Isatuximab (Sarclisa®) in combination with carfilzomib and dexamethasone for the treatment of patients with multiple myeloma (MM)

General information

Drug description [1]	Indication [2]
Isatuximab is an immunoglobulin G1 (IgG1) monoclonal antibody that targets a specific epitope on CD38.	Isatuximab combination with carfilzomib and dexamethasone is indicated for the treatment of adult patients with MM who have received at least one prior therapy.

Current treatment [3]

NICE guidelines recommend the use of a number of the following possible sequences of treatments for relapsed or refractory MM:

- In instances of first relapse, the guidelines recommend the use of:
  - Carfilzomib in combination with dexamethasone – only after one prior therapy, which did not include bortezomib.
  - Bortezomib – only after one prior therapy and for adults who have undergone, or are unsuitable for, bone marrow transplantation.
  - Second autologous stem cell transplant – suitability determined by response to first transplant, number of prior treatments, overall health and fitness, and ranking on ISS system.
- Subsequent relapse treatment may include:
  - Lenalidomide in combination with dexamethasone for adults who have received two or more prior therapies.
  - Ixazomib, with lenalidomide and dexamethasone, for adults who have already had two or three lines of therapy.
  - Panobinostat in combination with bortezomib and dexamethasone for adults who have received at least two prior regimens including bortezomib and an immunomodulatory agent.
  - Pomalidomide, in combination with low-dose dexamethasone for adults at third or subsequent relapse; that is, after three previous treatments including both lenalidomide and bortezomib.
  - Daratumumab monotherapy for adults whose previous therapy included a proteasome inhibitor and an immunomodulator, and whose disease progressed on the last therapy, only if they have daratumumab after 3 previous therapies.

Regulatory status

EMA [2]	FDA
Approval status for this indication: On 25 February 2021, the CHMP adopted a positive opinion recommending a change to the terms of the marketing authorisation for Sarclisa®. The CHMP adopted an extension to the existing indication as follows: ❖ Sarclisa® is indicated in combination with carfilzomib and dexamethasone, for the treatment of adult patients with MM who have received at least one prior therapy. **Other indications**: ❖ Sarclisa® is indicated in combination with pomalidomide and dexamethasone, for the treatment of adult patients with relapsed and refractory MM who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on the last therapy. ✓ **Medicine under additional monitoring**	**Approval status for this indication**: On 31 March 2021, the FDA approved isatuximab-irfc (Sarclisa®) in combination with carfilzomib and dexamethasone, for the treatment of adult patients with relapsed or refractory MM who have received one to three prior lines of therapy [4]. **Other indications**: ❖ Sarclisa® is indicated, 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 [5].

Costs

Sarclisa® 100 mg/5 ml concentrate for solution for infusion = **€ 664.00** (ex-factory price) [6]
Sarclisa® 500 mg/25 ml concentrate for solution for infusion = **€ 3,320.00** (ex-factory price) [6]

Premedication

- Premedication should be used prior to Sarclisa® infusion with the following medicinal products to reduce the risk and severity of infusion reactions:
  - Dexamethasone 40 mg oral or intravenous (or 20 mg oral or intravenous for patients ≥75 years of age): when administered in combination with isatuximab and pomalidomide, Dexamethasone 20 mg (intravenous on the days of isatuximab and/or carfilzomib infusions, and oral on the other days): when administered in combination with isatuximab and carfilzomib.
  - Acetaminophen 650 mg to 1000 mg oral (or equivalent).

- Diphenhydramine 25 mg to 50 mg intravenous or oral (or equivalent e.g., cetirizine, promethazine, dexchlorpheniramine). The intravenous route is preferred for at least the first 4 infusions.

❖ The above recommended dose of dexamethasone (oral or intravenous) corresponds to the total dose to be administered only once before the infusion, as part of the premedication and the backbone treatment, before isatuximab and pomalidomide and before isatuximab and carfilzomib administration.

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

Warnings and precautions [7]

❖ **Infusion-Related Reactions**: In case of grade ≥2, interrupt Sarclisa® and manage medically. Permanently discontinue for grade 4 infusion-related reactions or anaphylactic reaction.

❖ **Neutropenia**: Monitor complete blood cell counts periodically during treatment. Monitor patients with neutropenia for signs of infection. Sarclisa® dose delays and the use of colony-stimulating factor may be required to allow improvement of neutrophil count.

❖ **Second Primary Malignancies:** Monitor patients for the development of second primary malignancies.

❖ **Laboratory Test Interference**:

- Interference with Serological Testing (Indirect Antiglobulin Test): Type and screen patients prior to starting treatment. Inform blood banks that a patient has received Sarclisa®.
- Interference with Serum Protein Electrophoresis and Immunofixation Tests: Sarclisa® may interfere with the assays used to monitor M-protein, which may impact the determination of complete response.

❖ **Embryo-Foetal Toxicity**: Can cause foetal harm.

Study characteristics [1, 8-10]

Trial name	*n*	Intervention (I)	Comparator (C)	PE	Characteristics	Biomarker	Funding	Publication(s)
IKEMA, EFC15246 NCT03275285	302	Isatuximab (10 mg/kg weekly over 4 weeks, then given every 2 weeks) in combination with twice-weekly carfilzomib (3 weeks out of 4) and twice-weekly low-dose dexamethasone	carfilzomib and low-dose dexamethasone alone	PFS	**ongoing**, prospective, multinational, randomized, open-label, parallel-group, two-arm, phase III study	-	Sanofi	[1]

Efficacy (I vs. C)

PFS, months: NR vs. 19.5, HR 0.53, p=0.0007
Overall response: 86.6% vs. 82.9%, p=0.19
Time to next treatment: NR vs. NR, HR=0.56 (favouring triplet)
≥ VGPR: 72.6% vs. 56.1%, p=0.0011
≥ CR: 39.7% vs. 27.6%
MRD negativity: 29.6% vs. 13.0%, p=0.0004
MRD negativity in patients with ≥ VGPR: 41.4% vs. 22.9%
OS: data not mature at the time of data cut-off

HRQoL, as measured by QLQ-C30 Global Health Status score, was maintained with isatuximab plus carfilzomib–dexamethasone [11].

Safety (I vs. C)

Grade ≥3 TEAEs: n=136/177 (76.8%) vs. n=82/122 (67.2%)
Serious TEAEs: n=105/177 (59.3%) vs. n=70/122 (57.4%)
Fatal TEAEs: n=6/177 (3.4%) vs. n=4/122 (3.3%)

Risk of bias (study level) [12]

Adequate generation of randomisation sequence	Adequate allocation concealment	Blinding	Selective outcome reporting unlikely	Other aspects which increase the risk of bias	**Risk of bias**
unclear	unclear	No, open-label	unclear[1]	yes[2]	unclear

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[1] IKEMA trial is ongoing until 02/2023; currently only interim analysis data available.
[2] Industry-funded

Abbreviations: AE=adverse event, AJ=adjustment, C=comparator, CHMP=Committee for Medicinal Products for Human Use, CI=confidence interval, CR=complete response, EMA=European Medicines Agency, ESMO-MCBS=European Society of Medical Oncology – Magnitude of Clinical Benefit Scale, FDA=Food and Drug Administration, FM=final magnitude of clinical benefit grade, HR=hazard ratio, HRQoL=health-related quality of life, I=intervention, IG G1=immunoglobulin G1, Int.=intention, MG=median gain, MM=multiple myeloma, MRD=minimal residual disease, n=number of patients, NICE=National Institute for Health and Care Excellence, OS=overall survival, PE=primary endpoint, PFS=progression-free survival, PM=preliminary grade, QLQ-C30=quality-of-life questionnaire C30, QoL=quality of life, SAE=serious adverse event, ST=standard treatment, TEAE=treatment-emergent adverse events, VGPR=very good partial response.

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