Rare disease
Sector: Hospital

HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
21 JULY 2021

The legally binding text is the original French opinion version

nitisinone
ORFADIN 2 mg hard capsules
ORFADIN 5 mg hard capsules
ORFADIN 10 mg hard capsules
ORFADIN 20 mg hard capsules
ORFADIN 4 mg/mL oral suspension

New indication

Key points

Favourable opinion for reimbursement in the treatment of adult patients with alkaptonuria (AKU).

What therapeutic improvement?

No clinical added value in the therapeutic strategy.

Role in the care pathway?

Alkaptonuria is a genetic metabolic disease caused by a deficiency in homogentisate 1,2 dioxygenase, the third enzyme involved in the catabolism of tyrosine and the degradation of homogentisic acid (HGA). Alkaptonuria is characterised by an increase and systemic accumulation of HGA and its oxidation product (acetic benzoquinone acid) in various tissues (such as cartilage and connective tissue) and body fluids (such as urine and sweat). This accumulation leads to dark coloured urine and pigmentation (ochronosis) and is responsible for multiple clinical manifestations of the disease.

Alkaptonuria is a slow-progressing chronic disease. Life expectancy is not reduced but a gradual functional decline is observed in everyday activities, with progressive loss of mobility and a disabling pain syndrome.

The treatment of patients with alkaptonuria aims to prevent ochronosis, prevent the joint, genitourinary and cardiovascular complications of the disease and improve patients' quality of life.

At present, there are no medicinal products authorised in the treatment of alkaptonuria.

The treatment options used are based primarily on:

- symptomatic treatments of the clinical manifestations of the disease as they occur (analgesia, physiotherapy, joint replacement surgery),
- a low phenylalanine and tyrosine diet, although this is difficult for patients to maintain and has not been shown to be effective to improve symptoms of alkaptonuria,
- the off-label use of nitisinone as early as possible due to its mechanism of action leading to a reduction in the HGA formation and systemic accumulation that causes the clinical manifestations of the disease.

Role of the medicinal product in the care pathway

ORFADIN (nitisinone) is a medicinal alternative in the treatment of adult patients with alkaptonuria, which should be used in combination with a strict low-protein diet to limit hypertyrosinaemia. It is the only medicinal product to have an MA in this indication in France.

Treatment with nitisinone leads to an increase in tyrosine levels, which may be associated with ocular adverse effects (such as corneal opacity and keratopathy) and cutaneous adverse effects. It is essential to combine nitisinone treatment with a low tyrosine and phenylalanine diet in order to limit the toxicity associated with hypertyrosinaemia. According to the SPC, in patients who develop keratopathies, plasma tyrosine levels should be monitored and maintained below 500 micromol/L, and nitisinone should be temporarily discontinued. It may be reintroduced when the symptoms have been resolved.

The Committee regrets the absence of data in patients with alkaptonuria in the pre-ochronotic phase, during which the mechanism of action of nitisinone could be of interest.

Given the natural course of alkaptonuria and the need to treat patients as soon as possible, particularly during childhood, to prevent the disabling - and in some cases, irreversible - complications of the disease, the Committee nevertheless highlights:

- the importance of scheduling paediatric development in consultation with reference and expert centres, enabling, in particular, definition of the age at which it is pertinent to start this treatment,
- and to evaluate the appropriateness of compassionate access pending the results of the paediatric development plan.

Special recommendations

Considering the specificities of the management of this rare disease and the safety profile of nitisinone, the Committee recommends that the initial prescription of ORFADIN (nitisinone) be restricted to physicians experienced in the management of alkaptonuria (metabolic specialists), in consultation with reference and expert centres.

Regular follow-up of the disease and of nutrition is essential to ensure the therapeutic efficacy of nitisinone and monitor its safety.

COMMITTEE'S CONCLUSIONS

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

Clinical benefit

◗ Alkaptonuria is a rare genetic metabolic disease caused by an enzyme deficiency, characterised by the systemic accumulation of homogentisic acid and its oxidation product (acetic benzoquinone acid) from childhood, leading to an ochronosis process and the development of clinical manifestations. It is a rare disease that affects patients' quality of life (joint pain, symptoms, loss of mobility) and that may cause numerous complications associated with ochronotic joint disease (musculoskeletal, genitourinary and cardiac involvement).

◗ The proprietary medicinal product ORFADIN (nitisinone) is a preventive medicinal product.

◗ The efficacy/adverse effects ratio of nitisinone is low in adults, due to the limitations indicated in the Summary and Discussion section.

◗ There are no medicinal products authorised in this indication. Current treatment options are based on a low protein (tyrosine and phenylalanine) diet and symptomatic treatments of the disease.

◗ ORFADIN (nitisinone) is a medicinal alternative in the treatment of adult patients with alkaptonuria, which should be used in combination with a strict low-protein diet to limit hypertyrosinaemia.

Public health impact
Considering:
- the seriousness of the disease and its rarity,
- the very partially met medical need,
- the lack of response to the identified need in the absence of any demonstrated impact on morbidity and mortality, quality of life or the care pathway,

ORFADIN (nitisinone) is unlikely to have an additional impact on public health.

Given all these elements, the Committee deems that the clinical benefit of ORFADIN (nitisinone) is low in the MA indication.

The Committee issues a favourable opinion for inclusion in the hospital formulary list of reimbursed proprietary medicinal products approved for use in the MA indication and dosages.

Clinical Added Value

Considering:

- **the natural history of alkaptonuria and the very partially met medical need with a requirement to have access to effective, well tolerated medicinal products with an MA aimed at preventing the accumulation of homogentisic acid (HGA) in order to prevent harmful complications associated with the disease,**
- **demonstration of the efficacy of nitisinone in a randomised, open-label, comparative study versus no therapy (SONIA 2), in terms of the reduction in urinary HGA levels (primary endpoint assessed under blind conditions) in adult patients at an advanced clinical stage of the disease,**

but considering:

- **the low clinical relevance of the biological endpoint (HGA levels) in this specific population with established clinical sequelae,**
- **the absence of robust data documenting the clinical efficacy of nitisinone on the progression of the main complications of alkaptonuria (for example, AKUSSI clinical scores or their components) at this advanced stage of the disease,**
- **the absence of robust data on quality of life data, which is particularly impaired in this disease,**

the Committee deems that ORFADIN (nitisinone), in combination with a low tyrosine and phenylalanine diet, provides no clinical added value (CAV V) in the current treatment of adult patients with alkaptonuria.