HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
22 APRIL 2020

The legally binding text is the original French opinion version

daratumumab
DARZALEX 20 mg/mL concentrate for solution for infusion

New indication

Key points

Favourable opinion for reimbursement in combination with lenalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.

What therapeutic improvement?

Therapeutic improvement compared to the Rd protocol combining lenalidomide and dexamethasone.

Role in the care pathway?

The current classification for myeloma, developed on the basis of International Myeloma Working Group criteria, divides patients into two categories: asymptomatic patients for whom simple monitoring is generally recommended, and symptomatic patients requiring appropriate management adapted to age and comorbidities.

In symptomatic patients, first-line treatment is dependent on whether the subject is eligible or not for intensive chemotherapy combined with autologous peripheral blood stem cell transplantation.

When patients are not eligible for a transplant (in particular, due to their age, their comorbidities and/or their general condition), the therapeutic strategy is based on chemotherapy:

- either with bortezomib (VELCADE), melphalan and prednisone (VMP protocol) for a fixed duration, potentially combined with the anti-CD38 monoclonal antibody DARZALEX (daratumumab),
- or with lenalidomide (REVLIMID) combined with low doses of dexamethasone (Rd protocol) until disease progression.

Role of the medicinal product in the care pathway

Given the superiority of the DARZALEX (daratumumab) protocol, administered in combination with lenalidomide and dexamethasone (Rd protocol) until disease progression, demonstrated in comparison with the Rd protocol, the D-Rd protocol is a first-line treatment for patients with previously untreated multiple myeloma who are ineligible for autologous stem cell transplant.

In patients ineligible for autologous stem cell transplant, two different protocols based on daratumumab have an MA: D-VMP (combination with bortezomib, melphalan and prednisone) and now D-Rd. To date, only the D-VMP protocol has demonstrated a benefit in terms of overall survival compared to the VMP protocol. No comparative data are available or scheduled to assess these two protocols based on daratumumab. The choice should therefore be made taking into account the level of evidence of the demonstration, the profile and preferences of patients, the characteristics of the disease and its potential complications and the safety of the protocols.

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), is observed in the study arm including DARZALEX (daratumumab), and is also reported in the literature and according to expert opinion.

COMMITTEE'S CONCLUSIONS

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 lenalidomide and dexamethasone is high.
◗ There are medicinal alternatives (see chapter 05. Clinically relevant comparators).
◗ This is a first-line treatment in adult patients who are ineligible for autologous stem cell transplant in the context of its administration in combination with lenalidomide and dexamethasone until disease progression (see chapter 09 Role in the care pathway).

Public health impact
Considering:
- the seriousness of multiple myeloma,
- its incidence,
- the partially met medical need in the first-line treatment of patients ineligible for autologous stem cell transplant,
- the impact of DARZALEX (daratumumab) on progression-free survival in the context of its administration in combination with the Rd protocol, without any demonstrated benefit in terms of overall survival to date and hence the partial response to the medical need,
- the absence of demonstration of the impact on quality of life, an exploratory endpoint in the study,
- the dosage regimen for DARZALEX (daratumumab) requiring weekly IV infusion, every 2 weeks then every 4 weeks until progression, and the lack of evidence to support an improvement in the care pathway,

DARZALEX (daratumumab) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of DARZALEX (daratumumab) is substantial in the indication "in combination with lenalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant".

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 lenalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant" and at the MA dosages.

Clinical Added Value

Considering:
- **demonstration of the superiority of the addition of DARZALEX (daratumumab) to lenalidomide and dexamethasone (D-Rd protocol) compared to the Rd protocol, administered until progression, following a median follow-up of 28 months, in terms of progression-free survival (HR = 0.56 [$CI_{95\%}$: 0.43 – 0.73], median improvement not quantifiable at present),**
- **results obtained with respect to undetectable minimal residual disease (ranked secondary endpoint) with D-Rd compared to Rd (24% versus 7%) although it has not been demonstrated to date that MRD is a substitution criterion for overall survival,**

but in view of :
- **the absence of any demonstrated improvement in overall survival on the date of the analysis,**
- **the lack of demonstrated impact on quality of life,**

- **and the higher frequency of grade 3-4 adverse events with the D-Rd compared to the Rd protocol (90% versus 83%) having mainly concerned neutropenia (50% versus 35%) and pneumonia (14% versus 8%),**

the Committee considers that, pending results relating to overall survival, DARZALEX (daratumumab) in combination with lenalidomide and dexamethasone (Rd protocol), provides a minor clinical added value (CAV IV) compared to the Rd protocol in the treatment of adult patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant.