OPINION ON MEDICINAL PRODUCTS

daratumumab

DARZALEX 20 mg/ml and 1 800 mg,

concentrate for solution for infusion and solution for injection

Reassessment

Adopted by the Transparency Committee on 7 December 2022

SUMMARY

The legally binding text is the original French opinion version

Key points

Maintain favorable opinion on the reimbursement of DARZALEX (daratumumab) in combination with lenalidomide and dexamethasone, or bortezomib anddexamethasone, for the treatment of adult patientswith multiple myeloma who have received at least one prior therapy.

Therapeutic improvement?

Therapeutic improvement compared to the Vd [VELCADE (bortezomib), dexamethasone] and Rd [REVLIMID (lenalidomide), dexamethasone] combination.

Role in therapeutic strategy?

The current treatment of refractory or relapsed MM generally involves combinations of medicinal products of different and complementary mechanisms of action, as bi- or tritherapy including immunomodulatory agents (IMiDs) and/or proteasome inhibitors (PIs) and/or monoclonal antibodies, associated with dexamethasone.

The choice of relapse treatments accounts for the prior first-line treatment and the remaining options available, as well as age, duration of the first remission, and circumstances of the relapse, peripheral stem cell (PSC) availability, general health state, and comorbidities.

Role of DARZALEX (daratumumab) in the therapeutic strategy:

DARZALEX as tritherapy, in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, is a treatment option for multiple myeloma in adult patients having received at least one previous line treatment.

The choice between the different therapeutic options available for the treatment of multiple myeloma from the second-line treatment must take account particularly of the refractory or non-refractory status to lenalidomide and previous exposure to daratumumab as a first-line treatment, the patient's characteristics (age, comorbidities), as well as the level of evidence and the toxicity profile.

The Committee points out that the role of DARZALEX (daratumumab), now recommended in the first line of treatment, regardless of autologous peripheral blood stem cell transplantation eligibility status, is decreasing in the relapse setting and its benefit is considerably reduced in subsequent treatments. However, there are still patients who have not received DARZALEX (daratumumab) and are likely to receive it in a subsequent line.

The Committee would also like to point out the lack of direct comparison to KYPROLIS (carfilzomib) in association with Rd, meaning that it is not possible to place DARZALEX (daratumumab) versus to this alternative strategy in a context where there is also evidence of an improvement of overall survival with this regimen.

Committee's conclusions

Clinical Benefit

- Multiple myeloma is a blood disorder of almost always fatal outcome with a short median survival (3 to 5 years).
- The proprietary medicinal product DARZALEX (daratumumab) is a specific curative multiple myeloma treatment.
- The efficacy/adverse effect ratio is significant.
- Alternatives are available (see section on clinically relevant comparators).
- DARZALEX (daratumumab) as tritherapy, in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, is a treatment option for multiple myeloma in adult patients having received at least one previous lone of treatment. The choice between the different therapeutic options available for the treatment of multiple myeloma from the second-line treatment must take account particularly of the refractory or non-refractory status to lenalidomide and previous exposure to daratumumab as a first-line treatment, the patient's characteristics (age, comorbidities), as well as the level of evidence and the toxicity profile. The Committee points out that the role of DARZALEX (daratumumab), now recommended in the first line of treatment, regardless of autologous peripheral blood stem cell transplantation eligibility status, is decreasing in the relapse setting and its benefit is considerably reduced in subsequent treatments. However, there are still patients who have not received DARZALEX (daratumumab) and are likely to receive it in a subsequent line. The Committee would also like to point out the lack of direct comparison to KYPROLIS (carfilzomib) in association with Rd, meaning that it is not possible to place DARZALEX (daratumumab) versus to this alternative strategy in a context where there is also evidence of an improvement of overall survival with this regimen.

Public health benefit

Considering:

- the severity of the disease and its prevalence/ incidence,
- the partially covered medical need,
- the partial response to the identified need taking into account of:
  - the evidence of an improvement of progression-free survival with the addition of daratumumab to the Vd or Rd regimens,
  - the new overall survival data demonstrating an impact on mortality and given that a cross-over was possible for the patients in the comparator group (Vd or Rd regimen) who might receive daratumumab as monotherapy and subsequent treatments administered post-progression.
  - the lack of robust data on quality of life supporting an improvement of quality of life among treated patients,
- the lack of evidence of an impact on delivery of care,

DARZALEX (daratumumab) is not likely to have an additional impact on public health.

Considering all these elements, the Committee considers that the clinical added value of DARZALEX (daratumumab) remains significant in the marketing authorisation indication covered by this reassessment ""in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy."

The Committee gives a favorable opinion to the maintenance of the registration on the list of specialties approved for use in the community (hospital drug list) in the MA indication under reassessment and at the marketing authorization doses.

Clinical Added Value

Considering:

- **the evidence of superiority of the tritherapy associating DARZALEX (daratumumab), with lenalidomide and dexamethasone, or with bortezomib and dexamethasone, compared to the combinations of lenalidomide and dexamethasone (Rd), or bortezomib and dexamethasone in terms of progression-free survival in the CASTOR and POLLUX studies,**
- **the superiority now demonstrated over the combination of lenalidomide and dexamethasone or bortezomib and dexamethasone in terms of overall survival with an absolute gain of 11.1 months in the CASTOR study and 15.8 months in the POLLUX study,**

and despite:

- **the long-term safety profile confirming the higher frequency of grade 3-4 adverse events, in the daratumumab groups, and marked by haematological and infectious type AEs,**
- **the lack of robust data on quality of life,**

the Transparency Committee considers that DARZALEX (daratumumab) in association with lenalidomide and dexamethasone, or with bortezomib and dexamethasone, provides moderate clinical added value (CAV III) compared to each of these bitherapies used alone for the treatment of multiple myeloma, for adult patients, after at least one previous line of treatment.