OPINION ON MEDICINAL PRODUCTS

ambrisentan

VOLIBRIS 2,5 mg, 5 mg and 10 mg,

film-coated tablets

New indication and inclusion of addition to range

Adopted by the Transparency Committee on 9 November 2022

SUMMARY

The legally binding text is the original French opinion version

- **Pulmonary arterial hypertension**
- **Sector: Hospital**

Key points

Approval of reimbursement, alone or in association, for the treatment of pulmonary arterial hypertension (PAH) in functional class II and III (WHO classification) adolescent and paediatric patients (aged from 8 years to under 18 years). Efficacy has been demonstrated for idiopathic PAH and for PAH associated with systemic collagenosis.

Therapeutic improvement?

No therapeutic improvement.

Role in therapeutic strategy?

The objective of treatment is primarily to improve patient survival and quality of life.

PAH is treated in children based on risk stratification (symptom progression, WHO functional classification, certain ultrasound parameters). Given that PAH is a progressive disease in the short term, regular follow-up is required to ensure early detection of clinical exacerbation in order to allow therapeutic escalation at the earliest possible opportunity. Prognostic assessment is important for the choice of initial treatment and assessment of treatment response.

The paediatric PAH treatment algorithm is extrapolated from that for adults, despite limited paediatric data based on low-quality methodology (no randomised controlled clinical trials).

As a first-line approach, it is recommended to conduct acute vasoreactivity testing in order to identify potential responders (<10%) to calcium channel blocker treatment.

For non-responders, and low-risk patients, it is recommended to introduce monotherapy treatment (endothelin receptor antagonists, PDE5i inhibitors, or prostacyclin analogues), or bitherapy treatment from the outset. For high-risk patients, it is recommended to use intravenously or subcutaneously administered prostacyclin analogues from the outset.

At the present time, in addition to ambrisentan, only bosentan (orally administered endothelin receptor antagonist) and sildenafil (orally administered PDE5 inhibitors) have been granted a marketing authorisation for children, and are covered in France for this paediatric indication.

Creating a Potts shunt is an alternative or bridge to lung transplantation to be proposed for forms failing to respond to tritherapy.

Role of VOLIBRIS (ambrisentan)

VOLIBRIS (ambrisentan) must be used, alone or in association, for the treatment of pulmonary arterial hypertension (PAH) in functional class II and III adolescent and paediatric patients. **It is a first-line treatment**.

It is an alternative to TRACLEER (bosentan) and to REVATIO (sildenafil).

Note that this treatment must only be initiated and supervised by a medical practitioner experienced in the treatment of pulmonary arterial hypertension.

Committee's conclusions

Actual Clinical Benefit

- PAH is a rare, potentially life-threatening lung disease, characterised by an increase in pulmonary arterial pressures and potentially resulting in right heart failure. Asthenia, progressive exertional dyspnoea, chest pain, and fainting are the most common clinical signs.
- The proprietary medicinal product VOLIBRIS (ambrisentan) is a symptomatic medicinal product.
- Based on the data currently available, the efficacy/adverse effect ratio is poorly defined in this population given the lack of comparative data and the limitations of the studies submitted by the pharmaceutical firm. However, the safety profile of ambrisentan is known as it is similar to that observed in adults. Thus, the efficacy/adverse effect ratio is moderate,
- Therapeutic alternatives are available (see Section 5 "Clinically relevant comparators").
- First-line treatment (see role in therapeutic strategy section).

Public health benefit

Considering:

- the severity of the disease and its low prevalence;
- the partially met medical need among children with PAH;
- the lack of response to the identified need due to lack of evidence of an impact on morbidity-mortality among children in the absence of comparative data;
- the lack of evidence of an impact on quality of life and on delivery of care;

VOLIBRIS (ambrisentan) is not likely to have an additional impact on public health.

Considering all of these elements, the Committee deems that the actual clinical benefit of VOLIBRIS (ambrisentan) is moderate alone or in association, for the treatment of pulmonary arterial hypertension (PAH) in functional class II and III (WHO classification) adolescent and paediatric patients (aged from 8 years to under 18 years).

The Committee approves inclusion of VOLIBRIS 2.5 mg film-coated tablets in the list of proprietary medicinal products approved for community use for the marketing authorisation indication and dosages.

The Committee approves inclusion of VOLIBRIS 5 and 10 mg film-coated tablets in the list of proprietary medicinal products approved for community use for the marketing authorisation indication and dosages.

Clinical Added Value

Considering:

- the lack of evidence of the efficacy of VOLIBRIS (ambrisentan) among children and adolescents aged 8 years and over on account of the lack of comparative data;
- the consistency of the outcomes observed in children with those in adults, suggested by a Bayesian extrapolation analysis and pharmacokinetic data providing evidence of a modest improvement versus placebo in walking distance as monotherapy, and evidence of a reduced risk of first morbidity-mortality event onset of the ambrisentan/tadalafil association versus monotherapies;
- the safety profile, seemingly similar to that of adults, apart from several cases of pneumonia reported in children;

the Transparency Committee deems that VOLIBRIS (ambrisentan) provides no clinical added value (CAV V) in the therapeutic strategy for children and adolescents from 8 years of age with functional class II and III pulmonary arterial hypertension.