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 for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible for autologous stem cell transplant, in combination with bortezomib, thalidomide and dexamethasone.

What therapeutic improvement?

Therapeutic improvement compared to the VTD protocol combining bortezomib, thalidomide 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.

In patients eligible for intensive chemotherapy, the guidelines recommend induction treatment with four triple combination cycles, followed by an autologous stem cell transplant. The recommended treatments in this context are:
- the VTd protocol (bortezomib + thalidomide + dexamethasone),
- the VRd protocol (bortezomib + lenalidomide + dexamethasone), although this is off-label.

Post-ASCT consolidation treatment, with the same medicinal products used as induction treatment, may be proposed.

Role of the medicinal product in the care pathway

Given the demonstrated superiority of the D-VTd protocol combining DARZALEX (daratumumab) with bortezomib, thalidomide and dexamethasone in terms of progression-free survival compared to the VTd protocol, the D-VTd protocol is a first-line treatment for induction (16 weeks) and consolidation (8 weeks) in patients with previously untreated multiple myeloma who are eligible for autologous stem cell transplant.

Given the absence of comparative data between the two induction and consolidation protocols, the role of the D-VTd protocol compared to the VRd protocol (bortezomib, lenalidomide, dexamethasone), is not known.

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 bortezomib, thalidomide 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 eligible for autologous stem cell transplant, in the context of its administration as induction and consolidation treatment, in combination with bortezomib, thalidomide and dexamethasone (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 eligible for autologous stem cell transplant,
- the partial response to the identified medical need in terms of progression-free survival, without any demonstrated impact on mortality or quality of life at this stage,
- the dosage regimen for DARZALEX (daratumumab) requiring weekly IV infusion for 8 weeks then every 2 weeks until the end of consolidation, 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 bortezomib, thalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible 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 bortezomib, thalidomide and dexamethasone for the treatment of adult patients with newly diagnosed multiple myeloma who are eligible 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 bortezomib, thalidomide and dexamethasone (D-VTd protocol) compared to the VTd protocol administered alone, following 4 induction cycles followed by 2 consolidation cycles, in terms of progression-free survival (HR = 0.47, $CI_{95\%}$ [0.33 – 0.67], median increase not quantifiable to date),**
- **results obtained with respect to undetectable minimal residual disease (ranked secondary endpoint) with D-VTd compared to VTd (64% versus 44%) 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 in the group treated with the D-VTd protocol, in particular severe neutropenia (28% versus 15%), severe lymphopenia (17% versus 10%) and serious pneumonia (3.5% versus 1.7%),**

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