OPINION ON MEDICINAL PRODUCTS

fremanezumab

AJOVY 225 mg,

solution for injection in pre-filled syringe / solution for injection in pre-filled pen

Reassessment

Adopted by the Transparency Committee on 14 September 2022

SUMMARY

The legally binding text is the original French opinion version

- **Migraine**
- **Sectors: Community and Hospital**

Key points

Approved for reimbursement only for adult patients suffering from severe migraine with at least 8 migraine days per month, with previous failure to at least two prophylactic treatments and without cardiovascular disease (patients who have had clinically significant cardiovascular disease or vascular ischemia, or thromboembolic event).

Clinical benefit now substantial (previously it was moderate) in this indication.

Therapeutic improvement?

No therapeutic improvement.

Role in therapeutic strategy?

The treatment of migraine is based on treating acute episodes, and where applicable, setting up of a basic prophylactic treatment with a view to reducing 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. Amitriptyline (LAROXYL film-coated tablet and oral solution proprietary medicinal products) also has an indication in the basic treatment of migraine in adults. This indication has not been assessed 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 of episodic migraine where beta blocker treatment is inappropriate.

If these treatments fail, 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 migraine days per month, with previous failure to at least two prophylactic treatments and without cardiovascular disease,
- 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 the chronic migraine prophylaxis in patients who have failed to respond to 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 AJOVY (fremanezumab) in the therapeutic strategy within the scope of indications covered by this reassessment:

Considering:

- the efficacy data or fremanezumab *versus* placebo, based on the previously assessed FOCUS study, among patients failing to respond to 2 to 4 prophylactic treatments and mostly experiencing at least 8 days of migraine per month, and the medical need of these patients, particularly resulting in the recommendation of reimbursement in this context,
- the new efficacy data based on intermediate analyses of observational studies and their limitations, particularly in terms of transposability (proportion of missing data, lack of information on concomitant treatments received, etc.),

- the uncertainty as to the cardiac safety observed in patients from the different studies while patients with severe cardiovascular disease were excluded by the protocols; this uncertainty remains in spite of new safety data based on pharmacovigilance follow-up,

the Committee deems that AJOVY (fremanezumab) remains a medication option for adult patients suffering from severe migraine with at least 8 migraine days per month, with previous failure to at least two prophylactic treatments and without cardiovascular disease (patients who have had clinically significant cardiovascular disease or vascular ischemia, or thromboembolic event).

The new data are not liable to modify the role of AJOVY (fremanezumab) in the therapeutic strategy previously established by the Committee in its inclusion opinion of 16 September 2020.

The Committee stresses that, in accordance with the SPC, the benefit of the treatment must be assessed within 3 months following 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.

Efficacy data with more than one year of follow-up remain limited. Based on expert opinion, continued treatment beyond one year requires a neurological reassessment.

Committee's conclusions

Clinical Benefit

- Migraine is a debilitating chronic condition, which may severely impair quality of life according to the frequency and severity of acute episodes.
- The proprietary medicine product AJOVY (fremanezumab) is a medicinal product intended to prevent acute migraine episodes.
- Considering:
  - initial efficacy data obtained *versus* placebo for episodic migraine and for chronic migraine when studies versus active comparators were feasible, with a moderate short-term effect size versus placebo, particularly among patients failing to respond to 2 prophylactic treatments, among patients mostly presenting with more than 8 days of migraine per month,
  - new efficacy data based on intermediate analyses of observational studies and their limitations, particularly in terms of transposability,
  - updated safety data based on pharmacovigilance follow-up, and follow-up on the use of fremanezumab,

  the efficacy/adverse effect ratio of fremanezumab [AJOVY]) is significant for patients suffering presenting with at least 8 days of migraine per month, failing to respond to at least two prophylactic treatments, and free from cardiovascular impairment,
- Alternative treatments indicated for basic episodic migraine and chronic migraine treatment are available.
- AJOVY (fremanezumab) provides a medication option for adult patients suffering from at least 8 migraine days per month, with previous failure to at least two prophylactic treatments and without cardiovascular disease (patients who have had clinically significant cardiovascular disease or vascular ischemia, or thromboembolic event).

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 alternative basic treatments having fewer adverse effects,
- the lack of additional response to the identified need with:
  - the lack of additional impact on morbidity in severe migraine contexts after failure to respond to at least two prophylactic treatments,
  - the lack of new data in terms of impact on quality life in this debilitating chronic disease,
- the lack of data on the additional impact on patients' care pathway;

AJOVY (fremanezumab) is not likely to have an additional impact on public health.

Considering all of these elements, the Committee deems that the clinical benefit of AJOVY (fremanezumab) is substantial for patients with severe migraine and with at least 8 migraine days per month, with previous failure to at least two prophylactic treatments and without cardiovascular disease (patients who have had clinically significant cardiovascular disease or vascular ischemia, or thromboembolic event).

The Committee approves inclusion in the list of proprietary medicinal products qualifying for reimbursement under social security and in the list of proprietary products approved for community use for adult patients with at least 8 migraine days per month, with previous failure to at least two prophylactic treatments and without cardiovascular disease (patients who have had clinically significant cardiovascular disease or vascular ischemia, or thromboembolic event).

Recommended reimbursement rate: 65%

Clinical Added Value

Considering:

- the initial data demonstrating the superiority of fremanezumab versus placebo with a moderate effect size on the variation of the number of days of migraine per month in episodic and chronic migraine, including one study (FOCUS) specifically on patients failing to respond to 2 to 4 prophylactic treatments, and mostly with at least 8 days of migraine per month,
- the new efficacy data based on intermediate analyses of observational studies and their limitations, particularly in terms of transposability (proportion of missing data, lack of information on concomitant treatments received, etc.),
- the lack of robust quality-of-life data,
- and despite the medical need among this cohort,

the Committee deems that AJOVY (fremanezumab) does not provide clinical added value (CAV V) for adult patients with severe migraine and at least 8 migraine days per month, with previous failure to at least two prophylactic treatments and without cardiovascular disease (patients who have had clinically significant cardiovascular disease or vascular ischemia, or thromboembolic event).