Rare disease
Sector: Hospital

HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE

SUMMARY

2 DECEMBER 2020

The legally binding text is the original French opinion version

rituximab

MABTHERA 100 and 500 mg concentrate for solution for infusion

New indication

Key points

Favourable opinion for reimbursement for the induction of remission, in combination with glucocorticoids, in paediatric patients (aged ≥ 2 to < 18 years old) with severe, active granulomatosis with polyangiitis (Wegener's, GPA) and microscopic polyangiitis (MPA).

What therapeutic improvement?

Therapeutic improvement in management.

Role in the care pathway?

The objectives of treatment in ANCA-associated vasculitis are to induce remission and prevent relapses, at the same time limiting treatment-associated adverse effects and the sequelae of the disease.

There are no specific guidelines in children in France. The use of remission induction treatments in children with severe or active GPA and MPA is extrapolated from the guidelines in adults.

The treatment of severe forms of GPA and MPA combines corticosteroids with immunosuppressive therapies prescribed long-term for a duration of more than 18 months. A first induction phase lasting around 3 to 6 months aims to obtain disease remission.

The remission induction treatment of severe and active GPA and MPA is based primarily on the combination of oral prednisone, possibly preceded by a bolus of methylprednisolone, and IV cyclophosphamide for at least 3 months (usually 6 infusions).

Cyclophosphamide is liable to promote the development of infections and cancers - predominantly bladder cancers - and, at high doses, to cause sterility, sometimes permanent, particularly when cyclophosphamide is prescribed orally since the cumulative doses are higher than following intravenous administration. For a similar efficacy, the oral form is less well tolerated than the IV form.

As first-line treatment, rituximab may be prescribed in the same way as cyclophosphamide. The choice of treatment is left to the clinician's assessment when patients are treated for a first flare of the disease. The decision takes into account the patient's history, pre-existing morbidity factors, the disease to be treated and the patient's opinion.

According to the most recent revised 2019 French national diagnostic and care protocol (PNDS) guidelines, rituximab should be used preferentially as immunosuppressive therapy in combination with glucocorticoids in paediatric patients (children and adolescents) for the remission induction treatment of severe forms of GPA and MPA.

Role of the medicinal product in the care pathway

MABTHERA (rituximab) is a first-line treatment for the induction of remission, in combination with glucocorticoids, in paediatric patients (aged ≥ 2 to < 18 years old) with severe, active GPA (Wegener's) and MPA.

Special recommendations

In view of the complexity of treatment of these rare diseases and the absence of specific guidelines, the Committee recommends that children be treated following consultation of a paediatric "rare autoimmune diseases and systemic diseases" reference centre or specialist centre, possibly with the involvement of an adult reference or specialist centre, to discuss the therapeutic strategy to be adopted.

COMMITTEE'S CONCLUSIONS

Clinical benefit

◗ Severe, active granulomatosis with polyangiitis (GPA) (formerly called Wegener's disease) and microscopic polyangiitis (MPA) are serious and incapacitating rare diseases.

◗ MABTHERA (rituximab) is a curative treatment.

◗ Its efficacy/adverse effects ratio is high.

◗ There is an alternative with an MA: cyclophosphamide (ENDOXAN).

◗ MABTHERA (rituximab) is a first-line treatment for the induction of remission.

Public health impact

Considering:

- the seriousness and low prevalence of severe, active GPA and MPA, rare diseases that can be life-threatening in the absence of treatment,
- **the medical need to have access to effective medicinal products to induce remission with lower toxicity,** the available information on rituximab (MABTHERA) suggesting an efficacy and safety profile similar to that in adults and hence a low impact on morbidity without a demonstrated impact on mortality to date,
- the lack of demonstrated impact on quality of life,
- the lack of expected impact on the organisation of care.

MABTHERA (rituximab) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of MABTHERA (rituximab) is substantial in the MA indication extension to children aged ≥ 2 to < 18 years old.

The Committee issues a favourable opinion for inclusion in the hospital formulary list of reimbursed proprietary medicinal products approved for use in the paediatric indication extension (children aged ≥ 2 to < 18 years old) and at the MA dosages.

Clinical Added Value

Considering:

- **the available data in adults demonstrating the efficacy of rituximab for the induction of clinical remission,**
- **the available exploratory pharmacokinetic and efficacy data, from a phase 2 single-arm study, suggesting an efficacy and safety profile comparable to that described in adults,**
- **the absence of impact of rituximab on the fertility of patients of childbearing potential,**
- **the medical need partially met by a single alternative with an MA in children: ENDOXAN (cyclophosphamide),**

the Committee considers that, as in adults, MABTHERA (rituximab), in combination with glucocorticoids, provides a minor clinical added value (CAV IV) in the care pathway for the induction of remission in paediatric patients with severe, active GPA and MPA.