BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

EZETROL (ezetimibe), cholesterol-lowering agent

Therapeutic benefit in children aged over 6 years comparable to that of adults.

Main points

- As in adults, EZETROL is indicated in children aged over 6 years, in:
  - primary (heterozygous familial and non-familial) hypercholesterolaemia, in combination with a statin, for patients not controlled by a statin alone or in monotherapy for patients with a statin contraindication or a statin intolerance,
  - homozygous familial hypercholesterolaemia (HoFH),
  - homozygous sitosterolaemia.
- The efficacy of ezetimibe in combination with simvastatin has been demonstrated in terms of reduction of LDL-C levels in children aged 10 - 17 years with heterozygous familial hypercholesterolaemia and in monotherapy in children aged 6 to 10 years with primary hypercholesterolaemia, mostly familial. In the absence of a specific study in patients with HoFH or sitosterolaemia, the efficacy of ezetimibe cannot be clearly established for children with these two diseases.
- There is, to date, no long-term efficacy data justifying a decrease in morbidity and mortality at adult age in patients treated during childhood.
- The safety of use of EZETROL, in combination with simvastatin, was evaluated in particular in patients aged 10 to 17 years with heterozygous familial hypercholesterolaemia. In this study, no adverse effect on growth or sexual maturity of boys or girls adolescents, or on the length of the menstrual cycle of girls, was detected.

Therapeutic use

Hypercholesterolaemia and mixed dyslipidaemia

In the majority of patients with hypercholesterolaemia for whom lifestyle changes are not sufficient, therapeutic needs are theoretically covered by the use of the five statins currently available (pravastatin, simvastatin, fluvastatin, atorvastatin and rosuvastatin) and that have demonstrated a benefit in morbi-mortality, on the prevention of cardiovascular events and death due to all causes.

In adults not controlled despite regular use of an appropriate dosage of statins, cholesterol-lowering combinations can be proposed: statin + ezetimibe or statin + cholestyramine. There is no data about cholestyramine in children.

In adult patients with dyslipidaemia, and in case of statin intolerance, the therapeutic choice is between: fibrates, cholestyramine and ezetimibe. In children, data are available only for ezetimibe.

Role of the medicinal product in the therapeutic strategy

The efficacy of EZETROL has been demonstrated in children aged 6 to 17 years only in terms of LDL-C reduction. To date, there is no long-term efficacy data justifying a decrease in morbi-mortality at adult age in patients treated in childhood.

Homozygous familial hypercholesterolaemia and sitosterolaemia

These pathologies are treated by centres specialised in hereditary metabolic disorders. Their prognosis is correlate with the age of the patient, the LDL-c level and the ongoing arterial exposure to a chronic excess of LDL-C since birth. The treatment objective is to reduce the LDL-C levels to prevent the occurrence of cardiovascular events.

Treatment relies on the prescription of lipid-lowering agents; the first-line treatment are statins and these may be taken in combination with ezetimibe or cholestyramine (not recommended in children) if the goals are not met. Apheresis of LDL-C may also be considered. Pharmacological treatment must be combined with lifestyle and dietary modifications.

- **Role of the medicinal product in the therapeutic strategy**
  In children aged 6 years and older and in adolescents with HoFH uncontrolled or statin intolerant, there is no specific study demonstrating the efficacy of the treatment. However, a study conducted in 48 patients including seven children aged 10 to 17 years seemed to indicate that the efficacy of ezetimibe is no different between adults and children.

Clinical data

- In one study, the objective was to compare the efficacy of ezetimibe 10 mg in combination with simvastatin 10, 20 or 40 mg compared to simvastatin alone in terms of reduction in LDL-C at 6 weeks in 247 adolescents aged 10 to 17 years with heterozygous familial hypercholesterolaemia. After 6 weeks of treatment, a significantly greater reduction in the LDL-C level was observed in the ezetimibe + simvastatin group than in simvastatin alone: -49.45% ± 1.19 versus -34.43% ± 1.22, difference -15.03% 95% CI [-18.36; -11.70], p<0.01.
- In another study, the objective was to compare the efficacy of ezetimibe to placebo in terms of reduction in LDL-C levels at 12 weeks in 138 children aged 6 to 10 years with primary hypercholesterolaemia (familial or non-familial). After 12 weeks of treatment, a significantly greater reduction in the LDL-C level was observed in the ezetimibe group than in the placebo group: -27.7% [-30.80; -24.69] versus -0.95% [-4.94; 3.04], difference -26.74% [-30.80; -22.69], p<0.001.

- In HoFH and sitosterolaemia, no specific study has been conducted in children and adolescents aged 6 to 17 years. However, studies previously analysed by the Transparency Committee have included paediatric patients and have evaluated these two indications:
  - The study in HoFH conducted in 48 patients, including seven children aged 10 to 17 years,
  - The study in sitosterolaemia conducted in 37 patients, including five children aged 10 to 17 years.

  While the results of these studies seem to indicate that there is no difference in efficacy of ezetimibe in adults and children, to the extent that the patients were not stratified *a priori* by age, the results are purely exploratory.
- The effects of ezetimibe in a period of more than 12 weeks of treatment has not been studied in children aged 6 to 10 years. EZETROL has not been studied in children under 6 years old.

Special prescribing conditions

- Medicinal product subject to the prior approval of the medical control service.

Benefit of the medicinal product

- The actual clinical benefit of EZETROL in the Marketing Authorisation indications is substantial.
- Recommends inclusion on the list of reimbursable products for supply by pharmacists and for hospital use.

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* The actual clinical benefit (ACB) of a medicinal product describes its benefit primarily in terms of its clinical efficacy and the seriousness of the condition being treated. HAS Transparency Committee assesses the ACB, which can be substantial, moderate, low or insufficient for reimbursement for hospital use.
** The improvement of actual clinical benefit (IACB) describes the improvement in treatment provided by a medicinal product compared with existing treatments. HAS Transparency Committee assesses the degree of IACB on a scale from I (major) to IV (minor). A level V IACB (equivalent of “no IACB”) means "no clinical added value".