs was higher in IKd group compared to Kd group (86.4% versus 80.3%, respectively). The most frequent TEAEs of all Grades regardless of relationship with study treatment with ≥5% higher incidence in IKd group compared to the Kd group were upper respiratory tract infection (36.2% versus 23.8%), pneumonia (23.7% versus 19.7%), bronchitis 22.5% versus 12.3%), hypertension (36.7% versus 31.1%), dyspnoea

(27.7% versus 21.3%), cough (19.8% versus 13.9%), diarrhoea (36.2% versus 28.7%), vomiting (15.3% versus 9.0%), fatigue (28.2% versus 18.9% and IRRs (44.6% versus 3.3%).

The proportion of patients with serious TEAEs was numerically higher? In the IKd group compared to the Kd groups (59.3% versus 57.4% for all grades; 53.1% versus 47.5% for Grade ≥3). The serious TEAE related to pneumonia occurred with a higher incidence in the IKd group than in the Kd group (18.1% versus 11.5% respectively). The incidences of patients with TEAEs leading to treatment discontinuation was lower in the IKd group (8.5% versus 13.9% respectively), and the incidences of deaths due to TEAEs was similar between the IKd and Kd groups (3.4% versus 3.3% respectively).

In both studies, AEs IRRs, neutropenia, lower respiratory AEs and second primary malignancies (SPMs) were specially analysed. IRRs occurred in 38.2% of patients in Study ICARIA and most were Grade 2 (31.6%). Grade 3 or 4 IRRs were reported in 1.3% of subjects, respectively. IRRs led to isatuximab interruption in 28.9% of patients and discontinuation of isatuximab in 2.6% of patients. IRRs occurred at the first infusion in all patients and had a duration of 1 day in 98.4% of patients. In Study IKEMA, IRRs of any grades were reported more frequently in the IKd group (45.8%) than in the Kd group (3.3%). All IRRs were Grade 1 or Grade 2 except for 1 patient (in IKd group) who developed a Grade 3 IRR which was reported as carfilzomib induced. The most frequent symptoms of IRRs were dyspnoea, cough, nasal congestion, vomiting and nausea. Adequate warnings have been provided in the package insert.

The incidence of Grade 3-4 laboratory neutropenia was higher in the IPd group than the Pd group (84.8% versus 70.1%). The incidence of neutropenic complications was higher in IPd group compared to Pd group (30.3% versus 20% respectively). Grade 3 neutropenia events were reported more frequently in the IKd group than in the Kd group (17.5% versus 6.6% respectively). Neutropenia events were well managed with supportive care and through the use of colony-stimulating factors and most of them were reversible. Adequate warnings have been provided in the package insert.

In Study ICARIA, lower respiratory TEAEs were seen in 36.8% in IPd group versus 25.5% in the Pd group (Grade ≥3: 7.9 vs 3.4% respectively). In Study IKEMA, lower respiratory TEAEs excluding infections were also reported more frequently in the IKd group than in the Kd group (46.3% versus 36.1% all grades; 9.0% versus 3.3% for Grade ≥3). TEAEs of dyspnoea and cough were the main contributors to the imbalance.

Grade 3-4 thrombocytopenia was observed in 30.9% patients in the IPd group and 24.5% in the Pd group in Study ICARIA. In Study IKEMA, the incidences of Grade 3-4 thrombocytopenia were observed in 29.9% patients in IKd group and 23.8% in the Kd group. The package insert has included adequate warnings regarding these TEAEs.

SPMs were reported at a higher incidence in IPd group (6 patients) versus Pd group (1 patient) in Study ICARIA. In Study IKEMA, SPMs were reported in 7.3% in IKd group and 4.9% in Kd group mainly contributed by skin cancers (5.1% versus 2.5% respectively). SPMs are known risks for MM and associated with the other treatments like lenalidomide or alkylating agents used in the prior regimens. In Study IKEMA, SPMs were reported at a slightly higher incidence than the background rate. While the patients do have underlying risk factors for SPM due to the disease condition, prior therapies, pre-existing conditions, the increased risk associated with Isatuximab could not be ruled out. This information has been included in the package insert with recommendation for monitoring by healthcare professionals. Long-term data is

required to assess the risk and continued monitoring through routine pharmacovigilance activities would be necessary.

In ICARIA study, the Coomb's test was positive during IPd treatment in 67.7% of the 99 tested patients (47.5% were negative at baseline and 20.2% had missing test at baseline). In IKEMA study, a positive Coombs test was reported during IKd treatment in 63.3% of the 150 tested patients (negative at baseline). It is known that anti-CD38 monoclonal antibodies can bind to CD38 on red blood cells causing interference for blood typing and resulting in false positive test, which is also seen for isatuximab. Blood typing should be performed prior to the first infusion of isatuximab to avoid potential delay in case red blood cell transfusions are needed. Adequate warnings have been provided in the package insert regarding the interference with testing and the possibility of false positive results with Coomb's test.

The addition of isatuximab to Pd or Kd backbone increased the toxicity profile with higher incidences of overall TEAEs and Grade≥3 TEAES. Nevertheless, the SAEs, TEAES leading to discontinuation or deaths were comparable between the groups. The common AEs included pneumonia, upper respiratory tract infection, diarrhoea, bronchitis, dyspnoea, nausea, febrile neutropenia, and vomiting. The increased toxicity could be managed with dose modifications, use of growth factors, and anti-infectives. The IRRs observed were predominantly Grade 1-2 with onset most frequently at the first infusion and on the same day of the infusion. All IRRs were clinically manageable and recovered with no sequelae. Isatuximab caused a positive indirect Coombs test, but no RBC transfusion complications or haemolysis were observed. The incidence of SPMs was higher in treated groups and was also slightly higher than the background incidence as seen in MM especially with IKd combination. The package insert contains adequate warnings for active monitoring. Overall, the safety profile was considered acceptable for the proposed patient population.

## E ASSESSMENT OF BENEFIT-RISK PROFILE

Treatment of MM is challenging despite advances in treatment and many therapeutic options. This is due to high incidences of relapse and resistance to treatment regimens, leading to decreased duration of response and short survival times.

Study ICARIA conducted in RRMM patients with two or more prior therapies demonstrated that addition of isatuximab to Pd regimen resulted in statistically significant improvement in PFS with a 40.4% reduction in the risk of progression or death and a longer median PFS of 11.53 months with IPd compared to 6.47 months with Pd. The PFS benefit was consistently demonstrated in the subgroups with poor prognosis such as those with high-risk cytogenetics, elderly, ISS stage II and III, ECOG PS of 2, and heavily pre-treated patients (>3 prior lines). This improvement in PFS along with the higher ORR and the deeper response rates (VGPR, CR) compared to the comparator group were considered clinically meaningful.

While OS was not mature, a trend favouring IPd was observed. Notable adverse reactions were IRRs, pneumonia, upper respiratory tract infection, diarrhoea, bronchitis, dyspnoea, nausea, febrile neutropenia, and vomiting. Overall, the addition of isatuximab to pomalidomide and dexamethasone resulted in a significant and clinically meaningful benefit in PFS and response rates in patients with RRMM with a manageable safety profile. The final results of Study ICARIA will be required to further confirm the survival benefit with IPd regimen. Taken together, the benefit-risk profile of isatuximab in combination with pomalidomide and dexamethasone for use in RRMM with two or more prior therapies was considered favourable.

Study IKEMA conducted in RRMM patients with one to three prior lines of therapy demonstrated that addition of isatuximab to Kd regimen resulted in statistically significant improvement in the interim PFS with a 47% reduction in the risk of progression or death, with median PFS not reached for IKd compared to 19.1 months for Kd group. This improvement in PFS along with higher ORR and deeper response rates (VGPR, CR) compared to the comparator group was considered clinically meaningful. Consistent PFS was observed in the subgroups.

OS was not evaluated during the interim analysis and as pre-specified would be assessed at the final analysis. Nevertheless, the lower proportion of subjects with PFS2 events in the IKd group compared to Kd arm was reassuring. The final results of Study IKEMA will be required to further confirm the efficacy and safety with IKd regimen.

The safety profile was similar to that observed in ICARIA with slightly higher incidence of SPMs in IKd group which appeared to be higher than the background rate. While the SPM events could be confounded by the underlying risk factors such as the disease itself, prior therapies, pre-existing conditions, this risk could not be definitively ruled and would require further long-term monitoring. This information is presented factually in the package insert and the safety risk would be monitored through routine pharmacovigilance. Overall, the benefit-risk profile of isatuximab in combination with carfilzomib and dexamethasone was considered favourable for use in RRMM subjects with one to three prior lines of therapy.

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## F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefits of isatuximab have been demonstrated to outweigh the risks for the treatment of relapsed and refractory multiple myeloma. Approval of the product registration was granted on 13 October 2022. The approval of this application is subject to the submission of the final results of the Studies ICARIA and IKEMA to confirm the efficacy and safety of isatuximab in the treatment of patients with RRMM.

## G APPROVED PACKAGE INSERT AT REGISTRATION

**SARCLISA CONCENTRATE FOR SOLUTION FOR INFUSION 20MG/ML**

## 1. NAME OF THE MEDICINAL PRODUCT

SARCLISA Concentrate for Solution for Infusion 20mg/mL

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of concentrate for solution for infusion contains 20 mg of isatuximab.
Each vial contains 100 mg of isatuximab in 5 mL of concentrate (100 mg/5mL).
Each vial contains 500 mg of isatuximab in 25 mL of concentrate (500 mg/25mL).
Isatuximab is an immunoglobulin G1 (IgG1) monoclonal antibody (mAb) produced from a mammalian cell line (Chinese Hamster Ovary, CHO).
For the full list of excipients, see section 6.1

## 3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.
Colourless to slightly yellow solution, essentially free of visible particulates**.**

## 4. CLINICAL PARTICULARS

### 4.1 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 therapies 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 relapsed or refractory multiple myeloma who have received one to three prior therapies (see section 5.1).

### 4.2 Posology and method of administration

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

Premedication

Premedication should be used prior to SARCLISA infusion with the following medicinal products to reduce the risk and severity of infusion reactions:

- Dexamethasone 40 mg oral or intravenous (or 20 mg oral or intravenous for patients ≥75 years of age): when administered in combination with isatuximab and pomalidomide,
  Dexamethasone 20 mg (intravenous on the days of isatuximab and/or carfilzomib infusions, and oral on the other days): when administered in combination with isatuximab and carfilzomib.
- Acetaminophen 650 mg to 1000 mg oral (or equivalent).
- Diphenhydramine 25 mg to 50 mg intravenous or oral (or equivalent [e.g., cetirizine, promethazine, dexchlorpheniramine]). The intravenous route is preferred for at least the first 4 infusions.

The above recommended dose of dexamethasone (oral or intravenous) corresponds to the total dose to be administered only once before the infusion, as part of the premedication and the backbone treatment, before isatuximab and pomalidomide and before isatuximab 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 infusion reaction upon their first 4 administrations of SARCLISA may have their need for subsequent premedication reconsidered.

*Management of neutropenia*
The use of colony-stimulating factors (e.g. G-CSF) should be considered to mitigate the risk of neutropenia. In the event of grade 4 neutropenia, SARCLISA administration should be delayed until neutrophil count improves to at least 1.0 x 109/L (see section 4.4).

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

**Table 1: SARCLISA dosing schedule in combination with pomalidomide and dexamethasone or in combination with carfilzomib and dexamethasone**

| **Cycles** | **Dosing Schedule** |
|---|---|
| Cycle 1 | Days 1, 8, 15, and 22 (weekly) |
| Cycle 2 and beyond | Days 1, 15 (every 2 weeks) |

Each treatment cycle consists of a 28-day period. Treatment is repeated until disease progression or unacceptable toxicity.
For other medicinal products that are administered with SARCLISA, see section 5.1 and the respective current package insert.
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.

*Dose adjustments*
No dose reduction of SARCLISA is recommended.
Administration adjustments should be made if patients experience infusion reactions (see "Method of administration" below).
For other medicinal products that are administered with SARCLISA, the respective package insert should be considered.

Special populations

*Elderly*
Based on population pharmacokinetic analysis, no dose adjustment is recommended in elderly patients.

*Patients with renal impairment*
Based on population pharmacokinetic analysis and on clinical safety, no dose adjustment is recommended in patients with mild to severe renal impairment (see section 5.2).

*Patients with hepatic impairment*
Based on population pharmacokinetic analysis, no dose adjustment is recommended in patients with mild hepatic impairment. Data in patients with moderate and severe hepatic impairment are limited (see section 5.2), but there is no evidence to suggest that dose adjustment is required in these patients.

*Paediatric population*
The safety and efficacy of SARCLISA in children below 18 years of age have not been established. No data are available.

Method of administration
SARCLISA is for intravenous use. For instructions on dilution of the medicinal product before administration, see section 6.6.

Infusion rates
Following dilution, the SARCLISA infusion should be administered intravenously at the infusion rate presented in Table 2 below (see section 5.1). Incremental escalation of the infusion rate should be considered only in the absence of infusion reactions (see section 4.8).

**Table 2: Infusion rates of SARCLISA administration**

| | **Dilution Volume** | **Initial Rate** | **Absence of Infusion Reaction** | **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/hour |
| Subsequent infusions | 250 mL | 200 mL/hour | - | - | 200 mL/hour |

Administration adjustments should be made if patients experience infusion reactions (see section 4.4)

- In patients necessitating an intervention (Grade 2, moderate infusion reactions), a temporary interruption in the infusion should be considered and additional symptomatic medicinal products 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 supportive care, as needed. If symptoms do not recur after 30 minutes, the infusion rate may be increased to the initial rate, and then increased incrementally, as shown in Table 2.
- If symptoms do not resolve rapidly or do not improve to Grade ≤1 after interruption of SARCLISA infusion, persist or worsen despite appropriate medicinal products, or require hospitalization or are life-threatening, treatment with SARCLISA should be permanently discontinued and additional supportive therapy should be administered, as needed.

**4.3 Contraindications**
Hypersensitivity to the active substance or to any of its excipients listed in section 6.1.

**4.4 Special warnings and precautions for use**

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

Infusion reactions

Infusion reactions, mostly mild or moderate, have been observed in 38.2% of patients treated with SARCLISA in ICARIA-MM, and in 45.8% of patients treated with Isa-Kd in IKEMA (see section 4.8). In ICARIA-MM, all infusion reactions started during the first SARCLISA infusion and resolved on the same day in 98% of the infusions. The most common symptoms of an infusion reaction included dyspnoea, cough, chills and nausea. The most common severe signs and symptoms included hypertension, dyspnoea, and bronchospasm. In IKEMA, the infusion reactions occurred on the infusion day in 99.2% of episodes. In patients treated with Isa-Kd, 94.4% of those experiencing an IR experienced it during the first cycle of treatment. All infusion reactions resolved. The most common symptoms of an infusion reaction included cough, dyspnoea, nasal congestion, vomiting and nausea. The most common severe signs and symptoms included hypertension and dyspnoea (see section 4.8).

To decrease the risk and severity of infusion reactions, patients should be pre-medicated prior to SARCLISA infusion with acetaminophen, diphenhydramine or equivalent; dexamethasone is to be used as both premedication and anti-myeloma treatment (see section 4.2). Vital signs should be frequently monitored during the entire SARCLISA infusion. When required, interrupt SARCLISA infusion and provide appropriate medical and supportive measures (see section 4.2). In case symptoms do not improve to grade ≤1 after interruption of SARCLISA infusion, persist or worsen despite appropriate medicinal products, require hospitalization or are life-threatening, permanently discontinue SARCLISA and institute appropriate management.

Neutropenia

In patients treated with Isa-Pd, neutropenia occurred as a laboratory abnormality in 96.1% of patients and as an adverse reaction (1) in 46.7% of patients, with Grade 3-4 neutropenia reported as a laboratory abnormality in 84.9% of patients and as an adverse reaction in 45.4% of patients. Neutropenic complications have been observed in 30.3% of patients, including 11.8% of febrile neutropenia and 25.0% of neutropenic infections. In patients treated with Isa-Kd, neutropenia occurred as a laboratory abnormality in 54.8% of patients and as an adverse reaction (1) 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 4.8).
Complete blood cell counts should be monitored periodically during treatment. Patients with neutropenia should be monitored 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) should be considered to mitigate the risk of neutropenia (see section 4.2).

(1) Haematology laboratory values were recorded as adverse reactions only if they led to treatment discontinuation and/or dose modification and/or fulfilled a serious criterion.

Infection

A higher incidence of infections including grade ≥ 3 infections, mainly pneumonia, upper respiratory tract infection and bronchitis**,** occurred with SARCLISA (see section 4.8). Patients receiving SARCLISA should be closely monitored for signs of infection and appropriate standard therapy instituted. Antibiotics and antiviral prophylaxis can be considered during treatment.

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 (see section 4.8). 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 (see section 4.8). 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%. Physicians should carefully evaluate patients before and during treatment as per IMWG guidelines for occurrence of SPM and initiate treatment as indicated.

Interference with serological testing (indirect antiglobulin test)
Isatuximab binds to CD38 on red blood cells (RBCs) and may result in a false positive indirect antiglobulin test (indirect Coombs test). To avoid potential problems with RBC transfusion, patients being treated with SARCLISA should have blood type and screen tests performed prior to the first 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. Patients should be monitored for theoretical risk of haemolysis. If an emergency transfusion is required, non- cross- matched ABO/Rh-compatible RBCs can be given as per local blood bank practices (see section 4.5). There is currently no available information with regards to how long the interference with the indirect Coombs test may persist after the last infusion of SARCLISA. Based on the half-life of isatuximab, it is anticipated that isatuximab mediated positive indirect Coombs test may persist for approximately 6 months after the last infusion.

Interference with determination of complete response
Isatuximab is an IgG kappa monoclonal antibody that could be detected on both serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein (see section 4.5). This interference can impact the accuracy of the determination of complete response in some patients with IgG kappa myeloma protein. Twenty-two patients in the Isa-Pd arm who met Very Good Partial Response (VGPR) criteria with only residual immunofixation-positivity were tested for interference. Serum samples from these patients were tested by mass spectrometry to separate isatuximab signal from the myeloma M-protein signal. In the Isa-Kd arm, out of the 27 patients identified with potential interference and tested by mass spectrometry at the sensitivity level of the immunofixation test (25 mg/dL), 15 non-Complete Response (non-CR) patients as per Independent Response Committee (IRC) showed no detectable residual myeloma M-protein. Among these 15 patients, 11 patients had plasma cell <5% in bone marrow. This indicates that 11 additional patients out of the 179 Isa-Kd patients (6.1%) could have CR as best response leading to a potential CR rate of 45.8% (see section 4.5).

Elderly
Data are limited in the elderly population ≥ 85 years old (see section 4.2).

**4.5 Interaction with other medicinal products and other forms of interaction**
Isatuximab has no impact on the pharmacokinetics of pomalidomide or carfilzomib, or vice versa.

Interference with serological testing
Because CD38 protein is expressed on the surface of red blood cells, isatuximab, 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 isatuximab (see section 4.4). The interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt isatuximab binding or other locally validated methods. Since the Kell Blood group system is also sensitive

to DTT treatment, Kell-negative units should be supplied after ruling out or identifying alloantibodies using DTT-treated RBCs.

Interference with Serum Protein Electrophoresis and Immunofixation Tests
Isatuximab may be 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 section 4.4).

**4.6 Fertility, pregnancy and lactation**

Women of childbearing potential/Contraception
Women of childbearing potential treated with isatuximab should use effective contraception during treatment and for 5 months after cessation of treatment.

Pregnancy
There are no available data on isatuximab use in pregnant women. Animal reproduction toxicity studies have not been conducted with isatuximab. Immunoglobulin G1 monoclonal antibodies are known to cross the placenta after the first trimester of pregnancy. The use of isatuximab in pregnant women is not recommended.

Breast-feeding
It is unknown whether isatuximab is excreted in human milk. Human IgGs are known to be excreted in breast milk during the first few days after birth, which is decreasing to low concentrations soon afterwards; however, a risk to the breast-fed child cannot be excluded during this short period just after birth. For this specific period, a decision must be made whether to discontinue breast-feeding or to discontinue/abstain from isatuximab therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. Afterwards, isatuximab could be used during breast-feeding if clinically needed.

Fertility
No human and animal data are available to determine potential effects of isatuximab on fertility in males and females (see section 5.3).

For other medicinal products that are administered with isatuximab, refer to the respective current package insert

**4.7 Effects on ability to drive and use machines**
SARCLISA has no or negligible influence on the ability to drive and use machines.

**4.8 Undesirable effects**

Summary of the safety profile
In ICARIA-MM, the most frequent adverse reactions (>20%) are neutropenia (46.7%), infusion reactions (38.2%), pneumonia (30.9%), upper respiratory tract infection (28.3%), diarrhoea (25.7%) and bronchitis (23.7%). Serious adverse reactions occurred in 61.8% of patients receiving Isa-Pd. The most frequent serious adverse reactions are pneumonia (25.7%) and febrile neutropenia (6.6%). Permanent discontinuation of treatment because of adverse reactions was reported in 7.2% of patients treated with Isa-Pd. Adverse reactions with a fatal outcome during treatment were reported in 7.9% of patients treated with Isa-Pd (those occurring in more than 1% of patients were pneumonia occurring in 1.3% of patients and other infections occurring in 2.0% of patients).

In IKEMA, the most frequent adverse reactions (≥20%) are infusion reactions (45.8%), hypertension (36.7%), diarrhoea (36.2%), upper respiratory tract infection (36.2%), pneumonia (28.8%), fatigue (28.2%), dyspnoea (27.7%), insomnia (23.7%), bronchitis (22.6%), and back pain (22.0%). Serious adverse reactions occurred in 59.3% of patients receiving Isa-Kd. The most frequent serious adverse reaction is pneumonia (21.5%). Permanent discontinuation of treatment because of adverse reactions was reported in 8.5% of patients treated with Isa-Kd. Adverse reactions with a fatal outcome during treatment were reported in 3.4% of patients treated with Isa-Kd (those occurring in more than 1% of patients were pneumonia and cardiac failure both occurring in 1.1% of patients).

Tabulated list of adverse reactions

Adverse reactions are described using the NCI Common Toxicity Criteria, the 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); "frequency not known (cannot be estimated from available data)". Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

The adverse reactions were reported from the 152 patients who received Isa-Pd with a median duration of exposure of 41 weeks in ICARIA-MM study (see section 5.1).

**Table 3[a]: Adverse reactions reported in patients with multiple myeloma treated with isatuximab in combination with pomalidomide and dexamethasone (ICARIA-MM)**

| System Organ Class<br>Preferred Term | Adverse reaction | Frequency | Incidence (%) (N=152) | |
|---|---|---|---|---|
| | | | Any Grade | Grade ≥3 |
| **Infections and infestations** | Pneumonia[b c] | Very common | 47 (30.9) | 40 (26.3) |
| | Upper respiratory tract infection* | Very common | 43 (28.3) | 5 (3.3) |
| | Bronchitis* | Very common | 36 (23.7) | 5 (3.3) |
| **Neoplasms benign, malignant and unspecified (incl cysts and polyps)** | Skin squamous cell carcinoma | Common | 4 (2.6) | 2 (1.3) |
| **Blood and lymphatic system disorders** | Neutropenia[d] | Very common | 71 (46.7) | 70 (46.1) |
| | Febrile neutropenia | Very common | 18 (11.8) | 18 (11.8) |
| **Metabolism and nutrition disorders** | Decreased appetite* | Common | 15 (9.9) | 2 (1.3) |
| **Cardiac disorders** | Atrial fibrillation | Common | 7 (4.6) | 3 (2.0) |
| **Respiratory, thoracic and mediastinal disorders** | Dyspnoea* | Very common | 23 (15.1) | 6 (3.9) |
| **Gastrointestinal disorders** | Diarrhoea* | Very common | 39 (25.7) | 3 (2.0) |
| | Nausea* | Very common | 23 (15.1) | 0 |
| | Vomiting* | Very common | 18 (11.8) | 2 (1.3) |
| **Investigations** | Weight decreased* | Common | 10 (6.6) | 0 |
| **Injury, poisoning and procedural complications** | Infusion reaction[c] | Very common | 58 (38.2) | 4 (2.6) |

[a] Only TEAEs are reported in Table 3. The haematology laboratory values are reported in Table 4.

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

[c] See "Description of selected adverse reactions"
[d] Haematology laboratory values were recorded as TEAEs only if they led to treatment discontinuation and/or dose modification or fulfilled a serious criterion.
*No grade 4

The adverse reactions were reported from the 177 patients who received Isa-Kd with a median duration of exposure of 80.0 weeks in IKEMA study (see section 5.1).

**Table 4[a]: Adverse reactions reported in patients with multiple myeloma treated with isatuximab in combination with carfilzomib and dexamethasone (IKEMA)**

| System Organ Class<br>Preferred Term | Adverse reaction | Frequency | Incidence (%) (N=177) | |
|---|---|---|---|---|
| | | | Any Grade | Grade ≥3 |
| **Infections and infestations** | Pneumonia[b c] | Very common | 28.8% | 20.9 |
| | Upper respiratory tract infection* | Very common | 36.2% | 3.4% |
| | Bronchitis* | Very common | 22.6% | 2.3% |
| **Vascular disorders** | Hypertension* | Very common | 36.7% | 20.3% |
| **Neoplasms benign, malignant and unspecified (incl cysts and polyps)** | Skin cancers* | Common | 5.1% | 0.6% |
| | Solid tumours other than skin cancers | Common | 3.4 % | 1.7% |
| **Blood and lymphatic system disorders** | Neutropenia[d] | Common | 4.5% | 4.0% |
| **Respiratory, thoracic and mediastinal disorders** | Dyspnoea* | Very common | 27.7% | 5.1% |
| | Cough* | Very common | 19.8% | 0% |
| **Gastrointestinal disorders** | Diarrhoea* | Very common | 36.2% | 2.8% |
| | Vomiting* | Very common | 15.3% | 1.1% |
| **General disorders and administration site conditions** | Fatigue* | Very common | 28.2% | 3.4% |
| **Injury, poisoning and procedural complications** | Infusion reaction[c*] | Very common | 45.8% | 0.6% |

[a] Only TEAEs are reported in Table 4. The haematology laboratory values are reported in Table 6.
[b] The term pneumonia is a grouping of the following terms: atypical pneumonia, pneumocystis jirovecii pneumonia, pneumonia, pneumonia influenzal, pneumonia legionella, pneumonia streptococcal, pneumonia viral, and pulmonary sepsis.
[c] See "Description of selected adverse reactions"
[d] Haematology laboratory values were recorded as TEAEs only if they led to treatment discontinuation and/or dose modification or fulfilled a serious criterion.
*No grade 4 or 5.

Description of selected adverse reactions

*Infusion reactions*
In ICARIA-MM, infusion reactions were reported in 58 patients (38.2%) treated with SARCLISA. All patients who experienced infusion reactions, experienced them during the 1st infusion of SARCLISA, with 3 patients (2.0%) also having infusion reactions at their 2nd infusion, and 2 patients (1.3%) at their 4th infusion. Grade 1 infusion reactions were reported in 3.9%, Grade 2 in 31.6%, Grade 3 in 1.3%, and

Grade 4 in 1.3% of the patients. All infusion reactions were reversible and resolved the same day in 98% of the infusions. Signs and symptoms of Grade 3 or 4 infusion reactions included dyspnoea, hypertension, and bronchospasm.
The incidence of infusion interruptions because of infusion reactions was 28.9%. The median time to infusion interruption was 55 minutes. Discontinuations from treatment due to infusion reaction were reported in 2.6% of patients in Isa-Pd group.
In IKEMA, infusion reactions were reported in 81 patients (45.8%) treated with Isa-Kd. Grade 1 infusion reactions were reported in 13.6%, Grade 2 in 31.6%, and Grade 3 in 0.6% of the patients treated with Isa-Kd. All infusion reactions were reversible and resolved the same day in 73.8% of episodes in Isa-Kd patients and in more than 2 days in 2.5% of episodes in Isa-Kd patients. Signs and symptoms of Grade 3 infusion reactions included dyspnoea and hypertension. The incidence of patients with isatuximab infusion interruptions because of infusion reactions was 29.9%. The median time to isatuximab infusion interruption was 63 minutes. Isatuximab was discontinued in 0.6% of patients due to infusion reactions. (see sections 4.2 and 4.4).

*Infections*
In ICARIA-MM, the incidence of Grade 3 or higher infections was 42.8%. Pneumonia was the most commonly reported severe infection with Grade 3 reported in 21.7% of patients in the Isa-Pd group compared to 16.1% in the Pd group, and Grade 4 in 3.3% of patients in the Isa-Pd group compared to 2.7% in the Pd group. Discontinuations from treatment due to infection were reported in 2.6% of patients in the Isa-Pd group compared to 5.4% in the Pd group. Fatal infections were reported in 3.3% of patients in the Isa-Pd group and 4.0% in the Pd group. In IKEMA, the incidence of Grade 3 or higher infections was 38.4%. Pneumonia was the most commonly reported severe infection with Grade 3 reported in 15.8% of patients in the Isa-Kd group compared to 10.7% in the Kd group, and Grade 4 in 3.4% of patients in the Isa-Kd group compared to 2.5% in the Kd group. Treatment was discontinued due to infection in 2.8% of patients in the Isa-Kd group compared to 4.9% in the Kd group. Fatal infections were reported in 2.3% of patients in the Isa-Kd group and 0.8% in the Kd group. (see section 4.4).

*Cardiac failure*
In IKEMA, cardiac failure (including cardiac failure, cardiac failure congestive, cardiac failure acute, cardiac failure chronic, left ventricular failure, and pulmonary oedema) 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. Cardiac failure with a fatal outcome during treatment was reported in 1.1% of patients in the Isa-Kd group and not reported in the Kd group (see the current prescribing information for carfilzomib).

*Haematology laboratory values*

**Table 5: Haematology laboratory abnormalities in patients receiving isatuximab combined with pomalidomide and dexamethasone–versus pomalidomide and dexamethasone (ICARIA-MM)**

| **Laboratory Parameter** | **SARCLISA + Pomalidomide + Dexamethasone n (%) (N=152)** | | | **Pomalidomide + Dexamethasone n (%) (N=147)** | | |
|---|---|---|---|---|---|---|
| | **All Grades** | **Grade 3** | **Grade 4** | **All Grades** | **Grade 3** | **Grade 4** |
| Anaemia | 151 (99.3) | 48 (31.6) | 0 | 145 (98.6) | 41 (27.9) | 0 |
| Neutropenia | 146 (96.1) | 37 (24.3) | 92 (60.5) | 137 (93.2) | 57 (38.8) | 46 (31.3) |
| Lymphopenia | 140 (92.1) | 64 (42.1) | 19 (12.5) | 137 (93.2) | 52 (35.4) | 12 (8.2) |
| Thrombocytopenia | 127 (83.6) | 22 (14.5) | 25 (16.4) | 118 (80.3) | 14 (9.5) | 22 (15.0) |

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.

**Table 6: Haematology laboratory abnormalities in patients receiving isatuximab combined with carfilzomib and dexamethasone versus carfilzomib and dexamethasone (IKEMA)**

| **Laboratory Parameter** | **SARCLISA + Carfilzomib + Dexamethasone (N=177)** | | | **Carfilzomib + Dexamethasone (N=122)** | | |
|---|---|---|---|---|---|---|
| | **All Grades** | **Grade 3** | **Grade 4** | **All Grades** | **Grade 3** | **Grade 4** |
| Anaemia | 99.4% | 22.0% | 0% | 99.2% | 19.7% | 0% |
| Neutropenia | 54.8% | 17.5% | 1.7% | 43.4% | 6.6% | 0.8% |
| Lymphopenia | 94.4% | 52.0% | 16.9% | 95.1% | 43.4% | 13.9% |
| Thrombocytopenia | 94.4% | 18.6% | 11.3% | 87.7% | 15.6% | 8.2% |

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.

*Immunogenicity*
Across 9 clinical studies in multiple myeloma (MM) with isatuximab single agent and combination therapies including ICARIA-MM and IKEMA (N=1018), the incidence of treatment emergent ADAs was 1.9%. No effect of ADAs was observed on pharmacokinetics, safety or efficacy of isatuximab.

**4.9 Overdose**

Signs and symptoms
There has been no experience of overdosage of isatuximab in clinical studies. Doses of intravenous isatuximab 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 patients for signs or symptoms of adverse reactions and take all appropriate measures immediately.

**5. PHARMACOLOGICAL PROPERTIES**

**5.1 Pharmacodynamic properties**
Pharmacotherapeutic group: Antineoplastic agents, monoclonal antibodies, ATC code: L01XC38.

Mechanism of action
Isatuximab is an IgG1-derived monoclonal antibody that binds to a specific extracellular epitope of CD38 receptor. CD38 is a transmembrane glycoprotein that is highly expressed on multiple myeloma cells.

*In vitro*, isatuximab acts through IgG Fc-dependent mechanisms including: antibody dependent cell mediated cytotoxicity (ADCC), antibody dependent cellular phagocytosis (ADCP), and complement dependent cytotoxicity (CDC). Furthermore, isatuximab can also trigger tumour cell death by induction of apoptosis via an Fc-independent mechanism.

*In vitro*, isatuximab blocks the enzymatic activity of CD38 which catalyses the synthesis and hydrolysis of cyclic ADP-ribose (cADPR), a calcium mobilizing agent. Isatuximab inhibits the cADPR production from extracellular nicotinamide adenine dinucleotide (NAD) in multiple myeloma cells.

*In vitro*, isatuximab can activate NK cells in the absence of CD38 positive target tumour cells.

*In vivo, a* decrease in absolute counts of total CD16+ and CD56+ NK cells, CD19+ B-cells, CD4+ T-cells and $T_{REG}$ (CD3+, CD4+, CD25+, CD127-) was observed in peripheral blood of patients treated with isatuximab monotherapy.

In multiple myeloma patients, SARCLISA monotherapy induced clonal expansion of the T-cell receptor repertoire indicating an adaptive immune response.

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 that of isatuximab alone. *In vivo* animal experiments using a human multiple myeloma xenograft model in mice demonstrated that the combination of isatuximab and pomalidomide results in enhanced antitumour activity compared to the activity of isatuximab or pomalidomide alone.

Clinical efficacy and safety

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/or refractory multiple myeloma. Patients had received at least two prior therapies including lenalidomide and a proteasome inhibitor with disease progression on or within 60 days after the end of the previous therapy. 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 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 I.V. 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 (oral/intravenous) 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 between the two treatment groups, with some minor imbalances. The median patient age was 67 years (range 36-86), 19.9% of patients were ≥75 years. ECOG PS was 0 in 35.7% of patients in the isatuximab arm and 45.1% in the comparator arm, 1 in 53.9% in the isatuximab arm and 44.4% in the comparator arm, and 2 in 10.4% in the isatuximab arm and 10.5% in the comparator arm, 10.4% of patients in the isatuximab arm versus 10.5% in the comparator arm entered the study with a history of COPD or asthma, and 38.6% versus 33.3% of patients with renal impairment (creatinine clearance <60 mL/min/1.73 m²) were included in the isatuximab arm versus the comparator arm , respectively. The International Staging System (ISS) stage at study entry was I in 37.5% (41.6% in the isatuximab arm and 33.3% in the comparator arm), II in 35.5% (34.4% in the isatuximab arm and 36.6% in the comparator arm) and III in 25.1% (22.1% in the isatuximab arm and 28.1% in the comparator arm) of patients. Overall, 19.5% of patients (15.6% in the isatuximab arm and 23.5% in the comparator arm) had high-risk chromosomal abnormalities at study entry; del(17p), t(4;14) and t(14;16) were present in 12.1% (9.1% in the isatuximab arm and 15.0% in the comparator arm), 8.5% (7.8% in the isatuximab arm and 9.2% in the comparator arm) and 1.6% (0.6% in the isatuximab arm and 2.6% in the comparator arm) of patients, respectively.
The median number of prior lines of therapy was 3 (range 2-11). All patients received a prior proteasome inhibitor, all patients received prior lenalidomide, and 56.4% of patients received prior stem cell

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

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

Progression-free survival (PFS) was the primary efficacy endpoint of ICARIA-MM. The improvement in PFS represented a 40.4% reduction in the risk of disease progression or death in patients treated with Isa-Pd.

Efficacy results are presented in Table 7 and Kaplan-Meier curves for PFS and OS are provided in Figures 1 and 2:

**Table 7: 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** |
|---|---|---|
| **Progression-Free Survival** [a,b] | | |
| Median (months) [95% CI] | 11.53 [8.936-13.897] | 6.47 [4.468-8.279] |
| Hazard ratio[c] [95% CI] | 0.596 [0.436-0.814] | |
| p-value (stratified log-rank test)[c] | 0.0010 | |
| **Overall Response Rate**[d] Responders (sCR+CR+VGPR+PR) n (%) [95% CI][e] | 93 (60.4) [0.5220-0.6817] | 54 (35.3) [0.2775-0.4342] |
| Odds ratio vs comparator [95% exact CI] | 2.795 [1.715-4.562] | |
| 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][e] | 49 (31.8) [0.2455-0.3980] | 13 (8.5) [0.0460-0.1409] |
| Odds ratio vs comparator [95% exact CI] | 5.026 [2.514-10.586] | |
| p-value (stratified Cochran-Mantel Haenszel)[c] | <0.0001 | |
| **Duration of Response**[f *] Median in months [95% CI][g] | 13.27 [10.612-NR] | 11.07 [8.542-NR] |

[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] Patients without progressive disease or death before the analysis cut-off or the date of initiation of further anti-myeloma treatment were censored at the date of the last valid disease assessment not showing disease progression performed prior to initiation of a further anti-myeloma treatment (if any) or the analysis cut-off date, whichever came first.

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

[e] Estimated using Clopper-Pearson method.

[f] The duration of response was determined for patients who achieved a response of ≥PR (93 patients in the isatuximab arm and 54 patients in the comparator arm). Kaplan-Meier estimates of duration of response.
[g] CI for Kaplan-Meier estimates are calculated with log-log transformation of survival function and methods of Brookmeyer and Crowley.
*Cut-off date of 11-Oct-2018. Median follow-up time=11.60 months. HR<1 favours Isa-Pd arm.
NR: not reached

In patients with high-risk cytogenetics (central laboratory assessment), median PFS was 7.49 (95% CI: 2.628 to NC) in the Isa-Pd group and 3.745 (95% CI: 2.793 to 7.885) in the Pd group (HR=0.655; 95% CI: 0.334 to 1.283). PFS improvements in the Isa-Pd group were also observed in patients >75 years (HR=0.479; 95% CI: 0.242 to 0.946), with ISS stage III at study entry (HR=0.635; 95% CI: 0.363 to 1.110), with baseline creatinine clearance < 60 ml/min/1.73 m² (HR=0.502; 95% CI: 0.297 to 0.847), with > 3 prior lines of therapy (HR=0.590; 95% CI: 0.356 to 0.977), in patients refractory to prior therapy with lenalidomide (HR=0.593; 95% CI: 0.431 to 0.816) or proteasome inhibitor (HR=0.578; 95% CI: 0.405 to 0.824) and in those refractory to lenalidomide at the last line before to the study entry (HR= 0.601; 95%CI: 0.436 to 0.828).
Insufficient data is available to conclude on the efficacy of Isa-Pd in patients previously treated with daratumumab (1 patient in the isatuximab arm and no patient in the comparator arm).

The median time to first response in responders was 35 days in the Isa-Pd group versus 58 days in the Pd group. With a median duration of follow-up of 11.56 months in the Isa-Pd group and 11.73 months in the Pd group, median overall survival was not reached for either treatment group. The hazard ratio for OS was 0.687 (95% CI: 0.461-1.023, p-value=0.0631).

**Figure 1: Kaplan-Meier Curves of PFS – ITT population – ICARIA-MM (assessment by the IRC)**

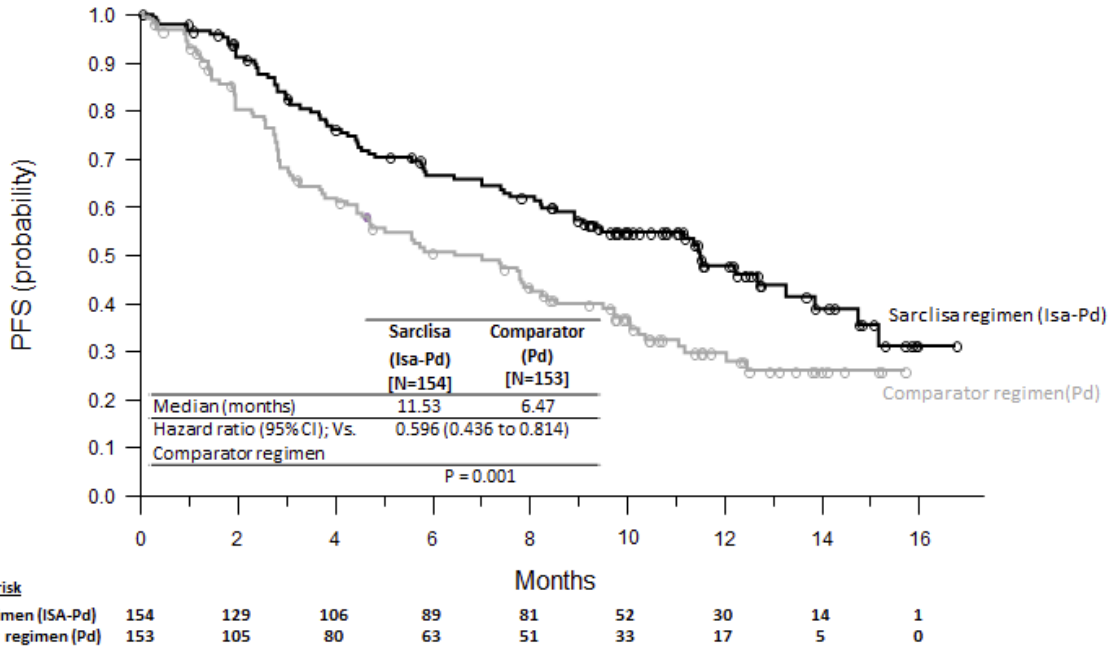
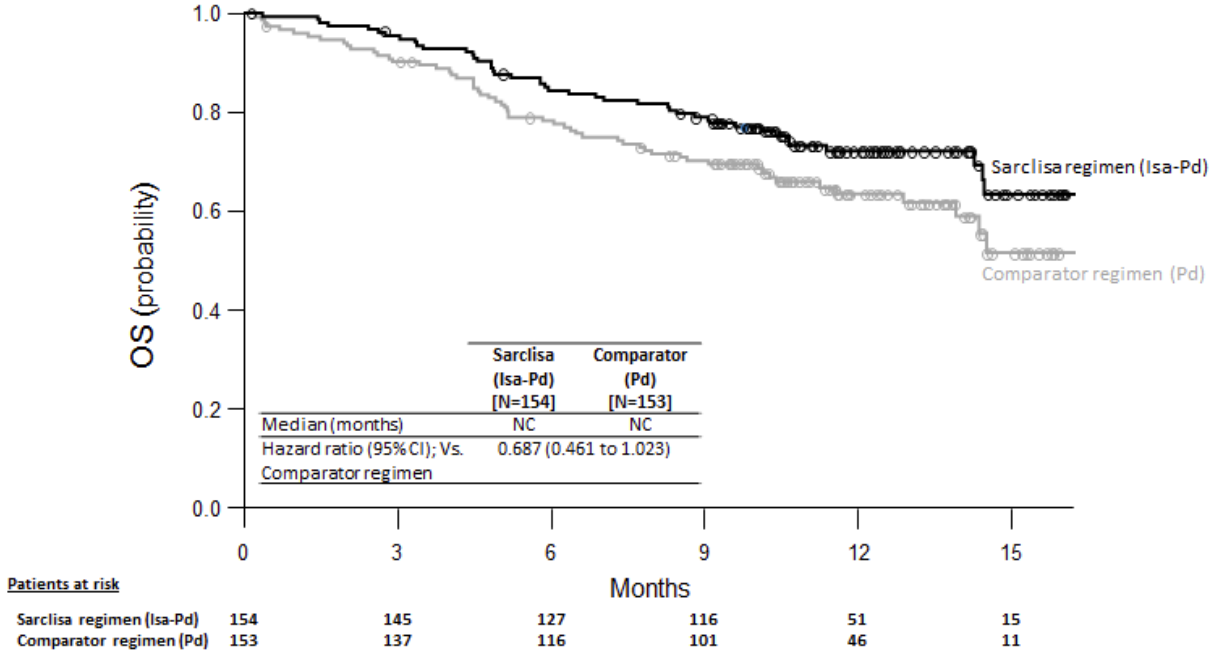


**Figure 2: Kaplan-Meier Curves of OS – ITT population – ICARIA-MM**




Cutoff date = 11 October 2018

In the ICARIA-MM (EFC14335) study, a weight-based volume was used for isatuximab infusion. The fixed volume infusion method as described in section 4.2 was evaluated in study TCD14079 Part B and pharmacokinetics simulations confirmed minimal differences between the pharmacokinetics following injection applying a volume based on patient weight and a fixed volume of 250 mL (see section 5.2). In study TCD14079 part B, there were no new safety signals or differences in efficacy and safety as compared to ICARIA-MM.

IKEMA (EFC15246)

The efficacy and safety of SARCLISA in combination with carfilzomib and dexamethasone were evaluated in IKEMA (EFC15246), a multicentre, 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 therapies. Patients with primary refractory disease, who had previously been treated with carfilzomib, or who were refractory to previous anti-CD38 monoclonal antibody treatment 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 I.V. infusion weekly in the first cycle and every two weeks thereafter. Carfilzomib was administered as an I.V. infusion at the dose of 20 mg/m² on days 1 and 2; 56 mg/m² on days 8, 9, 15 and 16 of cycle 1; and at the dose of 56 mg/m² on days 1, 2, 8, 9, 15 and 16 for subsequent cycles of each 28-day cycle. Dexamethasone (IV on the days of isatuximab and/ or carfilzomib infusions, and PO on the other days) 20 mg was given on days 1, 2, 8, 9, 15, 16, 22 and 23 for each 28-day cycle.

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. ECOG PS was 0 in 53.1% of patients in the Isa-Kd group and 59.3% in the Kd group, 1 in 40.8% in the Isa-Kd group and

36.6% in the Kd group, and 2 in 5.6% in the Isa-Kd group and 4.1% in the Kd group, and 3 in 0.6% in the Isa-Kd group and 0% in the Kd group. The proportion of patients with renal impairment (eGFR<60 mL/min/1.73 $m_2$) 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. The Revised-ISS (R-ISS) stage at study entry was I in 25.8%, II in 59.6%, and III in 7.9% of patients. Overall, 24.2% of patients had high -risk chromosomal abnormalities at study entry; del(17p), t(4;14), t(14;16) were present in 11.3%, 13.9% and 2.0% of patients, respectively. In addition, gain(1q21) was present in 42.1% 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. The improvement in PFS represented 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 8 and Kaplan-Meier curves for PFS are provided in the Figure 3:

**Table 8: Efficacy of SARCLISA in combination with carfilzomib and dexamethasone versus carfilzomib and dexamethasone in the treatment of multiple myeloma (intent-to-treat analysis)**

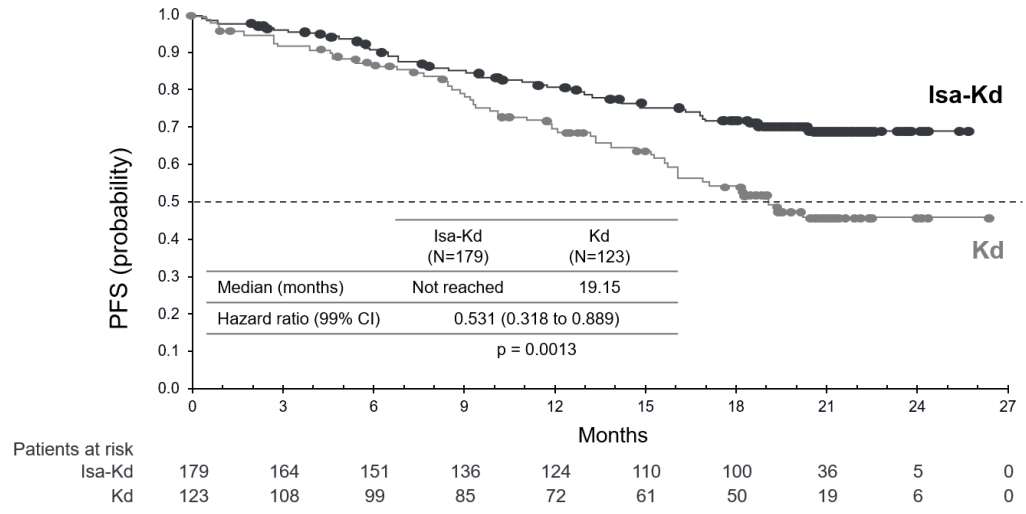
| **Endpoint** | **SARCLISA + Carfilzomib + Dexamethasone N=179** | **Carfilzomib + Dexamethasone N=123** |
|---|---|---|
| **Progression-Free Survival**[a] | | |
| Median (months) [95% CI] | NR [NR-NR] | 19.15 [15.77- NR] |
| Hazard ratio[b] [95% CI] | 0.531 [0.318-0.889] | |
| p-value (stratified log-rank test)[b] | 0.0013 | |
| **Overall Response Rate**[c]<br>Responders (sCR+CR+VGPR+PR) [95% CI][d] | 86.6%<br>[0.8071-0.9122] | 82.9%<br>[0.7509-0.8911] |
| p-value (stratified Cochran-Mantel-Haenszel)[b] | 0.3859 | |
| Complete Response (CR) | 39.7% | 27.6% |
| Very Good Partial Response (VGPR) | 33.0% | 28.5% |
| Partial Response (PR) | 14.0% | 26.8% |
| **VGPR or better** (sCR+CR+VGPR)<br>[95% CI][d] | 72.6%<br>[0.6547-0.7901] | 56.1%<br>[0.4687 -0.6503] |
| p-value (stratified Cochran-Mantel-Haenszel)[b e] | 0.0021 | |
| **CR**[f]<br>[95% CI][d] | 39.7%<br>[0.3244-0.4723] | 27.6%<br>[0.1996 to 0.3643] |
| **Minimal Residual Disease negative rate**[g]<br>[95% CI][d] | 29.6%<br>[0.2303-0.3688] | 13.0%<br>[0.0762-0.2026] |
| p-value (stratified Cochran-Mantel-Haenszel)[b e] | 0.0008 | |
| **Duration of Response**[h] *(PR or better)<br>Median in months [95% CI][i]<br>Hazard ratio[b] [95% CI] | NR [NR-NR]<br><br>0.425 [0.269-0.672] | NR [14.752-NR] |

[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] Nominal p-value.
[f] CR to be tested with final analysis.
[g] Based on a sensitivity level of 10-5 by NGS in ITT population.
[h] Based on Responders in the ITT population. Kaplan-Meier estimates of duration of response.
[i] CI for Kaplan-Meier estimates are calculated with log-log transformation of survival function and methods of Brookmeyer and Crowley.
* Cut-off date of 7 February 2020. Median follow-up time=20.73 months. HR<1 favours Isa-Kd arm.
NR: not reached.

PFS improvements in the Isa-Kd group were observed in patients with high -risk cytogenetics (central laboratory assessment, HR = 0.724; 95% CI: 0.361 to 1.451), with gain (1q21) chromosomal abnormality (HR=0.569; 95% CI: 0.330 to 0.981), ≥65 years (HR =0.429; 95% CI: 0.248 to 0.742), with baseline eGFR (MDRD) < 60 mL/min/1.73 m² (HR =0.273; 95% CI: 0.113 to 0.660), with >1 prior line of therapy (HR =0.479; 95% CI: 0.294 to 0.778), with ISS stage III at study entry (HR=0.650; 95% CI: 0.295 to 1.434), and in patients refractory to prior therapy with lenalidomide (HR=0.598; 95% CI: 0.339 to 1.055).
In the sensitivity analysis without censoring for further anti-myeloma therapy, the median PFS was not reached (NR) in the Isa-Kd group versus 19.0 months (95% CI: 15.38 to NR) in the Kd group (HR=0.572; 99% CI: 0.354 to 0.925, p=0.0025). Insufficient data is available to conclude on the efficacy of Isa-Kd in patients previously treated with daratumumab (1 patient in the isatuximab arm and no patient in the comparator arm).

The median time to first response was 1.08 months in the Isa-Kd group and 1.12 months in the Kd group. 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.

**Figure 3 – Kaplan-Meier Curves of PFS – ITT population – IKEMA (assessment by the IRC)**




Cutoff date = 07 February 2020.

Among patients with eGFR (MDRD) <50 mL/min/1.73 $m^2$ at baseline, complete renal response (≥60 mL/min/1.73 $m^2$ at ≥1 postbaseline assessment) was observed for 52.0% (13/25) of patients in the Isa-Kd group and 30.8% (4/13) in the Kd group. Sustained complete renal response (≥60 days) occurred in 32.0% (8/25) of patients in the Isa-Kd group and in 7.7% (1/13) in the Kd group. In the 4 patients in the Isa-Kd group and the 3 patients in the Kd group with severe renal impairment at baseline (eGFR (MDRD) >15 to <30 mL/min/1.73 $m^2$), minimal renal response (≥30 to <60 mL/min/1.73 $m^2$ at ≥1 postbaseline assessment) was observed for 100% of patients in the Isa-Kd group and 33.3% of patients in the Kd group.

**5.2 Pharmacokinetic properties**

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 and 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 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 every 2 weeks schedule, while no deviation to the dose proportionality is observed between 5 and 20 mg/kg following every week for 4 weeks followed by every 2 weeks schedule. This is due to the high contribution of nonlinear target-mediated clearance to the total clearance at doses below 5 mg/kg, which becomes negligible at higher doses. 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, clinical trial performed in relapsed and/or refractory multiple myeloma patients treated with isatuximab in combination with pomalidomide and dexamethasone, 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. Although the change from a weight-based volume administration method for isatuximab infusion to the fixed volume infusion method resulted in changes in the $t_{max}$, the change had a limited impact on pharmacokinetics exposure with comparable simulated $C_{max}$ at steady state (283 µg/mL vs 284 µg/mL) and $C_{trough}$ at 4 weeks (119 µg/mL vs 119 µg/mL) for a patient with median weight (76 kg). Also for other patient weight groups, $C_{max}$ and $C_{trough}$ were comparable. In IKEMA, clinical trial performed in relapsed and/or refractory multiple myeloma patients treated with isatuximab in combination with carfilzomib and dexamethasone, the mean (CV%) predicted maximum plasma concentration $C_{max}$ and AUC at steady state were 655 µg/mL (30.8%) and 159,000 µg.h/mL (37.1%), respectively.

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

Distribution

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

Metabolism

As a large protein, isatuximab is expected to be metabolized 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 9.55 mL/h (0.229 L/day). This is associated with a terminal half-life of 28 days.

Specific populations

*Age*
The population pharmacokinetic analyses of 476 patients aged 36 to 85 years showed comparable exposure to isatuximab in patients <75 years old (n=406) versus ≥ 75 years old (n=70).

*Gender*

The population pharmacokinetic analysis with 207 female (43.5%) and 269 male (56.5%) patients showed no clinically meaningful effect of gender on isatuximab pharmacokinetics.

*Race*
The population pharmacokinetic analysis with 377 Caucasian (79%), 25 Asian (5%), 18 Black (4%), and 33 other race (7%) patients showed no clinically meaningful effect of race on isatuximab pharmacokinetics.

*Weight*
Based on a population pharmacokinetics analysis using data from 476 patients, the clearance of isatuximab increased with increasing body weight, supporting the body-weight based dosing.

*Hepatic Impairment*
No formal studies of isatuximab in patients with hepatic impairment have been conducted. Out of the 476 patients of 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 4.2).

*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 $m_2$ ≤ estimated glomerular filtration rate (e-GFR) <90 mL/min/1.73 $m_2$), 163 patients with moderate renal impairment (30 mL/min/1.73 $m_2$≤ e-GFR < 60 mL/min/1.73 $m_2$) and 12 patients with severe renal impairment (e-GFR <30 mL/min/1.73 $m_2$). Analyses suggested no clinically meaningful effect of mild to severe renal impairment on isatuximab pharmacokinetics compared to normal renal function.

*Paediatric population*
Isatuximab was not evaluated in patients under 18 years of age.

### 5.3 Preclinical safety data
Non-clinical data reveal no special hazard for humans based on conventional studies of repeated dose toxicity, albeit the species selected is not pharmacologically responsive and therefore the relevance for humans is not known. Genotoxicity, carcinogenic potential and toxicity to reproduction and development studies have not been performed.

## 6. PHARMACEUTICAL PARTICULARS
### 6.1 List of excipients
Sucrose
Histidine hydrochloride monohydrate
Histidine
Polysorbate 80
Water for injections

### 6.2 Incompatibilities
This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

### 6.3 Shelf life
Unopened Vial
Please refer to outer carton.

After dilution
Chemical and physical in-use stability of SARCLISA infusion solution has been demonstrated for 48 hours at 2°C - 8°C, followed by 8 hours (including the infusion time) at room temperature (15°C - 25°C).
From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior use are the responsibility of the user and would normally not be longer than 24 hours at 2°C to 8°C, unless dilution has taken place in controlled and validated aseptic conditions. No protection from light is required for storage in the infusion bag.

### 6.4 Special precautions for storage
Store in a refrigerator (2°C - 8°C).
Do not freeze.
Store in the original package in order to protect from light.
For storage conditions after dilution of the medicinal product, see section 6.3.

### 6.5 Nature and contents of container
5 ml concentrate containing 100 mg of isatuximab in a 6 mL type I colourless clear glass vial closed with ETFE (copolymer of ethylene and tetrafluoroethylene)-coated bromobutyl stopper. The vials are crimped with an aluminium seal with a grey flip-off button. The fill volume has been established to ensure removal of 5 mL (i.e. 5.4 mL). Pack size of one or three vials.

25 ml concentrate containing 500 mg of isatuximab in a 30 mL type I colourless clear glass vial closed with ETFE (copolymer of ethylene and tetrafluoroethylene)-coated bromobutyl stopper. The vials are crimped with an aluminium seal with a blue flip-off button. The fill volume has been established to ensure removal of 25 mL (i.e. 26 mL). Pack size of one vial.

Not all pack sizes may be marketed.

**6.6 Special precautions for disposal and other handling**

Preparation for the intravenous administration

The preparation of the infusion solution must be done under aseptic conditions.

- The dose (mg) of SARCLISA concentrate should be calculated based on patient weight (measured prior to each cycle to have the administered dose adjusted accordingly, see section 4.2). More than one 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 discoloured.
- Do not shake vials.
- 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 the 250 mL infusion bag with sodium chloride 9 mg/mL (0.9%) solution for injection or glucose 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 homogenize the diluted solution by inverting the bag. Do not shake.

Administration

- The infusion solution must be administered by intravenous infusion using an intravenous tubing infusion set (in PE, PVC with or without DEHP, polybutadiene (PBD) or polyurethane (PU)) with an in-line filter (polyethersulfone (PES), polysulfone or nylon).
- The infusion solution should be administered for a period of time that will depend on the infusion rate (see section 4.2).
- 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

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

**Product Registrant**

Sanofi-aventis Singapore Pte Ltd, 38 Beach Road #18-11, South Beach Tower.

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