Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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NHS SCOTLAND

# Re-submission

tocofersolan, 50mg/mL (corresponding to 74.5 IU tocopherol) oral solution (Vedrop®) SMC No. (696/11)

**Orphan Europe UK**

**07 September 2012**

The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

**ADVICE**: following a resubmission

**tocofersolan oral solution (Vedrop®)** is not recommended for use within NHS Scotland.

**Indication under review:** 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.

In an open-label, single-arm study, 96% of patients had an improved or stable neurological score after 2.5 years of treatment with tocofersolan.

The submitting company did not present a sufficiently robust economic analysis and in addition their justification of the treatment's cost in relation to its health benefits was not sufficient to gain acceptance by SMC.

Overleaf is the detailed advice on this product.

**Chairman,**
**Scottish Medicines Consortium**

## Indication

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.

## Dosing Information

The recommended total daily dose in paediatric patients suffering from congenital chronic cholestasis or hereditary chronic cholestasis is 0.34mL/kg/day (i.e. 17mg/kg of d-alpha-tocopherol in the form of tocofersolan).

The dose should be adjusted according to plasma vitamin E level.

Bioavailability of vitamin E from Vedrop® differs from that of other medicinal products. The dose should be prescribed as volume of tocofersolan oral solution. 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.

The treatment with tocofersolan should be initiated and supervised by a physician experienced in the management of patients suffering from congenital chronic cholestasis or hereditary chronic cholestasis.

## Product availability date

January 2010

## Summary of evidence on comparative efficacy

Congenital or hereditary chronic cholestasis reduces intestinal lipid absorption, due to a reduction in bile secretion, leading to malabsorption of the fat-soluble vitamins, including vitamin E. In these patients deficiency of vitamin E can result in significant, though potentially reversible, neurological disorders.

Tocofersolan is a polymeric mixture prepared by esterification of d-alpha-tocopherol succinate with polyethylene glycol (PEG) 1000 to form a water soluble formulation, d-alpha-tocopheryl polyethylene glycol-1000 succinate, which is taken orally. It forms micelles in the absence of bile acids allowing tocofersolan to be absorbed from the aqueous intestinal lumen.

One open-label, single-arm study[1] was considered pivotal with supportive data from a second study which reported on the bioavailability of vitamin E in all patients plus an assessment of neurological function in a subgroup of patients.[2,3] Both studies enrolled patients with chronic forms of neonatal cholestasis and low plasma vitamin E concentration and/or vitamin E/total lipids ratio who had failed to respond to up to 70 to 200 units/kg/day of oral alpha-tocopherol or alpha-tocopheryl acetate, or required treatment with intramuscular vitamin E. In the pivotal study, patients were excluded if they had significant renal impairment. All patients received the study treatment, tocofersolan. The studies assessed biochemical endpoints and neurological function outcomes.

The pivotal study[1] included 60 patients aged 6 months to 20 years (mean age 6.4 years) and a mean vitamin E level at baseline of 3.9 ±0.5micromol/L and vitamin E/total lipid ratio of 11.6±1.6micromol/g. At study entry, in patients <4 years (n=28), 15 had no neurological dysfunction but in patients over 4 years (n=26), 24 had an abnormal neurological score. The exceptions in the >4 years group were two patients who had received parenteral vitamin E since infancy. The initial dose of tocofersolan was 25 units/kg/day adjusted during the study to maintain vitamin E levels and the vitamin E/total lipid ratio. Patients were assessed in respect of 12 neurological signs: hyporeflexia and areflexia, truncal and limb ataxia, impaired position and vibratory senses, loss of light touch and pain sensations, ophthalmoplegia, dysarthria, proximal muscle weakness, scoliosis and pes cavus, and scored from 0 (normal) to 3 (severely abnormal) for each. A change in neurological score was defined as an increase or decrease of ≥1 point. All patients achieved normalisation of vitamin E levels, with a mean of 27.6±1.9 micromol/L (range 21.6 to 39.9 micromol/L). Overall, in 54 patients assessed neurologically, scores improved significantly from 4.7±0.7 to 4.0±0.7 ($p<0.001$). After a mean of 2.5 years of treatment (range from 6 months to 7 years), neurological scores had improved in 25 patients, stabilised in 27 and deteriorated in two patients, thus neurological symptoms were improved or stabilised in 96% of patients overall. When patients were grouped by age (under 4 years, 4 to 10 years [n=13] and over 10 years [n=13]), linear regression analysis showed a strong correlation between age as well as score at study entry. In children under 4 years (15/28 of whom had no neurological dysfunction), neurological function improved in 11 patients and was unchanged in 17 patients; in the 4 to 10 years group, neurological function was improved in 7 patients and unchanged in 6 patients; and in the over 10 years group, neurological function improved in 7 patients, was unchanged in 4 patients and worsened in 2 patients. Within each age group, for those children whose scores improved, the differences from baseline were statistically significant.

The supporting study enrolled 22 patients, aged between 7 months and 19 years.[2] Nine patients had previously received intramuscular vitamin E. An oral vitamin E tolerance test in 16 patients showed a rise in vitamin E levels in all but one patient. There was no statistically significant difference in absorption between patients who had or had not previously received intramuscular therapy. Following the tolerance test, maintenance treatment was initiated with tocofersolan 50 units/kg/day, but subsequently reduced to 25 units/kg/day when the first patient's vitamin E levels exceeded the target level. Doses were adjusted to maintain vitamin E levels below 20.4 microgram/mL and vitamin E/total lipid ratio above 0.6mg/g in the <12 years group and above 0.8mg/g for the ≥12 years group. Within two to four weeks, vitamin E levels were normalised in all patients. Treatment continued for a mean of 10.6 months and vitamin E levels ranged from 6.7 to 26.4 microgram/mL, using tocofersolan doses of 10 to 25 units/kg/day.

Neurological outcomes were reported in a subgroup of 12 patients aged between 9 months and 6 years.[3] These patients were grouped according to baseline neurological function; group A, 3 years or under with normal neurological function (n=2); group B, 3 years or under with abnormal neurological function (n=7) or group C, aged over 3 years with abnormal neurological function (n=3). In this subgroup of 12 patients a dose of tocofersolan 20 units/kg/day was found to be effective after a mean of 19.3 months. Neurological scoring was as described for the pivotal study. Patients in group A remained neurologically normal and all but one patient in groups B and C showed statistically significant improvement in overall neurological function (mean of one point) when compared to baseline.

## Summary of evidence on comparative safety

The main concern was any potential toxicity, especially nephrotoxicity, from the PEG-1000 component, but this was not evident. In the supporting study in 22 patients, absorption of PEG-1000 was reported as 1.7±1.6% of the orally administered dose, based on its urinary excretion, and no potentially toxic PEGs of lower molecular weight were detected in the urine. However, the authors noted that tocofersolan was not administered to patients with evidence of renal failure or dehydration. Patients with significant renal impairment were excluded from the pivotal study.

No adverse events attributed to tocofersolan were reported in either of the studies discussed. In the pivotal study, three patients reported episodes of diarrhoea, two patients had a worsening of cholestasis and one patient developed a pruritic rash. There were small, but statistically significant, changes in serum potassium, chloride and carbon dioxide levels, but these were attributed to the underlying liver disease.

## Summary of clinical effectiveness issues

Vitamin E is essential for the normal functioning of the nervous system. Tocofersolan has been developed as a water-soluble oral preparation which is well-absorbed even when bile secretions are low in conditions such as cholestasis. In addition to tocofersolan, currently available vitamin E preparations include alpha-tocopheryl acetate which is available as an oral suspension and also as an unlicensed parenteral preparation. The oral alpha-tocopheryl acetate suspension is a fat soluble formulation with limited absorption in chronic cholestasis. The parenteral formulation of alpha-tocopheryl acetate necessitates regular intramuscular injections which can be unpleasant for children.

In both studies, tocofersolan was shown to normalise vitamin E levels in children with chronic cholestasis who were resistant to conventional oral vitamin E therapy. The economic case was based on the subgroup with neurological outcomes in the supportive study.

In the pivotal study, for all patients, the measured effect was relatively small, with the mean overall neurological score decreasing from 4.7±0.7 to 4.0±0.7. In the supporting study the overall improvement in neurological scores was modest, reported as a mean of one point.

All studies were of open-label, single-arm design, with no comparative data presented. Studies were small, and carried out by the same team of researchers around 20 years ago. Prior to the availability of a licensed preparation, the tocofersolan used in these studies was prepared in the hospital pharmacy of the study centres. Patients with renal function were excluded, so safety in these patients is unknown. Marketing authorisation was granted under ‘exceptional circumstances’, because, owing to the rarity of the disease, it was not possible to obtain complete information on this product. No dose-ranging studies were conducted. The licensed dose is an approximation of the effective maintenance dose used in the studies discussed.

The bioavailability of vitamin E in this preparation differs from that of other products therefore there is the potential for confusion between generic drug names and units of doses used. Vedrop® should be prescribed as milligrams of d-alpha-tocopherol in the form of tocofersolan.

## Summary of comparative health economic evidence

The submitting company presented a lifetime cost-utility analysis comparing tocofersolan with either usual care or alpha-tocopheryl acetate oral suspension for the treatment of vitamin E deficiency due to digestive malabsorption in paediatric patients suffering from congenital chronic cholestasis or hereditary chronic cholestasis. Expert responses have confirmed that alpha-tocopheryl acetate oral suspension is the most relevant comparator. While it is recognised that the unlicensed alpha-tocopheryl acetate injection is currently used as a treatment in NHS Scotland, it was not SMC policy at the time the submission was made to permit the use of an unlicensed medicine as a comparator.

The analysis was conducted separately for patients with normal neurological function and abnormal neurological function at baseline as the outcomes for these subgroups may differ. A decision tree was used to determine the pathway of patients in the short term following treatment. A Markov model was then used to model the outcomes over the longer term where the health states included normal neurological function, abnormal neurological function, and death. The abnormal neurological function health state was further divided according to the severity of neurological impairment. The source of clinical data for the tocofersolan arm was a subgroup of 12 patients from the supporting study where neurological outcomes were reported. Based on these data, the effectiveness of tocofersolan in preventing neurological impairment in the normal subgroup was assumed to be 100%. In the abnormal subgroup, 22% of patients were assumed to experience an improvement in neurological function following tocofersolan treatment. The relative effectiveness of alpha-tocopheryl acetate oral suspension compared with tocofersolan was assumed to be 98% in both subgroups.

The utility value for severe neurological impairment was estimated to be 0.584 based on a catalogue of EQ-5D scores for a variety of chronic conditions using UK-based preferences from a general population sample. The company selected the disease classification 'other hereditary and degenerative neurological conditions' as a proxy for severe neurological impairment. The utility value for patients with less severe neurological impairment was assumed to be 0.687. Patients with no neurological impairment were assumed to experience no reduction in their quality of life other than standard age adjustments. The resource use estimates included for patients with severe neurological impairment were taken from a previous SMC submission for carglumic acid. Patients with less severe impairment were assumed to require 50% less resource.

For patients with normal neurological function at the start of treatment the submitting company estimated the following results:

| **Tocofersolan vs** | **Incremental cost** | **Incremental QualityAdjusted Life Years (QALYs)** | **Incremental cost effectiveness ratio (ICER)** |
|---|---|---|---|
| Usual care | -£687,453 | 13.86 | dominant |
| Alpha-tocopheryl acetate oral suspension | £6,065 | 0.32 | £19,207 |

For patients with abnormal neurological function at the start of treatment, the submitting company estimated the following results:

| Tocofersolan vs | Incremental cost | Incremental QALYs | ICER |
|---|---|---|---|
| Usual care | -£608,964 | 3.13 | dominant |
| Alpha-tocopheryl acetate oral suspension | £5,841 | 0.08 | £74,267 |

The following limitations were noted:

- There are a number of weaknesses with the clinical data. In particular, there are no comparative data, the study used in the model was single-arm and was based on small patient numbers, and a number of assumptions were used to populate the model in the absence of robust data. In addition, for the normal neurological function subgroup, 100% effectiveness of tocofersolan was assumed based on the outcomes of two patients in the study. As a result, the effectiveness estimates in the model are uncertain.
- The results were very sensitive to small changes in the relative effectiveness of the oral suspension compared with tocofersolan. Assuming a relative effectiveness of 98.5% resulted in the ICER increasing to £38k per QALY in the normal subgroup and £140k in the abnormal subgroup. When the relative effectiveness was assumed to be 97.5%, the cost per QALY was £8k and £35k for the normal and abnormal subgroups respectively.
- The treatment duration assumed in the model may not be appropriate as patients may require treatment beyond 2 years. Due to the higher drug cost this may bias the analysis in favour of tocofersolan. SMC experts have suggested that for some patients, treatment may be life- long.
- It is difficult to validate the utility values used in the model. SMC clinical experts were asked to comment on the quality of life of patients with neurological impairment but the responses indicated they were unable to verify the assumptions used as there is limited experience of treating such patients given that neurological impairment is uncommon in practice.
- The resource use estimates were taken from a previous SMC submission for a different condition as a proxy for the level of impairment and support required for patients with neurological impairment. The resource use estimates included in the model ranged from £25k to £125k per year depending on the age of the patient and the severity of impairment. SMC experts were asked to comment on the severity of neurological impairment patients may experience and the impact of this on health care resource use. However, as noted above it was not possible to validate the assumptions the submitting company had used.
- The estimated cost per QALY compared with alpha-tocopheryl acetate in the abnormal neurological function subgroup is above acceptable thresholds.

Due to the significant weaknesses and uncertainties outlined, the economic case has not been demonstrated.

## Summary of patient and public involvement

A Patient Interest Group Submission was not made.

## Additional information: comparators

Oral vitamin E suspension and unlicensed vitamin E injection.

## Cost of relevant comparators

| Drug | Dose Regimen | Cost per year (£) |
|---|---|---|
| **tocofersolan oral solution** | **0.34mL/kg/day (17mg/kg/day), orally** | **3.5kg: 1,181**<br>**50kg: 16,878** |
| alpha-tocopheryl acetate suspension | 150 to 200 mg/kg/day, orally | 3.5kg: 764 to 1019<br>50kg: 10,917 to 14,556 |
| *tocopheryl acetate injection | 10mg/kg (max.100mg) monthly | Commercial in confidence |

Doses are for general comparison and do not imply therapeutic equivalence. *This preparation is unlicensed in the UK, cost is commercial in confidence (CIC). Cost from eVadis on 19.6.12. Costs calculated for 3.5kg (full term neonate) and 50kg (14 year old) children.

## Additional information: budget impact

The submitting company estimated the population eligible for treatment to be 12 each year, with an estimated uptake rate of 20% in year 1 and 80% in year 5. The gross impact on the medicines budget was estimated to be £42k in year 1 and £169k in year 5. As other drugs were assumed to be displaced, the net medicines budget impact is estimated to be £38k in year 1 and £102k in year 5.

References

The undernoted references were supplied with the submission. The reference shaded in grey is additional to those supplied with the submission.


1. Sokol RJ, Butler-Simon N, Conner C et al. Multicentre trial of d-alpha- Tocopherol polyethylene glycol 1000 succinate for treatment of vitamin E deficiency in children with chronic cholestasis. Gastroenterology 1993; 104: 1727-35.

2. Sokol RJ, Heubi JE, Butler-Simon N, et al. Treatment of vitamin E deficiency during chronic childhood cholestasis with oral d-alpha-tocopheryl polyethylene glycol-1000 succinate. Gastroenterology 1987; 93: 975-85.

3. Sokol RJ, Butler-Smith N, Bettis D et al. Tocopherol polyethylene glycol 1000 succinate therapy for vitamin E deficiency during chronic childhood cholestasis: Neurologic outcome. J Pediatr 1987, 111: 830-6.

4. The European Medicines Agency (EMA) European Public Assessment Report. Tocofersolan (Vedrop). 29/5/2009. EMEA/H/C/000920. www.ema.europa.eu


This assessment is based on data submitted by the applicant company up to and including 16 August 2012.

Drug prices are those available at the time the papers were issued to SMC for consideration. These have been confirmed from the eVadis drug database. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

***Advice context:***

*No part of this advice may be used without the whole of the advice being quoted in full.*

*This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.*