HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
20 APRIL 2022

The legally binding text is the original French opinion version

mepolizumab
NUCALA 100 mg powder for solution for injection, solution for injection in pre-filled syringe and solution for injection in pre-filled pen

New indication

Key points

Favourable opinion for reimbursement as an add-on treatment for adult patients with inadequately controlled lymphocytic or idiopathic hypereosinophilic syndrome.

Unfavourable opinion for reimbursement in the other MA situations.

What therapeutic improvement?

Therapeutic improvement in the management of inadequately controlled lymphocytic or idiopathic hypereosinophilic syndrome.

Role in the care pathway?

Hypereosinophilic syndromes (HES) are a group of rare diseases associated with tissue damage related to eosinophil infiltration, in which the clinical manifestations are heterogeneous and of variable severity. The main objectives of treatment are to reduce symptoms and control eosinophilia. It is also essential to prevent any adverse effects of the treatments used in order to ensure control of the disease and prevent long-term complications.

The therapeutic management should be adapted based on the severity of the disease and the type of HES:

- for reactional HES with an identified cause (iatrogenic, parasitic or cancer-related), management is specific and tailored to the aetiology;
- for F/P-positive chronic eosinophilic leukaemia clonal neoplastic HES, imatinib is the first-line treatment in patients with this rearrangement; for F/P-negative chronic eosinophilic leukaemia clonal neoplastic HES or MDS/MPD, imatinib or, in some cases, hydroxyurea may be used;
- for lymphocytic and idiopathic HES, the management is as follows:
  - as first-line treatment: corticosteroids are generally administered at moderate or high doses (0.5 to 1 mg/kg of prednisone equivalent); corticosteroids usually enable normalisation of eosinophil levels and an improvement in clinical signs, but it is common for the disease to reappear on gradual dose tapering;
  - as second-line treatment: immunomodulatory therapies, such as PEGylated interferon alfa or hydroxyurea, are proposed as corticosteroid-sparing treatments; these are used off-label.

Role of the medicinal product in the care pathway

NUCALA (mepolizumab) is a first-line treatment in patients with lymphocytic or idiopathic hypereosinophilic syndrome inadequately controlled by corticosteroids and/or immunomodulators.

Since it has not been assessed in these subpopulations, NUCALA (mepolizumab) has no role in the care pathway for clonal neoplastic HES (in particular F/P+ chronic eosinophilic leukaemias) for which the first-line treatment is imatinib.

Special recommendations

Given the specificities of treatment of this rare disease and the implementation of long-term patient follow-up in the context of the national COHESion cohort, the Committee recommends that decisions to initiate and discontinue treatment with mepolizumab be taken after a documented proposal resulting from a multidisciplinary team meeting within the national network of specialists involved in the diagnosis and treatment of hypereosinophilic syndromes (Hypereosinophilic syndrome reference centre - CEREO). Regular follow-up of patients within one of these centres is essential to ensure the efficacy of treatment and monitor its safety.

COMMITTEE'S CONCLUSIONS

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

Clinical benefit

- Inadequately controlled hypereosinophilic syndromes can have life-threatening complications.
- The proprietary medicinal product NUCALA (mepolizumab) is a symptomatic medicinal product.
- The efficacy/adverse effects ratio of NUCALA (mepolizumab) is:
  - high as an add-on treatment in inadequately controlled lymphocytic or idiopathic hypereosinophilic syndrome;
  - inadequately established in the other MA situations, which were not assessed.
- There are no therapeutic alternatives in the treatment of inadequately controlled lymphocytic or idiopathic hypereosinophilic syndrome. In the treatment of clonal neoplastic HES: imatinib is the first-line therapy.
- NUCALA (mepolizumab) is a first-line treatment in patients with lymphocytic or idiopathic hypereosinophilic syndrome inadequately controlled by corticosteroids and/or immunomodulators. Since it has not been assessed in these subpopulations, NUCALA (mepolizumab) has no role in the care pathway for clonal neoplastic HES (in particular F/P+ chronic eosinophilic leukaemias) for which the first-line treatment is imatinib.

Public health benefit

Considering:

- the seriousness of the disease,
- the low prevalence of the disease,
- the unmet medical need for inadequately controlled lymphocytic or idiopathic HES,
- the partial response to the identified need due to a demonstrated additional impact on morbidity and quality of life (fatigue severity), despite the absence of a demonstrated impact on mortality;
- the absence of demonstration of a potential impact on the organisation of care.

NUCALA (mepolizumab) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of NUCALA (mepolizumab) is:

- **substantial only as an add-on treatment for adult patients with inadequately controlled lymphocytic or idiopathic hypereosinophilic syndrome;**
- **insufficient in the other MA situations to justify public funding cover.**

The Committee issues a favourable opinion for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use as an add-on treatment for adult patients with inadequately controlled lymphocytic or idiopathic hypereosinophilic syndrome, and at the MA dosages.

The Committee issues an unfavourable opinion for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the other MA indications.

- **Recommended reimbursement rate: 65%**

Clinical Added Value

In patients with inadequately controlled lymphocytic or idiopathic hypereosinophilic syndrome (HES):

Considering:

- demonstration of the superiority of NUCALA (mepolizumab) compared to placebo in a randomised, double-blind study, on the proportion of patients having experienced an HES flare at 32 weeks, a clinically relevant endpoint, with a substantial effect size (OR=0.28; CI95% [0.12; 0.64]; p=0.003);
- demonstration of the superiority of mepolizumab compared to placebo on ranked secondary endpoints (time to first HES flare, proportion of patients who experienced an HES flare during week 20 through week 32, rate of HES flares), including a quality of life endpoint (fatigue severity);
- the acceptable safety profile;
- the unmet medical need in patients with lymphocytic or idiopathic hypereosinophilic syndrome inadequately controlled by standard treatments;

but in view of:

- the uncertainty with respect to the HES subtypes included in the study (other than F/P+ chronic eosinophilic leukaemias, which were excluded);
- the lack of data on oral corticosteroid consumption, which was not the subject of an endpoint despite the fact that this would have been relevant in the treatment of HES;
- the absence of data on the evolution of organ involvement;

the Transparency Committee considers that NUCALA (mepolizumab) provides a minor clinical added value (CAV IV) in the care pathway for inadequately controlled lymphocytic or idiopathic hypereosinophilic syndrome.