OPINION ON MEDICINAL PRODUCTS

eptinezumab
VYEPTI 100 mg,

dilutable solution for perfusion

First assessment

Adopted by the Transparency Committee on 5 October 2022

SUMMARY

The legally binding text is the original French opinion version

Key points

Approval of reimbursement only in preventive treatment of migraine in patients suffering from severe migraine with at least 8 migraine days per month, who have failed to respond to at least two prophylactic treatments and are free from cardiovascular impairment (patients having had myocardial infarction, stroke, TIA, unstable angina or coronary bypass surgery).

Disapproval of reimbursement in other marketing authorisation situations.

Therapeutic improvement?

No progress in management.

Role in therapeutic strategy?

Migraine management is based on both treating acute episodes and, if necessary, on introducing a basic prophylactic treatment to reduce the frequency of acute episodes.

The substances used for treating acute episodes are non-migraine-specific treatments (analgesics and non-steroidal anti-inflammatory drugs), and migraine-specific treatments (primarily triptans and ergot derivatives).

The choice of prophylactic treatment is based on the patient's adverse effects, contraindications, interactions, and associated conditions, if applicable. The substances authorised for migraine prophylaxis and used as a first-line treatment are beta blockers (metoprolol and propranolol) and topiramate. It should be noted that topiramate has been the subject of a recent report on the risk of autism spectrum disorders and intellectual disability in children exposed during pregnancy and is therefore contraindicated for migraine in pregnant women and in women of childbearing age who are not using a highly effective method of contraception, pending the conclusions of the European assessment. Amitriptyline (LAROXYL film-coated tablet and oral solution proprietary medicinal products) is also indicated for the basic treatment of migraine in adults. This indication has not been evaluated by the Committee to date. The recent 2021 guidelines issued by the French Society for the Study of Migraine and Headache rank amitriptyline as the first-line treatment for episodic migraine where beta blocker treatment is inappropriate.

In the event of failure to respond to these treatments, the alternative prophylactic migraine treatments are as follows:

- oral treatments authorised for basic treatment of migraine (pizotifen, oxetorone, flunarizine), but only used as an alternative treatment due to their safety profile in particular,
- anti-CGRP antibodies (erenumab [AIMOVIG], galcanezumab [EMGALITY] and fremanezumab [AJOVY]) providing alternatives for patients suffering from severe migraine with at least 8 days of migraine per month, failing to respond to at least two prophylactic treatments, and free from cardiovascular impairment,
- the proprietary medicinal product BOTOX (botulinum toxin A) for which an extension of indication was recently granted specifically for chronic migraine (presence of headache at least 15 days per month, including at least 8 days of migraine per month), and was recently assessed by the Committee (Transparency Committee opinion of 17 November 2021); this proprietary medicinal product provides a medication option for chronic migraine prophylaxis in patients who have failed to respond or are intolerant to other oral treatments for migraine prophylaxis.

Other substances are also used off-label for basic migraine treatment with a lower level of evidence of efficacy (high to moderate): antiepileptics (valproate and sodium divalproate), beta blockers (atenolol, nebivolol, timolol), candesartan.

Role of VYEPTI (eptinezumab) in the therapeutic strategy:

In view of:

- the efficacy data from the DELIVER study in patients who have failed to respond to 2-4 prophylactic regimens, and of the need in this clinical situation,

- the fact that patients with at least 8 migraine days per month represented the majority of patients included in the efficacy studies,
- the uncertainty about cardiac safety observed in patients from the different studies, while patients with severe cardiovascular disease were excluded by the protocols; this uncertainty remains despite the long-term data on the safety of the anti-CGRP antibody medicinal product class,

the Committee deems that VYEPTI (eptinezumab) provides a medication option for patients suffering from severe migraine with at least 8 migraine days per month, who have failed to respond to at least two prophylactic treatments and are free from cardiovascular impairment (patients having had myocardial infarction, stroke, TIA, unstable angina or coronary bypass surgery).

The Committee stresses, in accordance with the clinical guidelines, that the benefit of the treatment must be assessed within 6 months after the start of treatment, with a decision whether to continue treatment made on a case-by-case basis, and regular assessment of the clinical response recommended thereafter. It should be recalled that, unlike previous anti-CGRP antibodies evaluated by the Committee, which are administered subcutaneously, VYEPTI (eptinezumab) is administered as an intravenous infusion with the need for monitoring during and after the infusion, paying particular attention to anaphylactic reactions that may occur during treatment.

Furthermore, the Committee underlines that current data on the use of eptinezumab in pregnant women is limited (see clinical guidelines). As a precautionary measure, the use of VYEPTI (eptinezumab) should be avoided during pregnancy.

Committee's conclusions

Clinical Benefit

- Migraine is a chronic disabling condition which, due to the frequency and severity of attacks, can lead to severe impairment of quality of life.
- VYEPTI (eptinezumab) is a medicinal product intended to prevent acute migraine episodes.
- Considering:
  - the evidence of the superiority of eptinezumab only versus placebo in episodic and chronic migraine, and in particular in a study in patients who failed to respond to 2-4 prophylactic treatments with a moderate short-term effect size,
  - the evidence of superiority over placebo in terms of quality of life (adjusted secondary outcome measure) in patients who failed to respond to 2-4 prophylactic treatments with a moderate effect size: -3.8 to -5.4 points change in the 78-point HIT-6 migraine impact score, in patients with a score of 66 (major impact) at inclusion,
  - the available short-term safety data with reports of anaphylactic reactions and uncertainties about long-term safety, particularly in terms of cardiovascular risks in a context in which patients with severe cardiovascular disease were excluded from studies,

  the efficacy/adverse effect ratio of VYEPTI (eptinezumab) is substantial for adult patients with at least 8 migraine days per month, who have failed to respond to at least two prophylactic treatments and are free from cardiovascular impairment (patients having had myocardial infarction, stroke, TIA, unstable angina or coronary bypass surgery).

  In other clinical situations, including patients with fewer than 8 migraine days per month, patients who are treatment-naïve or have failed to respond to a single medicinal alternative, and patients with cardiovascular disease, the efficacy/adverse effect ratio of VYEPTI (eptinezumab) cannot be established.
- Medicinal alternatives are available, which are indicated as basic treatment for episodic and chronic migraine.
- VYEPTI (eptinezumab) is a drug option for adult patients suffering from severe migraine with at least 8 migraine days per month, who have failed to respond to at least two prophylactic treatments, and are free from cardiovascular impairment, (patients having had myocardial infarction, stroke, TIA, unstable angina or coronary bypass surgery).

In other clinical situations, including patients with fewer than 8 migraine days per month, patients who are treatment-naïve or have failed to respond to a single medicinal alternative, and patients with severe cardiovascular disease, VYEPTI (eptinezumab) has no role in the therapeutic strategy.

- **Public health benefit**

Considering:

- the severity of the disease and its prevalence,
- the partially met medical need in severe migraine contexts (≥ 8 days of migraine per month) after failure to respond to at least two prophylactic treatments with the need for more effective medicinal alternatives as basic treatments, with fewer adverse effects,
- the absence of an additional response to the identified need:
  - the demonstrated superiority in terms of efficacy versus placebo only in the prophylactic treatment of episodic and chronic migraine, mainly in adult patients who have failed to respond to at least two prophylactic treatments, albeit with a moderate effect size,
  - the lack of additional impact on quality of life given the robust data versus placebo only in patients who have failed to respond to 2-4 prophylactic treatments with a moderate effect size,
  - the lack of evidence of an impact on the delivery of care,

VYEPTI (eptinezumab) is not likely to have an additional impact on public health.

Considering all these elements, the Committee deems that the actual clinical benefit of VYEPTI (eptinezumab) is:

- **substantial only in the preventive treatment of migraine in patients suffering from severe migraine with at least 8 migraine days per month, who have failed to respond to at least two prophylactic treatments and are free from cardiovascular impairment (patients having had myocardial infarction, stroke, TIA, unstable angina or coronary bypass surgery).**
- **insufficient to justify public funding in the other marketing authorisation situations.**

The Committee approves inclusion in the list of proprietary medicinal products approved for community use only for the preventive treatment of migraine in patients suffering from severe migraine with at least 8 migraine days per month, who have failed to respond to at least two prophylactic treatments and are free from cardiovascular impairment (patients having had myocardial infarction, stroke, TIA, unstable angina or coronary bypass surgery).

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

Proposed reimbursement rate: 65%

Clinical Added Value

Considering:

- the evidence of superiority of eptinezumab 100 mg and 300 mg versus placebo only in episodic and chronic migraine, and in particular in a study involving patients who had failed 2-4 prophylactic treatments, with a moderate effect size on the change in the number of migraine days per month from baseline to 12 weeks (primary outcome measure): -2.7 days to -3.2 days, depending on dosage, in patients with 14 migraine days per month at baseline,
- the evidence of superiority over placebo in terms of quality of life (adjusted secondary outcome measure) in patients who failed to respond to 2-4 prophylactic treatments with a moderate effect size: -3.8 to -5.4 points change in the 78-point HIT-6 migraine impact score, in patients with a score of 66 (major impact) at inclusion
- the available short-term safety data (maximum follow-up of 96 weeks) with reports of anaphylactic reactions and uncertainties about long-term safety, particularly in terms of cardiovascular risks in a context in which patients with severe cardiovascular disease were excluded from studies,
- the lack of robust data in relation to an active comparator in a setting in which the majority of patients in the study who failed to respond to 2-4 treatments had failed to respond to only two treatments (62%),
- and despite the medical need in this population with severe migraine whose quality of life is particularly impaired,

The Committee deems that **VYEPTI (eptinezumab) provides no clinical added value (CAV V)** in the preventive treatment of migraine in patients suffering from severe migraine with at least 8 migraine days per month, who have failed to respond to at least two prophylactic treatments and are free from cardiovascular impairment (patients having had myocardial infarction, stroke, TIA, unstable angina or coronary bypass surgery).