HAUTE AUTORITÉ DE SANTÉ

# TRANSPARENCY COMMITTEE
## SUMMARY
## 24 JUNE 2020

*The legally binding text is the original French opinion version*

***givosiran***
**GIVLAARI 189 mg/1 mL solution for injection**

**First assessment**

### Key points

Favourable opinion for reimbursement only for patients aged 18 years and over with acute hepatic porphyria (AHP) and with active disease (at least 2 porphyria attacks requiring hospitalisation, an urgent healthcare visit or treatment with IV hemin at home, in the past 6 months).

Unfavourable opinion for reimbursement in the other MA situations, i.e., in patients not meeting the ENVISION study inclusion criteria, in particular in patients with intermittent acute attacks (1 to 3 attacks per year), as well as in patients aged 12 to 18 years.

### What therapeutic improvement?

Therapeutic improvement in management.

### Role in the care pathway?

The treatment of acute neurological attacks should be initiated as soon as possible. It is first necessary to identify and eliminate all trigger factors, in particular porphyrinogenic drugs, and then to initiate symptomatic treatment, identical irrespective of the type of porphyria. This treatment is aimed at treating pain (opioids), gastrointestinal disorders, hypertension and arrhythmia, anxiety, insomnia or seizures, and correcting any hyponatraemia and inadequate calorie intake (carbohydrates). The

intravenous administration of human hemin arginate (NORMOSANG), as an etiopathogenic treatment, is the treatment of choice for attacks in the event of signs of severity (neurological complications, hyponatraemia or persistent severe pain). The administration of exogenous haem suppresses ALAS1 and reduces ALA and PBG concentrations, resulting in the regression of symptoms within a few days. However, it should be noted that hemin arginate does not induce regression of existing neuropathy.

The prophylactic management of attacks is primarily based on the avoidance of trigger factors (alcohol, smoking, diets, etc.), as well as limitation of prescriptions to medicines that are authorised because they are non-porphyrinogenic. No treatment has an MA specifically in the prevention of attacks. In patients with recurrent (≥ 4 attacks per year) or intermittent attacks (1 to 3 attacks per year), off-label long-term prophylactic treatment (1 injection per month to 1 injection per week) with human hemin (NORMOSANG) is often considered in the absence of alternatives. However, this medicinal product is only indicated for the treatment of acute attacks and may cause damage to the superficial venous network, thrombosis and iron overload in the event of repeated administration. In very severe cases with major impairment of quality of life, particularly for recurrent acute intermittent porphyria (AIP), liver transplantation may be considered.

Finally, cutaneous involvement in variegate porphyria (VP) and hereditary coproporphyria (HCP) also require photoprotection (avoidance of sun, opaque creams, protective clothing, etc.).

**Role of the medicinal product in the care pathway**

**Considering:**

- **demonstration of the superiority of GIVLAARI (givosiran) compared to placebo in terms of the number of severe acute porphyria attacks (requiring hospitalisation, an urgent healthcare visit or treatment with IV hemin at home), the frequency of hemin administration for the curative treatment of attacks, and pain (ranked secondary outcome measures), and maintenance of this efficacy after 12 months,**
- **the absence of therapeutic alternatives to prevent acute porphyria attacks,**
- **demonstration of this efficacy only in patients with severe forms of AHP with repeated (≥ 2 porphyria attacks in the past 6 months) and severe attacks (requiring hospitalisation, an urgent healthcare visit or treatment with IV hemin at home)**
- **and the absence of data in patients aged 12 to 18 years,**

**the Committee considers that GIVLAARI (givosiran) is a treatment for acute hepatic porphyria (AHP) only for patients aged 18 years and over and with active disease, characterised by at least 2 porphyria attacks requiring hospitalisation, an urgent healthcare visit or treatment with IV hemin at home, in the past 6 months, in accordance with the inclusion criteria in the ENVISION study.**

**This corresponds to patients with recurrent attacks (≥ 4 attacks per year). For these patients, the long-term prophylactic treatment of attacks should no longer be based on the repeated administration of hemin, therefore.**

**The medicinal product has no role in the other clinical situations covered by the MA.**

The Committee highlights the fact that:

- given the complexity of the diagnosis and management of these diseases, the decision to initiate treatment with GIVLAARI (givosiran) should be taken after a documented proposal resulting from a treatment review meeting with a reference centre with expertise in the treatment of porphyria,
- the implementation of careful monitoring of hepatic and renal function in accordance with the SPC recommendations (sections 4.2, 4.4 and 4.8 of the SPC) is essential,
- on an occasional basis, the use of givosiran may be considered as a prophylactic treatment in patients with a concomitant neoplastic or infectious disease or with a surgical indication liable to trigger a neurovisceral attack that could have a particularly significant impact in terms of morbidity and mortality or limitation of treatments (expert opinion),
- the data with givosiran are very limited or even non-existent in patients with VP, HCP and ALA dehydratase-deficient porphyria (ADP), but these types of porphyria were included in the inclusion criteria for the ENVISION study and the treatment efficacy appears to be extrapolable given the pathophysiology of the attacks and the mechanism of action of givosiran,
- its efficacy on chronic neuropathic pain has not been determined

- given the unmet medical need, it encourages the pharmaceutical company to continue development in patients with acute hepatic porphyria, potentially with a simplified dosing regimen in certain situations.

## Special recommendations

The Committee reiterates that therapy should be initiated under the supervision of a healthcare professional experienced in the management of porphyria.

It also draws attention to the need to perform liver function tests before and during treatment with givosiran (so that treatment interruption or discontinuation can be considered in the event of clinically relevant transaminase elevations) and to implement careful monitoring of renal function in patients with pre-existing renal disease in accordance with the SPC recommendations (sections 4.2, 4.4 and 4.8 of the SPC).

## COMMITTEE'S CONCLUSIONS

### Clinical benefit

◗ Acute hepatic porphyrias are rare hereditary conditions that can lead to the development of sometimes irreversible and potentially fatal serious neurological symptoms. Recurrent acute attacks are incapacitating and result in a major impairment of quality of life.
◗ This is a prophylactic treatment for acute porphyria attacks.
◗ Based on available data with a 12-month follow-up period, the efficacy/adverse effects ratio of GIVLAARI (givosiran) is high in adult patients with AHP and with severe and recurrent acute attacks. The efficacy/adverse effects ratio has not been established in the other MA situations, in particular in patients aged 12 to 18 years. Longer-term data are expected.
◗ There is no medicinal alternative to GIVLAARI (givosiran) in the prophylaxis of acute attacks associated with acute hepatic porphyria (see paragraph 05 of the present opinion).
◗ GIVLAARI (givosiran) is a treatment for acute hepatic porphyria (AHP) only for patients aged 18 years and over and with active disease, characterised by at least 2 porphyria attacks requiring hospitalisation, an urgent healthcare visit or treatment with IV hemin at home, in the past 6 months (see paragraph 08 of this opinion). The medicinal product has no role in the other clinical situations and in patients aged 12 to 18 months.

**Public health impact**

Considering:
- the seriousness of the disease in terms of morbidity and quality of life, particularly in patients with recurrent acute attacks,
- the low prevalence of acute hepatic porphyria (AHP),
- the absence of therapeutic alternatives to GIVLAARI (givosiran) in the prophylaxis of acute attacks associated with AHP and hence the medical need considered to be unmet in this situation,
- demonstration of the superiority of givosiran compared to placebo after 6 months in terms of the number of severe acute attacks of porphyria, ALA and PBG levels, the use of hemin for etiological treatment of acute attacks, as well as pain, and the maintenance of this efficacy after 12 months,
- the expected improvement in the care and life pathway given the significant reduction in the number of acute porphyria attacks, pains, complications and associated hospitalisations, the elimination of IV hemin administration to prevent attacks and the associated risks, and hence an expected improvement in quality of life despite the exploratory nature of these analyses in the study,
- the partial response to the identified unmet medical need,

GIVLAARI (givosiran) is likely to have an additional impact on public health.

**Considering all these elements, the Committee deems that the clinical benefit of GIVLAARI (givosiran) is:**

- **substantial only for patients aged 18 years and over, for the treatment of acute hepatic porphyria (AHP) and with active disease characterised by at least 2 porphyria attacks requiring hospitalisation, an urgent healthcare visit or treatment with IV hemin at home, in the past 6 months.**
- **insufficient to justify its funding by the French national health insurance system in the other MA situations, i.e., in patients not meeting the ENVISION study inclusion criteria, in particular in patients with intermittent acute attacks (1 to 3 attacks per year), as well as in patients aged 12 to 18 years, in the absence of data.**

**The Committee issues a favourable opinion for inclusion in the hospital formulary list of reimbursed proprietary medicinal products approved for use in the treatment of patients aged 18 years and over with acute hepatic porphyria (AHP) and with active disease, characterised by at least 2 porphyria attacks requiring hospitalisation, an urgent healthcare visit or treatment with IV hemin at home, in the past 6 months.**

**Unfavourable opinion for inclusion in the hospital formulary list of reimbursed proprietary medicinal products approved for use in the other MA situations, i.e., in patients not meeting the ENVISION study inclusion criteria, in particular in patients with intermittent acute attacks (1 to 3 attacks per year), as well as in patients aged 12 to 18 years.**

## Clinical Added Value

**Considering:**

- **demonstration of the superiority of GIVLAARI (givosiran) compared to placebo in terms of the number of severe acute porphyria attacks (requiring hospitalisation, an urgent healthcare visit or treatment with IV hemin at home) during the first 6 months of treatment, with an effect size deemed to be substantial and clinically relevant (primary endpoint; 3.22 vs 12.52 attacks; RR = 0.26; $CI_{95\%}$ [0.16; 0.41]; p < 0.0001), in adult patients with AHP and with severe and recurrent acute attacks in a phase III randomised, double-blind study,**
- **maintenance of this efficacy after 12 months in the follow-up data**
- **the absence of therapeutic alternatives to prevent acute porphyria attacks and hence the medical need considered to be unmet in this situation,**

**and despite:**

- **the lack of long-term efficacy and safety data (> 12 months of treatment) and,**
- **the absence of robust data concerning patients' quality of life given the exploratory nature of the analyses,**

**the Transparency Committee considers that GIVLAARI (givosiran) provides an important clinical added value (CAV II) in the therapeutic strategy for adult patients with acute hepatic porphyria (AHP).**