CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761113Orig1s000

RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Division of Risk Management (DRM)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Application Type	BLA
Application Number	761113
PDUFA Goal Date	April 30, 2020
OSE RCM #	2019-829; 2019-840
Reviewer Name(s)	Till Olickal, Ph.D., Pharm.D.
Acting Team Leader	Naomi Boston, Pharm.D.
Division Director	Cynthia LaCivita, Pharm.D.
Review Completion Date	February 05, 2020
Subject	Review to determine if a REMS is necessary
Established Name	isatuximab-irfc
Trade Name	Sarclisa
Name of Applicant	Sanofi-aventis U.S. LLC
Therapeutic Class	CD38-directed cytolytic chimeric immunoglobulin G1 (IgG1) monoclonal antibody (mAb)
Formulation(s)	100 mg/5 mL (20 mg/mL) and 500 mg/25 mL (20 mg/mL) solution in a single-dose vial
Dosing Regimen	Administer isatuximab-irfc 10 mg/kg intravenously every week with pomalidomide and dexamethasone for 4 weeks followed by every 2 weeks

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EXECUTIVE SUMMARY

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity isatuximab-irfc is necessary to ensure the benefits outweigh its risks. Sanofi-aventis U.S. LLC submitted a Biologic Licensing Application (BLA) 761113 for isatuximab-irfc with the proposed indication in combination with pomalidomide and dexamethasone, for the treatment of adult patients with multiple myeloma (MM) who have received at least two prior therapies including lenalidomide and a proteasome inhibitor. The serious risks associated with the use of isatuximab-irfc are infusion-related reactions, neutropenia, second primary malignancies, laboratory test interference and embryo-fetal toxicity. The applicant did not submit a REMS with this application but proposed voluntary risk management activities along with the Prescribing Information that includes Warnings and Precautions, as well as information to be included in section 17, Patient Counseling Information, and a Patient Package Insert (patient labeling or PPI).

Division of Risk Management (DRM) and Division of Hematology Malignancies 2 (DHM2) have determined that if approved, a REMS is not necessary to ensure the benefits of isatuximab-irfc outweigh its risks. Multiple myeloma is the second most common hematological malignancy involving the skeleton, causing osteolytic lesions, bone pain, and pathological fractures that dramatically decrease MM patients' quality of life and survival. Despite significant advances and improvements in overall survival (OS), MM remains incurable and additional treatments are needed. Isatuximab-irfc appeared efficacious in both its primary outcome of progression-free survival and secondary outcome of overall response rate and its risks can be communicated and managed through labeling. Based on the efficacy and safety information currently available, the clinical reviewer recommends approval of isatuximab-irfc in combination with pomalidomide and dexamethasone for the treatment of adult patients with MM who have received at least two prior therapies including lenalidomide and a proteasome inhibitor. The most concerning adverse reactions observed with the use of isatuximab-irfc are of infusion-related reactions, neutropenia, second primary malignancies, laboratory test interference and embryo-fetal toxicity. If isatuximab-irfc is approved, labeling, including Warnings and Precautions, Patient Counseling Information to be included in section 17, and in the PPI will be used to communicate the safety issues and management of toxicities associated with isatuximab-irfc.

1 Introduction

This review evaluates whether a risk evaluation and mitigation strategy (REMS) for the new molecular entity (NME) isatuximab-irfc is necessary to ensure the benefits outweigh its risks. Sanofi-aventis U.S. LLC submitted a Biologic Licensing Application (BLA) 761113 for isatuximab-irfc with the proposed indication in combination with pomalidomide and dexamethasone, for the treatment of adult patients with MM who have received at least two prior therapies including lenalidomide and a proteasome inhibitor.[1] The applicant did not submit a REMS with this application but proposed voluntary risk management activities along with the Prescribing Information that includes Warnings and Precautions, as well as information to be included in section 17, Patient Counseling Information and a Patient Package Insert (patient labeling or PPI).

2 Background

2.1 PRODUCT INFORMATION

Isatuximab-irfc is a NME BLA type 351(a) pathway application.[a] It is a chimeric immunoglobulin G1 (IgG1) monoclonal antibody (mAb) against CD38 antigen. Isatuximab-irfc binds to CD38 expressed on the surface of hematopoietic and tumor cells, including multiple myeloma cells. Isatuximab-irfc acts by inducing apoptosis through Fc-dependent mechanisms including: antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and complement dependent cytotoxicity (CDC). The combination of isatuximab-irfc and pomalidomide enhances ADCC activity, and direct tumor cell killing compared to that of isatuximab-irfc alone in vitro and enhanced antitumor activity compared to the activity of isatuximab-irfc or pomalidomide alone in a human multiple myeloma xenograft model.[1] Isatuximab-irfc is prepared as 100 mg/5 mL (20 mg/mL) and 500 mg/25 mL (20 mg/mL) solution in a single-dose vial. The recommended dose of isatuximab-irfc is 10 mg/kg intravenously every week with pomalidomide and dexamethasone for 4 weeks followed by every 2 weeks until disease progression or unacceptable toxicity.[b] Isatuximab-irfc was granted orphan drug designation on May 22, 2014. Isatuximab-irfc is not currently approved in any jurisdiction.

2.2 REGULATORY HISTORY

The following is a summary of the regulatory history for isatuximab-irfc (BLA 761113) relevant to this review:

- 12/29/2009: Investigation New Drug (IND) 103217 submission for isatuximab-irfc (SAR650984) was received.
- 05/22/2014: Orphan Drug designation granted
- 04/30/2019: BLA 761113 submission for isatuximab-irfc with the proposed 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, received.
- 10/10/2019: A Post Mid-cycle meeting was held between the Agency and the Applicant via teleconference. The Agency informed the Applicant that based on the currently available data, there were no safety issues that require a REMS for isatuximab-irfc.

3 Therapeutic Context and Treatment Options

3.1 DESCRIPTION OF THE MEDICAL CONDITION

Multiple myeloma is the second most common hematological malignancy and is characterized by a clonal proliferation of neoplastic plasma cells within the bone marrow.[2,3] The expected number of new cases in the United States in 2019 is 32,110[c], with 12,960 expected deaths due to the disease[d]. Five-year

[a] Section 505-1 (a) of the FD&C Act: *FDAAA factor (F): Whether the drug is a new molecular entity.*

[b] Section 505-1 (a) of the FD&C Act: *FDAAA factor (D): The expected or actual duration of treatment with the drug.*

[c] Section 505-1 (a) of the FD&C Act: *FDAAA factor (A): The estimated size of the population likely to use the drug involved.*

survival for patients diagnosed with MM is approximately 52%.[4] MM is the most frequent cancer involving the skeleton, causing osteolytic lesions, bone pain, and pathological fractures that dramatically decrease MM patients' quality of life and survival.[2] Multiple myeloma is more common in men than women and among individuals of African American descent. Myeloma is most frequently diagnosed among people aged 65-74 with the average age of 69.[4] Patients with MM experience a variety of disease-related events and symptoms, such as bone destruction leading to pain, height reduction and body shape changes, and bone marrow failure, renal failure, immunodeficiency, as well as the psychosocial burden of a diagnosis of cancer.[5] A deterioration in quality of life is particularly marked in elderly frail patients, who represent approximately 30% of patients with MM.[6]

3.2 DESCRIPTION OF CURRENT TREATMENT OPTIONS

The treatment paradigms and outcomes for patients with MM have dramatically changed in the past decade with introduction of several new, more effective, and less toxic therapies and more than doubling of the survival.[7] Over the past decade, use of novel agents, including immunomodulatory drugs (IMiDs) and proteasome inhibitors (PIs) has resulted in high response rates and improvement in OS for patients with MM.[8] Multiple myeloma treatment has improved remarkably over the last 2 decades with the introduction of autologous stem cell transplantation (ASCT) and the introduction of numerous novel agents, including 3 generations of immunomodulator agents (thalidomide[9], lenalidomide[10], and pomalidomide[11]), 2 generations of proteasome inhibitors (bortezomib[12], then carfilzomib[13] and ixazomib[14]) and most recently, the anti-CD38 antibody (daratumumab[15]) and anti-signaling lymphocytic activation molecule F7 (anti-SLAMF7) antibody (elotuzumab[16]). The IMiDs, thalidomide, lenalidomide and pomalidomide are approved with REMS to mitigate the risk of teratogenicity.[9,10,11] The 2019 National Comprehensive Cancer Network (NCCN) guidelines[17] for multiple myeloma list the following combinations as preferred regimens for primary induction therapy in patients who are candidates for transplantation:

- Bortezomib/lenalidomide/dexamethasone (category 1)
- Bortezomib/cyclophosphamide/dexamethasone (preferred initial treatment in patients with acute renal insufficiency)

Other recommended regimens, according to the NCCN, are as follows:

- Carfilzomib/lenalidomide/dexamethasone
- Ixazomib/lenalidomide/dexamethasone (category 2B)

Primary therapy for non-transplant candidates are as follows:

- Bortezomib/lenalidomide/dexamethasone (category 1)
- Daratumumab/lenalidomide/ dexamethasone (category 1)
- Lenalidomide/low-dose dexamethasone (category 1)
- Bortezomib/cyclophosphamide/dexamethasone

Other NCCN-recommended regimens for these cases include the following:

- Carfilzomib/lenalidomide/dexamethasone
- Ixazomib/lenalidomide/dexamethasone
- Daratumumab/bortezomib/melphalan/prednisone (category 1)

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[d] Section 505-1 (a) of the FD&C Act: FDAAA factor (B): *The seriousness of the disease or condition that is to be treated with the drug.*

The introduction of novel agents that target both the tumor cell and its microenvironment[18] (surrounding blood vessels, immune cells, fibroblasts, signaling molecules and the extracellular matrix (ECM)) into the treatment of MM has considerably improved outcomes and it is now possible to aim for deep responses in a greater number of patients in an attempt to prolong remission duration and OS.[19] Despite substantial progress, MM remains a highly resistant disease given its propensity for clonal heterogeneity and its complex interaction with the surrounding bone marrow microenvironment[20]. Almost all patients eventually relapse despite therapeutic responses to a PI, IMiD or both.[21] There is a clear need for therapeutic strategies that encompass multiple modes of action.

4 Benefit Assessment

The efficacy of isatuximab-irfc in combination with pomalidomide and low-dose dexamethasone were evaluated in a multicenter, multinational, randomized, open-label, 2-arm, phase 3 study (ICARIA-MM [NCT02990338]) in patients with relapsed and refractory MM. Patients had received at least two prior therapies including lenalidomide and a proteasome inhibitor. A total of 307 patients were randomized in a 1:1 ratio to receive either isatuximab-irfc in combination with pomalidomide and low-dose dexamethasone (Isa-Pd, 154 patients) or pomalidomide and low-dose dexamethasone (Pd, 153 patients). Treatment was administered in both groups in 28-day cycles until disease progression or unacceptable toxicity. Isatuximab-irfc 10 mg/kg was administered as an intravenous infusion weekly in the first cycle and every two weeks thereafter. Pomalidomide 4 mg was taken orally once daily from day 1 to day 21 of each 28-day cycle. Low-dose dexamethasone (orally or intravenously) 40 mg (20 mg for patients ≥75 years of age) was given on days 1, 8, 15, and 22 for each 28-day cycle. The median duration of treatment was 41 weeks for Isa-Pd group compared to 24 weeks for Pd group.[1]

At the time of this review, labeling negotiations were still ongoing with the Applicant. The following section is a summary of relevant efficacy information to date for isatuximab-irfc. Efficacy was established on the basis of the progression-free survival (PFS) evaluated based on central laboratory data for M-protein and central radiologic imaging review using the International Myeloma Working Group (IMWG) criteria, as assessed by an Independent Response Committee. PFS was the primary efficacy endpoint of ICARIA-MM study. A statistically significant improvement in PFS was demonstrated for Isa-Pd group compared to the Pd group is shown in Table 1.[1,22,e] 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% of patients received prior stem cell transplantation. The majority of patients (92.5%) were refractory to lenalidomide, 76% to a proteasome inhibitor, and 73% to both an immunomodulator and a proteasome inhibitor, and 91% of patients were refractory to lenalidomide at last line of therapy.

PFS was significantly prolonged in the Isa-Pd group compared to the Pd group. The median PFS was 11.53 months (95% CI: 8.94-13.9) in Isa-Pd group versus 6.47 months (95% CI: 4.47-8.28) in Pd group (hazard ratio [HR]=0.6; 95% CI: 0.44-0.81, p=0.001), representing a 40% reduction in the risk of disease progression or death in patients treated with Isa-Pd. The key secondary end point was overall response rate, summarized in Table 1.[1,22,e] Other secondary end points included the overall survival.

[e] Section 505-1 (a) of the FD&C Act*: FDAAA factor (C): The expected benefit of the drug with respect to such disease or condition*

Table 1: Efficacy of isatuximab-irfc in Combination with Pomalidomide and Low-Dose Dexamethasone versus Pomalidomide and Dexamethasone in the Treatment of Multiple Myeloma (ICARIA-MM)[1,22,e]

Endpoint	Isatuximab-irfc + Pomalidomide + Dexamethasone (Isa-Pd) N=154	Pomalidomide + Dexamethasone (Pd) N=153
Progression-Free Survival Median (months) [95% CI]	11.53 [8.94-13. 9]	6.47[4.47-8.28]
Hazard ratio[c] [95% CI]	0.6 [0.44-0.81]	
p-value[c] (stratified log-rank test)	0.0010	
Overall Response Rate[a] Responders (sCR+CR+VGPR+PR) n(%) [95% CI][b]	93 (60.4) [52.2%-68.2%]	54 (35.3) [27.8%-43.4%]
p-value (stratified Cochran-Mantel Haenszel)[c]	<0.0001	
Stringent Complete Response (sCR) + Complete Response (CR) n(%)	7 (4.5)	3 (2)
Very Good Partial Response (VGPR) n(%)	42 (27.3)	10 (6.5)
Partial Response (PR) n(%)	44 (28.6)	41 (26.8)

[a] sCR, CR, VGPR and PR were evaluated by the IRC using the IMWG response criteria.
[b] Estimated using Clopper-Pearson method.
[c] Stratified on age (<75 years versus ≥75 years) and number of previous lines of therapy (2 or 3 vs >3) according to IRT. One -sided significance level of 0.025.

The median time to first response in responders was 35 days in the Isa-Pd group versus 58 days in the Pd group. The median duration of response was 13.3 months (95% CI: 10.6-NR) in the Isa-Pd group versus 11.1 months in the Pd group, and the median OS was not reached for either treatment group. At a median follow-up time of 11.6 months, 43 (27.9%) patients on Isa-Pd and 56 (36.6%) patients on Pd had died. The OS results at interim analysis did not reach statistical significance.[1,22,e]

5 Risk Assessment & Safe-Use Conditions

At the time of this review, labeling negotiations were still ongoing with the applicant. The following section is a summary of relevant safety information to date for isatuximab-irfc. The safety of isatuximab-irfc was evaluated in a randomized, open-label clinical trial in patients with previously treated multiple myeloma. A total of 301 patients in ICARIA-MM trial, in which patients received isatuximab-irfc 10 mg/kg as an intravenous infusion weekly in the first cycle and every two weeks thereafter in combination with pomalidomide and low dose dexamethasone (n=152) or pomalidomide and low dose dexamethasone (n=149). Among patients receiving isatuximab-irfc, 66% were exposed for 6 months or longer and 24% were exposed for greater than one year.[1]

The most common adverse reactions (incidence ≥20% of patients) noted in Isa-Pd group compared with Pd group were neutropenia (96% vs 92%), infusion-related reactions (38% vs 0), pneumonia (31% vs 23%), upper respiratory tract infection (57% vs 42%) and diarrhea (26% vs 19%).

Deaths

Overall, disease progression was the most common cause for death listed for both arms during treatment and post treatment. Other causes in the post treatment period in the Isa-Pd arm included 3 with pneumonia or lung infection in the Isa-Pd arm and 1 patient each with atrial fibrillation and cachexia. In the post treatment period on the Pd arm additional causes of death included cerebral hemorrhage, myocardial infarction, stroke and cardiac arrest (1 patient each), infection including sepsis, bronchopneumonia and respiratory tract infection (4 patients) and death due to aplasia in the post allogeneic transplant setting. Across all fatal TEAEs the incidence was similar for both arms, and most TEAEs occurred in only 1 patient, with the exception of septic shock, which occurred in 2 (1.3%) patients in the Pd arm and none in the Isa-Pd arm. Overall, there was a higher incidence of deaths due to infections in both arms (4 [2.6%] patients in Isa-Pd arm and 6 [4.0%] in Pd arm) compared to other system organ classes. One patient in the Isa-Pd arm with a history of hypertension developed general physical health deterioration leading to treatment withdrawal, followed by renal injury, and the patient died of unrelated cardiac failure and atrial fibrillation 41 days after last dose of study treatment. Sudden death occurred in 1 patient in the Pd arm. In the study, fatal TEAEs were considered treatment-related in 2 (1.3%) patients in the Pd arm (pneumonia and urinary tract infection), and in 1 (0.7%) patient in the Isa-Pd arm (sepsis).[23,24]

Serious Adverse Events (SAE)

Serious adverse reactions occurred in 62% of patients receiving isatuximab-irfc. Serious adverse reactions in > 5% of patients who received isatuximab-irfc included pneumonia and febrile neutropenia. Permanent discontinuation of the isatuximab-irfc regimen due to an adverse reaction (Grades 3-4) occurred in 7% of patients. In addition, isatuximab-irfc was discontinued in 3% of patients due to infusion-related reactions. Dosage interruptions due to an adverse reaction occurred in 31% of patients who received isatuximab-irfc. The most frequent adverse reaction requiring dosage interruption were infusion-related reactions (28%).[1]

If approved, labeling will include the following risks in the Warnings and Precautions section.

5.1 INFUSION-RELATED REACTIONS

Infusion-related reactions (defined as adverse reactions associated with the isatuximab-irfc infusions, with an onset typically within 24 hours from the start of the infusion) were reported in 58 patients (38%) treated with isatuximab-irfc in ICARIA-MM. The most common symptoms of an infusion-related reaction included dyspnea, cough, chills, and nausea. The most common severe signs and symptoms included hypertension and dyspnea. All patients who experienced infusion-related reactions, experienced them during the 1st infusion of isatuximab-irfc, with 3 patients (2%) also having infusion-related reactions at their 2nd infusion, and 2 patients (1.3%) at their 4th infusion and resolved on the same day in 98% of the cases. Grade 1 infusion-related reactions were reported in 3.9%, Grade 2 in 32%, Grade 3 in 1.3%, and Grade 4 in 1.3% of the patients. Signs and symptoms of Grade 3 or higher infusion-related reactions included dyspnea, hypertension, and bronchospasm. The incidence of infusion interruptions because of

infusion reactions was 29.6%. The median time to infusion interruption was 55 minutes. If approved, the risk of infusion related reactions will likely be communicated with in the Warnings and Precautions section of the label. Management of infusion-related reactions, including recommendations to premedicate patients prior to isatuximab-irfc infusion with acetaminophen, H2 antagonists, diphenhydramine, or equivalent and dexamethasone will be included in the Warnings and Precautions as well as in the Dosage and Administration sections of the label. Monitoring and infusion rate modifications for toxicities to address the safety issues with isatuximab-irfc will also be included in both Warnings and Precautions and the Dosage and Administration sections of the label.[1]

5.2 NEUTROPENIA

In ICARIA-MM trial, neutropenia AEs occurred in 96% of patients and grade 3-4 neutropenia occurred in 85% of patients treated with isatuximab-irfc compared with the Pdarm of 92% and 61%, respectively. Febrile neutropenia occurred in 12% of patients and neutropenic infections, defined as infection with concurrent grade ≥ 3 neutropenia, occurred in 25% of patients treated with isatuximab-irfc. The most frequent neutropenic infections included those of upper respiratory tract (10%), lower respiratory tract (9%), and urinary tract (3%). Labeling instructs to monitor patients with neutropenia for signs of infection and complete blood cell counts periodically during treatment, and to consider the use of antibiotics and antiviral prophylaxis during treatment. Labeling also recommends considering dose delays in case of grade 4 neutropenia until neutrophil count recovery to at least 1.0×10^9/L, and supportive care with growth factors, according to institutional guidelines.[1] If approved, the risk of neutropenia will likely be communicated with in the Warnings and Precautions section of the label.

5.3 SECOND PRIMARY MALIGNANCIES (SPM)

The incidence of SPMs in Study ICARIA-MM is 3.9% (6 of 152 patients) in the Isa-Pd arm and 0.7% (1 of 149) in the Pd arm, and consisted of skin squamous cell carcinoma in 4 patients in the Isa-Pd arm and one patient in the Pd arm.[1] All the patients in the Isa-Pd arm had been previously exposed to lenalidomide (for at least 26 months) and alkylating agents, which have been associated with the development of SPMs.[25] The risk of SPMs is MM is well characterized within official IMWG guidelines.[26] Labeling instructs to monitor patients for the development of second primary malignancies, as per IMWG guidelines.[1] If approved, the risk of SPM will likely be communicated with in the Warnings and Precautions section of the label.

5.4 LABORATORY TEST INTERFERENCE

Interference with Serological Testing (Indirect Antiglobulin Test):

Isatuximab-irfc binds to CD38 on red blood cells (RBCs) and may result in a false positive indirect antiglobulin test (indirect Coombs test). In ICARIA-MM, the indirect anti-globulin test (IAT) was performed during the treatment period in 99 (65.1%) patients in the IPd arm. In 32 of the 99 patients (32.3%) the IAT remained negative during treatment. In 67 of the 99 (67.7%) patients a positive test was observed, 47 (47.5%) of which were negative at baseline and 20 (20.2%) of which were missing at baseline. Twenty of the 67 (29.9%) patients with at least one positive post-baseline IAT test, received a red blood cell (RBC) transfusion. No complications of hemolysis were reported post-RBC transfusion in the IPd arm. One patient in the IPd arm of study EFC14335 experienced Grade 1 hemolysis, assessed as related to the use of sulperazone (third-generation cephalosporin); sulperazone was discontinued and

the patient continued on study treatment with no recurrence of the hemolysis. Labeling instructs to avoid potential problems with RBC transfusion, patients being treated with isatuximab-irfc should have blood type and screen tests performed prior to the first isatuximab-irfc infusion. If treatment with isatuximab-irfc has already started, labeling also recommends informing the blood bank that the patient is receiving isatuximab-irfc, and that isatuximab-irfc interference with blood compatibility testing can be resolved using dithiothreitol (DTT)-treated RBCs. If an emergency transfusion is required, non–cross-matched ABO/RhD-compatible RBCs can be given as per local blood bank practices.[1]

Interference with Serum Protein Electrophoresis and Immunofixation Tests:

Isatuximab-irfc is an IgG kappa monoclonal antibody that can be incidentally detected on both serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein. This interference can impact the accuracy of the determination of complete response in some patients with IgG kappa myeloma protein.[1]

If approved, the risk of laboratory test interferences will likely be communicated with in the Warnings and Precautions section of the label.

5.5 EMBRYO-FETAL TOXICITY

Based on its mechanism of action and findings from animal data, isatuximab-irfc can cause fetal harm when administered to a pregnant woman. Besides being communicated in the Warnings and Precautions section of the label, recommended guidance to use effective contraception for females of reproductive potential during treatment with isatuximab-irfc for 5 months after the last dose will be communicated in the Use in Specific Populations section of the label. Labeling instructs that the combination of isatuximab-irfc with pomalidomide is contraindicated in pregnant women because pomalidomide may cause birth defects and death of the unborn child.[1]

6 Expected Postmarket Use

According to the current proposed indication, if approved, isatuximab-irfc will be used in both inpatient and outpatient settings such as oncology infusion centers. It is expected that oncologists/hematologists, who should be familiar with the management of toxicities such as infusion-related reactions, neutropenia, second primary malignancies, laboratory test interference and embryo-fetal toxicity, will be the likely prescribers of isatuximab-irfc.

Healthcare providers and blood bank personnel need to know that isatuximab-irfc may interfere with serological testing. This ability to interfere with serological testing is not unique to isatuximab-irfc, and blood banks address similar interactions with other drugs such as daratumumab[15] that cause positive indirect Coombs tests. Isatuximab-irfc's capacity to interfere with serological testing is clinically important in that the patient population receiving isatuximab-irfc is subject to frequent serological testing to manage their disease and treatment. Recent articles published in the medical literature have highlighted this issue.[27,28,29]

7 Risk Management Activities Proposed by the Applicant

The applicant did not submit a REMS with this application but proposed voluntary risk management activities along with the Prescribing Information that includes Warnings and Precautions, as well as information to be included in section 17, Patient Counseling Information, and a PPI to address the risks of infusion-related reactions, neutropenia, second primary malignancies, laboratory test interference and embryo-fetal toxicity.

7.1 Other Proposed Risk Management Activities

The applicant has proposed the voluntary risk management activities[30] to further communicate that isatuximab-irfc may interfere with serologic testing.

A (b) (4) will be used as an additional resource (b) (4)

The Sponsor is also proposing (b) (4)

Reviewer's Comments: *These activities voluntarily proposed by the applicant are outside of a required REMS program, and we do not oppose the applicant's proposal* (b) (4)

8 Discussion of Need for a REMS

When evaluating factors of whether a REMS is necessary to ensure that the benefits outweigh the risks for isatuximab-irfc, this reviewer considered the patient population, seriousness of the disease, expected benefit of the drug, seriousness of known or potential adverse events, and the prescribing population. The likely prescribers for isatuximab-irfc will be oncologists or hematologists. The risks identified are risks that these providers have likely encountered in their practice experience.

Isatuximab-irfc is a CD38-directed cytolytic chimeric IgG1 mAb, with the proposed 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.[1] At the time this review was completed , labeling negotiations were still ongoing with the Applicant. Based on the efficacy and safety information currently available, the clinical reviewers stated that isatuximab-irfc shows clinically meaningful benefit, and recommends approval of isatuximab-irfc in combination with pomalidomide and dexamethasone for the treatment of adult patients with MM who have received at least two prior therapies including lenalidomide and a proteasome inhibitor.[23,24]

MM is the second most common hematological malignancy involving the skeleton, causing osteolytic lesions, bone pain, and pathological fractures that dramatically decrease MM patients' quality of life and survival. Despite significant advances and improvements in overall survival, multiple myeloma remains

incurable and additional treatments are needed. Isatuximab-irfc appeared efficacious in both its primary and secondary outcomes and its risks can be communicated and managed through labeling.

DRM and DHM2 have determined that if approved, a REMS is not necessary to ensure the benefits of isatuximab-irfc outweigh its risks. The most concerning adverse reactions observed with the use of isatuximab-irfc are of infusion-related reactions, neutropenia, second primary malignancies, laboratory test interference and embryo-fetal toxicity. If isatuximab-irfc is approved, labeling, including Warnings and Precautions, will be used to communicate the safety issues and management of toxicities associated with isatuximab-irfc, as well as information to be included in section 17, Patient Counseling Information and in the PPI, to inform patients. Management of infusion-related reactions, monitoring and infusion rate modifications for toxicities to address the safety issues with isatuximab-irfc will also be included in both Warnings and Precautions and the Dosage and Administration sections of the label. The interference with serological testing does not present a sufficient risk to outweigh the benefits of isatuximab-irfc, and additional requirements are not necessary to maintain a favorable benefit–risk balance. The applicant did not submit a REMS with this application but proposed voluntary risk management activities for interference with serologic testing. We do not oppose the applicant's proposal (b) (4) We note that articles have already appeared in the medical literature regarding this interference.[29] At this time, none of these risks will receive a boxed warning in the label.

9 Conclusion & Recommendations

If approved, DRM has determined that a REMS is not necessary to ensure the benefits outweigh the risks of isatuximab-irfc. The management of the risks associated with isatuximab-irfc treatment will be communicated through labeling. Please notify DRM if new safety information becomes available that changes the benefit-risk profile, so that this recommendation can be reevaluated if necessary.

10 References

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