HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
16 FEBRUARY 2022

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 newly diagnosed systemic light chain (AL) amyloidosis.

What therapeutic improvement?

Therapeutic improvement compared to the bortezomib/cyclophosphamide/dexamethasone combination.

Role in the care pathway?

The main objective of treatment of systemic AL amyloidosis is to slow down deterioration of the organs involved and improve overall survival. A reduction in levels of monoclonal protein (light chains) responsible for the formation of amyloid deposits and acting on the body's deposit formation-elimination balance is an intermediate endpoint of treatment.

The current care pathway is based on chemotherapies aimed at eliminating the plasma B cell clone responsible for the secretion of the amyloidogenic light chains, rather than the deposits themselves. Since this cell population is of plasma cell origin in 90% of cases, multiple myeloma treatments are recommended and used to treat systemic AL amyloidosis.

Treatments make it possible to eliminate the production of the pathological precursor of amyloid deposits, but reducing organ deterioration is an objective that it is difficult to achieve since the amyloid deposition process is often irreversible and diagnosis of the disease is often delayed. The management of systemic AL amyloidosis is a therapeutic emergency; effective treatment should be administered as soon as possible, before the development of irreversible damage.

The reduction in light chains is demonstrated by the achievement of at least a very good partial response (VGPR), defined as a difference between serum concentrations of pathogenic light chains and the other isotype (difference of free light chains, dFLC) of less than 40 mg/L.

Retrospective data have suggested that achieving a haematological response was associated with better long-term overall survival.

Hence non-response and achievement of a partial response (<VGPR) are considered to be suboptimal. If a patient still does not present at least a very good partial response after three cycles of initial treatment, it is recommended to change the treatment to prevent further organ injury.

In France, there are no official guidelines for the management of this disease; the treatment recommendations are based on expert consensus.

The introduction of bortezomib for the treatment of AL amyloidosis has led to response rates of over 80% being achieved; similarly, the substitution of prednisone by dexamethasone has increased the response rate from 30 to 60%. The currently recommended treatment in systemic AL amyloidosis is based on the bortezomib + cyclophosphamide + dexamethasone combination (VCd protocol) irrespective of the disease stage (expert opinion).

At present, there are no medicinal products with an MA in the treatment of systemic AL amyloidosis.

In the event of organ involvement, supportive treatments must not be overlooked (diuretics, elastic compression, nutritional support or even transplantation in certain situations).

Role of DARZALEX (daratumumab) in the care pathway:

Given the demonstration of the superiority of adding DARZALEX (daratumumab) to the VCd protocol including the bortezomib + cyclophosphamide + dexamethasone combination in terms of complete haematological response, and despite the absence of demonstration of a statistically significant difference for the risk of onset of a major organ deterioration progression-free survival (MOD-PFS) event, and the absence of robust results for overall survival, the DVCd protocol is currently the treatment to be favoured for adult patients with newly diagnosed systemic light chain (AL) amyloidosis.

The Committee recommends starting treatment with DARZALEX (daratumumab) in combination with bortezomib + cyclophosphamide + dexamethasone as soon as possible following diagnosis given the irreversible nature of organ deterioration once amyloid deposits become established.

COMMITTEE'S CONCLUSIONS

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

Clinical benefit

◗ Light chain (AL) amyloidosis is a rare and potentially fatal haematological disorder.

◗ The proprietary medicinal product DARZALEX (daratumumab) is a curative medicinal product.

◗ The efficacy/adverse effects ratio of DARZALEX (daratumumab) is high.

◗ There are therapeutic alternatives (see chapter 05).

◗ DARZALEX (daratumumab) in combination with bortezomib + cyclophosphamide + dexamethasone is the treatment to be favoured in this indication.

Public health impact

Considering:

- the seriousness of the disease and its rarity,
- the partially met medical need,
- the partial response provided by DARZALEX (daratumumab) to the identified need, in terms of:
    - the additional impact demonstrated only in terms of complete haematological response, but not in terms of organ involvement, in a context in which overall survival is exploratory,
    - the lack of impact on quality of life in the absence of robust data,
- the lack of demonstrated impact on the patient's care or life 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 treatment of adult patients with newly diagnosed systemic light chain (AL) amyloidosis, in combination with bortezomib + cyclophosphamide + dexamethasone.

The Committee issues a favourable opinion for inclusion in the hospital formulary list of reimbursed proprietary medicinal products approved for use in the treatment of adult patients with newly diagnosed systemic light chain (AL) amyloidosis, in combination with bortezomib + cyclophosphamide + dexamethasone, and at the MA dosages.

Clinical Added Value

Considering:

- demonstration of the superiority of the addition of DARZALEX (daratumumab) to the VCd protocol including the bortezomib + cyclophosphamide + dexamethasone combination (corresponding to the DVCd protocol) in terms of complete haematological response (a relevant primary endpoint), compared to the bortezomib + cyclophosphamide + dexamethasone combination (VCd protocol) with 53% versus 18% respectively, i.e. an OR=5.13, 95% CI [3.22; 8.18], p<0.0001) in a phase 3, randomised open-label study having included newly diagnosed patients with at least one organ involved,

but in view of:

- the absence of demonstration of a statistically significant difference between the DVCd protocol and the VCd protocol for the risk of onset of a major organ deterioration progression-free survival (MOD-PFS) event (first ranked secondary endpoint),
- the absence of robust data for overall survival (second ranked secondary endpoint), with the ranked analysis having been stopped before this endpoint,
- the absence of robust data on quality of life, which was an exploratory endpoint,

the Committee considers that **DARZALEX (daratumumab), in combination with bortezomib + cyclophosphamide + dexamethasone, provides a minor clinical added value (CAV IV) compared to the bortezomib + cyclophosphamide + dexamethasone combination, in the treatment of adult patients with newly diagnosed systemic light chain (AL) amyloidosis.**