Multiple myeloma
Sector: Hospital

HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
20 OCTOBER 2021

The legally binding text is the original French opinion version

daratumumab
DARZALEX 1,800 mg solution for injection

New indication

Key points

Favourable opinion for reimbursement in combination with pomalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received one prior therapy containing a proteasome inhibitor and lenalidomide and were lenalidomide-refractory, or who have received at least two prior therapies that included lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or after the last therapy

What therapeutic improvement?

No clinical added value in the therapeutic strategy as second-line treatment in patients who have received one prior therapy containing a proteasome inhibitor and lenalidomide and were lenalidomide-refractory.

Therapeutic improvement compared to the pomalidomide plus dexamethasone combination as third and later-line treatment in patients who have received at least two prior therapies that included lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or after the last therapy.

Role in the care pathway?

Over the last decade, numerous medicinal products have been added to the therapeutic arsenal for the second and later-line treatment of multiple myeloma, such as: daratumumab (DARZALEX), ixazomib (NINLARO), carfilzomib (KYPROLIS) or pomalidomide (IMNOVID), always in combination. At the first relapse, the choice between these treatments should take into account whether or not the patient is refractory to lenalidomide and prior exposure to daratumumab in first-line therapy, as well as the level of evidence and the toxicity profile.

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 place 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 du combination 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 multiple myeloma, having previously received two lines of treatment, including bortezomib and an immunomodulator. 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 available from first-line therapy) in combination with a proteasome inhibitor (PI) or an IMiD, substantially reduces the benefit of this monotherapy in subsequent treatment lines. Recently, SARCLISA (isatuximab) has been added to the care pathway, in combination with pomalidomide and dexamethasone in patients having received at least two prior treatments including lenalidomide and a PI.

Otherwise, in heavily pretreated patients in the very advanced stages of the disease, in particular those whose disease is refractory to at least one PI, one immunomodulatory agent, and an anti-CD38 monoclonal antibody such as daratumumab (DARZALEX), until recently there were no validated treatment options following the failure of an anti-CD38 antibody and patients were usually in a situation where all the treatment options had been exhausted. BLENREP (belantamab mafodotin) was recently added to the care pathway as monotherapy for the treatment of multiple myeloma in adult patients, who have received at least four prior therapies and whose disease is refractory to at least one proteasome inhibitor, one immunomodulatory agent, and an anti-CD38 monoclonal antibody, and who have demonstrated disease progression on the last therapy.

Role of the medicinal product in the care pathway

Given the demonstrated superiority of the DPd protocol combining DARZALEX (daratumumab) with IMNOVID (pomalidomide) and dexamethasone, administered until progression, compared to the Pd (pomalidomide + dexamethasone) combination, a clinically relevant comparator only from the third line of treatment, in terms of progression-free survival and pending the final results in terms of overall survival, the DPd combination is a 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 that included lenalidomide and a proteasome inhibitor (PI) and have demonstrated disease progression on the last therapy, i.e. as third and later-line therapy. As second-line therapy, in patients who have received prior therapy including lenalidomide and a PI and were lenalidomide-refractory, the DPd protocol is a treatment option.

Its place compared to the other protocols available at this stage in the care pathway, in particular the protocol combining SARCLISA (isatuximab) and Pd, cannot be determined in the absence of robust comparative data.

Given the similar mechanism of action, targeting the CD38 receptor, and the non-inclusion in the APOLLO study of patients refractory to an anti-CD38 antibody received in a prior treatment line, the Committee does not recommend the use of DARZALEX (daratumumab) in patients refractory to an anti-CD38 antibody. In addition, no robust data supports the value of re-using DARZALEX (daratumumab) in previously treated patients. Insofar as DARZALEX (daratumumab) has several marketing authorisations for the first and second-line treatment of myeloma, the Committee regrets that there are no ongoing studies tof define the optimal treatment sequence and encourages the implementation of a study of this type.

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 DARZALEX (daratumumab). An excess of sometimes severe infectious episodes, particularly respiratory tract infection (including with opportunistic microorganisms), has been observed in patients treated with DARZALEX (daratumumab) in the context of clinical studies, and is also reported in the literature and according to expert opinion. The benefit/risk ratio of the long-term continuation of DARZALEX (daratumumab) injections must therefore be reassessed regularly, before each administration, particularly in the event of an infectious episode.

COMMITTEE'S CONCLUSIONS

Considering all of this information and further to debate and voting, the Committee considers:

Clinical benefit

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

◗ DARZALEX (daratumumab) is a specific curative treatment for multiple myeloma.

◗ The efficacy/adverse effects ratio of DARZALEX (daratumumab) in combination with IMNOVID (pomalidomide) and dexamethasone (DPd protocol) is high considering the data available, with demonstration of a benefit in terms of progression-free survival compared to the Pd protocol (pomalidomide and dexamethasone), with no demonstration to date of a benefit in terms of overall survival, pending a final analysis pre-specified in the protocol.

◗ There are medicinal alternatives (see section 05 of this opinion).

◗ The DPd combination is a 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, i.e. as third and later-line therapy. As second-line therapy, in patients who have received prior therapy including lenalidomide and a PI and were lenalidomide-refractory, the DPd protocol is a treatment option (see section 09 of the present opinion).

Public health impact

Considering:

- the seriousness of multiple myeloma,
- its incidence,
- the partially met medical need at this stage of the disease,
- the expected impact on the organisation of care given the short administration time of the SC route compared to the IV route, but which may fluctuate depending on the combined protocols, and which has nonetheless not been demonstrated due to a lack of data,
- the lack of response to the identified need (no additional impact on morbidity and mortality or on quality of life demonstrated to date),

DARZALEX (daratumumab) subcutaneous, in combination with pomalidomide and dexamethasone, is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of DARZALEX (daratumumab) 1,800 mg solution for injection is SUBSTANTIAL in the indication "in combination with pomalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received one prior therapy containing a proteasome inhibitor and lenalidomide and were lenalidomide-refractory, or who have received at least two prior therapies that included lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or after the last therapy".

The Committee issues a favourable opinion for inclusion in the hospital formulary list of reimbursed proprietary medicinal products approved for use in the indication "in combination with pomalidomide and dexamethasone for the treatment of adult patients with multiple myeloma who have received one prior therapy containing a proteasome inhibitor and lenalidomide and were lenalidomide-refractory, or who have received at least two prior therapies that included lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or after the last therapy" and at the MA dosages.

Clinical Added Value

Considering:

- **the demonstration of the superiority of the addition of DARZALEX (daratumumab) to IMNOVID (pomalidomide) and dexamethasone (DPd protocol) compared to the IMNOVID (pomalidomide) and dexamethasone combination (Pd protocol), in the APOLLO study conducted in patients with multiple myeloma from the second line of treatment (89% of whom in third or later-line treatment), in terms of progression-free survival (primary endpoint), with a median increase deemed to be clinically relevant of + 5.5 months (HR = 0.63; $CI_{95\%}$ [0.47; 0.85]; p = 0.0018) after a median follow-up of 16.9 months,**
- **and the safety profile of this combination, consistent with that observed in the other indications of daratumumab and with other anti-CD38 antibodies, marked in particular by infections and febrile neutropenia,**

and despite:

- **the non-optimal nature in second-line therapy of the comparator used in the APOLLO study (Pd protocol), indicated in patients who have received two prior therapies containing lenalidomide and a proteasome inhibitor;**
- **the absence of any demonstration to date of a benefit in terms of overall survival (key secondary endpoint) in an intermediate analysis;**
- **and the absence of robust data on quality of life,**

the Committee considers that DARZALEX (daratumumab) in combination with IMNOVID (pomalidomide) plus dexamethasone (DPd protocol), provides a minor clinical added value (CAV IV) compared to the IMNOVID (pomalidomide) and dexamethasone combination (Pd protocol) 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 and have demonstrated disease progression on the last therapy.
In the absence of comparison with clinically relevant comparators used as second-line therapy, the Committee considers that DARZALEX (daratumumab) in combination with IMNOVID (pomalidomide) and dexamethasone (DPd protocol), provides no clinical added value (CAV V) in the care pathway for adult patients with relapsed and refractory multiple myeloma who have received one prior therapy containing a proteasome inhibitor and lenalidomide and were lenalidomide-refractory.