Medicines & Healthcare products Regulatory Agency

MHRA

EAMS 04425/0002 isatuximab

Early Access to Medicines Scheme – Treatment protocol – Information for healthcare professionals

Introduction

The aim of the Early Access to Medicines Scheme (EAMS) is to provide earlier availability of promising new unlicensed and 'off label' medicines to UK patients that have a high unmet clinical need. The medicinal products included in the scheme are those that are intended to treat, diagnose or prevent seriously debilitating or life-threatening conditions where there are no adequate treatment options or those with significant limitations. More information about the scheme can be found here: http://www.mhra.gov.uk/Howweregulate/Innovation/EarlyaccesstomedicinesschemeEAMS/index.htm

This information is intended for healthcare professionals and is provided by the pharmaceutical company that manufactures the medicine. This medicine does not yet have a license (marketing authorisation) and the information is provided to assist the doctor in prescribing an unlicensed medicine. Guidance on prescribing unlicensed medicines can be found on the GMC webpage: https://www.gmc-uk.org/guidance/ethical_guidance/14327.asp

The scientific opinion is based on the information supplied to the MHRA on the benefits and risks of a promising new medicine. As such this is a scientific opinion and should not be regarded as a medicine licensed by the MHRA or a future commitment by the MHRA to license such a medicine.

The prescribing doctor should also refer to the summary information on the pharmacovigilance system which is provided in the document 'Early Access to Medicines Scheme – Treatment protocol – Information on the pharmacovigilance system'.

Scientific opinion period: The MHRA will withdraw the EAMS positive scientific opinion when a marketing authorisation (drug license) is issued for the product covering the EAMS indication, or if following scientific assessment, the EAMS criteria are considered to be no longer met.

Contact information regarding queries on using this EAMS medicine can be found at the end of this document.

Information for the healthcare professionals:

1. NAME OF THE MEDICINAL PRODUCT

Isatuximab 20mg/mL concentrate for solution for infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One ml of isatuximab concentrate for solution for infusion contains 20 mg of isatuximab*.

Each vial of isatuximab concentrate contains 100 mg of isatuximab (20 mg/mL) in 5mL concentrate (100 mg/5mL).
Each vial of isatuximab concentrate contains 500 mg of isatuximab (20 mg/mL) in 25mL concentrate (500 mg/25 mL).

Isatuximab is an immunoglobulin G1 (IgG1) monoclonal antibody (mAb) CD38*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

Isatuximab is indicated in combination with pomalidomide and dexamethasone for the treatment of adult patients with relapsed and refractory multiple myeloma only if they have received 3 previous lines of therapies (that have included lenalidomide and a proteasome inhibitor) and have demonstrated disease progression on the last therapy.

4.2 Posology and method of administration

Under the EAMS program, treatment must be prescribed by physicians experienced in the treatment of patients with multiple myeloma (MM).

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

<u>Premedication</u>
Premedication should be used prior to isatuximab 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).
- Paracetamol 650 mg to 1000 mg oral.
- H2 antagonists (ranitidine 50 mg intravenous or equivalent [e.g., cimetidine]).

- 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 administration.

The recommended premedication agents should be administered 15-60 minutes prior to starting an isatuximab infusion. Patients who do not experience an infusion reaction upon their first 4 administrations of isatuximab may have their need for subsequent premedication reconsidered.

Posology
The recommended dose of isatuximab is 10 mg/kg body weight administered as an intravenous infusion in combination with pomalidomide and dexamethasone (isatuximab regimen), according to the schedule in the Table 1:

Table 1 - Isatuximab dosing schedule in combination with pomalidomide 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 isatuximab, refer to the respective current summary of product characteristics.

The administration schedule must be carefully followed. If a planned dose of isatuximab 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 isatuximab is recommended.
Administration adjustments should be made if patients experience infusion reactions (see "Method of administration" below).

Neutropenia
In the event of grade 4 neutropenia, isatuximab administration should be delayed until neutrophil count improves to at least 1.0 x 10^9/L. The use of colony-stimulating factors (e.g. G-CSF) should be considered, according to local guidelines (see section 4.4).

For other medicinal products that are administered with isatuximab, the respective current summary of product characteristics 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 isatuximab in children below 18 years of age have not been established. No data are available.

Method of administration

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

Infusion rates

Following dilution, the isatuximab infusion should be administered intravenously at the infusion rate presented in the Table 2 below. 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 isatuximab administration

	Dilution volume	Initial rate	Absence of infusion reaction	Rate increment	Maximum rate
First infusion	250 mL	175 mg/ hour	For 60 minutes	50 mg/hour every 30 minutes	400 mg/ hour
Subsequent infusions	250 mL	175 mg/ hour	For 60 minutes	100 mg/hour every 30 minutes	400 mg/ hour

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

- In patients who experience Grade 2 (moderate) infusion reactions, a temporary interruption in the infusion should be considered and additional symptomatic medicinal products can be administered. After improvement to grade ≤1 (mild), isatuximab 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 isatuximab infusion, recur after initial improvement with appropriate medicinal products, or require hospitalization or are life-threatening (Grade ≥3), treatment with isatuximab 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 the excipients listed in section 6.1.

Patients should be excluded from EAMS if they meet any of the following criteria:

1. Primary refractory multiple myeloma
2. Free Light Chain measurable disease only

3. Patient with prior anti-CD38 monoclonal antibody treatment (with progression on or within 60 days after end of anti-CD38 monoclonal antibody treatment (i.e refractory to anti-CD38 treatment)
4. Prior therapy with pomalidomide
5. Any anti-myeloma drug treatment within 14 days before EAMS treatment.
6. Prior allogenic HSC transplant with active graft versus host disease (GvHD)
7. Any major procedure within 14 days before the EAMS treatment: plasmapheresis, major surgery (kyphoplasty is not considered a major procedure), radiotherapy
8. Patient who has received any other investigational drugs or prohibited therapy for EAMS within 28 days or 5 half-lives from EAMS treatment, whichever is longer
9. ECOG status >2
10. Platelets <75 000 cells/µL if <50% of bone marrow (BM) nucleated cells are plasma cells and, <30 000 cells/µL if ≥50% of BM nucleated cells are plasma cells.
11. ANC <1000 µ/L (1 x 109/L). The use of G-CSF is not allowed to reach this level
12. Creatinine clearance <30 mL/min
13. Total bilirubin >2 x ULN
14. Corrected serum calcium >14 mg/dL (>3.5 mmol/L)
15. AST and/or ALT >3 x ULN
16. Ongoing toxicity (excluding alopecia and those listed in eligibility criteria) from any prior anti-myeloma therapy >G1 (NCI-CTCAE v4.03)
17. Significant cardiac dysfunction; myocardial infarction within 12 months; unstable, poorly controlled angina pectoris.
18. Diagnosed or treated for another malignancy within 3 years prior to EAMS with the exception of complete resection of basal cell carcinoma or squamous cell carcinoma of the skin, an in-situ malignancy, or low risk prostate cancer after curative therapy
19. Known to be HIV+ or hepatitis A, B or C active infection
20. Malabsorption syndrome or any condition that can significantly impact the absorption of pomalidomide
21. Active primary amyloid-light (AL) amyloidosis
22. Unable or unwilling to undergo to thromboprophylaxis
23. Daily requirement for corticosteroids (equivalent to 10 mg/day of prednisone) for more than 7 days (except for inhalation corticosteroids).
24. Pregnant or breastfeeding woman or female who intends to become pregnant during the participation in the study. Woman of childbearing potential (WOCBP) unwilling to prevent pregnancy by the use of 2 reliable methods of contraception for the duration of the treatment period.
25. Male participants who disagree to practice true abstinence or disagree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while receiving treatment.

26. Any potential allergy or hypersensitivity to the excipients of the isatuximab product (Sucrose, Histidine hydrochloride monohydrate, Histidine, Polysorbate 80 and Water for injection)

27. Unable to provide informed consent to receive isatuximab in combination with pomalidomide and dexamethasone as part of EAMS.

4.4 Special warnings and precautions for use

Infusion reactions
Infusion reactions , mostly mild or moderate, have been observed in 38.2% of patients treated with isatuximab (see section 4.8). All infusion reactions started during the first isatuximab infusion and resolved on the same day in 98% of the infusions . The most common symptoms of an infusion reactions included dyspnoea, cough, chills 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 isatuximab infusion with paracetamol, H2 antagonists, 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 isatuximab infusion. When required, interrupt isatuximab infusion and provide appropriate medical and supportive measures (see section 4.2). In case symptoms do not improve after interruption of isatuximab infusion, recur after initial improvement with appropriate medicinal products, require hospitalization or are life-threatening, permanently discontinue isatuximab and institute appropriate management.

Neutropenia
Grade 3-4 neutropenia reported as laboratory abnormalities (84.9%) and neutropenic complications (30.3%) have been observed in patients treated with isatuximab (see section 4.8). Monitor complete blood cell counts periodically during treatment. Antibiotics, antifungal and antiviral prophylaxis can be considered during treatment. Monitor patients with neutropenia for signs of infection. No dose reductions of isatuximab are recommended. Isatuximab dose delays and the use of colony-stimulating factors (e.g. G-CSF) may be required to allow improvement of neutrophil count (see section 4.2).

Interference with Serological Testing (indirect antiglobulin test)
Because CD38 protein is expressed on the surface of red blood cells (RBCs), 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.

In ICARIA-MM, the indirect antiglobulin test was positive during Isa-Pd treatment in 67.7% of the tested patients. In patients with a positive indirect antiglobulin test, blood transfusions were administered without evidence of haemolysis. ABO/RhD typing was not affected by isatuximab treatment. To avoid potential problems with RBC transfusion, patients being treated with isatuximab should have blood type and screen tests performed prior to the first isatuximab infusion. Phenotyping may be considered prior to starting isatuximab treatment as per local practice. If treatment with isatuximab has already started, the blood bank should be informed that the patient is receiving isatuximab and isatuximab 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 (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 isatuximab. Based on the half-life of

isatuximab, it is advised that isatuximab mediated positive indirect Coombs test may persist for approximately 6 months after the last isatuximab infusion.

Interference with determination of complete response
Isatuximab is an IgG kappa monoclonal antibody that can be incidentally detected on both serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein (see section 4.5) and could interfere with accurate response classification based on International Myeloma Working Group (IMWG) criteria. 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 isatuximab regimen 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 isatxumab signal from the myeloma M-protein signal. In 11 out of 22 patients, there was no residual myeloma M-protein detectable at the sensitivity level of the immunofixation test (25 mg/dL); 10 of the 11 patients had IgG subtype myeloma at baseline, showing isatuximab interference with the immunofixation assay (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 and 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).

Interference with Serum Protein Electrophoresis and Immunofixation Tests
Isatuximab may be incidentally detected by serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the monitoring of M-protein and could interfere with accurate response classification based on International Myeloma Working Group (IMWG) criteria (see 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 at least 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 infant cannot be excluded during this short period just after birth. 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.

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 summary of product characteristics.

4.7 Effects on ability to drive and use machines

Isatuximab has no or negligible influence on the ability to drive and use machines. Fatigue and dizziness, however, have been reported in patients taking isatuximab and this should be taken into account when driving or using machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequent adverse reactions (≥20%) are laboratory neutropenia (96.1%), infusion reactions (38.2%), pneumonia (30.9%), upper respiratory tract infection (28.3%), diarrhoea (25.7%) and bronchitis (23.7%).

The most frequent serious adverse reactions are pneumonia (9.9%) and febrile neutropenia (6.6%).

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); not known (cannot be estimated from available data).

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 3 - Adverse reactions reported in patients with multiple myeloma treated with isatuximab in combination with pomalidomide and low-dose dexamethasone (ICARIA-MM study)

System Organ Class Preferred Term	Adverse reaction	Frequency	Incidence (%) (N=152)		
			Any Grade	Grade 3	Grade 4
Infections and infestations	Upper respiratory tract infection	Very common	43 (28.3)	5 (3.3)	0
	Pneumonia [a]	Very common	47 (30.9)	33 (21.7)	5 (3.3)

	Bronchitis	Very common	36 (23.7)	5 (3.3)	0
Blood and lymphatic system disorders	Febrile neutropenia	Very common	18 (11.8)	16 (10.5)	2 (1.3)
Metabolism and nutrition disorders	Decreased appetite	Common	15(9.9)	2 (1.3)	0
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Very common	23 (15.1)	6 (3.9)	0
Gastrointestinal disorders	Diarrhoea	Very common	39 (25.7)	3 (2.0)	0
	Nausea	Very common	23 (15.1)	0	0
	Vomiting	Very common	18 (11.8)	2 (1.3)	0
Investigations	Weight decreased	Common	10 (6.6)	0	0
Injury, poisoning and procedural complications	Infusion reaction	Very common	58 (38.2)	2 (1.3)	2 (1.3)

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

Table 4 – Haematology Laboratory Abnormalities in Patients Receiving isatuximab combined with pomalidomide and low-dose dexamethasone–versus pomalidomide and low-dose dexamethasone (ICARIA-MM)

Laboratory parameter	**Isatuximab + Pomalidomide + low-dose Dexamethasone n(%) (N=152)**			**Pomalidomide + low-dose Dexamethasone n(%) (N=147)**		
	All grades	**Grade 3**	**Grade 4**	**All grades**	**Grade 3**	**Grade 4**
Anemia	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.

Description of selected adverse reactions

Infusion reactions
In ICARIA-MM, infusion reactions were reported in 58 patients (38.2%) treated with isatuximab. All patients who experienced infusion reactions, experienced them during the 1st infusion of isatuximab, 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 higher 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. The median duration of isatuximab infusion was 3.3 hours during the first infusion and 2.8 hours for the subsequent infusions.
Discontinuations from treatment due to infusion reaction were reported in 2.6% of patients in isatuximab regimen group.

In a separate study (TCD14079 Part B) with isatuximab 10 mg/kg administered from a 250 mL fixed infusion volume in combination with pomalidomide and low-dose dexamethasone, infusion reactions (all Grade 2) were reported in 47.1% of patients, at the first administration, the day of the infusion. The median duration of infusion was 3.94 hours for the first infusion, 1.88 hours for the second infusion, and 1.25 hours from third infusion onwards. Overall, the safety profile of isatuximab 10 mg/kg administered as a 250 mL fixed infusion volume was similar to that of isatuximab as administered in ICARIA-MM.

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 in isatuximab regimen group compared to 16.1% in comparator regimen (pomalidomide and low-dose dexamethasone) group, and Grade 4 in 3.3% of patients in isatuximab regimen group compared to 2.7% in comparator regimen group. Discontinuations from treatment due to infection were reported in 2.6% of patients in isatuximab regimen group compared to 5.4% in comparator regimen group. Fatal infections were reported in 3.3% of patients in isatuximab regimen group and 4.0% in comparator regimen group.

Immunogenicity
Across 6 clinical studies in multiple myeloma (MM) with isatuximab single agent and combination therapies including ICARIA-MM (N=564), the incidence of treatment emergent anti-drug antibodies (ADAs) was 2.3%. 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 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 isatuximab overdose. In the event of overdose of isatuximab, 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: CD38 directed monoclonal antibodies, ATC code: not yet assigned

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.

Isatuximab acts through IgG Fc-dependent mechanisms including: antibody dependent cell mediated cytotoxicity (ADCC), antibody dependent cellular phagocytosis (ADCP), and

complement dependent cytotoxicity (CDC). Isatuximab can also trigger tumour cell death by induction of apoptosis via an Fc-independent mechanism.

Clinical efficacy and safety

ICARIA-MM (EFC14335)

The efficacy and safety of isatuximab in combination with pomalidomide and low-dose dexamethasone were evaluated in ICARIA-MM (EFC14335), a multicentre, multinational, randomised, open-label, 2-arm, phase III study in patients with relapsed and refractory multiple myeloma. Patients had received at least two prior therapies including lenalidomide and a proteasome inhibitor 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 isatuximab in combination with pomalidomide and low-dose dexamethasone (isatuximab regimen, 154 patients) or pomalidomide and low-dose dexamethasone (comparator regimen , 153 patients). Treatment was administered in both groups in 28-day cycles until disease progression or unacceptable toxicity. Isatuximab 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. Low-dose 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 isatuximab arm and 45.1% in comparator arm, 1 in 53.9% in isatuximab arm and 44.4% in comparator arm, and 2 in 10.4% in isatuximab arm and 10.5% in comparator arm, 10.4% of patients entered the study with a history of COPD or asthma, and 38.6% versus 33.3% of patients with renal impairment (creatinine clearance <60 mL/min/1.73 m^2) were included in isatuximab arm versus comparator arm groups, respectively. The International Staging System (ISS) Stage at study entry was I in 37.5 % (41.6% in isatuximab arm and 33.3% in comparator arm), II in 35.5% (34.4% in isatuximab arm and 36.6% in comparator arm) and III in 25.1% (22.1% in isatuximab arm and 28.1% in comparator arm) of patients. Overall, 19.5% of patients (15.6% in isatuximab arm and 23.5% in 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 isatuximab arm and 15.0% in comparator arm), 8.5% (7.8% in isatuximab arm and 9.2% in comparator arm) and 1.6% (0.6% in isatuximab arm and 2.6% in 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 91.2% of patients were refractory to lenalidomide at last line of therapy. One patient treated with isatuximab regimen received a prior treatment with daratumumab versus no patient in the comparator regimen group.

The median duration of treatment was 41.0 weeks for isatuximab regimen group compared to 24.0 weeks for comparator regimen 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 isatuximab regimen .

Efficacy results are presented in the table 5and Kaplan-Meier curves for PFS and OS are provided in Figures 1 and 2:

Table 5 - Efficacy of isatuximab in combination with pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in the treatment of multiple myeloma (intent-to-treat analysis)

Endpoint	**Isatuximab + pomalidomide + low-dose dexamethasone N =154**	**Pomalidomide + low-dose dexamethasone N = 153**
Overall Response Rate[a] Responders (sCR+CR+VGPR+PR) n(%) [95% CI] [b]	93 (60.4) [0.5220-0.6817]	54 (35.3) [0.2775-0.4342]
Odds ratio vs Pd [95% exact CI]	2.795 [1.715-4.562]	
p-value (stratified Cochran-Mantel-Haenszel) [d]	<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][c]	49 (31.8) [0.2455-0.3980]	13 (8.5) [0.0460-0.1409]
Odds ratio vs Pd [95% exact CI]	5.026 [2.514-10.586]	
p-value (stratified Cochran-Mantel-Haenszel)[d]	<0.0001	
Duration of Response[e] ***** (PR or better) Median in months [95% CI] [f]	13.27 [10.612-NR] (N=93)	11.07 [8.542-NR] (N=54)

[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] sCR, CR, VGPR and PR were evaluated by the IRC using the IMWG response criteria.
[c] Estimated using Clopper-Pearson method.
[d] Stratified on age (<75 years versus ≥75 years) and number of previous lines of therapy (2 or 3 versus >3) according to IRT. One-sided significance level is 0.025.
[e] based on Responders in the ITT population. Kaplan-Meier estimates of duration of response.
[f] CI for Kaplan-Meier estimates are calculated with log-log transformation of survival function and methods of Brookmeyer and Crowle.
* Cut-off date of 11-Oct-2018. Median follow-up time=11.60 months. HR<1 favours isatuximab regimen arm.
NR: not reached

The median time to first response in responders was 35 days in isatuximab regimen group versus 58 days in comparator regimen 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)

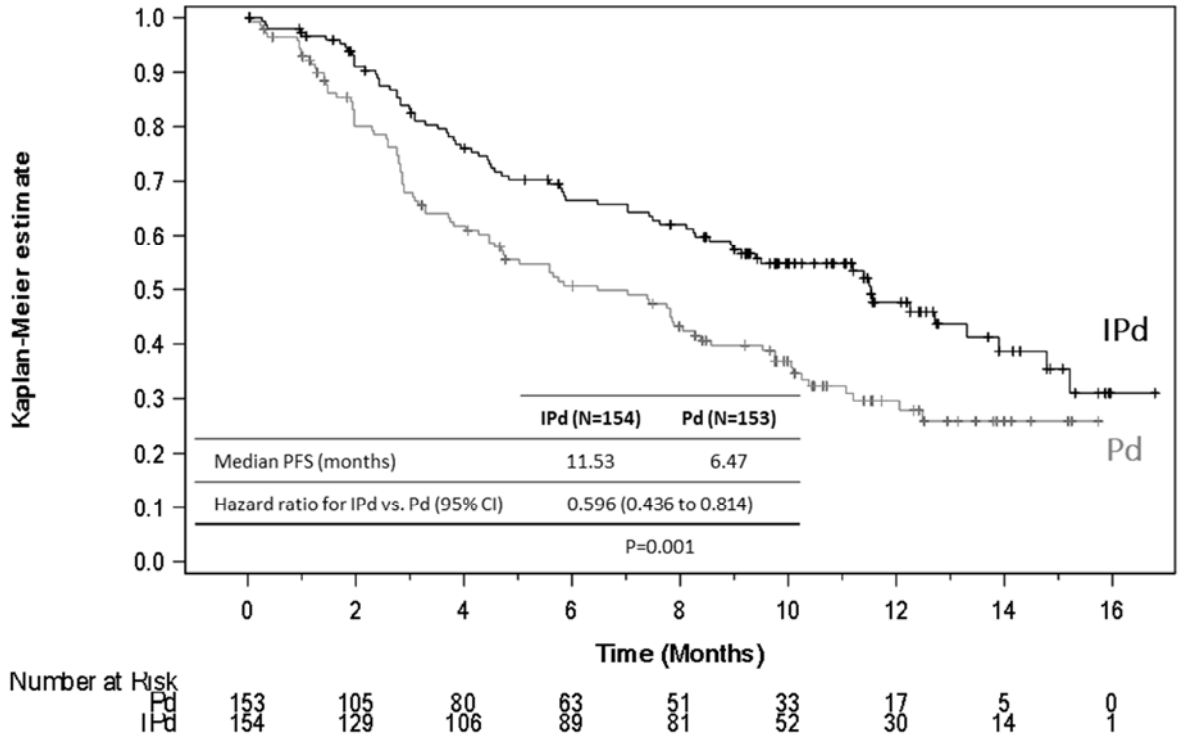
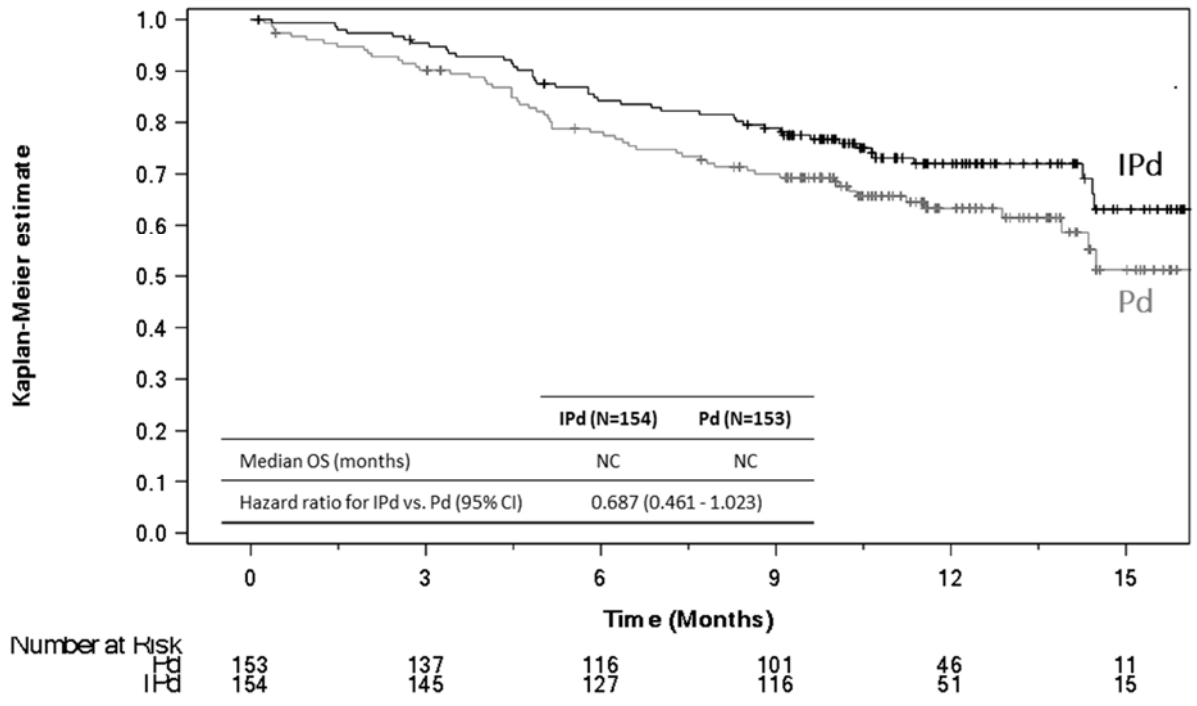


Figure 2 – Kaplan-Meier curves of OS – ITT population – ICARIA-MM



Cut-off date = 11 October 2018

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/ 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 8 weeks with a 3.1-fold accumulation., 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.

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 0.00955 L/h 9.55 mL/h (0.229 L/day). This is associated with a terminal half-life of 28 days.

Drug Interactions
The pharmacokinetics of isatuximab and pomalidomide were not influenced by their coadministration.

Specific populations

Age
The population pharmacokinetic analyses of 476 patients aged 36 to 85 years showed comparable exposure to isatuximab in patients $\leq$ 75 years old (n=406) versus $\geq$ 75 years old (n=70). Gender and race had no clinically meaningful effect on isatuximab pharmacokinetics.

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
Isatuximab exposure (AUC) at steady state decreased with increasing body weight.

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
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. However, scientific knowledge on the role of CD38 in embryofoetal development cannot exclude potential risk in humans.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sucrose
Histidine hydrochloride monohydrate
Histidine
Polysorbate 80
Water for injection

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

36 months

After dilution
Microbiological, chemical and physical in-use stability of isatuximab infusion solution has been demonstrated after dilution with 0.9% sodium chloride or 5% glucose solution for 48 hours at 2°C - 8°C, followed by 8 hours (including the infusion time) at room temperature. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user and would not normally be longer than 24 hours at 2 - 8°C, unless reconstitution/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.
Do not shake.
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

Isatuximab 100 mg/5mL concentrate for solution for infusion vial

- 5 ml concentrate containing 100 mg of isatuximab (fill volume: 5.4 mL) in a 6 mL type I colourless clear glass vial closed with ETFE (copolymer of ethylene and tetrafluoroethylene)-coated bromobutyl stoppers. The stoppered 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.
- Pack size of one single-use vial.

Isatuximab 500 mg/25 mL concentrate for solution for infusion vial

- 25 ml concentrate containing 500 mg of isatuximab (fill volume: 26.0 mL) in a 30 mL type I colourless clear glass vial closed with ETFE (copolymer of ethylene and tetrafluoroethylene)-coated bromobutyl stoppers. 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.
- Pack size of one single-use vial.

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 required isatuximab 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 isatuximab concentrate vial may be necessary to obtain the required dose for the patient.

- Vials of isatuximab concentrate should be visually inspected before dilution to ensure they don't contain any particles and are not discoloured.
- Do not shake vials.
- The appropriate volume of isatuximab concentrate should be withdrawn and diluted in an infusion bag with 250 mL of 9 mg/mL (0.9%) of sodium chloride or glucose 5% solution to achieve the appropriate isatuximab concentration for infusion.
- 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 (polyether sulfone (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).
- Prepared isatuximab infusion solution should be used within 48 hours when stored at 2° - 8°C, followed by 8 hours (including the infusion time) at room temperature (typically 15°C - 25°C). From a microbiological point of view, the product should be used immediately.
- No protection from light is required for the prepared infusion bag in a standard artificial light environment.
- Do not infuse isatuximab 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.

7. SCIENTIFIC OPINION HOLDER

Aventis Pharma limited
410 Thames Valley Park Drive,
Reading, Berkshire,
RG6 1PT,
UK
Trading as Sanofi,
410 Thames Valley Park Drive,
Reading, Berkshire,
RG6 1PT,
UK.

8. EAMS NUMBER(S)

04425/0002

9. DATE OF SCIENTIFIC OPINION

To be completed.

Additional information:

- Each prescribing haematologist will be provided with a **physician pack** containing all the relevant documents needed to manage patients receiving isatuximab under EAMS.

- As each patient signs the Informed Consent Form, they must be issued with a Patient Alert Card. This is a wallet-card sized and patients must be instructed to carry it with them at all times. It alerts any other healthcare professional that may treat the patient that they are receiving isatuximab through an early access scheme and provides information about their healthcare professional out of hours contact details and the Company's contact information. Prescribers will be provided with training on the EAMS program, the important identified risks associated with isatuximab treatment and guidance on reporting safety information.

Contact information:
To request access to EAMs: https://www.sanofi.com/en/compassionate-use/

For other EAMS information:
Email: GB-eams-oncology@sanofi.com
Tel: 0845 372 7101