HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE

SUMMARY

18 NOVEMBER 2020

The legally binding text is the original French opinion

pegvaliase

PALYNZIQ 2.5 mg, 10 mg and 20 mg solution for injection in pre-filled syringe

First assessment

Key points

Favourable opinion for reimbursement in the treatment of patients with phenylketonuria (PKU) aged 16 years and older who have inadequate blood phenylalanine control (blood phenylalanine levels greater than 600 micromol/l) despite prior management with available treatment options.

What therapeutic improvement?

Therapeutic improvement in the management of the disease.

Role in the care pathway?

Since the clinical - in particular, neurological - consequences of phenylketonuria (PKU) are directly related to phenylalanine (Phe) levels, the objective of treatment is to maintain Phe levels within the recommended range, either via a phenylalanine-restricted diet, or using medicinal treatment (sapropterin) or by a combination of the two therapeutic approaches.

All young women with PKU should be informed about the risk of maternal phenylketonuria (maternal PKU) in the event of pregnancy without strict control of Phe levels.

Patients with levels > 600 µmol/L [10 mg/dL] require treatment because their outcome without treatment clearly demonstrates impairment of cognitive functions. The outcome of patients with levels of between 360 and 600 µmol/L [6-10 mg/dL] is less clear. The various studies conducted reveal conflicting results. In conclusion, and as a precaution in the absence of large-scale studies on this subject, the 2018 French national diagnostic and care protocol (PNDS) proposes compliance with the 2017 European consensus, which recommends the following target levels:

- 120-360 µmol/L [2-6 mg/dL] in children up to the age of 12 years,
- **120-600 µmol/L [2-10 mg/dL] from 12 years of age and in adults,**
- 120-360 µmol/L [2-6 mg/dL] during pregnancy,

Phe levels of 600-900 µmol/L [10-15 mg/dL] are acceptable in adult patients with no clinical consequences and who cannot manage to remain below 600 µmol/L, when they find it difficult to tolerate strict dietary measures. In the event of excessively low Phe levels (< 120 µmol/L) Phe deficiency should be suspected, and corrected if necessary.

To control the metabolic balance of patients with PKU, foods with a high protein - and hence Phe - content should be excluded from the diet. The daily amount of phenylalanine (Phe tolerance) should be supplied by natural foods in controlled quantities. Protein intake should be supplemented by amino acid mixtures in order to compensate for deficiencies related to the exclusion of high-protein foods. The strictness of the diet depends on the individual Phe tolerance of each patient.

Adolescence is a key period in the management of patients with PKU. Phe levels should remain ≤ 600 µmol/L [10 mg/dL] after the age of 12 years and there should be no relaxing of dietary measures. Dietary measures should be continued for life, and not be discontinued in adulthood as was previously the case. These guidelines require the continuation of low-protein foods and amino acid mixtures in patients with severe PKU.

Medicinal treatment with sapropterin (KUVAN) in patients identified as responders from birth may also be initiated, the aim being to make the diet less restrictive or even avoid it completely in some cases. This medicinal product, which is a synthetic form of enzymatic cofactor BH4, is currently the only product authorised in the treatment of hyperphenylalaninaemia in children from birth and in adults. The proportion of responders is limited in practice because residual phenylalanine hydroxylase (PAH) activity is required for it to be effective, and it rarely proves to be effective in the most severe forms of the disease.

Role of the medicinal product in the care pathway

PALYNZIQ (pegvaliase) is a last-resort option for the treatment of patients from 16 years of age with phenylketonuria and inadequate blood phenylalanine control (levels > 600 µmol/L) despite prior management with available treatment options.

In view of the variability of the therapeutic response, the safety profile and the treatment constraints, the Committee considers that the patients most likely to benefit from pegvaliase are those with hyperphenylalaninaemia > 900 µmol/L. It is also recommended not to prescribe this medicinal product in pregnant women or women planning a pregnancy, in the absence of assessment in these populations. In this context, a strict dietary approach should be employed to maintain the target level of <360 µmol/L.

Considering the specificities of management of this rare disease, and the characteristics of this new medicinal product (safety profile and burden of implementation), the Committee recommends that decisions to initiate or discontinue pegvaliase treatment should be taken during multidisciplinary team meetings within a reference or expert centre and that initial treatment be managed by physicians experienced in the management of PKU in liaison with one of these centres.

Regular metabolic, nutritional and neurological monitoring is essential to ensure the therapeutic efficacy of treatment, its safety and patients' compliance with treatment, in order to adapt it if necessary. Particularly close monitoring is required during adolescence, a key period that is often a source of treatment failure due to the difficulties maintaining it. This monitoring should be carried out by a medical and nutritional team specialised in the management of phenylketonuria.

Special recommendations

Considering the specificities of management of this rare disease, and the characteristics of this new medicinal product (safety profile and burden of implementation), the Committee recommends that decisions to initiate or discontinue pegvaliase treatment should be taken during multidisciplinary team meetings within a reference or expert centre and that initial treatment be managed by physicians experienced in the management of PKU in liaison with one of these centres.

COMMITTEE'S CONCLUSIONS

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

Clinical benefit

◗ Phenylketonuria is a rare hereditary metabolic disease, characterised, in particular, by mental retardation and serious neurological disorders in the absence of treatment in the first few weeks of life.
◗ PALYNZIQ (pegvaliase) is a symptomatic treatment.
◗ Its efficacy/adverse effects ratio is modest. Its efficacy, demonstrated versus placebo in terms of reduction of phenylalanine levels in the short term in a selected population of responder patients, should be weighed up against its safety profile.
◗ There are currently no therapeutic alternatives in the MA indication.
◗ This is a last-resort treatment for patients from 16 years of age with phenylketonuria and inadequate blood phenylalanine control (blood phenylalanine levels > 600 µmol/L) despite prior management with available treatment options (see section 8).

Public health impact
Considering:
- the seriousness of phenylketonuria,
- its low incidence,
- the unmet medical need in patients with inadequate blood phenylalanine control despite prior management with available treatment options,
- the potential impact on the organisation of care, given the burden of the administration and monitoring protocol,
- the partial response provided to the identified need considering the additional demonstrated impact on morbidity (short-term reduction of phenylalanine levels versus placebo), but without a demonstrated impact on neurological complications and quality of life taking into account its safety profile,

PALYNZIQ (pegvaliase) is unlikely to have an additional impact on public health.
Considering all these elements, the Committee deems that the clinical benefit of PALYNZIQ (pegvaliase) is moderate in the MA indication.

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 patients with phenylketonuria (PKU) aged 16 years and older who have inadequate blood phenylalanine control (blood phenylalanine levels greater than 600 micromol/l) despite prior management with available treatment options, and at the MA dosages.

◗ **Recommended reimbursement rate: 30%**

Clinical Added Value

Considering:

- **the efficacy of pegvaliase, robustly demonstrated in terms of reduction of blood phenylalanine in the short term in comparison with placebo and in a highly selective population of responder patients among whom the treatment was initiated,**
- **the improvement of neurocognitive symptoms expected in the long term in symptomatic patients achieving and managing to maintain the recommended target phenylalanine levels,**
- **the unmet medical need in the MA indication of pegvaliase,**

but considering:

- **the very common adverse effects, particularly the high risk of potentially serious acute hypersensitivity reactions, and of hypophenylalaninaemia in the event of overdose,**
- **the absence of a quality of life assessment for these patients,**
- **the absence of any demonstrated impact on the daily natural protein intake,**

the Committee considers that PALYNZIQ (pegvaliase) provides a <u>minor clinical added value (CAV IV)</u> in the strategy for the treatment of patients with phenylketonuria (PKU) aged 16 years and older who have inadequate blood phenylalanine control (blood phenylalanine levels greater than 600 micromol/l) despite prior management with available treatment options.