OPINION ON MEDICINAL PRODUCTS

inebilizumab

UPLIZNA 100 mg,

solution for dilution for infusion

First assessment

Adopted by the Transparency Committee on 19 October 2022

SUMMARY

The legally binding text is the original French opinion version

- **Neuromyelitis optica**
- **Sector: Hospital**

Key points

Approval of reimbursement as monotherapy for the treatment of neuromyelitis optica spectrum disorders (NMOSD) in adult patients seropositive for anti-aquaporin 4 immunoglobulin G (AQP4-IgG).

Therapeutic improvement?

Therapeutic improvement in the care pathway excluding rituximab.

Role in therapeutic strategy?

As per the 2021 national diagnosis and treatment protocol (PNDS) for NMOSD, the treatment of an attack of neuromyelitis optica (NMO) is a therapeutic emergency, due to the risk of incapacitating sequelae and, besides its potential functional outcomes, its potentially life-threatening nature. In parallel, long-term treatment (background therapy) is key in reducing the risk of attacks, the recurrence of which is liable to result in severe functional sequelae.

The initial treatment for attacks is based on high-dose methylprednisolone (1g/day) intravenous corticosteroid therapy for 5 to 10 days, followed by long-term oral treatment (1 mg/kg/day) and plasma exchanges for severe attacks**Erreur ! Signet non défini.**.

The basic treatments used in practice (off-label) and recommended to prevent relapses are the following immunosuppressant treatments:

- rituximab, an anti-CD20 therapy, administered by IV every 6 months (beneficial effect on episode prevention, significant reduction in annualised rate of attacks),
- azathioprine, in association with corticosteroid therapy administered orally for the first six months (decrease in annualised rate of attacks),
- mycophenolate mofetil, in association with corticosteroid therapy administered orally for the first six months (decrease in annualised rate of attacks),
- mitoxantrone (reduction in annualised rate of attacks).

Other medicinal products such as cyclophosphamide and ciclosporin are also used to a more limited extent.

The treatments used in MS (interferons, glatiramer acetate, natalizumab or fingolimod) appear to be ineffective or even harmful.

Tocilizumab, an anti-IL6 therapy, is also used off-label for conventional immunosuppressant-refractory NMOSD.

Two monoclonal antibodies were recently granted marketing authorisations for the treatment of NMOSD in adult patients exhibiting anti-aquaporin 4 (AQP4) antibodies;

- anti-complement protein C5 antibody, SOLIRIS (eculizumab) indicated for adults for the treatment of neuromyelitis optica spectrum disorder (NMOSD) in patients exhibiting anti-aquaporin 4 (AQP4) antibodies with the recurrent form of the disease
- anti-interleukin 6 antibody, ENSPRYNG (satralizumab) indicated as monotherapy or in association with an immunosuppressant treatment (IST) for the treatment of neuromyelitis optica spectrum disorders (NMOSD) in adult patients and adolescents from 12 years, who are seropositive for anti-aquaporin-4 IgG (AQP4IgG)"

The Transparency Committee assessed these two proprietary medicinal products on 16 September 2020 (SOLIRIS) and 17 January 2022 (ENSPRYNG), respectively, and approved reimbursement within a restricted scope of their respective marketing authorisations reserved for patients with recurrent forms of the disease and failing to respond to conventional immunosuppressant treatments.

Role of the medicinal product

Considering:

- **the evidence of the superiority of inebilizumab monotherapy versus placebo assessed in a double-blind randomised study on the time to relapse (clinically relevant primary outcome measure) and on reduced worsening of incapacity following the 6.5-month double-blind phase (adjusted secondary outcome measure),**
- **that the large majority of the patients included in this study (93%) were seropositive for anti-aquaporin-4 IGG,**
- **the similarity of the mechanism of action of inebilizumab to that of rituximab, predominantly used as a first-line approach,**

and despite,

- **the limited percentage of treatment-naive patients (34%) at the time of inclusion in the study,**
- **the lack of direct comparative data versus the immunosuppressant treatments used in practice (off-label), of which rituximab, or treatments with a marketing authorisation (satralizumab, eculizumab) reserved for recurrent forms as a second-line approach, the latter having been developed concomitantly,**
- **the uncertainties around long-term efficacy and safety and around the optimal treatment duration in a context in which the mechanism of action of the medicinal product exposes the patient to a risk of hypogammaglobulinaemia and severe associated infections,**

UPLIZNA (inebilizumab) monotherapy is a first-line treatment for NMOSD in adult patients seropositive for anti-aquaporin 4 immunoglobulin G (AQPA-IgG).

The Committee stresses that, in the absence of comparative data, it is not possible to specify the role of UPLIZNA (inebilizumab) in relation to rituximab based on the data available.

Moreover, despite the similarity of their mechanism of action, the Committee points out the uncertainties around a potential risk of hypogammaglobulinaemia when treated with UPLIZNA (inebilizumab) associated with its additional action on plasmablasts and certain plasmocytes and in a context in which severe infection and three deaths, including two associated with infections, have been reported. Unlike the current follow-up available on the use of rituximab, the follow-up on the safety of UPLIZNA (inebilizumab) is limited (open-label extension phase up to a median follow-up period of 3.15 years).

In this context, in accordance with the SPC, particular attention must be placed on the risk of infection and the need for full blood count monitoring (including leukocyte and immunoglobulin counts) prior to commencing treatment, during treatment, and after discontinuing treatment until B-cell repopulation has been achieved. The summary of product characteristics (SPC) and the Risk Management Plan (RMP) must be adhered to.

Special recommendations

The Committee recommends that UPLIZNA (inebilizumab) treatment be administered in a multiple sclerosis expert centre or a centre of the MIRCEM network (rare inflammatory brain and bone marrow disease), with prescription restricted to neurologists within the framework of multidisciplinary review meetings, justified with regard to the risk of UPLIZNA (inebilizumab) use beyond the scope defined by the Committee, especially use for patients with no anti-AQP4 antibodies (off-label).

Committee's conclusions

Clinical Benefit

- Neuromyelitis optica spectrum disorder (NMOSD) is a severe, incapacitating, potentially life-threatening disease.
- The proprietary medicinal product UPLIZNA (inebilizumab) as a monotherapy is a symptomatic background therapy.
- The efficacy/adverse effect ratio of UPLIZNA (inebilizumab) is significant as monotherapy for the treatment of NMOSD in adult patients seropositive for anti-aquaporin 4 immunoglobulin G (AQPA-IgG).
- Therapeutic alternatives are available (see Section 05 "Clinically relevant comparators").
- UPLIZNA (inebilizumab) as monotherapy is a first-intention treatment for NMOSD in adult patients seropositive for anti-aquaporin 4 immunoglobulin G (AQPA-IgG).

Public health benefit

Considering:

- the seriousness of the disease and its low prevalence,
- the medical need partially met by the available alternatives,
- the partial response to the identified need due to:
  - the demonstrated additional impact on morbidity in terms of time to the first relapse and on reduced worsening of incapacity, with no demonstrated impact on mortality,
  - the lack of demonstrated impact on quality of life, in the absence of robust data,
- the lack of demonstrated impact on organisation of care,

UPLIZNA (inebilizumab) is not likely to have an additional impact on public health.

Considering all of these elements, the Committee deems that the actual clinical benefit of UPLIZNA (inebilizumab) is substantial in the marketing authorisation indication.

The Committee approves inclusion in the list of proprietary medicinal products approved for community use for the marketing authorisation indication and at the marketing authorisation dosages.

Clinical Added Value

Considering:

- the evidence of the superiority of inebilizumab monotherapy *versus* placebo for the treatment of NMOSD:
  - on the time to relapse (clinically relevant primary outcome measure)
  - on reduced worsening of incapacity measured with the EDSS scale following the 6.5-month double-blind phase (adjusted secondary outcome measure),
- the need for authorised medicinal products with evidence of efficacy, with regard to the strategy currently based on immunosuppressants prescribed off-label as a first-line approach and on eculizumab and satralizumab, that are authorised but reserved for recurrent forms failing to respond to immunosuppressants,

and despite:

- the absence of robust data on the annualised rate of relapses, assessed as an exploratory outcome measure,
- the absence of demonstrated benefit on patient quality life,
- the uncertainties remaining around long-term efficacy and safety and around the optimal treatment duration in a context in which the mechanism of action of the medicinal product exposes the patient to a risk of hypogammaglobulinaemia and severe associated infections,
- the uncertainties around the strategy of use in the absence of comparison versus the basic treatments used in practice, particularly rituximab,

the Transparency Committee deems that UPLIZNA (inebilizumab) monotherapy provides moderate clinical added value (CAV III) in the therapeutic strategy, excluding rituximab, for NMOSD in adult patients seropositive for anti-aquaporin 4 immunoglobulin G (AQPA-IgG).