HAUTE AUTORITÉ DE SANTÉ

TRANSPARENCY COMMITTEE
SUMMARY
21 APRIL 2021

The legally binding text is the original French opinion version

lumasiran
OXLUMO 94.5 mg/0.5 mL solution for injection

First assessment

Key points

Favourable opinion for reimbursement in the treatment of primary hyperoxaluria type 1 (PH1) in all age groups.

What therapeutic improvement?

Therapeutic improvement in the management of the disease.

Role in the care pathway?

Conservative therapy should be initiated early, from the time a diagnosis of PH1 is suggested, in patients with preserved renal function. The aim is to maintain renal function by reducing the production of calcium oxalate, reducing urinary concentrations of calcium oxalate and inhibiting its crystallisation. The recommended conservative treatments are:

- Hyperhydration (approximately 3 L/m² per 24 h), which is an essential treatment to dilute urine, both day and night. This is a burdensome treatment approach, particularly in infants and young children, which generally requires the use of a nasogastric tube or gastrostomy to guarantee adequate hydration.

- A calcium oxalate crystallisation inhibitor (potassium citrate), as long as renal function is preserved. In the event of impaired renal function, it may be replaced by sodium citrate, adapted to the glomerular filtration rate (eGFR) and plasma potassium levels.

- Pyridoxine (vitamin B6), an AGT cofactor, in responder patients, to obtain a ≥ 30% reduction in urinary oxalate excretion. All patients should be tested for reactivity to pyridoxine; however, only a subset of patients with a precise AGXT gene mutation (in particular with genotype G170Arg) is more likely to respond effectively to pyridoxine. Responder patients should continue taking pyridoxine as long-term therapy.

Reducing the intake of oxalate-rich foods is of little benefit insofar as the role of exogenous oxalate is minimal compared to endogenous over-production. Excessive vitamin C and D intake should be avoided.

When renal function deteriorates, it is recommended to consider preventive liver and kidney transplantation in patients with renal impairment at a sufficiently early stage (eGFR < 40 ml/min/1.73 m²) to prevent the complications of systemic oxalosis.

Combined liver and kidney transplantation is recommended in most patients, either simultaneously or sequentially depending on the patient's condition and the renal function stage. However, despite its efficacy, this invasive procedure exposes patients to life-long immunosuppression and surgery-related risks.

It may nonetheless be necessary to use dialysis in certain situations, such as severe infantile forms pending organ transplantation or when preventive transplantation is not possible. In these cases, it is recommended to use high-efficiency dialysis, such as daily haemodialysis, night-time dialysis or a combination of daily haemodialysis and peritoneal dialysis. Dialysis may also be recommended during and after organ transplantation in patients with systemic oxalosis and/or an inadequate urine output at the start of the post-transplantation period.

Role of the medicinal product in the care pathway

OXLUMO (lumasiran) is a first-line therapy in the treatment of primary hyperoxaluria type 1 (PH1) in all age groups. It is the only medicinal product to have an MA in this indication in France.

According to the SPC, treatment with lumasiran increases plasma glycolate levels, which may increase the risk of metabolic acidosis or worsening of pre-existing metabolic acidosis in patients with severe or end-stage renal disease. These patients should therefore be monitored for signs and symptoms of metabolic acidosis.

COMMITTEE'S CONCLUSIONS

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

Clinical benefit

◗ Primary hyperoxaluria type 1 (PH1) is a serious disease with an impact on patients' quality of life of (symptoms, hospitalisation for urological procedures, treatments), and which may progress to end-stage kidney failure with the consequences of systemic oxalosis. This seriousness has been reported by patients in the context of a patient association contribution.

◗ The proprietary medicinal product OXLUMO (lumasiran) is a medicinal product with a curative intent.

◗ Considering the efficacy of lumasiran in terms of reduction in urinary and blood oxalate levels and its safety profile, the efficacy/adverse effects ratio is high.

◗ There are therapeutic alternatives (see section 05 Clinically relevant comparators).

◗ OXLUMO (lumasiran) is a first-line therapy in the treatment of primary hyperoxaluria type 1 (PH1) in all age groups.

Public health impact

Considering:
- the seriousness of the condition,
- its rarity,
- the very partially met medical need,
- the partial response to the identified need given an expected impact on morbidity and mortality and on the care and/or life pathway, but which is still to be demonstrated in the absence of clinical data,

OXLUMO (lumasiran) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of OXLUMO (lumasiran) is substantial 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 marketing authorisation indication and dosages.

◗ **Recommended reimbursement rate: 65%**

Clinical Added Value

Considering:

- **demonstration of a superiority of lumasiran after 6 months of treatment in terms of reduction in urinary and serum oxalate levels, endpoints deemed to be relevant,**
    - **compared to placebo in patients aged 6 years or older, with PH1 and relatively preserved renal function (eGFR > 30 ml/min/1.70 m²), with a relevant effect size (urinary oxalate: mean difference of -53.5% [-62.3; -44.8], p<0.0001; serum oxalate: mean difference of -39.5% [-50.1; -28.9], p< 0.0001),**
    - **before/after treatment with lumasiran in patients aged under 6 years, with PH1 and relatively preserved renal function (eGFR > 45 ml/min/1.70 m²), with a relevant effect size (urinary oxalate: mean reduction of 71.7% [-77.5; -66.4]; serum oxalate: mean reduction of 31.7% [-39.5; -23.9]),**
- **the very partially met medical need and the need for effective alternatives that are less restrictive than conservative treatment,**

but considering:

- **the immaturity of the data in patients with PH1 with advanced renal disease (with or without dialysis),**
- **the absence of data on clinically relevant endpoints in this disease (renal lithiasis, deterioration of renal function, clinical manifestations at the systemic oxalosis stage),**
- **the absence of robust data on quality of life,**
- **uncertainties with respect to the longer-term safety, particularly concerning the development of anti-lumasiran antibodies,**

the Committee considers that OXLUMO (lumasiran) provides a moderate clinical added value (CAV III) in the current care pathway for primary hyperoxaluria type 1.