HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
18 NOVEMBER 2020

The legally binding text is the original French opinion version

isatuximab
SARCLISA 20 mg/ml concentrate for solution for infusion

First assessment

Key points

Favourable opinion for reimbursement in combination with pomalidomide and dexamethasone, for the treatment of adult patients with relapsed and refractory multiple myeloma (MM) who have received at least two prior therapies including lenalidomide and a proteasome inhibitor (PI) and have demonstrated disease progression on the last therapy.

What therapeutic improvement?

Therapeutic improvement compared to the pomalidomide plus dexamethasone combination.

Role in the care pathway?

From the second relapse, in patients who have already been treated with VELCADE (bortezomib) and REVLIMID (lenalidomide), IMNOVID (pomalidomide) has an MA in combination with dexamethasone. However, given the evolution of the care pathway in multiple myeloma, with new medicinal products having been added to the therapeutic arsenal in earlier treatment lines, the role of IMNOVID (pomalidomide) in combination with dexamethasone has become more limited. In addition, earlier use of IMNOVID (pomalidomide) from the second line of treatment in combination with bortezomib and dexamethasone is likely to substantially reduce the benefit of pomalidomide-dexamethasone dual therapy in subsequent treatment lines. FARYDAK (panobinostat) combined with bortezomib and dexamethasone, represents a last-resort treatment option for patients with relapsed and/or refractory myeloma, having previously received two lines of treatment, including bortezomib and an immunomodulator. Finally, DARZALEX (daratumumab) is also an option in patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent; however, its earlier use (currently possible from first-line therapy) in the context of combination with a proteasome inhibitor (PI) or an IMiD, substantially reduces the benefit of this monotherapy in subsequent treatment lines.

Role of the medicinal product in the care pathway

Given the demonstrated superiority of the Isa-Pd protocol combining SARCLISA (isatuximab) with IMNOVID (pomalidomide) plus dexamethasone (Pd) until progression compared to the Pd combination in terms of progression-free survival and pending the final results in terms of overall survival, the Isa-Pd combination is the treatment option to be favoured over the Pd combination in adult patients with relapsed and refractory multiple myeloma (MM) who have received at least two prior therapies including lenalidomide and a proteasome inhibitor (PI) and have demonstrated disease progression on the last therapy.

However, the Committee regrets that the available study does not enable definition of the optimal treatment sequence between the use of a triple combination of an anti-CD38 antibody along with pomalidomide and dexamethasone from the outset and the sequential use of pomalidomide plus dexamethasone and an anti-CD38 antibody from the second relapse. In fact, DARZALEX (daratumumab), as monotherapy, is still an option in patients having received an IP and an immunomodulatory agent.

Given the similar mechanism of action, targeting the CD38 receptor, and the non-inclusion in the ICARIA-MM study of patients refractory to an anti-CD38 antibody received in a prior treatment line, the Committee does not recommend the use of SARCLISA (isatuximab) in patients refractory to an anti-CD38 antibody. In addition, no robust data supports the value of re-using SARCLISA (isatuximab) in patients previously treated with an anti-CD38 antibody but not refractory to an anti-CD38 antibody.

The Committee wishes to draw the attention of prescribers to the need for specific vigilance with respect to the risk of immune deficiency induced by the long-term administration of SARCLISA (isatuximab), as it did for DARZALEX (daratumumab). An excess of sometimes severe infectious episodes, particularly respiratory tract infection (including with opportunistic microorganisms), was observed in the study arm receiving SARCLISA (isatuximab). The benefit/risk ratio of the long-term continuation of SARCLISA (isatuximab) injections must also be reassessed regularly, particularly in the event of an infectious episode.

COMMITTEE'S CONCLUSIONS

Clinical benefit

◗ Multiple myeloma is a serious blood disease that is life-threatening.

◗ SARCLISA (isatuximab) is a specific curative treatment for multiple myeloma, targeting the CD38 receptor. It is the second representative of the anti-CD38 monoclonal antibody class of drugs, which also includes DARZALEX (daratumumab).

◗ Its efficacy/adverse effects ratio is high considering the data available, with demonstration of a benefit in terms of progression-free survival of SARCLISA (isatuximab) plus pomalidomide and dexamethasone (Isa-Pd) compared to Pd (absolute difference of + 5 months), with no demonstration to date of a benefit in terms of overall survival, pending a final analysis scheduled in the protocol.

◗ There are alternatives in patients who have received at least two prior therapies including lenalidomide and a proteasome inhibitor (PI) and have demonstrated disease progression on the last therapy, in particular IMNOVID (pomalidomide) in combination with dexamethasone, as well as DARZALEX (daratumumab) as monotherapy, and supportive care.

◗ Given the superiority of the Isa-Pd protocol combining SARCLISA (isatuximab) with IMNOVID (pomalidomide) plus dexamethasone (Pd) until progression, demonstrated compared to the Pd combination in terms of progression-free survival and pending final results in terms of overall survival, the Isa-Pd combination is the treatment option to be favoured over the Pd combination in adult patients with relapsed and refractory multiple myeloma (MM) who have received at least two prior therapies including lenalidomide and a proteasome inhibitor (PI) and have demonstrated disease progression on the last therapy (see chapter 08).

Public health impact

Considering:

- the seriousness of the disease, particularly from the second relapse,
- its incidence,
- the partially met medical need at this stage of the disease,
- the absence of an expected additional impact on the organisation of care compared to the protocols used from the second relapse (which may include intravenous treatments) despite the fact that this medicinal product is administered by intravenous infusion every 2 weeks,
- the lack of response to the identified need (no additional impact on morbidity and mortality or on quality of life demonstrated to date),

SARCLISA (isatuximab) in combination with pomalidomide and dexamethasone is unlikely to have an additional impact on public health.

Given all these elements, the Committee deems that the clinical benefit of SARCLISA (isatuximab) is substantial in the MA indication.

The Committee issues a favourable opinion for inclusion in the hospital formulary list of reimbursed proprietary medicinal products approved for use in the MA indication and dosages.

Clinical Added Value

Considering:

- **demonstration of the superiority of the addition of SARCLISA (isatuximab) to IMNOVID (pomalidomide) plus dexamethasone (Isa-Pd protocol) compared to the IMNOVID (pomalidomide) plus dexamethasone (Pd) combination, in terms of progression-free survival (primary endpoint), with a median improvement of + 5 months (HR = 0.596; CI95% [0.436 - 0.814]), after a median follow-up of 11.6 months, deemed to be clinically relevant,**
- **and the safety profile, consistent with the known profile for anti-CD38 antibodies, marked by infections and febrile neutropenia, in particular,**

but:

- **the absence of any demonstration to date of a benefit in terms of overall survival (ranked secondary endpoint) in two interim analyses, pending the final overall survival analysis,**
- **and the lack of demonstrated impact on quality of life,**

the Committee considers that SARCLISA (isatuximab) in combination with IMNOVID (pomalidomide) plus dexamethasone (Isa-Pd protocol), provides a minor clinical added value (CAV IV) compared to the IMNOVID (pomalidomide) plus dexamethasone combination in the treatment of adult patients with relapsed and refractory multiple myeloma (MM) who have received at least two prior therapies including lenalidomide and a proteasome inhibitor (PI) and have demonstrated disease progression on the last therapy.