HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
27 OCTOBER 2021

The legally binding text is the original French opinion version

odevixibat
BYLVAY 200, 400, 600, 1,200 micrograms hard capsules

First assessment

Key points

Favourable opinion for reimbursement for the treatment of progressive familial intrahepatic cholestasis (PFIC) type 1 or 2 (with the exception of the BSEP3 subtype) in patients aged 6 months or older.

Unfavourable opinion for reimbursement in other types of PFIC.

What therapeutic improvement?

Therapeutic improvement in the management of patients aged 6 months or older with PFIC type 1 or 2 (with the exception of the BSEP3 subtype).

Role in the care pathway?

The current treatment for PFIC is based on treatments with a non-specific action, used to control clinical symptoms and signs: nutritional supplements, prevention of vitamin deficiencies, treatment of hepatic manifestations, including severe pruritus. Medicinal products use off-label for the disease include ursodesoxycholic acid (except in PFIC type 3 for which it has an MA in France), rifampicin, hydroxyzine, antihistamines, naltrexone. None of these medicinal products have demonstrated a long-term effect or modify the prognosis. Hence, recourse to surgery is necessary in the majority of patients, with, in particular, the performance of external biliary diversion surgery, and liver transplant as a last-resort.

The main reason for recourse to biliary diversion is pruritus not controlled by medicinal products, particularly in the event of PFIC type 2. In addition, patients having undergone successful biliary diversion surgery can still have high serum bile acid levels and severe pruritus.

As a last resort, liver transplantation is considered: this eliminates cholestasis in patients with PFIC types 1 et 2. However, in the event of PFIC type1, extra-hepatic manifestations can occur following transplantation.

Therefore, there is currently no medicinal product specifically indicated in the event of PFIC (in particular types 1 and 2, which are the most common) and the medical need in these sometimes rare genetic conditions remains high.

Role of the medicinal product in the care pathway

In patients with PFIC type 1 and 2, the Transparency Committee considers that BYLVAY (odevixibat) is a second-line treatment that should be prescribed in addition to first-line medical treatment (UDCA +/- rifampicin), when the prescriber deems it necessary to continue therapeutic efforts in order to reduce serum bile acid levels and/or reduce pruritus in order to improve the patient's quality of life.

In patients with the BSEP3 subtype of PFIC type 2 (odevixibat not effective), and in other types of PFIC, the role of BYLVAY (odevixibat) cannot be determined in the absence of clinical data.

COMMITTEE'S CONCLUSIONS

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

Clinical benefit

◗ Progressive familial intrahepatic cholestasis (PFIC types 1 to 6 depending on the genetic mutation) is a rare genetic disease that directly or indirectly affects the canalicular transport of bile acids and/or the transport of phospholipids; it evolves towards progressive cholestasis with liver damage. PFIC, particularly type 1, 2 and 3, can cause severe pruritus, growth disorders and irreversible liver damage. PFIC significantly impairs the quality of life of patients, their caregivers and their family. In the absence of appropriate treatment, it causes the patient's death.

◗ BYLVAY (odevixibat) is a symptomatic (pruritus) and preventive (complications) treatment. It also reduces serum bile acid levels.

◗ Its efficacy/adverse effects ratio in the treatment of PFIC type 1 and 2, in patients aged 6 months or older, is high after 24 weeks of treatment. It is still to be established beyond this time and in other types of PFIC. The safety data are very limited.

◗ There are medicinal alternatives (used off-label except for UDCA in the event of PFIC3) and non-medicinal, surgical alternatives, including biliary diversion and, as a last resort, liver transplantation.

◗ BYLVAY (odevixibat) is a second-line treatment that must be prescribed in combination with first-line medicinal treatment (UDCA +/- rifampicin) when control of serum bile acid levels and/or pruritus is insufficient.

Public health impact

Considering:

- the seriousness of PFIC and its rarity,
- the very poorly met medical need,
- the partial response to the identified need, with a non-demonstrated additional impact on morbidity and mortality, but an expected impact on quality of life,
- the lack of established additional impact on the patient's care (recourse to surgery) and/or life (in particular schooling) pathway,

BYLVAY (odevixibat) is likely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of BYLVAY (odevixibat) is:

- **Substantial in the treatment of progressive familial intrahepatic cholestasis (PFIC) type 1 or 2 (with the exception of the BSEP3 subtype) in patients aged 6 months or older.**
- **Insufficient to justify public funding cover in the other types of PFIC.**

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 in the treatment of progressive familial intrahepatic cholestasis (PFIC) type 1 or 2 (with the exception of the BSEP3 subtype) in patients aged 6 months or older and at the MA dosages.

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 in the other types of PFIC.

◗ **Recommended reimbursement rate: 65%**

Clinical Added Value

Within the reimbursement scope:

Considering:
- the methodological quality of the study (controlled, randomised, double-blind) having assessed the efficacy and safety of odevixibat in PFIC type 1 and 2, which are very rare genetic diseases,
- the demonstrated superiority in terms of efficacy of odevixibat, at the dosage of 40 µg/kg/d after 24 weeks of treatment in addition to first-line medical treatment (UDCA +/- rifampicin mainly, prescribed off-label), in comparison with placebo on the proportion of patients having presented a reduction in serum bile acid levels (primary endpoint: 10/23 (43.5%) versus 0/20 (0%) under placebo, p = 0.0015) and the proportion of positive pruritus assessments (secondary endpoint: 58.31% versus 28.74% under placebo),
- exploratory data suggesting an improvement in quality of life of patients and their caregivers due to the reduction in pruritus, and
- the substantial medical need concerning improvement of pruritus reported by the patient association;

and despite:
- the lack of solid efficacy and safety data beyond 24 weeks,
- uncertainties with respect to the treatment to replace or delay recourse to biliary diversion surgery and/or liver transplantation;

the Transparency Committee considers that BYLVAY (odevixibat) in combination with the medicinal treatments currently used, such as ursodesoxycholic acid (UDCA) or rifampicin (off-label) provides a moderate clinical added value (CAV III) in the treatment of PFIC type 1 and 2 (excluding subtype BSEP3).