HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
3 NOVEMBER 2021

The legally binding text is the original French opinion version

berotralstat
ORLADEYO 150 mg hard capsules

First assessment

Key points

Favourable opinion for reimbursement only as a second-line treatment for routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older.

What therapeutic improvement?

No clinical added value in the routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older.

Role in the care pathway?

The avoidance of identifiable trigger factors is the first measure for the prevention of attacks in all patients (mechanical trauma, psychological stress and airway infections primarily). Teething or some medicinal products, such as angiotensin-converting enzyme inhibitors, may also be trigger factors. Therapeutic education plays an essential role in prophylaxis of attacks. In the event of a minor procedure, the following may be considered: the administration of danazol 600 mg/d orally for 5 days before the procedure and 5 days after, in combination with tranexamic acid 1 g x3/d orally starting the day before surgery and continuing until the day after. Danazol is contraindicated in pregnant or breastfeeding women and its use is not recommended in children. In addition, its adverse effects, related to its androgenic effect, mean that it is not appropriate in women. In case of a procedure affecting the upper airways, especially dental care, or which may lead to tissue trauma and cause oedema, the preventive use of a human C1 esterase inhibitor (Berinert or Cinryze) is recommended.

Basic treatment in the event of recurrent attacks is based on long-term, regular prophylaxis in addition to avoidance of trigger factors. In adults and adolescents aged 12 years and older, preventive treatment mainly involves the following oral treatments: danazol in men, macroprogestin contraception in women, tranexamic acid in all patients. As second-line treatment, the alternatives are CINRYZE, a plasma-derived C1 inhibitor administered by the IV route every 3 or 4 days in patients aged 6 years or older, and TAKHZYRO (lanadelumab), a monoclonal antibody administered by the SC route every 2 weeks in patients aged 12 years or older, particularly in the event of recurrent severe attacks.

Role of the medicinal product in the care pathway

ORLADEYO (berotralstat) has no role in the first-line prevention of recurrent HAE attacks.

In adults and adolescents aged 12 years and older, ORLADEYO (berotralstat) represents an alternative to second-line preventive treatment of recurrent attacks of hereditary angioedema (HAE), but its role compared to CINRYZE (human C1-esterase inhibitor) and TAKHZYRO (lanadelumab SC) cannot be specified in the absence of direct comparative data and given the significant methodological limitations of the indirect comparison available.

The choice should be guided by the severity of the attacks (with TAKHYRO having demonstrated the highest effect size for this criterion versus placebo), the safety profile, the administration methods (self-administration possible by patients after training by the SC route with TAKHZYRO or by the oral route with ORLADEYO), and the patient's preferences.

COMMITTEE'S CONCLUSIONS

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

Clinical benefit

◗ Hereditary angioedema (HAE) is characterised by episodes of subcutaneous and/or submucosal oedema, which are transient and recurrent and affect variable locations (cutaneous, gastrointestinal, pharyngeal, etc.). HAE is a rare and incapacitating, chronic genetic disease, which can be life-threatening in the event of laryngeal location with a risk of asphyxia. The impact on quality of life can be substantial, depending on the symptoms, and repeated HAE attacks in children can result in schooling difficulties.

◗ ORLADEYO (berotralstat) is a preventive medicinal product.

◗ The efficacy/adverse effects ratio of berotralstat in the routine prevention of recurrent attacks of HAE is moderate in adult and adolescent patients aged 12 years and older. The efficacy has been established in comparison with placebo in terms of reduction of the number of attacks (primary endpoint) but not in terms of quality of life or severity of attacks.

◗ There are medicinal alternatives, such as second-line treatment: CINRYZE (IV route) and TAHKZYRO (SC route).

◗ This is a second-line treatment. ORLADEYO (berotralstat) has no role as a first-line preventive treatment.

Public health impact

Considering:

- the seriousness of hereditary angioedema (HAE) attacks, which can be life-threatening in the event of laryngeal location,
- the fact that HAE is a rare disease;
- the partially met medical need;

but in view of:

- the lack of response to the identified need with, in particular:
    - the absence of an expected additional impact on morbidity and mortality via the reduction of HAE attacks, with efficacy data only versus placebo, without any comparative data versus the medicinal alternatives available, and given that the effect on the prevention of severe attacks has not been adequately established,
    - the absence of an additional impact on quality of life in view of inconclusive quality of life results versus placebo,
    - an impact on the organisation of care and patient's pathway that remains to be established: potential better long-term compliance is possible given the oral administration, but no data capable of quantifying this, in particular versus TAKHZYRO (lanadelumab), is available,

ORLADEYO (berotralstat) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of ORLADEYO 150 mg hard capsules (berotralstat) is moderate only as a second-line treatment for routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older.

The Committee issues a favourable opinion for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use as a second-line treatment and at the MA dosages.

- **Recommended reimbursement rate: 35%.**

The Committee issues an unfavourable opinion for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use as a first-line treatment for routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older.

Clinical Added Value

Considering:

- demonstration of the superiority of berotralstat 150 mg only compared to placebo in a randomised study in parallel groups to reduce the number of HAE attacks, mainly in adults, the primary endpoint,
- the absence of demonstration of superiority for quality of life, whereas this was a robustly analysed secondary endpoint,
- the absence of robust demonstration of the reduction in the severity of HAE attacks (exploratory secondary endpoint), a relevant clinical endpoint in this disease,
- the medical need already met by the existence of alternatives, and the absence of comparative data versus the other medicinal products used as second-line treatment, despite these comparisons being possible (except for TAKHYZYRO (lanadelumab) due to its simultaneous development),
- the safety profile of berotralstat, with gastrointestinal effects (abdominal pains also observed in this disease),

the Transparency Committee considers that **ORLADEYO (berotralstat) provides no clinical added value (CAV V) in adult and adolescent patients aged 12 years and older, as a second-line treatment for routine prevention of recurrent attacks of hereditary angioedema (HAE).**