TRANSPARENCY COMMITTEE

OPINION

8 September 2009

VEDROP 50 mg/ml, oral solution
B/20 ml bottle with 1 ml oral syringe (CIP code: 398 969-0)
B/60 ml bottle with 2 ml oral syringe (CIP code: 398 970-9)

Applicant: ORPHAN EUROPE
tocofersolan
ATC code: A11HA08

List I
Medicinal product reserved for hospital use. Prescription restricted to specialists in gastroenterology or paediatric medicine.
Medicine requiring special monitoring during treatment.

Date of the Marketing Authorisation (centralised procedure): 24 July 2009

This medicine has been authorised under “Exceptional Circumstances”. This means that, because of the rarity of this disease, it has been impossible to get complete information on this medicine. The EMA will review any new information on the medicine every year and the SPC will be updated as necessary.

Reason for request: Inclusion on the list of medicines approved for hospital use.
1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient
tocofersolan

1.2. Indication

“VEDROP is indicated in vitamin E deficiency due to digestive malabsorption in paediatric patients suffering from congenital chronic cholestasis or hereditary chronic cholestasis, from birth (in term newborns) to 16 or 18 years of age, depending on the region”.

1.3. Dosage

“The treatment with VEDROP should be initiated and supervised by a physician experienced in the management of patients suffering from congenital chronic cholestasis or hereditary chronic cholestasis. Bioavailability of vitamin E from VEDROP differs from that of other medicinal products. The dose should be prescribed in mg of d-alpha-tocopherol in the form of tocofersolan. Plasma vitamin E level should be monitored monthly for at least the first few months of therapy, thereafter at regular intervals and the dose adjusted accordingly if necessary.

Posology
The recommended total daily dose in paediatric patients suffering from congenital chronic cholestasis or hereditary chronic cholestasis is 0.34 ml/kg/day (17 mg/kg of d-alpha-tocopherol in the form of tocofersolan). The dose should be adjusted according to plasma vitamin E level.

To calculate the dose of VEDROP to be administered, divide the prescribed dose of d-alpha-tocopherol (in mg) by 50. The result is the volume of VEDROP in ml:

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\text{Dose of VEDROP (in ml)} = \frac{\text{dose of d-alpha-tocopherol (in mg)}}{50}
\]

In congenital chronic or hereditary chronic cholestasis patients, the posology is 17 mg/kg/day of d-alpha-tocopherol in the form of tocofersolan; the following table gives the volume of VEDROP in function of patients' weights.

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>VEDROP volume (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>1.0</td>
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<tr>
<td>4</td>
<td>1.4</td>
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<tr>
<td>5</td>
<td>1.7</td>
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<td>6</td>
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<td>7</td>
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<td>8</td>
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<td>9</td>
<td>3.1</td>
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<td>10</td>
<td>3.4</td>
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<tr>
<td>15</td>
<td>5.1</td>
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</tbody>
</table>

1 tocofersolan is a synthetic form of vitamin E made water-soluble by binding it to polyethylene glycol, enabling it to be absorbed from the gastrointestinal tract.
Method of administration
VEDROP is administered orally with or without water. The 1-ml or 2-ml oral syringes included in the container are designed to assist in measuring out the exact dose in accordance with the prescribed posology.

Note: No dose-finding study was put in place during product development. The recommended dosage is based on an analysis of the bibliographic data.

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2010)
A Alimentary tract and metabolism
A11 Vitamins
A11H Other plain vitamin preparations
A11HA Other plain vitamin preparations
A11HA08 Tocofersolan

2.2. Medicines in the same therapeutic category
VEDROP is the only oral formulation available at present which is indicated in the treatment of chronic cholestasis.

One other medicinal product is indicated and used in the treatment of cholestasis. This is Vitamin E NEPALM 100 mg/2 ml, injectable solution of alpha-tocopherol acetate, indicated in the “treatment of vitamin E deficiency when oral administration is not possible:
- gastrointestinal malabsorption of vitamin E: cystic fibrosis, hepatic cholestasis, pancreatic insufficiency, other malabsorption states
- intramuscular injection of vitamin E during elemental enteral nutrition.”

Note: the other oral presentations of vitamin E, based on α-tocopherol acetate or succinate, are not absorbed in children with chronic cholestasis because they are liposoluble.

2.3. Medicines with a similar therapeutic aim
Not applicable
3. ANALYSIS OF AVAILABLE DATA

The pharmaceutical company submitted a dossier comprising a large quantity of bibliographic data, including pharmacokinetic and clinical studies. Of the latter, the Sokol study was retained because it evaluated the efficacy and tolerance of tocofersolan in a sufficient number of patients in the indication in the Marketing Authorisation.

3.1 Efficacy

The objective of the open-label, multicentre Sokol study conducted in the United States was to determine the long-term efficacy and tolerance of tocofersolan in the treatment of vitamin E deficiency states in 64 patients with cholestasis aged between 0.5 and 20 (average age: 6.4 ± 0.8) years who had not responded to supplementation with other oral formulations of vitamin E (vitamin E intake of 70-212 IU/kg/day for at least 2 months) or to intramuscular vitamin E treatment.

The tocofersolan administered in this study was a hospital preparation in some centres. Doubts exist regarding the similarity between these preparations and VEDROP in terms of pharmaceutical formulation.

Of these patients, 19 had biliary atresia, 17 had Alagille syndrome (bile duct paucity) and 13 had Byler’s disease (progressive familial intrahepatic cholestasis).

The results are available for 60 patients.

The comparison is of the “before/after treatment” type.

The main endpoints for the study were the change in serum vitamin E concentrations and the patients’ neurological status (measured using a score) between the start and end of treatment. No primary endpoint was defined.

The neurological score used a scale of 0 (normal) to 3 (severe) and evaluated the neurological signs and symptoms (including hyporeflexia, areflexia, ataxia of the limbs, coordination problems, pain, dysarthria, muscle weakness, etc.) which are characteristic of vitamin E deficiency states.

A change in this score was defined as an increase or decrease of more than 1 point.

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4 Jacquemin E. et al. Bioavailability of oral vitamin E formulations in adult volunteers and children with chronic cholestasis or cystic fibrosis, J Clinical Pharmacy and Therapeutics, 2009; 34: 515-522
5 Sokol RJ et al. Treatment of vitamin E deficiency during chronic childhood cholestasis with oral d-alpha-tocopheryl polyethyleneglycol 1000 succinate. Gastroenterology, 1987a; 93: 975-985
12 four patients had previously received intramuscular vitamin E treatment for at least one year and 7 for more than 20 months
13 the data are missing for 4 patients owing to poor compliance, a change of address or death following liver transplantation
The children received tocofersolan in a daily dosage of 25 IU/kg (a dose which could be adjusted). The average duration of treatment was 2.3 ± 0.2 years. On inclusion, the serum vitamin E concentration was 3.9 ± 0.5 µmol/l. After 6 months of treatment, it was 27.6 ± 1.9 µmol/l (p<0.05 – final value compared with baseline value)\(^\text{14}\).

At the end of the study, the dose administered was 20.6 ± 1.1 IU/kg/day.

The neurological score was evaluated in the patients (54/60) treated for more than 6 months with tocofersolan. This score changed from 4.8 ± 0.7 on inclusion to 4.0 ± 0.7 at the end of the treatment. Stabilisation of this score was observed in 27 patients, an improvement in 25 patients and deterioration in 2 patients.

### 3.2 Adverse effects

No adverse effects were mentioned in the data from the literature. Within the context of VEDROP use under temporary authorisation for use by a named patient (ATU nominative), no VEDROP-related serious adverse effects have been reported. The SPC mentions frequent gastrointestinal disorders (diarrhoea).

### 3.3 Conclusion

A study of the “before/after treatment” comparison type, conducted in 64 patients with cholestasis aged between 0.5 and 20 years who had not responded to oral or intramuscular vitamin E treatment, evaluated tocofersolan administered for 2.3 ± 0.2 years. Doubts exist regarding the similarity between the tocofersolan formulations administered in this study and VEDROP.

Administration of VEDROP in a dosage of between 20 and 25 IU/kg/day resulted in normalisation of serum vitamin E concentrations in all the patients and a stable or improved neurological status in around 50/60 of them.

The data available are very limited. The level of evidence of this study, on the basis of its methodology, is questionable. The advantage to the patient is difficult to assess but the benefit of vitamin E is long established.

VEDROP is well tolerated. Because polyethylene glycols are potentially nephrotoxic, however, VEDROP should be administered with caution and under strict supervision in children who are dehydrated or have renal impairment. The risk management plan (RMP) requires a database to be set up for the acquisition of demographic data, diagnostic information, blood and laboratory test findings, serum vitamin E levels before the instigation of treatment, treatment follow-up, changes in clinical signs and symptoms, vitamin E status and adverse effects in patients with hereditary or congenital chronic cholestasis.

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\(^{14}\) normal serum vitamin E concentrations are between 11.1 and 46.4 µmol/l. These target values were achieved in all the patients after 1 month of treatment
4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

Congenital or hereditary chronic cholestasis is a rare, severe disease which can cause irreversible neurological disability. It can be secondary to liver, biliary or, more rarely, extrahepatic diseases. Biliary atresia is the primary cause of neonatal cholestasis. Chronic cholestasis is defined by a reduction in bile flow, the main consequences of which are related to reduced intraluminal bile acid concentrations and the cellular toxicity of the accumulated bile acids. This results on the one hand in malabsorption of lipids and liposoluble vitamins and vitamin E in particular, a deficiency which leads notably to a neurological syndrome which can become permanent if the deficiency is not corrected in time. On the other hand, deficient bile acid secretion leads to cholestasis followed by hepatomegaly, hepatocellular injury, fibrosis of the liver and possibly cirrhosis. The prognosis depends on the cause, how early the condition is diagnosed and on management.

VEDROP is intended as curative therapy.

The efficacy/adverse effects ratio for VEDROP is high.

There is a treatment alternative to this medicinal product: vitamin E administered by intramuscular injection.

Public health benefit:

Congenital or hereditary chronic cholestasis is responsible for severe disorders, including lipid malabsorption resulting in a deficiency of liposoluble vitamins (particularly vitamin E). These diseases, the hepatic and neurological consequences of which in particular are severe, constitute only a low public health burden because of their rarity.

Improving the management of these clinical conditions constitutes a public health need which comes within the scope of an established priority (Rare diseases plan).

On the basis of the limited clinical data available (derived notably from a clinical study of the “before/after” type in 60 patients), the medicinal product VEDROP might be expected to have an additional impact in terms of ease of use, quality of life and morbidity/mortality. This impact can only be low, however, from a population viewpoint. The medicinal product VEDROP should therefore be capable of partly meeting the identified public health need.

Consequently, it is expected that the medicinal product VEDROP will benefit public health in this indication. This benefit is low.

The actual benefit of VEDROP is substantial.

4.2. Improvement in actual benefit (IAB)

Because of its pharmaceutical form, VEDROP, oral solution, is likely to improve the conditions of use compared with vitamin E NEPALM administered by intramuscular injection. Consequently, the transparency Committee considers that VEDROP provides a minor improvement in actual benefit (IAB IV) by comparison with vitamin E NEPALM.

4.3. Therapeutic use

The objective of treatment is to restore serum vitamin E levels to normal and to limit the development of tissue lesions caused by vitamin E deficiency, notably in nerve tissue, and the development of neurological disorders.
It has been demonstrated that the neurological deficits in patients with cholestasis are correlated directly with vitamin E deficiency and that these deficits are reversible if serum vitamin E concentrations are restored in the child’s first few years of life, these neurological disorders becoming irreversible with age and with increasing level of vitamin E deficiency. The duration of treatment depends on the duration of the chronic cholestasis. The patient is hospitalised in the first few months of disease management to ensure stabilisation of his/her nutritional regime and vitamin supplementation while the patient is awaiting a Kasai procedure and/or liver transplantation. The prognosis depends on how early the diagnosis is made and how early surgical treatment is carried out (< 45 days)\textsuperscript{15}.

While the patient is awaiting surgical treatment, if this treatment fails and until liver transplantation is performed, supplementation with liposoluble vitamins and vitamin E in particular is vital. At present, this supplementation takes the form of deep intramuscular injection of vitamin E\textsuperscript{16,17}. This medication is effective but the dose administered is difficult to adjust, the injection is very painful, has to be given frequently (every 15 days) and, because of the presence of Cremophor (polyethoxylated hydrogenated castor oil), causes sudden drops in arterial blood pressure and anaphylactoid reactions, notably in children under the age of 3.

VEDROP is the only oral formulation available for the treatment of vitamin E deficiency caused by gastrointestinal malabsorption in the paediatric population with chronic cholestasis. This medicinal product is an alternative to intramuscular vitamin E injections. Once corrective surgery has been performed (Kasai procedure and/or liver transplantation), the rationale for treatment with VEDROP disappears because the reestablishment of bile flow restores the absorption of liposoluble vitamins.

4.4. Target population

VEDROP is used to treat or prevent vitamin E deficiency in children with congenital or hereditary chronic cholestasis who cannot absorb vitamin E through their gut, from birth (full-term neonates) up to the age of 16 or 18, depending on the country. The incidence of neonatal cholestasis is estimated at 1/2,500 births. Based on 821,000 live newborns/year in France (INSEE 2009), the number of newborns per year affected by chronic cholestasis is probably around 330.

4.5. Transparency Committee recommendations

The transparency Committee recommends inclusion on the list of medicines approved for hospital use and various public services in the indication and at the dosage in the Marketing Authorisation.

The transparency Committee draws attention to the benefit of making the medicinal product VEDROP available in the community and would like this medicinal product to form the subject of an application for inclusion on the list of medicines refundable by National Health Insurance.

\textsuperscript{15} Surgical treatment is sequential: during the neonatal period, the Kasai procedure, a form of biloenteric bypass, can be followed subsequently, if necessary, by liver transplantation in the event of failure to restore bile flow into the intestine and/or complications of cirrhosis. Biliary atresia is the main indication for liver transplantation in children and is globally the main cause of liver transplantation in children – 90% of children recover and lead a normal life


\textsuperscript{17} Perlmutter et al. Intramuscular vitamin E repletion in children with chronic cholestasis. Am J Dis Child 1987;141: 170-174