Taiwan Food and Drug Administration

Assessment Report

Trade Name：多髓易濃縮輸注液 20 毫克/毫升 /
SARCLISA concentrate for solution for infusion 20 mg/mL

Active Ingredient：Isatuximab

License Number：MOHW-BI 001147

Applicant：賽諾菲股份有限公司

Approval Date：110/1/21

Indication：
與 pomalidomide 及 dexamethasone 併用，適用於先前曾接受過至少 2 種治療(包括 lenalidomide 及一種蛋白酶體抑制劑)的多發性骨髓瘤成年病人。

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

Background Information

Trade Name	多髓易濃縮輸注液 20 毫克/毫升 / SARCLISA concentrate for solution for infusion 20 mg/mL
Active Ingredient(s)	Isatuximab
Applicant	賽諾菲股份有限公司
Dosage Form & Strengths	注射液劑
Indication	與 pomalidomide 及 dexamethasone 併用，適用於先前曾接受過至少 2 種治療(包括 lenalidomide 及一種蛋白酶體抑制劑)的多發性骨髓瘤成年病人。 SARCLISA is indicated in combination with pomalidomide and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor.
Posology	詳如仿單。
Pharmacological Category **ATC Code**	L01XC38

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

Isatuximab is an IgG1 derived-monoclonal antibody binding selectively the human CD38 membrane protein. Isatuximab potentially induces apoptosis of tumor cells and activation of immune effector mechanisms including antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and complement dependent cytotoxicity (CDC). Isatuximab is produced from a CHO cell line using a fed-batch production process and the theoretical molecular mass is 148 kDa. Each HC contains a predominant N-linked oligosaccharide attached at the consensus glycosylation site at N300.

Manufacturing

The isatuximab DS is manufactured at Sanofi Chimie, France, in accordance with GMP. The manufacturing process of isatuximab DS consists of cell culture, harvest, purification, and formulation. A production run begins with WCB vials thawed, through the cell culture expansion and harvest of the production culture, followed by purification by a series of chromatography steps. Additional steps are introduced for inactivation and removal of the potential viral contaminants. The DS solution is then adjusted to its final formulation and

filtered into storage containers

Controls

- Sufficient details were provided on the source and history of the cell substrate. The generation of the production cell line and the expression vectors is described in detail.
- The details of raw and starting materials used in the manufacturing process as well as quality standards (compendial monograph or in-house specifications) were presented.
- The in-process controls and critical process parameter were provided sufficiently.
- The results of the virus clearance study, retroviral like particles observed in unprocessed bulk, and the estimated safety margin retroviral contamination per clinical dose is considered acceptable.
- The risk for transmission of TSE/BSE is inferred to be minimal or negligible.

Process validation

The validation of the manufacturing process was carried out on 4 PPQ lots. Results obtained from these batches meet the pre-defined criteria and demonstrate the process consistency.

Manufacturing process development

The process was developed to enhance the productivity, improve robustness and ease of operation while meeting product quality at large scale manufacturing. Based on the comprehensive comparability studies, it is confirmed that DS manufactured by the commercial process has a highly comparable quality with those made by previous developmental manufacturing processes.

Characterization

The followings are included in characterization studies：

- Physicochemical characterization: primary sequences, post-translational modifications, size variants, sequence variants, charge variants and higher-order structure.
- Biological and immunochemical characterization: the ability of DS binding to CD38, the ADCC, CDC and ADCP activity.
- The potential produced- and process-related impurities have been analyzed and are considered sufficiently controlled.

DS specification

The release testing of isatuximab DS includes identity, appearance, carbohydrate profile, charge heterogeneity, purity, potency, pH, osmolality, polysorbate 80 content and contaminants. These tests are performed either according to compendial methods or by in-house analytical methods. Descriptions of the non-compendial analytical procedures validation summaries were provided. The proposed specifications of DS are considered adequate and acceptable.

Reference materials

The qualification reports of current RSs have been provided.

Stability

The stability data from production batches revealed that the DS is stable under storage condition for 36 months at −30±5°C.

2.1.2 Drug product

The isatuximab DP is available as a sterile 20 mg/mL concentrate for solution for infusion in two single-use vial presentations: 500 mg/25 mL and 100 mg/5 mL. The excipients for DP solution contain L-histidine, L-histidine hydrochloride monohydrate, sucrose, polysorbate 80 and water for injection.

Manufacturing

Isatuximab DP is manufactured, packaged, and released at Sanofi-Aventis Deutschland GmbH, Germany. The manufacturing process consists of FDS thawing, pooling, sterile filtration, aseptic filling, inspection, and packaging.

Controls

The critical process parameters and in-process control tests have been provided.

Process validation and/or evaluation

The process validation summaries on three consecutive production batches were provided. The aseptic processing and the suitability of the equipment are ensured. The results of shipping validation study were also provided to state that no noticeable impact of the transport (vibration, shock, acceleration and pressure differences) on DP quality, container closure integrity and stability and suitability of the primary and secondary packaging.

DP Specification

The release testing of isatuximab DP includes identity, appearance, purity, charge heterogeneity, potency, pH, particulate matter, polysorbate 80 content, contaminants, and extractable volume. These tests are performed either according to compendial methods or by in-house analytical methods. The proposed specifications of DP are considered adequate and acceptable. Batch analysis data of finished product batches are provided, and the results reveal a satisfactory batch to batch consistency.

Reference materials

Same reference standards as used for testing of the FDS are used for testing of the DP.

Stability of the DP

The long-term, accelerated and stress stability data for DP were provided. The photo stability and Freeze/Thaw studies were performed on DP batches. Overall, the stability data provided

could support the proposed shelf-life of 36 months when the DP is stored at the recommend condition (2-8°C) and the secondary packaging carton could provide adequate protection from light. The in-use stability results showed that the solutions of isatuximab diluted in 0.9% NaCl or 5% dextrose bags are stable for 48 hours at 5 ± 3°C followed by 8 hours at room temperature non-protected from light exposure.

2.2 Preclinical Pharmacology/Toxicology Evaluation

2.2.1 Pharmacological Studies

Isatuximab specifically bound to human CD38 with sub-nanomolar dissociation constants. Isatuximab exhibited its antitumor activity through ADCP, ADCC, CDC and apoptosis induction in various cell lines. The antitumor activity of isatuximab as a single agent or in combination with pomalidomide has been demonstrated in vitro and in vivo. Besides, isatuximab triggered various immunomodulatory mechanisms upon binding to CD38 on normal immune cells from peripheral blood, including promoting the lytic activity of NK cells, polarizing macrophages towards M1 in the presence of NK cells, and restoring the proliferation of conventional T cells inhibited by regulatory T cells.

Two isatuximab clinical formulations, C1P1F1 and C1P2F2, had comparable biological activity regarding CDC, ADCC, ADCP, apoptosis, and inhibition of nicotinamide adenine dinucleotide to cADPR conversion. Comparison between isatuximab and daratumumab (an approved anti-CD38 antibody) showed that both antibodies induce similar ADCC against CD38 expressing cell lines and are equipotent at inducing CDC; however, the extent of the complement-mediated lysis is greater for daratumumab. Isatuximab exhibited a greater ability to induce direct tumor cell killing and to inhibit CD38 enzymatic activity. Human CD38 protein expression and isatuximab binding to normal human tissues and human blood cells were investigated. On human blood cells, no significant release of cytokines or induction of proliferation was detected; an increase in the percentage of apoptotic cells of isolated NK cells was observed.

2.2.2 Toxicological Studies

Based on a detailed survey, only the chimpanzee could be considered a relevant species for toxicity testing. However, conventional toxicology studies were not conducted in the chimpanzee due to ethical reasons. In a 3-week repeated-dose intravenous toxicity study conducted in cynomolgus monkeys (a non-pharmacologically-relevant species), isatuximab in its clinical formulation did not produce compound-related changes in any parameters evaluated up to the highest dose tested. No isatuximab-related effects were noted in this study on ECG parameters, blood pressure, gross behavior profile (including body temperature), and respiratory function.

No genotoxicity, carcinogenicity, or developmental and reproductive toxicology study was conducted with isatuximab. Isatuximab, in its clinical formulation, was well tolerated locally in a single dose rabbit study and the 3-week monkey study. No hemolytic potential was identified for isatuximab in its clinical formulation in an in vitro study.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

Following the administration of isatuximab at the recommended dose and schedule, the steady state isatuximab mean (CV %) predicted maximum plasma concentration (C_{max}) was 351 μg/mL (36.0%) and area under the plasma concentration-time curve (AUC) was 72,600 μg·h/mL (51.7%). The median time to reach steady state of isatuximab was 18 weeks with a 3.1-fold accumulation.

Isatuximab AUC increases in a greater than dose proportional manner over a dosage range from 1 mg/kg to 20 mg/kg every 2 weeks. While isatuximab AUC increases proportionally over a dosage range from 5 mg/kg to 20 mg/kg every week for 4 weeks followed by every 2 weeks.

The mean (CV %) predicted total volume of distribution of isatuximab is of 8.13 L (26.2%). And isatuximab is expected to be metabolized into small peptides by catabolic pathways. Isatuximab total clearance decreased with increasing dose and with multiple doses. The elimination of isatuximab was similar when given as a single agent or as combination therapy.

2.3.2 Interaction Studies

No formal drug-drug interaction studies have been conducted for isatuximab. Since isatuximab is a monoclonal antibody and is not expected to have immunomodulatory activities, drug-drug interactions through inhibition or induction of metabolizing enzymes or transporter systems are not anticipated.

2.3.3 Special Populations

Isatuximab exposure (AUC) at steady state decreases with increasing body weight. The following factors have no clinically meaningful effect on the exposure of isatuximab: age (36 to 85 years, 70 patients were >75 years old), sex, race (Caucasian, Black, Asian), renal impairment (eGFR<90 mL/min/1.73 m^2), and mild hepatic impairment (total bilirubin >1 to 1.5 times upper limit of normal [ULN] or aspartate amino transferase [AST] > ULN). The effect of moderate (total bilirubin >1.5 times to 3 times ULN and any AST) and severe (total bilirubin >3 times ULN and any AST) hepatic impairment on isatuximab pharmacokinetics is unknown. No dose adjustments are recommended in these specific patient populations.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

The sponsor provided a pivotal study (Study [EFC14335]) to support the efficacy of isatuximab for the claimed indication. Study [EFC14335] is a phase III, multi-national, open label, randomized, two-arm study. Patients were randomized in a 1:1 ratio to receive either isatuximab with pomalidomide and low-dose dexamethasone (IPd) or pomalidomide and low-dose dexamethasone (Pd). The primary endpoint is PFS. Key secondary endpoint is ORR and OS.

Median PFS in the IPd arm was 11.53 months (95% CI: 8.936 to 13.897) and in the Pd arm was 6.47 months (95% CI: 4.468 to 8.279). The stratified HR was 0.596 (95% CI: 0.436 to 0.814). The p-value of 1-sided stratified log rank test was 0.001. The ORR was 60.4% in the IPd arm and 35.3% in the Pd arm. The 1-sided stratified CMH p-value was <0.0001. At the time of the OS interim analysis, the median follow-up time was 11.6 months with a total of 99 events (45% of the targeted 220 events). There were 43 OS events in IPd arm and 56 OS events in Pd arm, and the observed p-value of 0.0631 did not cross the pre-specified stopping boundary (≤0.0008).

In conclusion, adding isatuximab to Pd treatment statistically significant increased PFS compared to Pd (log rank test p-value = 0.001). Patients who received IPd compared with Pd shown a significant improvement in ORR (CMH p-value <0.0001). However, the OS interim analysis (p-value = 0.0631) did not reach the pre-specified stopping boundary (≤0.0008).

2.4.2 Safety Results

Although the duration of exposure was longer in the IPd arm compared with the Pd Arm, cycle delays occurred more frequently in the IPd arm (57.9% with at least 1 cycle delay) than in the Pd arm (43.0%). Pomalidomide and dexamethasone dose reductions and omissions occurred more frequently in the IPd arm compared with the Pd arm. However, the occurrence of treatment discontinuation (discontinue all study medications) in the IPD arm were lower than the in the PD arm.

Grade ≥ 3 TEAEs, SAE were reported more frequently in the IPd arm than on the Pd arm. Treatment discontinuation due to TEAEs occurred at a similar rate in both treatment arms. Grade ≥3 related TEAEs were reported more frequently in the IPd than in the Pd arm (71.7% versus 47.7%). Grade ≥3 related TEAEs reported at a ≥5% incidence in either treatment arm were neutropenia (42.1% and 30.9% in the IPd and Pd arms, respectively), thrombocytopenia (10.5% and 11.4%), febrile neutropenia (10.5% and 2.0%), and pneumonia (9.9% and 6.0%). The most common serious TEAEs in the IPd arm were pneumonia, febrile neutropenia,

disease progression, acute kidney injury, urinary tract infection, infusion related reaction, and pathological fracture.

Fatal AEs other than disease progression were comparable between the two arms (5 cases versus 8 cases).

Isatuximab infusion reactions occurred in 38.2% of patients, were predominantly Grade 1-2, and all had onset at first infusion. The IRs were managed with medication or temporary infusion interruption, with only 4 patients discontinuing isatuximab due to infusion reaction. All IRs were reversible and no delayed-onset infusion reactions were observed.

Isatuximab caused a positive indirect Coombs test in approximately two-thirds of patients. In patients with a positive indirect Coombs test, blood transfusions were administered without evidence of hemolysis.

No patient receiving isatuximab had a positive ADA sample during treatment.

In conclusion, the safety profile of IPd combination was comparable to the drug of the same class.

2.5 Bridging Study Evaluation

The evaluations of race/ethnicity effect on isatuximab PK by population PK analysis suggesting that race (Asian versus Non-Asian) was a significant covariate influencing isatuximab PK with 24% smaller V1 in Asian patients. However, the impact was limited based on the exposure difference between Asian and Caucasian was only less than 18%. Moreover, race was not found to be a significant covariate on non-specific elimination parameters. Overall, there was no significant race/ethnicity different in isatuximab PK.

The sponsor submitted Asian subgroup analysis of the pivotal study, Study EFC14335, as the bridging data for clinical assessment. There were 36(11.7%) Asians, all from East Asian including Taiwan, participating in Study EFC14335. Compared to non-Asian subgroup and overall population, Asian subgroup demonstrated similar efficacy and acceptable safety. It is considered reasonable that no significant race/ethnicity difference will cause clinical impact.

The conclusion is no need for bridging study for isatuximab.

2.6 Conclusion

After reviewing complete data package, the review team recommends approval of isatuximab (SARCLISA®) for the following indication: in combination with pomalidomide and dexamethasone, for the treatment of adult patients with multiple myeloma who have received

at least two prior therapies including lenalidomide and a proteasome inhibitor.

3. Post-Marketing Requirements

Submit the following data while available:

1) Overall survival analysis with the Study EFC14335 final report.
2) The final report of long term safety monitoring required by US FDA to determine the incidence of acute myeloid leukemia, myelodysplastic syndrome and other second primary malignancies in patients receiving isatuximab in combination with pomalidomide and dexamethasone and it's potential to have a detrimental impact on overall survival.