Recommendation No. 131/2021
of 29 November 2021
of the President of the Agency for Health Technology Assessment and Tariff System
on the reimbursement of Sarclisa (isatuximab) under the drug programme: "Treatment of patients with relapsed/refractory multiple myeloma (ICD-10 C90.0) with isatuximab"

The President of the Agency does not recommend the reimbursement of Sarclisa (isatuximab) under the drug programme: "Treatment of patients with relapsed/refractory multiple myeloma (ICD-10 C90.0)" as currently proposed in the application.

Grounds for the recommendation

Clinical analysis was based on the ICARIA-MM randomised clinical trial, which compared the efficacy and safety of isatuximab in conjunction with pomalidomide and dexamethasone (ISA+POM+DEX) versus pomalidomide and dexamethasone (POM+DEX). Two comparator studies were additionally included (CASTOR for the daratumumab+bortezomib + dexamethasone (DAR+BOR+DEX) vs bortezomib+dexamethasone regimen and ARROW for the carfilzomib with dexamethasone (KAR+DEX) regimen administered once a week vs carfilzomib with dexamethasone administered twice a week).

Major limitations to the clinical analysis include the incomplete results of the ongoing ICARIA-MM study, which should be interpreted with caution, and the lack of comparability with results from comparator studies. The studies included in the analysis mainly differed in follow-up periods, number of therapies previously used by patients, while different subpopulations for which results were reported make it impossible to draw reliable conclusions from the compiled results. [information protected as a trade secret]

[information protected as a trade secret]

The clinical analysis included a review of the results from the ICARIA-MM, CASTOR and ARROW publications, but due to a considerable heterogeneity of the studies, it was impossible to perform a comparison and draw conclusions regarding differences between the results of these studies.

When reading the results for each endpoint, it is important to note different median follow-ups and group populations. [information protected as a trade secret] In the CASTOR study, the results presented for other endpoints concern the entire population included in the study. Nominally higher results for the ORR, sCR, CR and VGPR were reported for the DAR+BOR+DEX regimen (population-wide results), while a nominally higher result for the PR was observed for the KAR70+DEX40 regimen.

According to the applicant's estimates, the use of Sarclisa instead of the selected comparators from the perspective of the public payer is [information protected as a trade secret] ICUR for the option with the RSS is [information protected as a trade secret] for comparison with POM+DEX [information protected as a trade secret] for comparison with DAR+BOR+DEX. These values are [information protected as a trade secret] the cost-effectiveness threshold.

Given [information protected as a trade secret] underlying the applicant's economic model, as well as the lack of studies directly comparing the assessed therapy with DAR+BOR+DEX and KAR+DEX regimens and the impossibility of conducting an indirect comparison, it was decided to provide a list of costs of all therapies. The annual cost of ISA+POM+DEX, POM+DEX, DAR+BOR+DEX, KAR+DEX regimens for 1 patient is [information protected as a trade secret] approx. PLN 146,000, approx. PLN 317,000 and approx. PLN 288,000 respectively.

It should be borne in mind, however, that the ICARIA-MM study in the general population demonstrated statistically significantly longer progression-free survival as assessed by researchers and as assessed centrally (11.53 vs 6.47 months and 11.14 vs 6.54 months respectively). [information protected as a trade secret]

In the general population, the ISA+POM+DEX vs POM+DEX treatment group also achieved a statistically significantly higher proportion of patients with: minimal residual disease negativity; complete response (as assessed by the researcher); overall response rate; very good partial response; very good partial response or better. [information protected as a trade secret]

[information protected as a trade secret]

The Polish Myeloma Group 2021 guidelines indicate that ISA+POM+DEX can be used in patients with recurrence/progression after two lines of treatment, which is in line with the National Comprehensive Cancer Network 2021 guidelines, in which the ISA+POM+DEX regimen is recommended in patients who have received at least 2 prior therapies, including lenalidomide and a proteasome inhibitor. By contrast, according to the National Institute for Health and Care Excellence (NICE) 2021 guidelines, this regimen is indicated for fourth-line treatment of patients with relapsed/refractory multiple myeloma (RRMM), who have previously received three lines of treatment, including lenalidomide and a proteasome inhibitor, and who have experienced disease progression after the last treatment. ISA+POM+DEX therapy is recommended by the European Hematology Association, European Society for Medical Oncology (EHA-ESMO) 2021 for the treatment of second and subsequent recurrences (≥3 lines of RRMM treatment), for patients refractory to LEN and BOR, and refractory to LEN and sensitive to a proteasome inhibitor.

All reimbursement recommendations are positive in terms of funding the proposed technology; however, the Canadian Agency for Drugs and Technologies in Health (CADTH) 2021 funding condition is cost-effectiveness improvement, and the NICE 2020 recommendation refers to funding under the Cancer Drugs Funds programme, not for routine use in the NHS.

In view of the Council position, clinical guidelines and the possible benefits of introducing an additional therapeutic option for patients with relapsed/refractory multiple myeloma, the President of the Agency considers it possible to fund the therapy in question if the costs are equal to the three-drug regimen constituting the comparator [information protected as a trade secret] and proposing an additional risk mechanism based on the results obtained [information protected as a trade secret]

Subject of the application

The order of the Minister of Health concerns the assessment of the appropriateness of public reimbursement of the following medicinal product:

- Sarclisa (isatuximab), 20mg/mL concentrate for infusion solution, 1 5 mL vial EAN: 05909991427818, for which the proposed net sales price is [information protected as a trade secret]
- Sarclisa (isatuximab), 20mg/mL concentrate for infusion solution, 1 5 mL vial 25 mL, EAN: 05909991427832, for which the proposed net sales price is [information protected as a trade secret]

Proposed payment and dispensing category: free of charge, the drug is to be applied under the drug programme as part of a new limit group. The applicant has submitted a proposal for a risk-sharing scheme.

Sarclisa was assessed by the Agency in 2021 as part of the development of a list of highly innovative drug health technologies (TLI) in a similar indication to that being assessed [information protected as a trade secret] [information protected as a trade secret]. According to the Position of the Council, this product did not finally qualify for the list as it did not meet the criteria adopted by the Transparency Council.

Health problem

Multiple myeloma (ICD-10 C90.0) is an excessive and abnormal proliferation of abnormal plasma cells usually located in flat bones. Complete blood count (CBC), bone marrow count and immunophenotype, cytogenetic and molecular tests, other laboratory tests and ancillary tests (e.g. bone X-ray, computed tomography, magnetic resonance imaging or positron emission tomography combined with computed tomography) are performed for diagnosis. Symptoms are caused by hyperplasia of neoplastic cells and proteins and cytokines that they secrete. The most common symptom is bone pain (lumbar spine, pelvis, ribs) accompanied by neurological symptoms (limb paresis and paralysis), hypercalcaemia and its sequelae, recurrent respiratory and urinary tract infections, renal failure (in approx. 30% at diagnosis), peripheral neuropathy (usually motor-sensory), hyperviscosity syndrome (<10%), liver enlargement, rarely enlargement of peripheral lymph nodes and spleen, and yellows on hands and soles of the feet.

Multiple myeloma accounts for approx. 1% of all malignant tumours and approx. 14% of cancers of the haematopoietic system. The annual incidence in Europe ranges from 4.5/100,000 to 5.8/100,000. It is slightly more common in men, with a peak incidence in the 7th decade of life (median age 70 years). Approximately 5% of patients are aged < 60 years and 2% before 40 years of age.

The median survival time for patients with relapsed disease is 1.5 years and the clinical course is characterised by shortened duration of response as the number of rescue therapy regimens increases.

Alternative health technology

Considering clinical guidelines, opinion of clinical experts and currently publicly funded technologies, the comparators included:

- pomalidomide with dexamethasone (POM+DEX);
- daratumumab+bortezomib+dexamethasone (DAR+BOR+DEX);
- carfilzomib+dexamethasone KAR+DEX.

Description of the proposed intervention

Isatuximab is an IgG1 monoclonal antibody that binds to the specific extracellular epitope of the CD38 receptor. CD38 is a transmembrane glycoprotein that is highly expressed on the surface of

multiple myeloma cells.

In vivo, reductions in absolute numbers of CD16+ and CD56+ NK cells, CD19+ B cells, CD4+ T cells and TREG cells (CD3+, CD4+, CD25+, CD127-) were observed in the peripheral blood of patients treated with isatuximab in monotherapy.

According to the Summary of Product Characteristics (SmPC), Sarclisa is indicated for use:

- in combination with pomalidomide and dexamethasone for the treatment of adult patients with relapsed/refractory multiple myeloma who have received at least two prior lines of treatment, including lenalidomide and a proteasome inhibitor and who have experienced disease progression after the last treatment;
- in combination with carfilzomib and dexamethasone for the treatment of adult patients with multiple myeloma who have received at least one prior line of therapy.

The proposed reimbursement indication is [information protected as a trade secret] from the registration indication, as it includes patients who [information protected as a trade secret]

Efficacy, effectiveness and safety assessment

This assessment involves collecting data on the health consequences (efficacy and safety) of the new therapy for the health problem in question and of other therapies that are currently reimbursed from public funds and represent alternative therapies available for the health problem. Furthermore, this assessment requires determination of the reliability of data collected and a comparison of the efficacy and safety results of the new therapy against the therapies already available to treat the health problem in question.

On the basis of the above, the efficacy and safety assessment allows answering the question of the scale of the health outcome (both in terms of efficacy and safety) to be expected from the new therapy compared with other therapeutic options under consideration.

The applicant based its clinical and economic analysis on a randomised clinical trial comparing isatuximab used in combination with pomalidomide and dexamethasone (ISA+POM+DEX regimen, IPd) with pomalidomide and dexamethasone (POM+DEX regimen, Pd) in a population of adult patients with relapsed/refractory multiple myeloma - ICARIA-MM. The study included 307 patients [information protected as a trade secret] The study is still ongoing - the results published so far derived from Attal 2019 and NICE 2020 publications for the period of 10 January 2017 to 11 October 2018 (for efficacy analysis) and to 22 November 2018 (for safety analysis). The median follow-up was 11.6 months (IQR 10.1 - 13.9).

The ITT (intention-to-treat) population covers all patients included in the study who were subject to randomisation. [information protected as a trade secret]

Due to the lack of studies directly comparing the efficacy and safety of the IPd regimen with other comparators, the review included:

- CASTOR - study comparing the KAR+BOR+DEX regimen with bortezomib and dexamethasone (BOR+DEX regimen, Vd). The study included 498 patients.
- ARROW - study comparing the efficacy of the KAR+DEX regimen used once a week with the same regimen used twice a week. The study included 478 patients.

As assessed by the Cochrane Collaboration recommendations, the ICARIA-MM, CASTOR, ARROW studies have a low risk of bias in most of the domains assessed. For all studies, the risk of bias in the "blindness of researchers and patients" domain was defined as unclear - these were open-label studies (in the ICARIA-MM study, those analysing the results were subject to blinding). Moreover, in the ARROW study, the risk of bias in the "blinding of effect assessment" domain was assessed as unclear because no information was provided whether those analysing the results knew what therapy the patients received.

Efficacy [information protected as a trade secret]

[information protected as a trade secret]

ITT population from the ICARIA-MM study

According to the results of the ICARIA-MM study, the use of ISA+POM+DEX vs POM+DEX was associated with statistically significantly higher efficacy in terms of:

- progression-free survival:
    - In the Independent Response Review Committee (IRC) assessment - 11.53 months (95% CI: 8.9; 13.9) vs 6.47 months (95% CI: 4.5; 8.3) and HR=0.596 (95% CI: 0.446; 0.814);
    - In researcher's assessment, 11.14 months (95% CI: 7.5; 14.8) vs 6.54 months (95% CI: 4.7; 7.9), and HR=0.602 (95% CI: 0.444; 0.816);
- MRD negativity:
    - For a sensitivity threshold of 1 per 10^{-4} leukocytes, OR=22.38 (95% CI: 1.29; 387.19), NNT=16 (95% CI: 9 38);
    - For a sensitivity threshold of 1 per 10^{-5} leukocytes, OR=17.87 (95% CI: 1.02; 318.84), NNT=20 (95% CI: 11; 60);
- response rate:
    - ORR:
        - in the IRC assessment - OR=2.795 (95% CI: 1.75; 4.56) NNT=4 (95% CI: 3; 8);
        - as assessed by the researcher - – OR=3.612 (95% CI: 2.195; 5.953), NNT=4 (95% CI: 3; 6);
    - CR:
        - as assessed by the researcher - OR=8.33 (95% CI: 1.03; 67.42), NNT=23 (95% CI: 11; 156);
    - ≥VGPR
        - in the IRC assessment - OR=5.026 (95% CI: 2.514; 10.586) NNT=5 (95% CI: 4; 7);
        - as assessed by the researcher - OR=6.581 (95% CI: 3.179; 14.611), NNT=4 (95% CI: 3; 6);
    - VGPR
        - in the IRC assessment – OR=5.36 (95% CI: 2.58; 11.16), NNT=5 (95% CI: 4; 8);
        - as assessed by the researcher – OR=6.20 (95% CI: 2.90; 13.25), NNT=5 (95% CI: 4; 8);
- time to next treatment (TNT) - the median in the intervention arm was not reached, and in the comparator arm it was 9.10 months (95% CI: 6.374; 12.255) - HR=0.538 (95% CI: 0.382; 0.758);

[information protected as a trade secret]

According to the ICARIA-MM study, the use of ISA+POM+DEX vs POM+DEX was associated with a statistically significantly lower efficacy in terms of:

- response to treatment:

- MR:
  - as assessed by the researcher - – OR=0.39 (95% CI: 0.17; 2.07), NNT=13 (95% CI: 7; 85);
- disease stabilisation:
  - as assessed by the researcher – OR=0.55 (95% CI: 0.33; 0.91), NNT=9 (95% CI: 5; 52).

The ICARIA-MM study found no statistically significant differences between ISA+POM+DEX and POM+DEX in terms of:

- overall survival;
- MRD negativity for a sensitivity threshold of 1 per 10^{-6} leukocytes;
- response rate: CR as assessed by the IRC, sCR (both IRC- and researcher-assessed), PR (both IRC- and researcher-assessed), MR as assessed by the IRC, disease stabilisation as assessed by the IRC, PD (both IRC- and researcher-assessed);

[information protected as a trade secret] time to progression (TTP); [information protected as a trade secret]

- quality of life for the domain relating to fatigue.

Comparison of ISA+POM+DEX vs KAR+DEX vs DAR+BOR+DEX (studies: ICARIA-MM, ARROW, CASTOR)

Due to the considerable heterogeneity of the studies resulting, among other things, from differences between the analysed populations, different definition of endpoints or follow-up period in the ICARIA-MM, ARROW and CASTOR studies, it was not possible to perform an indirect comparison. The applicant presented a summary of findings [information protected as a trade secret] for selected endpoints. Results for the selected efficacy endpoints from the three studies under analysis are summarised below.

Endpoint	Parameters	ISA+POM+DEX	KAR70+DEX40	DAR+BOR+DEX
PFS	median follow-up [months].	[information protected as a trade secret]	[information protected as a trade secret]	[information protected as a trade secret]
	n/N	[information protected as a trade secret]	[information protected as a trade secret]	[information protected as a trade secret]
	median (95% CI) [months]*.	[information protected as a trade secret]	[information protected as a trade secret]	[information protected as a trade secret]
	HR (95% CI)*; p-value	[information protected as a trade secret]	[information protected as a trade secret]	[information protected as a trade secret]
ORR	median follow-up [months].	[information protected as a trade secret]	[information protected as a trade secret]	7.4 40
	n/N (%)	[information protected as a trade secret]	[information protected as a trade secret]	199/240 (83)^ 203/240 (85)^
	OR (95% CI); p-value	[information protected as a trade secret]	[information protected as a trade secret]	p<0.001 p<0.0001
sCR	median follow-up [months].	[information protected as a trade secret]	[information protected as a trade secret]	7.4 40
	n/N (%)	[information protected as a trade secret]	[information protected as a trade secret]	11/240 (4.6)^ 23/240 (10)^
	OR (95% CI); p-value	[information protected as a trade secret]	[information protected as a trade secret]	- -

CR	median follow-up [months].	[information protected as a trade secret]	[information protected as a trade secret]	7.4 40
	n/N (%)	[information protected as a trade secret]	[information protected as a trade secret]	35/240 (14.6) 49/240 (20)
	OR (95% CI), p-value	[information protected as a trade secret]	[information protected as a trade secret]	- -
VGPR	median follow-up [months]. n/N (%)	[information protected as a trade secret] [information protected as a trade secret]	[information protected as a trade secret] [information protected as a trade secret]	7.4 40 96/240 (40)^ 79/240 (33)^
	OR (95% CI), p-value	[information protected as a trade secret]	[information protected as a trade secret]	-
PR	median follow-up [months].	[information protected as a trade secret]	[information protected as a trade secret]	7.4 40
	n/N (%)	[information protected as a trade secret]	[information protected as a trade secret]	57/240 (23,8)^ 52/240 (22)^
	OR (95% CI), p-value	[information protected as a trade secret]	[information protected as a trade secret]	- -

[information protected as a trade secret]

Safety

Comparison of ISA+POM+DEX vs POM+DEX (ICARIA-MM study)

Adverse events occurred in almost all patients, both in the ITT population, [information protected as a trade secret] In the ITT population, for the group treated with the IPd regimen relative to the group treated with the Pd regimen, the following were reported statistically significantly more often:

- grade ≥3 serious adverse events - OR=1.59 (95% CI: 1.01; 2.51), NNH=9 (95% CI: 9; 330);
- grade ≥3 adverse events - OR=2.77 (95% CI: 1.54; 4.98), NNH=7 (95% CI: 4; 14);
- overall serious adverse effects - OR=2.87 (95% CI: 1.66; 4.97) NNH=6 (95% CI: 4; 11);
- overall adverse effects - OR=2.48 (95% CI: 1.26; 4.91), NNH=10 (95% CI: 6; 35);
- grade ≥3 adverse effects - OR=2.78 (95% CI: 1.73; 4.49) NNH=5 (95% CI: 3; 8);

With regard to treatment discontinuation, this event was statistically significantly less frequent in the group treated with the IPd regimen than in the group treated with the Pd regimen:

- overall - OR=0.41 (95% CI: 0.25; 0.68) NNH=6 (95% CI: 4; 12);
- due to disease progression - OR=0.53 (95% CI: 0.34; 0.84) NNH=7 (95% CI: 4; 24).

Adverse events that occurred statistically significantly more frequently among patients treated with the IPd regimen than with the Pd regimen included overall and grade 3≥ neutropenia; vomiting in total; overall and grade 3≥ neutropenic fever; overall reduction in body weight.

Comparison of ISA+POM+DEX vs DAR+BOR+DEX vs KAR+DEX (studies: ICARIA-MM, CASTOR, ARROW)

For the CASTOR study, only the median follow-up and the incidence (%) of respective endpoints are given. For overall adverse events, the incidence (%) was similar in the compared interventions. For grade ≥3 adverse events, there was a nominally higher incidence of this endpoint in the ICARIA-MM study. Adverse events leading to death nominally occurred most frequently in the ARROW study and least frequently in the CASTOR study.

Limitations

The main limitation of the analyses presented here is that there are no direct studies comparing the assessed technology with all comparators, and the available studies prevent a reliable indirect

comparison. The studies for the selected comparators – DAR+BOR+DEX (CASTOR) and KAR70+DEX40 (ARROW) – had such different inclusion criteria (also including populations: disease refractoriness to specific drugs, line of treatment, which was the studied therapy), different assumptions regarding e.g. the line of treatment in which the given regimen would be used, and the follow-up period that this resulted in the impossibility of an indirect comparison, even for the comparison of specific subpopulations (as the population in question). In addition, the assessment of the efficacy of ISA+POM+DEX vs POM+DEX was based on data from the ICARIA-MM study, which is currently an ongoing clinical study. The data included in this review are for a cut-off date of 11 October 2018. The median follow-up is 11.6 months. The planned study completion date is March 2021.

The uncertainty in the results presented was affected by the following aspects:

- [information protected as a trade secret]
- In the ICARIA-MM study, all patients previously received a proteasome inhibitor (100% of them received bortezomib) and lenalidomide, whereas in the CASTOR study, 67.3% of patients previously received a proteasome inhibitor (64.5% of them received bortezomib) and 71.3% of them received an immunomodulatory drug (35.5% of them received lenalidomide).
- Patients refractory to bortezomib were excluded from the CASTOR study, with 32% of patients reporting refractoriness to the last line of treatment; 33% of the patients were refractory to the immunomodulatory drug only; and 28% of the patients were refractory to lenalidomide. In the case of the ICARIA-MM study, 98% of the patients were refractory during the last line of treatment, the vast majority of the patients (93%) were refractory to lenalidomide treatment; as many as 76% to proteasome inhibitor treatment (71% to lenalidomide + proteasome inhibitor treatment) and 59% of the patients were refractory to lenalidomide treatment at the last therapy applied.
- Survival analysis in the ICARIA-MM study was performed using data not yet mature. Therefore, the above conclusion should be confirmed once the data are mature. The EMA document indicates that the patients will continue to be followed for the assessment of overall survival (OS) and updated information will be provided in the final CSR (Clinical Study Report).
- Quality-of-life scores on the EORTC QLQ-C30 scale [information protected as a trade secret] of the patients were presented in a descriptive way, making statistical calculations impossible.
- [information protected as a trade secret]
- There are no effectiveness studies for isatuximab administered in combination with pomalidomide and dexamethasone in the proposed patient population.
- For the part of patient-centred health outcomes for the general population, i.e. data on quality-of-life assessment (EORTC QLQ-C30 for GHS/QoL; EORTC QLQ-MY20, EQ-5D-5L), data available on the ClinicalTrials.gov registry website were used. as well as unpublished data received from the Customer.
- The applicant extrapolates results of MRD determination in 16 patients to the entire population so these results should be interpreted with caution as they may not reflect the true efficacy of the proposed health technology.

Proposed risk-sharing scheme

[information protected as a trade secret]

Economic evaluation, including a cost-effectiveness estimation

Economic evaluation involves estimating and comparing the costs and health outcomes that may be associated with the administration of the new therapy to an individual patient instead of already reimbursed therapies.

The costs of therapy are estimated in Polish currency, and health outcomes are usually expressed in life-years gained (LYG) or quality-adjusted life years (QALY) as a result of the therapy.

By comparing cost and outcome values associated with the new therapy and comparing them to the costs and outcomes of already reimbursed therapies, it is possible to answer the question of whether the health outcome achieved for an individual patient due to a new therapy involves a higher cost compared to already reimbursed therapies.

The obtained results of the cost-effectiveness ratio are compared with the so-called cost-effectiveness threshold, i.e. a result that indicates that given the wealth of Poland (expressed in GDP), the maximum cost of the new therapy that is expected to produce a unit of health outcome (1 LYG or 1 QALY) compared to already available therapies should not exceed three times GDP per capita.

Currently, the cost-effectiveness threshold is PLN 166,758 (3 x PLN 55,586).

The cost-effectiveness ratio does not estimate or determine the value of life, but it only enables its assessment and the use of this assessment to choose the therapy associated with the potential best use of the currently available resources.

The aim of the analysis was to assess the cost-effectiveness of Sarclisa (isatuximab), used in combination with pomalidomide and dexamethasone to treat adult patients with relapsed/refractory multiple myeloma (RRMM), [information protected as a trade secret] Cost-utility analysis (CUA) over a lifelong (20-year) time horizon was presented. Furthermore, cost-consequence analysis (CCA) was carried out. The NHF perspective and the joint perspective were considered. Considering the method according to which the drug is financed (i.e. the drug programme), the patient does not pay for the therapy, so the two perspectives are the same.

The following cost categories were included in the applicant's basic analysis:

- costs of interventions and comparators,
- costs of administering drugs,
- costs of monitoring therapy,
- costs of adverse event treatment,
- transfusion costs (platelets and red blood cells),
- costs of administering granulocyte colony-stimulating factor,
- costs of palliative care,
- costs of drugs used after disease progression.

According to the applicant's estimates, the use of the ISA+POM+DEX combination therapy instead of the comparators, i.e. POM+DEX and DAR+BOR+DEX, is more expensive and more effective. The estimated ICUR was:

- ISA+POM+DEX vs. POM+DEX:
    - [information protected as a trade secret] PLN/QALY without the RSS;

- [information protected as a trade secret] PLN/QALY including the RSS;

- ISA+POM+DEX vs. DAR+BOR+DEX:
  - [information protected as a trade secret] PLN/QALY without the RSS;
  - [information protected as a trade secret] PLN/QALY including the RSS.

Considering the above ICUR values, the threshold price is:

- ISA+POM+DEX vs. POM+DEX
  - [information protected as a trade secret] PLN/per pack. 100 mg/5 ml;
  - [information protected as a trade secret] PLN/per pack. 500 mg/25 ml;
- ISA+POM+DEX vs. DAR+BOR+DEX:
  - [information protected as a trade secret] PLN/per pack. 100 mg/5 ml;
  - [information protected as a trade secret] PLN/per pack. 500 mg/25 ml.

Results of the sensitivity analysis confirm the basic analysis results -ISA+POM+DEX therapy is more expensive and more effective than both comparators and at the same time [information protected as a trade secret]

The most significant impact on the increase in the ICUR value for the comparison of ISA+POM+DEX vs. POM+DEX in both analysed variants (i.e. without/without the RSS) is to adopt a 5-year time horizon [information protected as a trade secret] in turn, the biggest impact on the decline in the ICUR value in both options is the adoption of zero discount rates [information protected as a trade secret] The estimated ICUR values range from [information protected as a trade secret] in the variant without the RSS and from [information protected as a trade secret] in the variant with the RSS.

For the comparison of ISA+POM+DEX vs. DAR+BOR+DEX, the ICUR increase is most influenced by assuming a median overall survival of 25 months [information protected as a trade secret], while a median overall survival of 13.3 months causes the biggest drop in the ICUR value [information protected as a trade secret]. The estimated ICUR values range from [information protected as a trade secret] in the variant without the RSS and from [information protected as a trade secret] in the variant with the RSS.

Probabilistic analysis was also carried out as part of the sensitivity analysis - according to its results, the probability of the cost-effectiveness of ISA+POM+DEX was:

- for comparison with POM+DEX:
  - in the variant without the RSS: [information protected as a trade secret]
  - in the variant with the RSS: [information protected as a trade secret]
- for comparison with DAR+BOR+DEX:
  - in the variant without the RSS: [information protected as a trade secret]
  - in the variant with the RSS: [information protected as a trade secret]

The table below presents cost–consequence analysis for the comparison: ISA+POM+DEX vs. KAR+DEX.

Parameter	**ISA+POM+DEX**		**KAR+DEX**
Total costs, including:	**without the RSS**	**with the RSS**	[information protected as a trade secret]
	[information protected as a trade secret]	[information protected as a trade secret]	

drug costs	**overall**	[information protected as a trade secret]	[information protected as a trade secret]	[information protected as a trade secret]
	including ISA	[information protected as a trade secret]	[information protected as a trade secret]	
Progression-free survival	**Percentage of patients: 2 month**	[information protected as a trade secret]		0.830
	Percentage of patients: 4 month	[information protected as a trade secret]		0.715
	Percentage of patients: 6 month	[information protected as a trade secret]		0.655
	Percentage of patients: 8 month	[information protected as a trade secret]		0.557
	Percentage of patients: 10 month	[information protected as a trade secret]		0.496
	Percentage of patients: 12 month	[information protected as a trade secret]		0.459
	Percentage of patients: 14 month	[information protected as a trade secret]		0.360
	Median PFS [months]	[information protected as a trade secret]		8.9
Overall survival (OS)	**Percentage of patients: 3 month**	[information protected as a trade secret]		no data available
	Percentage of patients: 6 month	[information protected as a trade secret]		no data available
	Percentage of patients: 9 month	[information protected as a trade secret]		no data available
	Percentage of patients: 12 month	[information protected as a trade secret]		no data available
	Percentage of patients: 15 month	[information protected as a trade secret]		no data available
	Median OS [months]	[information protected as a trade secret]		no data available
Adverse events [information protected as a trade secret]	**Anaemia**	3.3%		
	Neutropenia	46.1%		[information protected as a trade secret]
	Neutropenic fever	11.8%		[information protected as a trade secret]
	Thrombocytopenia	11.8%		[information protected as a trade secret]
	Hypertension	1.3%		[information protected as a trade secret]
	Pneumonia	16.4%		[information protected as a trade secret]

Limitations

The main limitation to the estimates is the lack of studies comparing the proposed technology with all comparators. Moreover, given the lack of studies directly comparing ISA+POM+DEX therapy with DAR+BOR+DEX therapy, as well as the impossibility of conducting an indirect comparison, there is insufficient justification for conducting incremental analysis for the above-mentioned comparison on the basis of a naive comparison.

Furthermore, the following aspects affect the uncertainty of the results presented:

- As the follow-up of patients enrolled in the ICARIA-MM clinical study was not completed, it was necessary to predict progression-free survival (PFS) curves, PFS during treatment, time to treatment discontinuation (TTD) and overall survival (OS) by in the model, particularly for overall survival, are associated with significant uncertainty that can have a significant impact adjusting parametric survival distributions to source data to determine long-term survival.

[information protected as a trade secret] on the cost-effectiveness estimates for Sarclisa;

- [information protected as a trade secret]; therefore, overall survival for the DAR+BOR+DEX arm was estimated with the use of the results of a publication proving that PFS is a reliable predictor for OS in multiple myeloma (Felix 2013).

Agency's own calculations

Given the lack of statistically significant results for the comparison of ISA+POM+DEX vs. POM+DEX, which is the basis of applicant's economic model, as well as the lack of studies directly comparing the assessed therapy with DAR+BOR+DEX and KAR+DEX regimens, and the impossibility of conducting an indirect comparison, it was decided to present a list of the costs of all therapies. Annual cost of using the regimens in 1 patient:

- ISA+POM+DEX – [information protected as a trade secret];
- POM+DEX - approx. PLN 146,000
- DAR+BOR+DEX - approx. PLN 317,000
- KAR+DEX - approx. PLN 288,000.

Indication whether the circumstances referred to in Art. 13 sec. 3 of the Act of 12 May 2011 on the reimbursement of drugs, foodstuffs for particular nutritional uses and medical devices (Dz. U. /Journal of Laws/ of 2021, item 523 as amended) do arise.

If the applicant's clinical analysis does not include randomised clinical trials proving the superiority of the drug over health technologies already reimbursed, the official selling price of the drug must be calculated so that the cost of the drug to be reimbursed is not higher than the cost of the health technology with the most favourable cost–effectiveness ratio.

The applicant submitted the randomised trial proving the superiority of ISA+POM+DEX over POM+DEX, so the circumstances described in Art. 13 of the Act on Reimbursement do not arise.

Assessment of the impact on the healthcare system, including the budget impact

Healthcare system impact assessment has two major parts.

First, the analysis of the impact on the payer's budget allows estimating the potential expenses associated with public reimbursement of the new therapy.

Estimates of the expenses associated with the new therapy (the "tomorrow" scenario) are compared to how much is currently spent on treating the health problem (the "today" scenario). On this basis, it is possible to assess whether a new therapy will require more resources allocated to the treatment of the given health problem or whether it will result in savings in the payer's budget.

The budget impact assessment makes it possible to establish whether the payer has adequate resources to fund a particular technology.

Healthcare system impact assessment in the second part answers the question of how the decision on the reimbursement of a new therapy may affect the organisation of the provision of services (particularly in terms of adaptation to the requirements of the implementation of the new therapy) and the availability of other healthcare services.

Budget impact analysis (BIA) in the case of a positive reimbursement decision for Sarclisa (isatuximab) for the treatment of adult patients with relapsed/refractory multiple myeloma (RRMM), [information protected as a trade secret] was conducted over a 3-year time horizon from the public payer perspective and from the joint perspective (public payer + patient). Due to the marginal cost on the patient side, the estimate from the joint perspective differs slightly from the patient perspective.

The following cost categories were included in the analysis:

- costs of active substances,

- costs of administering drugs,
- costs of monitoring therapy,
- costs of adverse event treatment,

[information protected as a trade secret]

According to the applicant's estimates, in the event of reimbursing Sarclisa as proposed in the application, the expenditure from the payer perspective

[information protected as a trade secret]:

Limitations

The uncertainty of the presented estimates is affected by the following aspects:

[information protected as a trade secret]

- A relatively high number of analysis parameters were estimated based on the opinions of clinical experts. However, this approach was necessary as no reliable data presenting Polish clinical practice [information protected as a trade secret] for treating multiple myeloma treatment are published.

Comments on the proposed risk-sharing scheme

[information protected as a trade secret]

Comments on the drug programme

It seems justified to include isatuximab in the already existing B.54 drug programme "Treatment of patients with refractory/relapsed multiple myeloma (ICD10 C90.0)", in which other drug health technologies reimbursed for the treatment of RRMM are available, including therapies indicated as the comparators.

Discussion on the solutions proposed in the rationalisation analysis

The subject of the rationalisation analysis is the identification of a mechanism, the introduction of which will result in the release of public funds in an amount corresponding to at least the increase in costs resulting from a positive decision on the reimbursement of the health technology covered in this recommendation.

The rationalisation analysis is submitted if the budget impact analysis for the entity responsible for funding indicates an increase in reimbursement costs.

As part of the rationalisation analysis, the applicant proposed a solution involving the reimbursement of the first reimbursable equivalent in a given indication due to the expiry of patent protection of the original drug and/or the current registration of equivalents at EMA (i.e. generic products). Implications of the implementation of the proposed savings solution in the following limit groups were presented:

- 1105.0, Fingolimod
- 1059.0, Dazatynib
- 1079.0, Sunitynib
- 1057.0, Cetuximab

Applying the above solution will generate approximately PLN 57 million in savings annually. Cleared funds will cover the estimated costs of funding Sarclisa to be incurred each year by the public payer.

Overview of recommendations in relation to the assessed technology

Ten clinical guidelines relating to the management of relapsed/refractory multiple myeloma were identified:

- Polish Myeloma Group (PGSz) 2021;
- Polish Society of Clinical Oncology (PTOK) 2020;
- National Comprehensive Cancer Network (NCCN) 2021;
- National Institute for Health and Care Excellence (NICE) 2021;
- European Hematology Association, European Society for Medical Oncology (EHA-ESMO) 2021;
- International Myeloma Working Group (IMWG) 2021;
- National Cancer Institute (NCI) 2021;
- Mayo Stratification 2020;
- Medical Scientific Advisory Group (MSAG) 2019;
- American Society of Clinical Oncology (ASCO) 2019.

The guidelines found do not present a uniform standard of procedures. All guidelines indicate that the choice of treatment depends on a number of factors and requires individual patient approach.

Both Polish and foreign guidelines emphasise the efficacy of regimens based on the combination of pomalidomide with dexamtezone (in the form of two- and three-drug therapies). The Polish Myeloma Group 2021 guidelines indicate that ISA+POM+DEX can be used in patients with recurrence/progression after two lines of treatment, which is in line with the NCCN 2021 guidelines, in which the ISA+POM+DEX regimen is recommended in patients who have received at least 2 prior therapies, including lenalidomide and a proteasome inhibitor. In contrast, according to the NICE 2021 guidelines, this regimen is indicated in fourth-line treatment, i.e. patients with RRMM who have previously received three lines of treatment, including lenalidomide and a proteasome inhibitor, and who have experienced disease progression after the last treatment. ISA+POM+DEX therapy is recommended by EHA-ESMO 2021 for the treatment of second and subsequent relapses (≥3 lines of RRMM treatment), for patients refractory to LEN and BOR as well as patients refractory to LEN and sensitive to a proteasome inhibitor.

Five reimbursement recommendations were found:

- 4 positive:
    - NICE 2020 - recommendation refers to funding under thr Cancer Drugs Funds programme, not for routine use in the NHS;
    - Haute Autorité de Santé (HAS) 2021;
    - Scottish Medicines Consortium (SMC) 2021;
    - Gemeinsamer Bundesausschuss (G-BA) 2021;
- 1 conditionally positive:
    - Canadian Agency for Drugs and Technologies in Health (CADTH) 2021 – pan-Canadian Oncology Drug Review Expert Review Committee (pERC) conditionally recommends the reimbursement of ISA+POM+DEX for the treatment of patients with relapsed/refractory multiple myeloma who have received at least two lines of treatment including lenalidomide and a proteasome inhibitor when the following conditions are met:
        - cost-effectiveness improvement to reach an acceptable level;

- feasibility of the budget impact adopted. [information protected as a trade secret]

Legal basis for the recommendation

The recommendation was prepared based on the order of the Minister of Health of 9 September 2021 (ref. no.: PLR.4500.645.2021.12.APR) regarding the preparation of the President's recommendation on the reimbursement of Sarclisa (isatuximab) under the drug programme: "Treatment of patients with relapsed/refractory multiple myeloma (ICD-10 C90.0) with isatuximab" pursuant to Art. 35 sec. 1 of the Act of 12 May 2011 on the reimbursement of drugs, foodstuffs intended for particular nutritional uses and medical devices (Dz. U. /Journal of Laws/ of 2021, item 523 as amended), having obtained Position of the Transparency Council No. 131/2021 of 29 November 2021 on the assessment of Sarclisa (isatuximab) under the drug programme "Treatment of patients with relapsed/refractory multiple myeloma (ICD-10 C90.0) with isatuxima

References

1. Position of the Transparency Council No. 131/2021 of 29 November 2021 on the assessment of Sarclisa (isatuximab) under the drug programme "Treatment of patients with relapsed/refractory multiple myeloma (ICD-10 C90.0) with isatuximab"
2. Report No. OT.4231.43.2021. Application for the reimbursement of Sarclisa (isatuximab) under the drug programme: "Treatment of patients with refractory/relapsed multiple myeloma (ICD- 10 C90.0) with isatuximab". Verification analysis