OPINION RELATIVE TO MEDICINAL PRODUCTS

Voxelotor
OXBRYTA 500 mg

film-coated tablets

First assessment

Adopted by the Transparency Committee on 20 July 2022

SUMMARY

The legally binding text is the original French opinion version

- **Sickle cell disease**
- **Sectors: Retail and hospital**

Key points

Favourable opinion for reimbursement **only** in the treatment of **severe** haemolytic anaemia due to sickle cell disease (SCD) in adults and paediatric patients 12 years of age and older as monotherapy or in combination with hydroxycarbamide.

Unfavourable opinion for reimbursement in the other populations of the MA (non-severe form of haemolytic anaemia).

What therapeutic improvement?

No clinical added value in the therapeutic strategy.

Role in the care pathway?

No medicinal products are currently specifically authorised in the treatment of haemolytic anaemia in patients with sickle cell disease. The medicinal products specifically authorised in the treatment of sickle cell disease are only for the prevention of vaso-occlusive crises (VOCs): hydroxycarbamide (SIKLOS and XROMI) and crizanlizumab (ADAKVEO).

The treatment of haemolytic anaemia is currently based on:

- Simple transfusions or exchange transfusions in the event of symptomatic or poorly tolerated chronic anaemia.
- Hydroxycarbamide (also known as hydroxyurea) off-label. According to the French national diagnostic and care protocols (PNDS) issued by the HAS in 2014, hydroxycarbamide can be offered in the event of anaemia:
  - in children and adolescents: in the event of severe anaemia (Hb < 6 g/dl or < 7 g/dl with poor clinical or functional tolerance)
  - in adults: in the event of severe chronic anaemia after having ruled out a curable cause for exacerbation and if the anaemia is symptomatic or combined with organ damage, in particular renal or cardiac.

It should be noted that in 2021, after the publication of the PNDS, the application for extension of the MA for SIKLOS (hydroxycarbamide) in the treatment of haemolytic anaemia was assessed by the CHMP. The latter concluded that the use of hydroxycarbamide could not be recommended in this indication, in view of the clinical data not enabling its benefit-risk balance to be adequately documented.

- Erythropoietin (EPO) off-label. EPO is not cited as a therapeutic option in the PNDS for children and adolescents. According to the PNDS for adults, EPOs are used following the opinion of reference and expert centres in certain off-label situations, in particular chronic anaemia, in combination with hydroxycarbamide.

The only curative treatment currently is a bone transplant. This is reserved for the most severe forms of the disease, particularly in children, and remains exceptional in adults.

Role of the medicinal product in the care pathway

OXBRYTA (voxelotor) is the first medicinal product to have a specific MA in the treatment of haemolytic anaemia in patients with sickle cell disease.

As knowledge currently stands, the Committee considers that the prescription of OXBRYTA (voxelotor) should be reserved for the treatment of **severe** haemolytic anaemia, in combination with hydroxycarbamide or as monotherapy. Since there is currently no consensus definition of severe haemolytic anaemia, prescriptions will depend on the assessment and experience of the specialist prescriber in the treatment of sickle cell disease, based on both clinical and laboratory criteria.

To date, only a benefit in terms of increase in haemoglobin and reduction in certain haemolysis markers in the short term (24 weeks) has been demonstrated versus placebo in the HOPE study, a study with a low level of evidence in a population predominantly treated with hydroxycarbamide at baseline and with a low rate of vaso-occlusive crises in the previous year.

The clinical impact of improving these laboratory parameters under voxelotor is not currently known. In fact, no benefit versus placebo was demonstrated in the HOPE study on clinical endpoints reflecting the severity of the disease or patient well-being (in particular the number of VOCs, disease symptoms, quality of life, need for blood transfusions and use of opioids).

Given its oral use, voxelotor could be useful in the care pathway of transfused patients if a benefit in terms of transfusion-sparing were to be demonstrated, although this is not yet the case.

The mechanism of action of voxelotor is a source of uncertainties in terms of the expected clinical benefits of increasing haemoglobin levels, and the potential risks of tissue hypoxia in the long term and of VOCs in the event of temporary interruption of treatment.

Voxelotor could lead to an excessive increase in haemoglobin levels in some patients, with a risk of blood hyperviscosity and associated complications that cannot be totally excluded, in view of the data from the HOPE study, during which 41.1% of patients treated at the dose of 1,500 mg/day achieved a haemoglobin level of > 10 g/dL at 24 weeks and in which a higher incidence of acute chest syndromes and priapism was observed in the voxelotor group than under placebo. Although a reduction in dose would appear to be justified in practice, no dosage reduction regimen has been validated in this situation and only the fixed dose of 1,500 mg/day is recommended in the SPC. The Committee highlights that, in sickle disease patients, it is not recommended to exceed an Hb level of 10 to 11 g/dL with the treatments currently used to correct haemoglobin[5], since there is a risk of complications associated with blood hyperviscosity above this level. The Committee considers that the clinical data available is still inadequate to be able to conclude that this risk cannot be transposed to voxelotor.

Special attention must be paid to ensuring good compliance with treatment, particularly in adolescents and young adults and especially since there are questions concerning the existence of a risk of VOC, related to the mechanism of voxelotor, in the event of temporary interruption of treatment.

Special recommendations

The Committee regrets that no dosage reduction regimen has been evaluated during clinical trials in the event of an excessive increase in haemoglobin levels and that only the fixed dose of 1,500 mg/day is recommended in the SPC, given data in the HOPE study demonstrating a concentration > 10 g/dL after 24 weeks of treatment in over 40% of patients treated at this dosage.

Committee's conclusions

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

Clinical benefit

➔ Sickle cell disease is a condition with a very variable course. It is associated with the development of haemolytic anaemia, the acute and chronic complications of which significantly impair the quality of life of patients and can ultimately be life-threatening.

➔ The proprietary medicinal product OXBRYTA (voxelotor) is a symptomatic medicinal product.

➔ Considering:

- The not very robust demonstration of a benefit versus placebo on haemoglobin levels and certain haemolysis markers, without a demonstrated impact on clinical criteria or on the need for transfusions, in a heterogeneous population in terms of disease severity, with or without concomitant hydroxycarbamide treatment,
- The available safety data, which is limited beyond 72 weeks, and uncertainties relative to the risk of tissue hypoxia in the long term, or the risk of blood hyperviscosity and associated complications in the event of an excessive increase in haemoglobin in a context in which a higher incidence of acute chest syndromes and priapism has been observed under voxelotor than under placebo, and relative to the risk of VOCs in the event of temporary treatment interruption,

the Committee considers that the efficacy/adverse effects ratio of OXBRYTA (voxelotor) is **low only in the event of severe haemolytic anaemia.**

➔ There is a non-medicinal therapeutic alternative: red cell concentrate transfusion (simple transfusions or exchange transfusions).

➔ As knowledge currently stands, the Committee considers that (see section 08 of the opinion):

- the use of OXBRYTA (voxelotor) should be reserved for the treatment of severe haemolytic anaemia, in combination with hydroxycarbamide or as monotherapy,
- this treatment has no role in the treatment of non-severe haemolytic anaemia.

➔ Public health benefit

Considering:

- the seriousness of severe haemolytic anaemia due to sickle cell disease and its low incidence,
- the partially met medical need,
- the partial response provided to the identified partially met need in view of:
  - the additional demonstrated impact on morbidity on laboratory endpoints (haemoglobin increase and reduction in certain haemolysis parameters, versus placebo), but the low robustness of this demonstration,
  - the lack of demonstrated impact on clinical criteria and on quality of life,
  - the potential additional impact on the care pathway of patients requiring regular transfusions given the oral administration, if a benefit in terms of transfusion-sparing were to be demonstrated, although this is not yet the case,

OXBRYTA (voxelotor) is unlikely to have an additional impact on public health.

Considering all these elements, the Committee deems that the clinical benefit of OXBRYTA (voxelotor) in the treatment of haemolytic anaemia due to sickle cell disease in adults and paediatric patients 12 years of age and older is:

- **low only** in the treatment of **severe** haemolytic anaemia, as monotherapy or in combination with hydroxycarbamide;
- **insufficient** to justify public funding cover in the other populations of the MA (non-severe form of haemolytic anaemia).

The Committee issues the following opinions:

- **favourable** for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use **only** in the treatment of **severe** haemolytic anaemia due to sickle cell disease in adults and paediatric patients 12 years of age and older, as monotherapy or in combination with hydroxycarbamide,
- **unfavourable** for inclusion in both the hospital formulary list and the retail formulary list of reimbursed proprietary medicinal products approved for use in the other populations of the MA (non-severe form of haemolytic anaemia).

Recommended reimbursement rate: 15%

Clinical Added Value

Treatment of severe haemolytic anaemia due to sickle cell disease in adults and paediatric patients 12 years of age and older, as monotherapy or in combination with hydroxycarbamide

Considering:

- Demonstration of the superiority of voxelotor compared to placebo in terms of response rate at 24 weeks, defined by an increase in haemoglobin of at least 1 g/dL, and a reduction in haemolysis, in the phase 3 HOPE study having included patients not very representative of a population with severe haemolytic anaemia, with or without concomitant hydroxycarbamide treatment,
- The low robustness of these results given the poor internal validity of the study in terms of control of bias risks,
- The debatable clinical relevance of the laboratory primary endpoint “haemoglobin increase of at least 1 g/dL”, its use as a surrogate endpoint in place of a clinical endpoint not being demonstrated to date,
- The absence of demonstrated benefit on the clinical complications of the disease, such as vaso-occlusive events and pulmonary hypertension, on quality of life or need for blood transfusions or exchange transfusions,
- The globally acceptable safety profile in the short term, but uncertainties in the longer term concerning the risk of tissue hypoxia, along with the risk of complications associated with blood hyperviscosity in a context in which 41.1% of patients in the HOPE study treated with voxelotor 1,500 mg achieved a haemoglobin level > 10 g/dL at 24 weeks and where a higher incidence of acute chest syndrome and priapism was observed under voxelotor than under placebo,

the Transparency Committee considers that OXBRYTA (voxelotor) provides no clinical added value (CAV V) in the care pathway for the treatment of severe haemolytic anaemia due to sickle cell disease in adults and paediatric patients 12 years of age and older, as monotherapy or in combination with hydroxycarbamide.