**OPINION ON MEDICINAL PRODUCTS**

# efgartigimod alfa
# VYVGART 20 mg/mL,

**concentrate for solution for infusion**

First assessment

**Adopted by the Transparency Committee on 14 December 2022**

**SUMMARY**

**The legally binding text is the original French opinion version**

## Key points

Approval of reimbursement only in addition to standard therapy, including first-line immunosuppressants, in adult patients with generalised myasthenia gravis who are anti-acetylcholine receptor (AChR) antibody positive who remain symptomatic.

Disapproval of reimbursement for other marketing authorisation indication cohorts.

## Therapeutic improvement?

Therapeutic improvement in the care pathway.

## Role in therapeutic strategy?

Therapeutic management of myasthenia is based on several objectives: reducing symptoms and their impact on personal and work life as much as possible, managing serious life-threatening complications, limiting disease progression.

In cases where myasthenia is suspected or established, setting up symptomatic treatment with orally administered cholinesterase inhibitors, based on pyridostigmine bromide or ambenonium chloride, is recommended as a first-line approach.

Long-term immunotherapy should be envisaged as soon as symptoms are not sufficiently or sustainably improved by cholinesterase inhibitors. First-line immunomodulatory treatment is based:

- either on corticosteroids (prednisone or prednisolone),

- or on immunosuppressants used off-label (azathioprine or alternatively mycophenolate mofetil),
- or an association of both.

The choice of treatment is based on the onset of action, contraindications, and patient preferences.

In cases where myasthenia is uncontrolled under first-line immunomodulatory treatment or of intolerance to these treatments, the patient should be referred to a reference centre with a view to confirming the diagnosis, optimising the previous treatment and screen for exacerbating factors (contraindicated medicinal products, associated autoimmune disease, etc.). An off-label second-line immunotherapy regimen shall then be discussed with, as therapeutic options listed by the 2015 PNDS:

- rituximab, proposed in forms resistant to corticosteroids and to azathioprine,
- ciclosporin and tacrolimus, proposed in cases of myasthenia refractory to other treatments,
- and cyclophosphamide, reserved for specific indications (failure with other therapeutics, association with severe lupus).

The choice of treatment depends on the severity of the clinical profile, diathesis, onsets of action, and side-effects. Their efficacy must be assessed over 9 to 12 months.

Non-medicinal alternatives are also available with surgical treatment (thymectomy) in cases of urgent thymoma regardless of myasthenia severity, except for elderly patients. Complementary radiotherapy is indicated in cases of macroinvasive thymoma. Chemotherapy is reserved for targeted indications, in particular for very extensive thymomas and in the case of metastases. International consensus recently updated[5] the positioning of thymectomy in non-thymomatous generalised MG, based in particular on the MGTX randomised trial, and lists it as a therapeutic option to be envisaged at an early stage for patients aged 18 to 50 years with acetylcholine receptor (AChR) antibody-positive non-thymomatous generalised MG with the aim of minimising immunotherapy use. It is worth noting that thymectomy should be performed on neurologically stabilised patients.

In specific refractory myasthenia contexts, only the proprietary medicinal product SOLIRIS (eculizumab) has been granted a marketing authorisation for the treatment of refractory generalized myasthenia gravis in adult patients who are anti-acetylcholine receptor antibody-positive. However, as the pharmaceutical firm did not apply for its inclusion in the list for community use in this indication, the proprietary medicinal product is not currently covered for this indication (Transparency Committee opinion of 27 June 2018). Note that a pre-marketing authorisation early-access authorisation was granted for the proprietary medicinal product ULTOMIRIS (ravulizumab) on 19 May 2022 for the “treatment of generalised myasthenia gravis (gMG) in symptomatic refractory generalised myasthenia gravis patients, i.e. non-responders, ineligible for or intolerant to the treatments currently available and who are anti-acetylcholine receptor (AChR) antibody-positive”, and for the proprietary medicinal product VYVGART (efgartigimod alfa) on 21 July 2022 “in association with standard therapy in adult patients with generalised myasthenia gravis who are anti-acetylcholine receptor (AChR) antibody-positive who remain symptomatic, and who are non-responders, ineligible for or intolerant to the alternatives currently available”.

The 2021 international consensus[5] cites thymectomy as a therapeutic option in cases of failure to respond to an initial immunotherapy treatment or of intolerance to this treatment.

Finally, in the case of acute and severe myasthenia episodes (including myasthenic crises), rapid, albeit temporary, improvement may be obtained with plasma exchanges (PLEX) or intravenous immunoglobulin injection (IVIG). The choice between IVIG and PLEX depends on their respective contraindications and hospital availability, particularly for PLEX. For some patients, regular

(monthly) PLEX or IVIG may be required as a basic treatment (off-label use) in cases of intolerance or inefficacy of other treatments.

### Role of VYVGART (efgartigimod alfa) in the therapeutic strategy:

**Within the scope of reimbursement**

VYVGART (efgartigimod alfa) is a first-line treatment in addition to standard therapy, including first-line immunosuppressants, in adult patients with generalised myasthenia gravis who are anti-acetylcholine receptor (AChR) antibody-positive who remain symptomatic, despite well-managed treatment.

Based on the current data, it is not possible to rank VYVGART (efgartigimod alfa) with respect to rituximab and anti-C5 treatments (SOLIRIS [eculizumab] and ULTOMIRIS [ravulizumab]), in the absence of comparative data.

**Within the scope included in the marketing authorisation but not approved for reimbursement**

VYVGART (efgartigimod alfa) has no role in such a context, given the lack of data in this cohort.

The summary of product characteristics (SPC) and the Risk Management Plan (RMP) must be adhered to.

## Special recommendations

The Committee recommends updating the ‘Myasthenia’ PNDS and setting up a national Autoimmune Myasthenia registry.

# Committee's conclusions

## Clinical Benefit

- Myasthenia is an debilitating, rare, serious autoimmune disease causing fluctuating muscle weakness and excessive fatigability which can impair patients' quality of life and autonomy. Severe forms may progress towards life-threatening myasthenic crises.
- The proprietary medicinal product VYVGART (efgartigimod alfa) is a symptomatic medicinal product.
- The efficacy/adverse effect ratio is:
  - significant in addition to standard therapy, including first-line immunosuppressants, in adult patients with generalised myasthenia gravis who are acetylcholine receptor (AChR) antibody-positive who remain symptomatic.
  - not defined for the other marketing authorisation indication cohorts, given a lack of data.
- Therapeutic alternatives are available.
- VYVGART (efgartigimod alfa) is a first-line treatment in addition to standard therapy, including first-line immunosuppressants, in adult patients with generalised myasthenia gravis who are anti-acetylcholine receptor (AChR) antibody-positive who remain symptomatic, despite well-managed treatment.

  VYVGART (efgartigimod alfa) has no role for the other marketing authorisation indication cohorts.

### Public health benefit

Considering:

- the severity of the disease,
- its low prevalence,
- the partially met medical need,
- the partial response to the identified need with:
  - evidence of an additional impact on morbidity and quality of life only in the short term versus placebo, during the first treatment cycles, with no evidence of an impact on morbidity,
  - the lack of evidence of an additional impact on long-term morbidity-mortality considering the limited data available,
  - the lack of evidence of an additional impact on delivery of care, even though an increased burden was possible, on account of the need for administration in weekly IV infusion cycles for 4 weeks and, according to the clinical assessment of the patient for subsequent cycles.

VYVGART (efgartigimod alfa) is not likely to have an additional impact on public health.

**Considering all of these elements, the Committee deems that the clinical benefit of VYVGART (efgartigimod alfa) is:**

- **significant only in addition to standard therapy, including first-line immunosuppressants, in adult patients with generalised myasthenia gravis who are anti-acetylcholine receptor (AChR) antibody-positive who remain symptomatic,**
- **insufficient in other marketing authorisation clinical contexts.**

**The Committee approves inclusion in the list of proprietary medicinal products approved for community use in addition to standard therapy, including first-line immunosuppressants, in adult patients with generalised myasthenia gravis who are anti-acetylcholine receptor (AChR) antibody-positive who remain symptomatic, and at the marketing authorisation dosages.**

**The Committee disapproves inclusion in the list of proprietary medicinal products approved for community use for the other marketing authorisation clinical contexts.**

## Clinical Added Value

Considering:

- the evidence of the superiority of efgartigimod alfa versus placebo in terms of:
  - percentage of responder AChR+ patients on the MG-ADL quality-of-life score for the first treatment cycle (primary outcome measure): 67.7% (44/65) versus 29.7% (19/64) (OR=4.95; 95%CI [2.21; 11.53], p<0.0001),
  - percentage of responder AChR+ patients on the QMG quality-of-life score for the first treatment cycle (ranked secondary outcome measure): 63.1% (41/65) versus 14.1% (9/64) (OR=10.84; 95%CI [4.18; 31.20], p<0.0001),
  - mean proportion of time during which AChR+ patients have a clinically relevant improvement in the total MG-ADL quality of life score, defined by a decrease ≥ 2 points in the total MG-ADL score (up to day 126 of treatment) (ranked secondary outcome measure): 48.7% (6.2) versus 26.6% (6,3), representing a mean difference of 22.1% (95%CI [10.95; 33.18], p=0.0001).

but in view of:

- the lack of evidence of continuation of the long-term effect on the reduction in the MG-ADL quality of life score, given a lack of robust data,
- the short-term safety profile (median follow-up of 21 weeks) marked by infection type adverse events,
- the limited nature of the long-term safety data (only 28% of patients were followed up for more than 24 months in the extension study),
- the lack of comparison versus rituximab or eculizumab even though it was possible; also the lack of comparison versus ravulizumab on account of concomitant development,

**the Committee deems that VYVGART (efgartigimod alfa), in addition to standard therapy including first-line immunosuppressants, provides minor clinical added value (CAV IV) in the therapeutic strategy for the treatment of adult patients with generalised myasthenia gravis who are anti-acetylcholine receptor (AChR) antibody-positive who remain symptomatic, excluding rituximab and anti-C5 treatments (SOLIRIS [eculizumab] and ULTOMIRIS [ravulizumab]).**