HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
17 NOVEMBER 2021

The legally binding text is the original French opinion version

Type A botulinum toxin
BOTOX 50 UNITS ALLERGAN powder for solution for injection
BOTOX 100 UNITS ALLERGAN powder for solution for injection
BOTOX 200 UNITS ALLERGAN powder for solution for injection

New indication

Key points

Favourable opinion for reimbursement in the prophylactic treatment of chronic migraine in adult patients who have not responded or are intolerant to other prophylactic migraine treatments.

What therapeutic improvement?

No clinical added value in the therapeutic strategy.

Role in the care pathway?

The management of migraine is based on both the treatment of attacks and, if necessary, the initiation of long-term prophylactic treatment to reduce the frequency of attacks.

The medicinal products used in the treatment of attacks are non-specific migraine treatments (analgesics and nonsteroidal anti-inflammatories) and specific treatments (triptans, mainly and ergot derivatives).

The prevention of the onset of attacks will, first and foremost, take into consideration the identification and avoidance of trigger factors. Thereafter, the initiation of long-term treatment will depend, in particular, on the frequency and intensity of attacks and the resulting disability in terms of quality of life, as well as the prevention of any risk of abuse of medication to treat attacks. The choice of prophylactic treatment is based on the side effects, contraindications, interactions and any concomitant conditions the patient may have. The drugs with an MA in the prophylactic treatment of migraine that are used as first-line treatment are beta-blockers (metoprolol and propranolol) and topiramate. The recent 2021 guidelines issued by the French Society for Migraine and Headache Studies specify the preferential care pathway depending on the episodic or chronic nature of the migraine and position topiramate as a first-line treatment for chronic migraine, since this medicinal product has efficacy data derived from specific studies in this clinical form.

Another three drugs also have an MA for the prophylactic treatment of migraine (pizotifen, oxetorone, flunarizine) but are used as salvage therapies only due to their safety profile, in particular. Other drugs without a marketing authorisation in the prophylactic treatment of migraine are also cited in the national guidelines with a lower level of evidence of efficacy (grade B or C, with the exception of sodium valproate and divalproate, with grade A): anti-epileptic drugs (sodium valproate and divalproate, gabapentin), antidepressants (amitriptyline, venlafaxine), other beta-blockers (atenolol, nadolol, nebivolol, timolol), candesartan, naproxen sodium.

Anti-CGRP antibodies (erenumab [AIMOVIG], galcanezumab [EMGALITY] and fremanezumab [AJOVY]), recently assessed by the Committee, represent alternatives in patients with severe migraine who have at least 8 migraine days per month, with previous failure to at least two prophylactic treatments and without cardiovascular disease.

Alternative therapies, such as relaxation and cognitive and behavioural stress management therapies can also be used in some patients.

Role of the medicinal product in the care pathway

BOTOX (botulinum toxin type A) is a medicinal option for the prophylactic treatment of chronic migraine (presence of headaches at least 15 days per month, including at least 8 migraine days per month) in adult patients who have not responded or are intolerant to other prophylactic oral migraine treatments, in accordance with the characteristics of the patients included in the study.

In the absence of comparative data versus anti-CGRP antibodies, the choice of treatment should be made based on the patient's characteristics, the efficacy of the drugs and their safety profile, along with the different contraindications.

Special recommendations

Given the specificities of the injection procedure and in accordance with the SPC, the Committee highlights the need to administer BOTOX (botulinum toxin type A) in the context of multidisciplinary global management by specialist physicians already experienced in the use of the toxin in these indications and with appropriate technical facilities.

COMMITTEE'S CONCLUSIONS

Considering all of this information and further to debate and voting, the Committee considers:

Clinical benefit

◗ Migraine is a chronic, disabling disease that, due to the frequency and severity of attacks, can cause a severe deterioration in quality of life.
◗ BOTOX (botulinum toxin type A) medicinal products are preventive medicines for chronic migraine.
◗ Considering:
- the efficacy demonstrated with a moderate effect size, in the short term, and only versus placebo in only one of two studies in chronic migraine, whereas studies versus active comparators would have been possible,
- the demonstrated superiority in terms of quality of life compared to placebo, and the value of this result in this chronic disease,
- the safety data in this indication for the prophylaxis of chronic migraine,

the efficacy/adverse effects ratio of BOTOX (botulinum toxin type A) is moderate in the prophylactic treatment of chronic migraine (presence of headaches at least 15 days per month, including at least 8 migraine days per month) in adult patients who have not responded or are intolerant to other prophylactic migraine treatments.
◗ There are alternatives indicated in the long-term prophylactic treatment of chronic migraine.
◗ BOTOX (botulinum toxin type A) is a medicinal option for the prophylactic treatment of chronic migraine (presence of headaches at least 15 days per month, including at least 8 migraine days per month) in adult patients who have not responded or are intolerant to other prophylactic oral migraine treatments.

Public health impact

Considering:
- the seriousness of the condition and its prevalence
- the partially met medical need, with the need to have access to more effective long-term alternatives with fewer adverse effects,
- the lack of partial response to the identified need with:
    - the absence of an additional impact on morbidity and mortality, with a superiority demonstrated versus placebo only, in one of two studies, in terms of efficacy in the prophylactic treatment of chronic migraine and with a moderate effect size in the short term,
    - an additional impact on quality of life with a superiority demonstrated versus placebo on quality of life in a debilitating chronic condition,
    - the absence of an expected impact on the care pathway in the absence of data,

BOTOX (botulinum toxin type A) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of BOTOX (botulinum toxin type A) is moderate in the indication for the prophylactic treatment of chronic migraine (presence of headaches at least 15 days per month, including at least 8 migraine days per month) in adult patients who have not responded or are intolerant to other prophylactic migraine treatments.

The Committee issues a favourable opinion for inclusion in the hospital formulary list of reimbursed proprietary medicinal products approved for use in the indication for the prophylactic treatment of chronic migraine (presence of headaches at least 15 days per month, including at least 8 migraine days per month) in adult patients who have not responded or are intolerant to other prophylactic migraine treatments, and at the MA dosages.

Clinical Added Value

Considering:

- **demonstration of the superiority of botulinum toxin type A, only in the short term, compared to placebo in only one of two randomised, double-blind studies in chronic migraine on:**
    - **the reduction of the number of headache days per month after 24 weeks (primary endpoint) with a nonetheless moderate effect size (difference of -2.3 days compared to placebo in patients presenting an average of 20 headache days per month at inclusion)**
    - **the following ranked secondary endpoints assessed after 24 weeks with a moderate effect size: change in the number of migraine/probable migraine days per month, change in the number of moderate/severe headache days per month, change in the cumulative number of headache hours on headache days per month and change in the frequency of headache episodes per month**
- **demonstration of the superiority compared to placebo in this same study on the ranked secondary quality-of-life endpoint of the percentage of patients having obtained a severe HIT-6 headache impact score (*i.e.,* ≥ 60),**

but in view of:

- **the absence of comparison versus salvage treatments, including anti-CGRP antibodies,**

the Committee deems that BOTOX (botulinum toxin type A) provides no clinical added value (CAV V) in the current care pathway for the prophylactic treatment of chronic migraine in adult patients who have not responded or are intolerant to other prophylactic migraine treatments.