European Medicines Agency
Evaluation of Medicines for Human Use

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CHMP ASSESSMENT REPORT

FOR

Vedrop

International Nonproprietary Name: tocofersolan

Procedure No. EMEA/H/C/000920

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Orphan Europe S.A.R.L. submitted on 07 September 2007 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Vedrop, through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMEA/CHMP on 24 January 2007. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of interest of patients at Community level.

The applicant applied for the following indication (as initially proposed): Vedrop is indicated in vitamin E deficiency due to digestive malabsorption in paediatric patients suffering from cystic fibrosis, congenital chronic cholestasis or hereditary chronic cholestasis.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

The application submitted is a complete dossier composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Scientific Advice
The applicant did not seek scientific advice at the CHMP.

Licensing status:
The product was not licensed in any country at the time of submission of the application.

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: **Ian Hudson** Co-Rapporteur: **János Borvendég**

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 07 September 2007.
- The procedure started on 27 September 2007.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 14 December 2007. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 14 December 2007.
- During the meeting on 21-24 January 2008, the CHMP agreed on the consolidated List of Questions (LOQ) to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 24 January 2008.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 25 July 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 5 September 2008.
- During the CHMP meeting on 22-25 September 2008, the CHMP agreed on a list of outstanding issues to be addressed in writing and in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP list of outstanding issues on 17 November 2008.
- The Rapporteurs circulated the updated Joint Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 1 December 2008 and a further update on 10 December 2008.

- During the CHMP meeting on 15-18 December 2008, the outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- During the meeting on 19-22 January 2009, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a Marketing Authorisation to Vedrop on 22 January 2009.

1.3 Steps taken for the re-examination procedure

The Rapporteur and Co-Rapporteur appointed by the CHMP and their evaluation teams were:

Rapporteur: **David Lyons** Co-Rapporteur: **Jean-Louis Robert** and **Jan Mazag**

- The Applicant submitted a letter to the EMEA dated 09 February 2009 requesting the re-examination of Vedrop CHMP Opinion of 22 January 2009.
- During its meeting on 16-19 February 2009, the CHMP appointed David Lyons as Rapporteur and Jean-Louis Robert and Jan Mazag as Co-Rapporteurs for the re-examination procedure.
- The detailed grounds for the re-examination request were submitted by the applicant on 30 March 2009. The re-examination procedure started on 31 March 2009.
- The Rapporteur's Assessment Report on the detailed grounds for the re-examination was circulated on 30 April 2009. The Co-Rapporteur's Assessment Report was circulated on 04 May 2009.
- An Ad-hoc expert meeting was convened at the EMEA on 12 May 2009 to consider the grounds for re-examination.
- During the meeting on 26-29 May 2009, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a final positive Opinion recommending the granting of a Marketing Authorisation under exceptional circumstances for Vedrop. The applicant provided the letter of undertaking on the specific obligations and follow-up measures to be fulfilled post-authorisation on 29 May 2009.

2. SCIENTIFIC DISCUSSION

2.1 Introduction

Chronic congenital or hereditary cholestasis is a clinical condition where vitamin E deficiency results from an impaired bile secretion. This impairment may result from bile duct malformation such as Alagille syndrome or extra-hepatic biliary atresia resulting in defective bile acid production and defective absorption of lipids by the intestine. Biliary atresia with an incidence of 1/8000 to 1/15000 live births is the most frequent cholestatic disorder of congenital or hereditary origin. Decreased intestinal absorption observed in chronic congenital or hereditary cholestatic patients is due to decreased bile secretion and the resulting decrease in intestinal cellular absorption. As a result, fat-soluble vitamins (*i.e.* A, D, E and K) are not absorbed properly and deficiency can occur. Among these vitamin deficiencies, vitamin E deficiency is one of the most severe, and starts early during childhood.

Cystic fibrosis (CF) is an autosomal recessive disease caused by a defective protein (Cystic Fibrosis Transmembrane Regulator Factor, CFTR) affecting the respiratory and gastrointestinal tract as well as the exocrine glands. Cystic fibrosis is one of the most common causes of lipid malabsorption syndrome. The most recent incidence estimation is approximately 1 in 2500 live births in Europe, where 1 out of 20 persons is a carrier of the CF gene mutation.

Vedrop (tocofersolan) or d-alpha-Tocopheryl Polyethylene Glycol 1000 Succinate (TPGS) is a water-soluble derivative of the natural active (d-alpha) isomer of vitamin E. The active constituent of the medicinal product is essentially vitamin E (alpha tocopherol). This constituent has a well established medicinal use, with recognized efficacy and acceptable safety.

Extensive experience exists with alpha-tocopherol. It was first synthesized in 1938, and 30 years later was granted by the FDA with the status of essential supplement in human nutrition. The degree of scientific interest in a hydro-soluble formulation was highlighted in the scientific literature in the eighties and nineties for the treatment of patients with lipid malabsorption diseases. Vitamin E is essential for the normal organization and functioning of the nervous system.

Because of the lack of micellar formation within the intestine, fat-soluble vitamin E preparations are not appropriate for patients with lipid malabsorption. In children with chronic cholestasis several studies demonstrated that only the intra-muscular formulation was able to achieve this objective before the availability of the oral formulation of tocofersolan. The existing water-miscible formulations were not able to properly restore vitamin E blood levels.

2.2 Quality aspects

Introduction

Vedrop contains tocofersolan in an amount equivalent to 50 mg/ml tocopherol as the active ingredient. It is presented in the form of 50 mg/ml oral solution.
Other ingredients included are potassium sorbate, sodium methyl parahydroxybenzoate, sodium propyl parahydroxybenzoate, glycerol, disodium phosphate dodecahydrate, hydrochloric acid and purified water. The primary container consists of 10 ml, 20 ml or 60 ml, coloured glass type III amber glass bottle with a white, HDPE tamper proof cap. A 1-ml or a 2 ml oral syringe CE marked is enclosed in the carton box respectively for the 10 ml/20 ml bottles and the 60 ml bottles.

Active Substance

The active substance is tocofersolan its chemical name is Poly(oxy-1,2-ethanediyl), *a* -[4-[[(2R)-3,4-dihydro-2,5,7,8-tetramethyl-2-[(4R,8R,12R)-(4,8,12-trimethyltricedyl]-2H-1-benzopyran-6-yl]oxy}-1,4-dioxobutyl]- ω –hydroxy. Tocofersolan is a polymeric mixture prepared by esterification of d-alpha tocopherol succinate with polyethylene glycol 1000 (PEG). This results in a mixture of three components; approximately 80 % mono esters (in which tocopherol succinate adds to one end of the

PEG); approximately 12 % di esters (2 tocopherol succinates add, one to each end of the PEG) and unreacted PEGs. It was not demonstrated that the active substance used in the pre-clinical and clinical studies is identical to the present active substance in terms of ratio of monoesters, diesters, free PEG, free tocopherol (succinate) and the molecular weight distribution of PEG.
Tocofersolan is a white to light brown, stable to air but reacts with alkali and miscible with water. Following some stability studies, it was noticed that the active substance is stable in aqueous solutions, However, it was noticed some slow degradation by ester hydrolysis between pH 4 and 8 but rapid at pH 10 and 12.
The active substance contains three chiral centres, is presented as a solid and the melting point is near body temperature.

- **Manufacture**

The synthesis of tocofersolan is a straightforward esterification reaction following purification by re-crystallisation. The reaction results in a polymeric mixture of components. It was verified that no intermediates have been isolated. The manufacturing process has been described and specifications for starting materials, reagents, and solvents have been provided.
It was noticed that the length of PEG could influence the quality, safety and efficacy of the finished product. Therefore, reassurance that either the starting materials, active and/or finished product will be controlled with respect to the PEG chain length must be further demonstrated.
Structure elucidation has been performed by infrared absorption spectroscopy, mass spectroscopy, ^{1}H-NMR spectroscopy, elemental analysis and ultraviolet spectroscopy. It is important to underline that there are some outstanding issues regarding the quality of the active substance. No information has been provided regarding the composition of the clinical trial batches in terms of the quantities of active species present or with regard to impurities present. Furthermore, the applicant should identify and qualify, if necessary the impurities present in the active substance. It was noticed that the active substance is a mixture of mono-ester, diester and free PEG. Therefore, there are some concerns regarding the uncertainty as to their similarity between clinical trial batches and the product intended for commercialisation. In this context, further clarification is needed.

- **Specification**

The active substance specifications include tests for appearance (waxy solid, white to light brown), identification (IR), identification of the D (+) enantiomer, acid value, colour gardner, heavy metals, solubility, impurities (HPLC), residual solvents (GC) and assay. The impurities presented in the active substance should be controlled in the specifications and their limits should be appropriately justified. The applicant should further justify why the molecular mass could not be part of the specification. Regarding formaldehyde the applicant should confirm that none of their stocks of tocofersolan have levels of formaldehyde present which exceed 20µg/ml.
An analytical method for determination of tocopherol succinate, succinic acid and the other impurities is needed.
The non-pharmacopoeia analytical methods, which were used in the routine controls, were described and their validations were presented. Nevertheless, it is important to underline that further validation is needed for some analytical methods. The limit for impurities above the ICH qualification level should be tightened if applicable or the proposed limit should be qualified. As already mentioned the applicant should identify and qualify, if necessary the impurities present in the active substance. Certificates of analyses for the active substances were provided and batch analysis results were presented. However, further batch analysis results are needed following further clarification on the unknown impurities and the agreement on the revised specifications.

- **Stability**

Taking into account that no accelerated data are available and stability studies at ICH conditions are limited it was agreed that the storage temperature for the active substance should be limited to 25 °C. Furthermore, it was agreed that the active substance will be reanalysed according to the revised specifications before the manufacturing of the finished product.

Medicinal Product

- **Pharmaceutical Development**

All information regarding the choice of the active substance and the excipients have been submitted.
This particular pharmaceutical form, oral solution, was chosen since this medicinal product might be in the paediatric population. Therefore, an oral solution is easier to administer than solid dosage forms.
The solubility of the active substance makes it possible to carry out easily an aqueous solution at the relatively high concentration. It was verified that the obtained solution was clear and had physical characteristics (viscosity, pH) suitable for an oral preparation. Taking into account the slight bitterness and insufficient antimicrobial activity this plain solution could not be used. Therefore, the first attempt to improve taste and microbiological stability was addition propylene glycol, but this formula did not meet the expectations. The next attempts to develop the appropriate medicinal product were adding glycerol and to find a preservative system to maintain the microbiological quality of the solution throughout the proposed shelf-life and usage. In this context more preservative systems were studied in different concentrations. In order to guarantee the stabilization of the pH throughout the shelf life optimization of buffer concentration was also considered.
The level of propylparaben in the proposed formulation is higher than in other authorised product and in July 2006 the European Parliament agreed to withdraw propylparaben from food products based on advice from EFSA. In this context, it was agreed that the inclusion of this preservative has not been adequately justified.
All other excipients used are well known and commonly used in the pharmaceutical industry.

- **Manufacture of the Product**

The manufacturing process for this particular oral solution consists of two main steps (compounding and filling operations) and involves standard technology using standard manufacturing processes such as mixing, blending, pH adjusting, melting, filtering and filling.
The proposed commercial process was validated by two process validation batches.
The batch analysis data show that these new pharmaceutical form can be manufactured according to the proposed finished product specification, which will need to be revised.

- **Product Specification**

The finished product specifications were established according the ICH guidelines and include the following tests: appearance, colour, pH, assay (HPLC), potassium sorbate, sodium methyl parahydroxybenzoate, sodium propyl parahydroxybenzoate, impurities (HPLC), microbial limits (Ph Eur). Following the assessment it was agreed that more clarification regarding the proposed specifications are needed. In this context, the applicant should consider to update specifications for the finished product. Therefore, an updated batch analysis data according to the revised specification should be submitted.
All analytical procedures that were used for testing the finished product were described and some of them were satisfactorily validated in accordance with the relevant ICH guidelines.
However, further clarifications regarding some analytical methods are needed.
The batch analysis data for two production scale and two pilot scale batches confirm that the oral solution can be manufactured according to the proposed finished product specifications.

- **Stability of the Product**

The stability studies were conducted according to the relevant ICH guidelines. Two laboratory batches, 2 pilot batches and 2 production batches have been stored at long term, intermediate and accelerated conditions. All batches were packed in the proposed market packaging. It was verified that the following parameters were controlled: colour, pH, assay, content of preservatives, impurities, microbial purity and viscosity. Based on the available stability data, the initial proposed shelf life could not be accepted. However, it was agreed that 24 months shelf-life might be acceptable without

special storage conditions. Furthermore, it was agreed that after first opening of the container an in-use shelf life of 1 month would be acceptable.

Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture, control of the active substance and the finished product has been submitted. There are some outstanding issues regarding the quality of the active substance and finished product. The applicant must consider revising the specification of the active substance and finished product. In this context, an updated batch analysis data for the active substance and finished product should have been submitted according to the revised specifications.
No information has been provided regarding the composition of the clinical trial batches in terms of the quantities of active species present or with regard to impurities present. Furthermore, the applicant should identify and qualify, if necessary the impurities present in the active substance. It was noticed that the active substance is a mixture of mono-ester, diester and free PEG. Therefore, there are some concerns regarding the uncertainty as to their similarity between clinical trial batches and the finished product intended for commercialisation. In this context, further clarification will be needed.
Taking into account that this particular medicinal product will be used by a paediatric population and that propylparaben was withdrawn from food products there are some concerns regarding the presence of this preservative at high levels in the final formulation. Therefore, the inclusion of propylparaben in the proposed formulation had not been adequately justified and the inclusion of a different preservative system should be considered.

2.3 Non-clinical aspects

Introduction

Vedrop has been developed over several years and many of the nonclinical studies are old and were not conducted to GLP standards. Exceptions, where GLP status is confirmed, include a single dose toxicity study in dogs, repeat dose toxicity studies in rats and dogs, all genotoxicity tests and one reproductive and developmental toxicity study in rats.

Pharmacology

- Primary pharmacodynamics

No new pharmacology studies have been provided and the applicant refers to published literature. In vitro studies using fibroblasts, enterocytes and Caco-2 cells conclude that tocofersolan is taken up as the intact molecule and undergoes a slow hydrolysis reaction, intracellularly, to give PEG 1000 and Vitamin E (d-α tocopherol). The Applicant has provided a summary of relevant published data on Vitamin E, which describes its transport and metabolism. In summary, Vitamin E is absorbed in the small intestine by passive diffusion processes which require bile salts and transferred to the lymph. Peak levels of activity in the lymph are reached at 4 hours and remain at a plateau until 15 hours. This delay is attributed to the time required for micelle formation and the transport across the intestinal mucosa into the lymph. Vitamin E is packaged in chylomicrons and enters the bloodstream where 15 – 45% of the total vitamin E can be absorbed by cells. Chylomicrons are broken down by lipoprotein lipase and the Vitamin E is dispersed towards a variety of pathways or is stored in adipose tissue. It is reasonable to assume that the d-α tocopherol moiety released from tocofersolan would be distributed and metabolised in the same way as Vitamin E.
Studies using the bile duct-ligated rat demonstrated the successful absorption of d-α tocopherol following tocofersolan administration in the absence of bile salts. Whilst this finding provides some reassurance that tocofersolan administration enhances the absorption of d-α tocopherol, only one animal was used and the study was not conducted to GLP standards. The applicant also refers to the existence of clinical data following administration of tocofersolan in vitamin E deficient children. Such clinical data supersede nonclinical data and obviate the need for further nonclinical studies.

- Secondary pharmacodynamics

No secondary pharmacology studies or safety pharmacology studies were conducted, which is considered acceptable given that treatment with Vedrop is effectively a replacement therapy.

- Safety pharmacology

No safety pharmacology studies were conducted. This is considered acceptable given that treatment with Vedrop is effectively a replacement therapy. Furthermore, it is not anticipated that Vedrop will have any pharmacological effects other than the intended primary effects of development and maintenance of the central nervous system and skeletal muscle.

- Pharmacodynamic drug interactions

No pharmacodynamic drug interactions have been discussed by the applicant; none are anticipated as the active substance is a vitamin which is present in healthy individuals.

Pharmacokinetics

Plasma levels of α-tocopherol were measured in dogs and pregnant rabbits and T_{max}, C_{max} and AUC were determined. Large variations were seen in the dog study where only two animals were used. More specifically one animal eliminated α-tocopherol from the blood biphasically whereas the other appeared to show monophasic elimination. Such variations are not unexpected as the animals were not vitamin deficient and were on a diet supplemented with α-tocopherol.

ADME studies were conducted using radiolabelled tocofersolan administered to rats. The radiolabel was placed in the PEG1000 moiety which is cleaved from α-tocopherol following absorption in the intestine, therefore the studies only describe the fate of PEG1000. This is reasonable given that a wealth of published data on Vitamin E distribution and metabolism are available and it follows that the α-tocopherol from tocofersolan will have a similar fate to that absorbed from the diet. Distribution studies conclude that PEG1000 is not taken up or retained in the tissues when administered on its own or as tocofersolan.

No metabolism studies have been submitted in support of this application. However it is known that tocofersolan is cleaved intracellularly to give α-tocopherol, succinic acid and PEG1000, all of which have been described in the literature. As such, the lack of metabolism studies is accepted, although that insufficient detail of the proposed intracellular cleavage was provided in the original dossier.

Oral administration of [^{14}C] tocofersolan and PEG1000 allowed the excretion of PEG1000 to be investigated. Whether administered as tocofersolan or on its own the majority of [^{14}C] PEG1000 was detected in the faeces with values of 76.9 and 95.3 %, respectively. The percentage of dose detected in the urine was higher following administration of tocofersolan than when PEG1000 was administered alone (13.1% compared with 6.7%), which corresponds to the amount of dose absorbed.

No pharmacokinetic drug interaction studies have been carried out, however the ability of tocofersolan to enhance the bioavailability of other drugs is well known.

Toxicology

- Single dose toxicity

Single dose toxicity studies were conducted in rats, rabbits, guinea pigs and dogs using oral (both gavage and dietary), intramuscular, intraperitoneal, subcutaneous, ocular and dermal routes of administration. No treatment-related findings were reported, as all clinical observations and findings at autopsy were similar in treatment and control groups. In many of the studies, the LD_{50} was not determined as tocofersolan was well tolerated.

- Repeat dose toxicity (with toxicokinetics)

In repeat dose studies in the rat and dog using dietary and oral (gavage) routes of administration no treatment-related effects were seen. Consequently there are no toxicity concerns following chronic treatment with tocofersolan.
The plasma concentration of α–tocopherol was determined at 3, 6, 9 and 12 months in the repeat dose toxicity studies in the rat and dog. No T_{max}, C_{max} or AUC values were presented and no animal:human exposure multiples have been calculated. A high variation between animals in the same treatment group was seen and therefore α–tocopherol concentration and dose proportionality was difficult to discern. This could be due to the measurement of both α–tocopherol following tocofersolan administration and endogenous Vitamin E absorbed from the diet. No relationship between the doses used and the proposed therapeutic doses has been discussed, although in light of the results of acute and chronic toxicity studies it is highly unlikely that any toxicity will be observed at the doses proposed for each indication.

- Genotoxicity

A standard battery of genotoxicity tests has been conducted, which produced negative results. Therefore tocofersolan does not appear to be genotoxic.

- Carcinogenicity

No carcinogenicity studies were conducted, however tocofersolan is not mutagenic and no hormone disturbances have been reported in the repeat dose toxicity studies. Reassuringly, there are data to suggest that Vitamin E inhibits cell proliferation, and overall it is considered unlikely that tocofersolan possesses any carcinogenic potential.

- Reproduction Toxicity

A battery of reproductive toxicity tests were conducted in rats and rabbits using the dietary and oral routes. No treatment-related effects were seen on the fertility of male and female rats, embryo-fetal development or on peri- and post-natal development. Toxicokinetic analysis following oral administration of tocofersolan in pregnant rabbits confirmed exposure to α-tocopherol, therefore tocofersolan is not considered to be toxic to reproduction.

The proposed Marketing Authorisation Application is for the use of Vedrop in two paediatric indications. Only one acute toxicity study has been conducted to assess the potential effects on juvenile rats using the oral route. This study was carried out some time ago and is not of a currently acceptable standard. Many deaths were seen across all treatment groups which were attributed to mechanical injury.

- Local tolerance and other toxicity studies

No local tolerance or other toxicity studies were conducted, which is acceptable as the results from the repeated dose toxicity studies do not raise any antigenicity or immunogenicity concerns. Additionally, no metabolism studies were conducted which is acceptable given that there are only 3 possible metabolites. Two of which are endogenous substances (α–tocopherol and succinic acid) and the other is PEG 1000, which has been used in several pharmaceutical products.

Several impurities associated with the drug substance (impurities 3, 6 and 9) have been detected in stability studies, that are above the qualification threshold in the ICH guideline on impurities in new drug products and appropriate toxicological qualification is lacking.

The proposed excipients are well known and are used in several pharmaceutical products.
High levels of preservatives are included in the proposed drug product. While the total amount of ethyl and methylparabens is below the daily limit of 10 mg/kg/day, the EC Scientific Committee for Food

(SCF) was unable to recommend an Acceptable Daily Intake (ADI) for propylparaben. Taking into account the high level of propylparaben in the proposed paediatric formulation and the withdrawal of propylparaben from food products by the European Parliament it was considered that the inclusion of this preservative has not been adequately justified.

Ecotoxicity/environmental risk assessment

The applicant has provided a revised environmental risk assessment. The marketing of Vedrop is unlikely to pose a risk to the environment.

2.4 Clinical aspects

Introduction

The applicant's own data is limited to two pharmacokinetic studies. The published efficacy and safety data have been gathered mostly in the USA but also from publications in the EU and Japan.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.
No issues regarding GCP aspects have been identified during the review of the dossier.

Pharmacokinetics

- Absorption / Distribution/ Elimination

The applicant has submitted two studies which aim to describe the pharmacokinetic characteristics of Vedrop. The first study investigated the bioavailability of two vitamin E formulations (Test versus Reference preparations) following a single oral dose in 12 healthy volunteers. The second study investigated the pharmacokinetics and tolerability of the two vitamin E formulations after a single oral dose administration in 12 paediatric patients (6 with chronic cholestasis, 6 with cystic fibrosis).

In addition, data from the literature comprising several pharmacokinetic studies in healthy volunteers were submitted. These involved different study designs and were performed during different time periods. As such it is not possible to draw any firm conclusions from the findings of these studies.

Study No. 1 (In Healthy Subjects)

This was an open; two-way cross-over randomized study which investigated the pharmacokinetic profiles of single oral doses of two vitamin E formulations, the Vitamin E TPGS Orphan Europe formulation (tocofersolan) and the Vitamin E Cambridge formulation. Both treatments were administered at an equivalent dose of 1200 I.U. to twelve healthy male volunteers. However Vitamin E TPGS Orphan Europe contains d-alpha tocopherol, for which bio-availability is about 1.33 times higher than the dl-alpha-tocopheryl acetate contained in the Vitamin E Cambridge formulation. Therefore, subjects received 800 mg d-alpha tocopherol and 1200 mg dl-alpha tocopheryl acetate (corresponding to 1093 mg of dl-alpha tocopherol). This implies that 37% less tocopherol was administered with the Vitamin E TPGS Orphan Europe formulation than with the Vitamin E Cambridge formulation. The doses of 800 mg and 1093 mg were used to calculate normalized pharmacokinetic parameters in this report. Between each drug administration, there was a washout period of 14 days. Blood samples were collected prior to Vitamin E intake and 3, 6, 9, 12, 12, 24, 48, 72 and 96 hours post dosing. The following pharmacokinetic parameters have been determined during this study: Peak plasma concentration (C_{max}), time to peak plasma concentration (t_{max}), $AUC_{(0-t)}$, half life parameters for absorption ($t_{½abs}$), distribution ($t_{½\lambda 1}$) and elimination ($t_{½\beta}$) and $AUC_{(0-\infty)}$.

The mean delta plasma profiles (after subtracting baseline endogenous vitamin E concentrations) in healthy male volunteers following a single administration of 1200 I.U. (International Units) are presented in the Table 1 and Figure 1 below.

Table 1

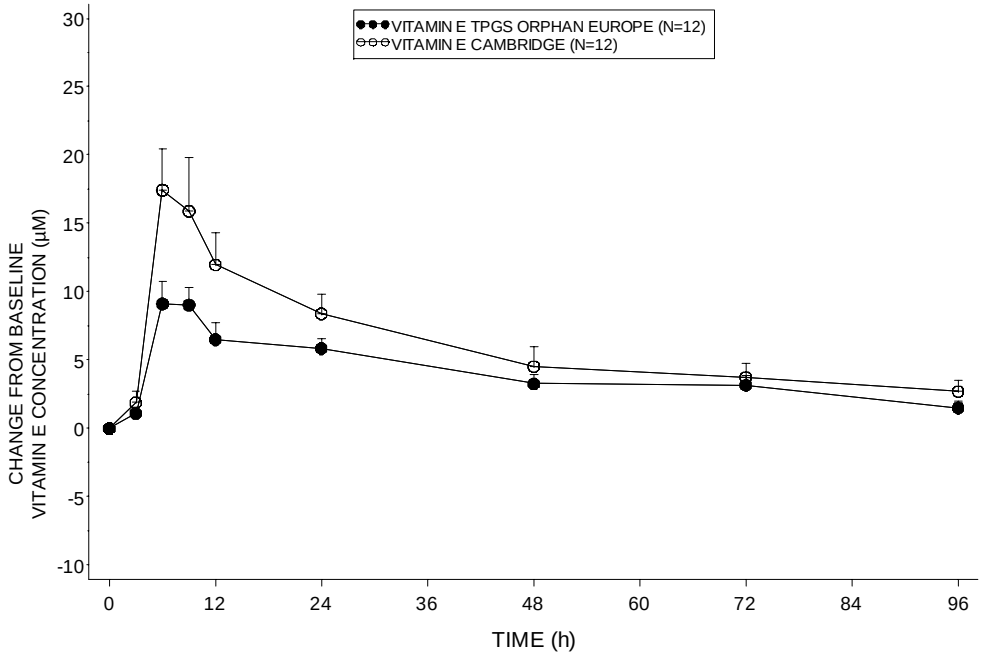
Mean delta vitamin E pharmacokinetics parameters after a single administration of 1200 I.U. vitamin E as test (Vitamin E TPGS Orphan Europe-800 mg d-alpha tocopherol) and reference (Vitamin E Cambridge-1093 mg dl-alpha tocopherol) formulation in 12 healthy subjects

Parameter	Treatment group	Number of values	Mean* ± sd
AUC_{0-t} (μM.hr)	Test formulation	12	367.1 ± 162.7
	Reference formulation	12	567.6 ± 411.03
C_{max} (μM)	Test Formulation	12	11.2 ± 4.4
	Reference formulation	12	19.7 ± 13.0
t_{max} * (hr)	Test Formulation	12	6.00 (6.0 oe 24.0)
	Reference formulation	12	6.00 (6.0 oe 12.0)
$t_{1/2}$ * (hr)	Test Formulation	4	29.7 (16.0 oe 59.5)
	Reference formulation	3	36.6 (24.7 oe 41.9)

*For tmax and t1/2 median (min-max) Test formulation : Vitamin E TPGS Orphan Europe Reference Formulation : Vitamin E Cambridge

Figure 1

Mean delta vitamin E plasma profile after single administration of 1200 IU of vitamin E as test and reference formulation in 12 healthy subjects



Statistical analysis after single doses of each formulation is summarized in Table 2 below.

Table 2

Statistical analysis results for delta vitamin E pharmacokinetic parameters after a single administration of 1200 IU vitamin E as test (Tocofersolan) and reference formulation in 12 healthy subjects

Parameter	Treatment group	Geometric mean ± SD (Dose normalized)*	90% Confidence Interval Dose normalization **	Relative bio-availability F_{rel}
AUC_{0-t} (µmol/L.h/mg)	Test formulation	0.383 ± 0.203	[0.54 – 1.86]	1.01 ± 1.74
	Reference formulation	0.381 ± 0.376		
C_{max} (µmol/L/mg)	Test formulation	0.013 ± 0.006	[0.59 – 1.28]	
	Reference formulation	0.015 ± 0.012		

*after normalization of the Cmax and AUC values by the dose administered (800 mg for the test and 1093 mg for the reference formulation)
**ANOVA was performed after normalization of the Cmax and AUC by the dose administered (800 mg for the test and 1093 mg for the reference formulation)

The statistical analysis was performed after normalization of the Cmax and AUC values by the dose administered as the administered tocopherol doses were 800 mg alpha-tocopherol for tocofersolan and 1093 mg alpha-tocopherol for the reference formulation, both corresponding to 1200 IU and as the biochemical determination was on alpha-tocopherol, without any stereo-isomeric separation.

In this small population of 12 healthy volunteers, bioequivalence of the two formulations was not established. However, the dose strengths of the two products appear to be of comparable Vitamin E activity.

Study No. 2 (In Paediatric Patients)

The objective of the study was to compare the pharmacokinetics and tolerability of two vitamin formulations given orally in 6 chronic cholestatic and 6 cystic fibrosis paediatric patients at a vitamin E dose of 100 I.U./kg in an open; two-way cross-over randomized study. Chronic cholestatic patients were already hospitalised at the time of their inclusion in the present study. No change was made to the on-going hospitalisation conditions. Cystic fibrosis patients were hospitalised on each drug administration day. They then remained in the clinical unit under permanent medical and nursing supervision for 24 hours after each administration. Pharmacokinetic profiles were obtained following administration of single oral doses of two vitamin E formulations, the Orphan Europe Vitamin E TPGS formulation and the Cambridge Vitamin E formulation.

After dosage adjustment for equipotency, the subjects received 66.7 mg/kg dl-alpha tocopherol and 91.1 mg/kg dl-alpha tocopherol (as tocopherol acetate in water- miscible formulation). Between each drug administration, there was a washout period of 7 days. Blood samples were collected prior to Vitamin E intake and 3, 6, 9, 12, 12 and 24 hours post dosing. One of the 6 patients with chronic cholestasis was excluded from the analysis because plasma concentrations were considered as not reliable by the analytical laboratory (CVs of the triplicate at baseline determination not fulfilling pre-established criterion for acceptability of the data).

In patients with chronic cholestasis, the mean (± SD) peak plasma concentrations were higher following Vedrop than following reference vitamin E with values of 25.5 (± 4.3) µmol/L, after test formulation *versus* 16.1 (± 3.2) µmol/L after the reference formulation. Similarly, AUC_{0-t} values were higher with mean (± SD) of 459 (± 90) µmol/L.hr *versus* 310 (± 66) µmol/L.hr following administration of the test and reference formulations respectively. The results of the main pharmacokinetic parameters for chronic cholestasis are summarised in the following table 3 and figure 2.

Table 3

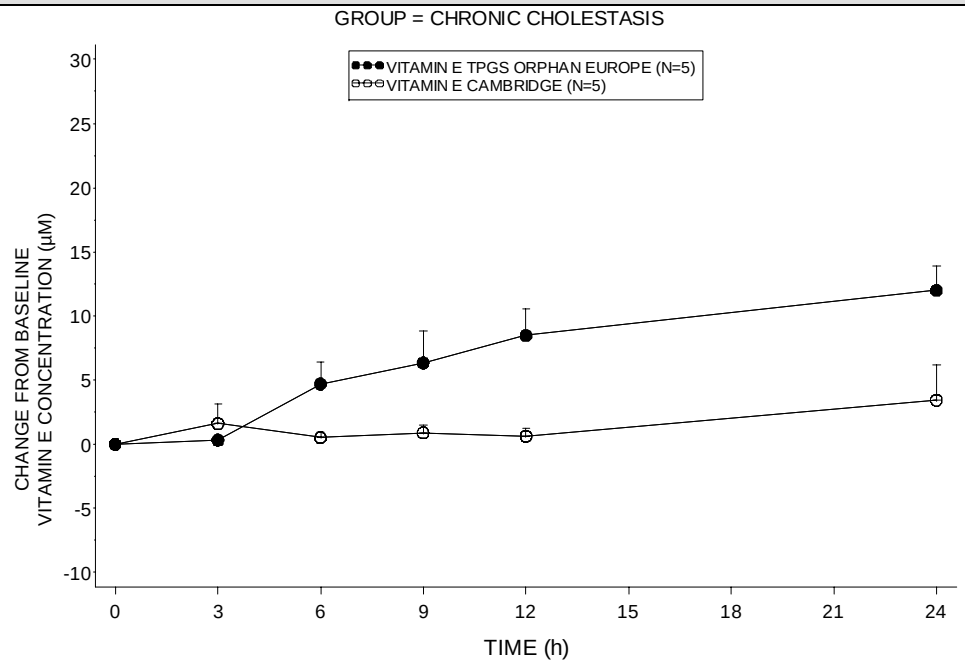
Mean Vitamin E and delta vitamin E pharmacokinetics parameters in paediatric patients with chronic cholestasis

Parameter	Treatment group	Number of values	Mean* ± SD Calculated on vitamin E concentrations	Mean* ± SD Calculated on Delta vitamin E concentrations
AUC0-t (µmol/L.h)	Test Formulation	5*	459 ± 90	167 ± 48.5
	Reference Formulation	5	310 ± 66	37.9 ± 56.5
C_{max} (µM)	Test Formulation	5*	25.5 ± 4.3	13.1 ± 4.2
	Reference Formulation	5	16.1 ± 3.2	3.9 ± 5.9
t_{max} ** (hr)	Test Formulation	5*	24.0 (12.0 – 24.0)	24.0 (12.0 – 24.0)
	Reference Formulation	5	9.00 (0.0 – 24.3)	16.5 (6.0 – 24.3)

* The data is also available for all 6 patients for test formulation but shows no difference from the 5 patient calculation (AUC0-t = 460 ± 81 µM.hr and Cmax = 24.8 ± 4.2 µM) **For tmax median (min-max) Test formulation : Vitamin E TPGS Orphan Europe Reference formulation : Vitamin E Cambridge

Figure 2

Mean (+SEM) vitamin E plasma profile expressed in changes from baseline: pediatric patients with chronic cholestasis



Results for patients with cystic fibrosis are presented below. Vitamin E plasma concentrations peaked between 9 and 12 hours following tocofersolan and between 6 and 9 hours after the reference formulation. Mean (± SD) peak plasma concentrations following Reference and Test are shown in table 4 and figure 3.

Table 4

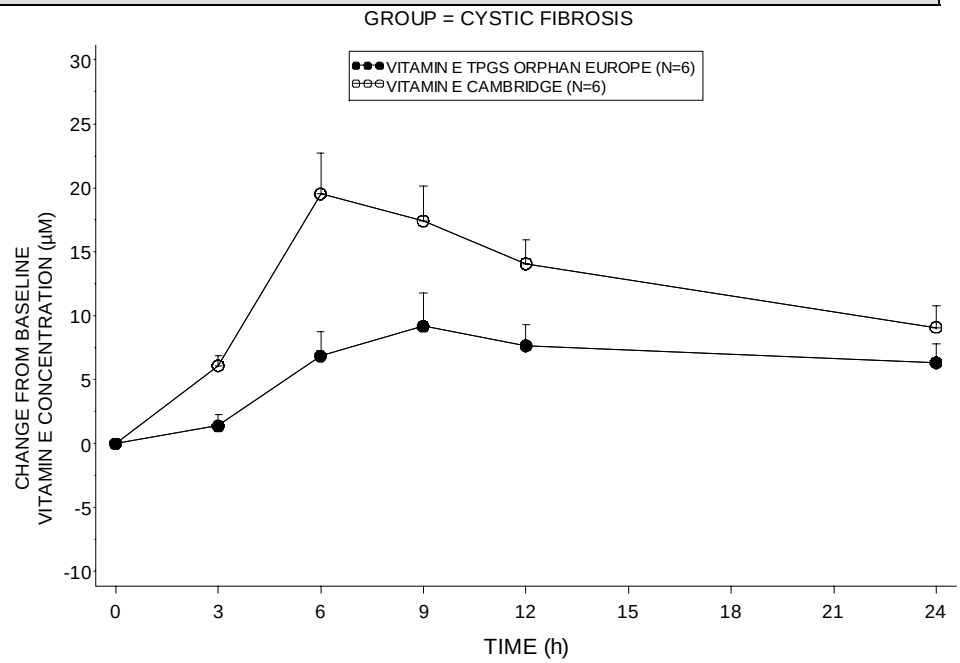
Mean vitamin E and delta vitamin E pharmacokinetic parameters in pediatric patients with cystic fibrosis

Parameter	Treatment group	Number of values	Mean* ± SD Calculated on vitamin E concentrations	Mean* ± SD Calculated on Delta vitamin E concentrations
AUC0-t (µmol/L.h)	Test Formulation	6	653 ± 121	148 ± 86
	Reference Formulation	6	771 ± 181	290 ± 94
Cmax (µmol/L)	Test Formulation	6	30.8 ± 6.5	9.8 ± 5.8
	Reference Formulation	6	40.0 ± 11.0	20.0 ± 7.4
tmax * (h)	Test Formulation	5	9.05 (9.0 – 12.0)	9.05 (9.0 – 12.0)
	Reference Formulation	5	7.55 (6.0 – 9.2)	7.57 (6.0 – 9.2)

*For tmax median (min-max)
Test formulation: vitamin E TPGS Orphan Europe
Reference formulation: vitamin E Cambridge

Figure 3

Mean (+SEM) delta vitamin E plasma profile in pediatric patients with cystic fibrosis



The test product, d-alpha tocopherol contained in Vitamin E TPGS, has higher bioavailability than the reference product, dl-alpha-tocopherol contained in the Vitamin E Cambridge formulation. The applicant made weight/dosage adjustments to enable comparing the pharmacokinetic parameters between the two formulations. The weight-base dose normalizing is not acceptable because after this adjustment the biological activities of the two formulations to be compared will be different.

Thus after taking into account the dosage adjustments, plasma Vitamin E concentrations of the Test and Reference preparations were largely comparable in healthy subjects, but the methodology for the comparison was incorrect. In children with chronic cholestasis, the plasma Vitamin E levels of the Test product were clearly higher compared with Reference formulation. In children with cystic fibrosis, this relationship was reversed; the plasma Vitamin E levels of the Test product were demonstrably lower compared with the Reference formulation.

- Dose proportionality and time dependencies

This issue has not explicitly been studied. However the data provided indicate non-linear kinetics. No further studies are required as this issue does not seem to generate any safety issue.

- Special populations

Studies in special populations were not performed. The applicant was requested to comment on the absence of pharmacokinetic data in patients with renal impairment (given the known nephrotoxic effects of glycol molecules). The applicant was also asked to discuss the possible influence of hepatic impairment on the pharmacokinetics for Vitamin E preparations, as the main metabolic pathways of tocofersolan involve the liver.

Based on additional literature review submitted in response to CHMP questions, the CHMP agreed that this could be resolved by a relevant precautionary statement in the product information, were the product to be marketed.

- Pharmacokinetic interaction studies

Specific PK interaction studies were not performed. The applicant provided a discussion of literature data. Tocofersolan is a strong P-gp inhibitor even at therapeutic doses, and consequently a bioavailability enhancer. Co-administration with immunosuppressants such as tacrolimus or cyclosporine can lead to possible interactions.

- Pharmacokinetics using human biomaterials

Not applicable

Pharmacodynamics

- Mechanism of action

The applicant has submitted several publications which describe the pharmacodynamic actions of alpha tocopherol both in healthy subjects and in patients with cystic fibrosis and chronic congenital cholestasis.

Vitamin E is the principal lipo-soluble antioxidant in the living organism. It acts as a free radical chain breaking molecule, stopping the peroxidation of polyunsaturated fatty acids. Vitamin E is also involved in maintaining the stability and integrity of cell membranes via the phytyl side chain which interacts with polyunsaturated fatty acids especially arachidonic acids.

- Primary and Secondary pharmacology

The mechanism of action in patients with cystic fibrosis and chronic cholestasis has sufficiently been investigated and is well known (resistance to oxidative reactions and to tissue damage). The influence of plasma alpha-tocopherol on neurological complications was described on histo-pathological studies and confirmed in the population of children with chronic cholestasis. No additional data are therefore required.

Clinical efficacy

- Dose response study(ies)

There are no dose-ranging studies available in this patient population with any of formerly tested formulations of vitamin E, neither with tocofersolan. In this regard, the dosing regimen has been derived from the doses administered to study patients.

- Main study (ies)

Several publications of the main efficacy clinical trials (from published literature) involving 130 patients have been submitted with the current application, and are summarized in the table below. Three of these were considered as pivotal (in bold type), while some of the other studies are not more than case reports. All three key studies involve paediatric patients with chronic cholestasis. Apart from one small study, there are no clinical trial data in patients with cystic fibrosis. Most of studies appear to have been conducted by the same clinical team in the US (Sokol *et al.*).

Given that these diseases are relatively rare, the applicant cannot reasonably be expected to provide comprehensive data on the efficacy. In the absence of an established active comparator as reference treatment and, considering the limited number of patients, the majority of studies were of open trials design. Most children in these studies had a long history of resistance to conventional treatment, *i.e.*

very high vitamin E dosage (100 to 400 mg/day when recommended FDA daily intakes are 5 to 15 mg/day). Usually, comparisons were made before and after treatment by tocofersolan after oral vitamin E absorption evaluation and then during the long-term treatment of these patients.

Table 5
Tocofersolan (TPGS-1000) vitamin E clinical efficacy main trials in the literature*

Publication	Design	Number of subjects with age and sex	Diagnosis at inclusion	Duration of treatment	Test product Dosage regimen Route of administration	Criteria for evaluation	Results (Efficacy)
Sokol 1987	**Open**	**12 9 mo-6 y 5 M, 7 F**	**Chronic cholestasis**	**19-34 mo**	**Oral liquid form TPGS 50 →25 IU/kg/d**	**Neurological evaluation tocopherolemia**	**Improved neurological score Tocopherolemia normalized**
Sokol 1987	**Open**	**22 7 mo-19 y 6 M, 16 F**	**Chronic cholestasis**	**19 mo**	**Oral liquid form TPGS 15 →25 IU/kg/d**	**Tocopherolemia**	**Tocopherolemia normalized**
Sokol 1993	**Open**	**60 6 mo-20 y 26 M, 38 F**	**Chronic cholestasis**	**2.5 y**	**Oral liquid form TPGS 25 IU/kg/d**	**Neurological evaluation tocopherolemia**	**Improved neurological score Tocopherolemia normalized (4→28 µmol/L)**
Argao 1992	Open	5 5 mo-19 y 1 M, 7 F	Chronic cholestasis	1 y	Oral liquid form TPGS 25 IU/kg/d vitamin D without then with TPGS	Tocopherolemia	Tocopherolemia normalized in 4 out of 5 patients with TPGS Positive effect on Vit D (enhancement of absorption)
Melhorn 1973	Open	1 F of 12	Cystic fibrosis	2 w	Oral liquid form TPGS 100 IU /kg/d	Tocopherol blood level Hemolysis rate (% RBC)	0.15 → 0.65 mg % (N= 0.7 – 1.40 % RBC varies from 68 → 24 % (N= 0 – 19 %)
Rosenblum 1981	Open	3	Chronic cholestasis	+/- 3 months	Oral liquid form TPGS 75 to 300 UI/kg/d	Vitamin E blood level	Blood levels moved from 5.32 µg/ l to 16.25
Socha 1997	Open	15, 9 mo-3.4 y	Chronic cholestasis	1 y	Oral liquid form TPGS 20 IU/kg/d	Vitamin E / lipid at 1 y.	Tocopherolemia normalized within 1 mo At 1 y.: 0.2→1.69mg/g
Traber 1986	Open	1, F 8 y	Chronic cholestasis	1 y	Oral liquid form MCTE 100 mg/kg/d x 2 wks then TPGS 100→60 mg/kg/d after 6 wks of TPGS therapy 11 mo of treatment with TPGS	Tocopherolemia	Failure of MCTE Tocopherolemia normalized after 1 w of TPGS

* This table describes only the most important clinical efficacy trials in the literature. The three "key" publications are in bold print.
TPGS: d-alpha-tocopheryl polyethylene glycol-1000 succinate. RBC: red blood cells.
MCTE: Medium Chain Triglyceride vitamin E

Clinical efficacy of TPGS /tocofersolan in chronic cholestasis

Several clinical observations and a few studies have been published which demonstrate clinical efficacy of tocofersolan in chronic cholestasis. Apart from the three pivotal studies, some of these publications are no more than case reports. One of three pivotal trials appears comprehensive and is summarized below.

METHODS

This multicentre trial in children with chronic cholestasis (Sokol, 1993) investigated 60 vitamin E-deficient patients unresponsive to massive (up to 200 IU/kg/day) dosages of oral dl-alpha-tocopheryl acetate. The patients were recruited over 8 centers in the USA and diagnoses included 17 patients with Alagille syndrome, 19 with extra-hepatic biliary atresia, 13 with intra-hepatic progressive cholestasis, 5 with non-syndromic paucity of interlobular bile ducts (PIBD) and 6 with persisting neonatal hepatitis. The age range of the patients was 0.5 to 20 years (mean 6.4 ± 0.8 years). All had a history of resistant vitamin E-deficiency and had baseline biochemical and neurological tests. Subjects were monitored first at 2 and 4 weeks and then every 3 to 4 months.

Neurological scoring was performed every 6 months and a minimum of 6-month follow-up was necessary to assess the clinical response. Scores were given for 12 symptoms (hyporeflexia, ataxia, impairment of vibratory sensation, dysarthria, etc.) and ranged from normal (0) to severely abnormal (3 +). The initial dosage of tocofersolan was 25 IU/kg/day and was adjusted throughout the study to achieve a vitamin E/total lipid ratio ≥0.8 mg/g (≥18.6 µmol/g). However two different vitamin E products were used in this trial. Between 1985-1989 a d-alpha-tocopherol succinate formulated in the hospital pharmacy from pure TPGS and since 1989 a commercial preparation (Ligui-E Qine Laboratories Ronconcome N.Y.)

Plasma vitamin E levels/total lipids ratio before treatment ranged from 6.5 to 17.9 µmol/g depending on the severity of the disease with a mean (± SD) of 11.6 (± 1.6) µmol/g. Patients with Alagille syndrome and with PIBD presented higher vitamin E plasma concentrations but vitamin E/lipid ratio within the range of patients with other diagnoses.

All patients receiving tocofersolan reached the biochemical target (0.8 mg/g) within 1 month: with plasma vitamin E ranging from 20.7 to 39.7 µmol/g of lipids depending on the clinical form. Patients with progressive intra-hepatic cholestasis and patients with neonatal hepatitis presented the highest responses (both 39.7 µmol/g). Mean (± SD) values for all 60 patients were 1.4 ± 0.1 mg/g with a significant ($p < 0.05$) increase by comparison to values at entry.

The mean duration of treatment was 2.3 ± 0.2 years and treatment was carried out up to 7 years in some patients.

RESULTS

Fifty four patients completed neurological scoring (mean duration of treatment: 2.5 years). All patients older than 4 years (except two) on entering the study presented an abnormal neurological score. The two remaining patients had received parenteral vitamin E since infancy and had no vitamin deficiency and no neurological symptoms at entry.

Mean neurologic score decreased significantly from 4.7 ± 0.7 to 4.0 ± 0.7 ($p < 0.001$). Twenty five patients improved, 27 were stabilized and only two worsened.

Neurological response to tocofersolan was also analyzed by age of patients at entry. Age groups were: <4 years (N=28); from 4 to 10 years (N=13); and >10 years (N=13). Results are presented in Table 6 below. Outcome under treatment strongly correlated with age at entry into the study ($r = 0.78$; $p < 0.001$).

Table 6
Neurological response to long term treatment with TPGS by age categories

Age at entry (years)	Neurological outcome	N	Duration of treatment (years)	Neurological score at entry	Neurological score under TPGS
<4	Improved No change Worsened	11 17 0	2.9 ± 0.7 2.2 ± 0.4 -	2.7 ± 0.3 0.6 ± 0.1 -	0.9 ± 0.3 (*) 0.6 ± 0.1 -
4 to 10	Improved No change Worsened	7 6 0	2.3 ± 0.4 2.2 ± 0.7 -	5.4 ± 1.5 4.3 ± 1.7 -	2.9 ± 1.3 (*) 4.3 ± 1.7 -
>10	Improved No change Worsened	7 4 2	3.6 ± 0.8 2.0 ± 0.2 0.6	12.8 ± 1.7 8.0 ± 3.3 15.5	11.5 ± 1.9 (*) 8.0 ± 3.3 17.8

Values are mean ± SEM or mean if less than three values
(*) $p < 0.05$ vs neurological score at entry

The results of this study showed that:

All 60 children responded to 20-25 IU/kg/day TPGS solution with normalization of vitamin E/total lipid blood levels.

Neurological symptoms were either improved or stabilized in 96% of patients. This study confirmed the critical role of vitamin E deficiency in neurological abnormalities in patients with chronic congenital or hereditary cholestasis.

Clinical efficacy of TPGS /tocofersolan in Cystic fibrosis

Very little data have been submitted to demonstrate clinical efficacy of tocofersolan in patients with cystic fibrosis.

In response to the CHMP LOQs the applicant has provided an additional 6 months open-label ongoing study in cystic fibrosis patients which is essentially a safety study. Although interim analysis of the 3 months results appear to show maintenance of normal plasma levels of alpha-tocopherol after 3 months of administration of Vedrop, it is not possible to assess whether this treatment is effective, even when considering plasma Vitamin E levels as a biochemical surrogate marker of efficacy. Another problem is that it was an open study without using any comparator preparation.

- Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

- Clinical studies in special populations

No data has been submitted. Please refer to discussion under Pharmacokinetics

- Supportive study(ies)

Please refer to the table under section "Main studies"

- Discussion on clinical efficacy

The available clinical efficacy data appear to indicate that in patients with congenital chronic cholestasis, tocofersolan may lead to an improvement in neurological symptoms or at least prevent the

deterioration of neurological symptoms. The same is not the case with regards to patients with cystic fibrosis (CF) as there is virtually no efficacy data in these patients.

Clinical safety

- Patient exposure

With regards to safety, experience concerning the clinical safety of tocofersolan is mainly based on published papers in the literature (in 27 healthy volunteers and 116 patients) and on the applicant's sponsored studies (in 12 healthy volunteers and 12 patients).

- Adverse events

Tocofersolan is taken up by cells as the intact molecule, hydrolyzed intra-cellularly and the alpha-tocopherol moiety then appears in chylomicrons in the lymph in a manner identical to vitamin E absorbed from the diet as shown *in vitro*. Therefore, safety issues from clinical experience both with tocofersolan or TGPS and with vitamin E were presented.
The other constituent of Vedrop, Polyethylene Glycol 1000, has also been used for decades in the preparations of several medicinal products. It does not contribute to the pharmacological action of Vedrop. It only acts as a vector of vitamin E to its intestinal absorption sites (*i.e.* the apical membrane of the enterocytes) in cases where physiological lipo-solubilizing agents are missing because of an underlying disease.

Overall, adverse effects seen with tocofersolan therapy appear to be not serious and are mostly related to the gastrointestinal tract. These AEs are often dose-related. Vitamin E and tocofersolan have been used as supplements in many patients over many years. However data from controlled trials are sparse.

- Serious adverse event/deaths/other significant events

No serious adverse events or deaths related to tocofersolan have been reported

- Laboratory findings

The clinically relevant laboratory findings observed in the submitted data were: abnormal serum sodium, abnormal serum potassium and 1 case of transaminase increase.

- Safety in special populations

Please refer to discussion under Pharmacokinetics.

- Safety related to drug-drug interactions and other interactions

Due to limited data and lack of systematic controlled studies, no definite conclusions can be drawn regarding drug-drug or other interactions. However, available evidence indicates that tocofersolan increases plasma levels of fat soluble vitamins (vitamin D or vitamin A) when these substances are concomitantly administered with tocofersolan.

- Discontinuation due to adverse events

From the limited number of controlled data provided no conclusions can be drawn on discontinuation due to adverse events.

- Post marketing experience

The product was not licensed in any country at the time of submission of the application.
Up to End of November 2008, 173 patients have been treated with tocofersolan in Europe on a name-patient basis. Orphan Europe has received clinical information for 62 of these 173 patients. Only 1 patient experienced one adverse event (diarrhea).

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan.

The CHMP, having considered the data submitted in the application was of the opinion that it was not appropriate to consider risk minimisation activities at this time.

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of this product is not considered to be acceptable. There are some outstanding issues regarding the quality of the active substance and the finished product, which need further clarification. It can be concluded that the unresolved quality issues have negative impact on the benefit/risk balance.

Non-clinical pharmacology and toxicology

No pharmacokinetic drug interaction studies were carried out. However the ability of tocofersolan to enhance the bioavailability of other drugs is well known. This has been addressed by incorporation of appropriate warnings in section 4.4 of the SPC.

Appropriate toxicological qualification should be provided for the drug substance impurities that have been detected above the qualification threshold in the ICH guideline on impurities in new drug products.

Efficacy

The clinical part of the application is essentially based on publications. The applicant's own data is limited to two pharmacokinetic studies – one in 12 healthy subjects and the other in 12 patients (6 with chronic cholestasis, 6 with cystic fibrosis). Pharmacodynamic, efficacy and safety data have been gathered mostly in the USA but also from publications in the EU and Japan.

Several publications have been submitted which describe the pharmacodynamic actions of alpha tocopherol both in healthy subjects and in patients with cystic fibrosis and chronic congenital cholestasis.

There are no dose-ranging studies available in this patient population with any of formerly tested formulations of vitamin E, neither with tocofersolan. The proposed dosing regimen has been derived from the doses administered to study patients in published literature.

Several publications of the main efficacy clinical trials involving 130 patients have been submitted with this application. Three of these were considered as pivotal. All three studies involve paediatric patients with chronic cholestasis. Apart from one small study, there are no clinical trial data in patients with cystic fibrosis. Most studies have been conducted by the same clinical team in the US.

From the data provided it appears that in patients with congenital chronic cholestasis, tocofersolan may lead to an improvement in neurological symptoms or at least prevent the deterioration of neurological symptoms. The same is not the case with regards to patients with cystic fibrosis (CF) as there is virtually no efficacy data in these patients. The applicant has provided a 3 months interim analysis of an additional 6 months open-label ongoing clinical trial in CF patients. However, this is essentially a safety study.

There are also concerns that the material used in the publications has not been sufficiently characterised, such that it is uncertain whether the product intended for marketing is the same or sufficiently similar to that used in the studies submitted as publications. Taking into account that the so called "pivotal" studies in chronic cholestasis had been performed more than 15-20 years ago and that the pegilation of vitamin E was partly done in a local hospital pharmacy ("home-made" preparation), the bridging data between the preparation used in those clinical studies and the product intended for marketing are missing.

Safety

Experience concerning the clinical safety of tocofersolan is mainly based on published papers in the literature (in 27 healthy volunteers and 116 patients) and on the applicant's sponsored studies (in 12 healthy volunteers and 42 patients).

Tocofersolan is taken up by cells as the intact molecule, hydrolyzed intra-cellularly and the alpha-tocopherol moiety then appears in chylomicrons in the lymph in a manner identical to vitamin E absorbed from the diet as shown *in vitro*. The other constituent of Vedrop, Polyethylene Glycol 1000, does not contribute to the pharmacological action of Vedrop. It only acts as a vector of vitamin E to its intestinal absorption sites (*i.e.* the apical membrane of the enterocytes) in cases where physiological lipo-solubilizing agents are missing because of an underlying disease.

Overall, adverse effects seen with tocofersolan therapy appear to be not serious, are mostly related to the gastrointestinal tract, and are often dose-related. Vitamin E and tocofersolan have been used as supplements in many patients over many years. However data from controlled trials are sparse. Due to limited data and lack of systematic controlled studies, no definite conclusions can be drawn regarding drug-drug interactions or other interactions. However, available evidence indicates that tocofersolan increases plasma levels of Vitamin D when the two substances are concomitantly administered (which would require an appropriate warning statement in the SPC).

Risk-benefit assessment

Chronic congenital or hereditary cholestasis and cystic fibrosis are responsible for severe deficit in lipid absorption by the gastrointestinal tract. One of the consequences is a deficit in liposoluble vitamins which gives rise to numerous related clinical symptoms. Vitamin E deficiency has been identified as being responsible for severe and evolving neurological disorders, which may be preventable when treated properly early in the child's life.

Due to failing lipid-dependent absorption mechanisms, dl-alpha-tocopheryl acetate formulations of vitamin E are not absorbed properly by these patients, leading to incomplete correction of the deficiency. This situation generates persistent and worsening neurological symptoms. Tocofersolan is a water-soluble derivative of the natural active (d-alpha tocopherol) isomer of vitamin E, in which polyethylene glycol is esterified to d-α-tocopherol via a succinic acid bridge.

Tocofersolan has been shown to be effective in correcting blood vitamin E levels in patients presenting with lipid malabsorption (at least in patients with chronic cholestasis) and appears appropriate for treating the affected children. From the historical data submitted, tocofersolan may be effective in correcting or preventing neurological symptoms in patients with congenital chronic cholestasis. The extent of regression of neurological symptoms depends on the age of the patients and the duration of malabsorption. Tocofersolan seems effective in preventing neurological complications when given early to patients, preferably before the age of 3 years.

The following main risks were identified:

- Nephrotoxicity is an established adverse effect of glycols, particularly small glycol molecules, e.g. ethylene and diethylene glycol or low-molecular-weight PEG. Results from animal and human studies appear not to substantiate this risk with regard to the high-molecular-weight PEG 1000. An appropriate precautionary statement in the SPC could address this.
- The composition of the clinical trial batches has not been sufficiently characterised in terms of active species and impurities, and it was not established whether the impurities had been adequately qualified.
- The demonstration of efficacy, both clinically and biochemically, in patients with cystic fibrosis is insufficient.
- The inclusion of propylparaben in the proposed paediatric formulation has not been adequately justified.
- There was insufficient evidence that the formulation of the investigational product was the same as Vedrop intended for marketing.

The applicant addressed the above points (with the exception of the first) during an oral explanation and proposed to drop the Cystic Fibrosis indication. However, after the oral explanation the CHMP was still of the opinion that these remaining issues were not satisfactorily addressed. In addition, there was a long list of further questions (as outlined in the post day 180 assessment report) that had not been satisfactorily addressed.

- Quality issues regarding the quality of the starting materials, the quality of the active substance, validation of analytical methods, further clarification on analytical methods, updated batch analysis and impurities.

- Outstanding issues regarding the finished product, which were raised in the Day 180 Joint AR, including clarification regarding the control of the ionic strength by osmolarity, updated specifications of the finished product, clarification on the method used for the determination of the free PEG 1000, description and validation of aspecific method to control PEG content of the finished product, further clarification regarding the release specification and updated batch analysis according to the revised specification.

- Appropriate toxicological qualification for the drug substance impurities which have been detected above the qualification threshold in the ICH guideline on impurities in new drug products.

- The Risk-management plan should be further revised.

Tocofersolan seems effective in correcting blood vitamin E levels in patients presenting with lipid malabsorption due to chronic cholestasis; historical data suggests that tocofersolan may be effective in correcting or preventing neurological symptoms in patients with congenital chronic cholestasis. Approval of congenital chronic cholestasis due to "exceptional circumstances" on the basis of "unmet medical need" for this rare condition (which has an incidence of approximately 1/8000 to 1/15000 live births) was considered. However, approval was deemed not possible as many outstanding issues remain, particularly relating to quality aspects, characterisation of the clinical trial material, bridging between the material used in the publications and the product intended for marketing. In any case there is insufficient information to consider a positive opinion for cystic fibrosis.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP during their meeting of January 2009 considered by consensus that the risk-benefit balance of Vedrop in the treatment *of vitamin E deficiency due to digestive malabsorption in paediatric patients suffering from cystic fibrosis, congenital chronic cholestasis or hereditary chronic cholestasis* was unfavourable and therefore did not recommend the granting of the marketing authorisation.

GROUNDS FOR REFUSAL

QUALITY

- The inclusion of propylparaben in the proposed paediatric formulation has not been adequately justified

- The composition of the clinical trial batches has not been sufficiently characterised in terms of active species and impurities, and it was not established whether the impurities had been adequately identified and qualified.

- The specification of the active substance and finished product should be revised and updated batch analysis data for the active substance and finished product should have been resubmitted according to the revised specifications.

EFFICACY AND SAFETY:

- The demonstration of PK and clinical efficacy in patients with cystic fibrosis was insufficient

- There was insufficient evidence that the formulation of the investigational product was the same as Vedrop intended for marketing.

In view of the above the CHMP, during their meeting of January 2009, has recommended the refusal of the granting of the Marketing Authorisation for Vedrop.

In addition, there were the unresolved questions, as outlined in the post day 180 assessment report (summarised above in the section 3.6 Risk-benefit assessment).

2.7 Re-examination of the CHMP opinion of January 2009

Following the CHMP Opinion concluding that the benefit risk of Vedrop administered for *vitamin E deficiency due to digestive malabsorption in paediatric patients suffering from cystic fibrosis, congenital chronic cholestasis or hereditary chronic cholestasis* was not favourable, the applicant submitted detailed grounds for the re-examination of the grounds for refusal.

Detailed grounds for re-examination submitted by the applicant

QUALITY

Ground for re-examination 1: The inclusion of propylparaben in the proposed paediatric formulation has not been adequately justified

Applicant`s position
The antimicrobial preservative system combines three preservatives selected for their well known antimicrobial and antifungal efficacy. The combination of propylparaben (0.09%) /methylparaben (0.3%) is widely used as being known to be the most effective antimicrobial system against moulds and bacteria. It was noted that propylparaben can be found in more than one hundred oral pharmaceutical formulations.
The selected concentrations in potassium sorbate (0.5%), sodium methyl parahydroxybenzoate (0.3%) and sodium propyl parahydroxybenzoate (0.09%) were justified on the basis of studies of efficacy according to monograph 5.1.3 "Efficacy of antimicrobial preservation" of the current European Pharmacopoeia edition.
The concentrations of both parabens were optimized in order to have the minimal effective concentration regarding the antimicrobial test. Methylparaben and propylparaben in Vedrop

formulation were also associated to potassium sorbate in order to amplify the antimicrobial efficacy of the preservative system.
During the pharmaceutical development, different formulations containing increasing concentrations of methylparaben/propylparaben were tested with 5.1.3 of the Ph.Eur. None of the formulations was compliant with the requirements. Therefore, a third preservative system, which included potassium sorbate was selected since it is in compliance with the Ph.Eur. requirements.
The formulation with methylparaben (0.3%) /propylparaben (0.09%) and of potassium sorbate (0.50%) was studied at different pH. The formulations found compliant with the requirements were those at pH 6.0 and 6.3 only. The disodium phosphate has been used as a buffer in order to stabilize the pH. After 6 months stability in accelerated conditions (40°C/75% RH), it was verified that the formulation at pH 6.0 was found to be the more stable. In this context, this formulation at pH 6.0 was selected and then developed.
It is important to underline that during the evaluation of the dossier, some parameters were studied in order to assess the robustness of the preservative system during the manufacturing of the drug product. It was concluded that at the lowest concentration of 90% in the parabens, the system was not compliant with the Ph.Eur. test but at minimum 93% for a pH range of 5.5 to 6.0.
The influence of the ionic strength showed that the efficacy of the preservative system was maintained in the range of 2600 to 4500 mOsm/Kg.
Furthermore, according to the micellar structure of the TPGS, at the concentration in Vedrop (i.e. 17.8 %), the preservative system was found to be more potent at lower concentrations down to 0.5% of TPGS in Vedrop solution, and being efficient even at 80% of the nominal concentrations of the parabens. The micellar structure of TPGS has probably an inactivating effect of a fraction of the parabens that are hydrophobic, justifying the level of the efficient concentration for the parabens needed for the preservation of the system.
This preservative system was shown to be compliant with the specifications through all the shelf-life of the finished product formulation with a good stability over time.

Acute toxicity studies in animals indicate that propylparaben is relatively non-toxic by both oral and parenteral routes, although it is mildly irritating to the skin. Furthermore, according to some scientific publications propylparaben is not carcinogenic, mutagenic or clastogenic (*Soni 2001*).
The applicant quotes an analysis of preclinical data by the Afssaps, which concluded in June 2004 that the safety profile of the parabens is good, with several years of clinical experience (*Afssaps site – bulletins de vigilance*). Recently, studies have demonstrated that parabens can bind to oestrogenic receptors, activate them and induce a physiological response in some animal models. Nevertheless, these compounds are from 1,000 to 1,000,000 times less potent than the 17 beta-estradiol (*Golden 2005*).
From a theoretical point of view, this oestrogenic activation may induce two types of risks in humans: 1) the potential promotion of oestrogenic-dependent tumors, in particular mammary tumors, and 2) the potential alteration of fertility. Regarding the risk of tumors, no valid experimental data can support an increased risk of breast cancer. Regarding potential alteration of fertility, studies conducted in 2001 and 2002 (*Oishi 2001, Oishi 2002a*) have shown a decrease in the number of spermatozoids in the testis of the juvenile rat with propylparaben and butylparaben (*Oishi 2002b*). No effect was observed following administration of methyl or ethylparaben. An additional study, conducted according to good laboratory practices, was conducted with butylparaben and showed no testicular effects in the juvenile rat (*Hoberman 2008*).

Review and analysis of the above-mentioned literature has been performed by two independent and recognized experts (Prof. Jacques Descotes and Dr. Richard Lee) and have been submitted.
In humans, the main risk related to the use of parabens is sensitization occurring when medications containing parabens are applied to the damaged or broken skin. Parabens have been implicated in numerous cases of contact sensitivity associated with cutaneous exposure, but high concentrations of 5-15% in patch testing are needed to elicit reaction in susceptible individuals. Allergic reactions to ingested parabens have been reported, although rigorous evidence of the allergenicity of ingested parabens is lacking (*Soni 2001*).
Review of the available data on the potential reproductive toxicity of parabens in animals and in humans have raised some concerns about the potential health risk, although it is questionable whether these concerns have any relevance to human exposure (*Hoberman 2008).*

To assess this potential health risk of propylparaben contained in Vedrop, different parameters should be taken into consideration, including maximal daily intake of propylparaben, treatment duration with Vedrop and therapeutic alternatives.
First of all, the recommended total daily dose in paediatric patients suffering from cystic fibrosis is 0.13 ml/kg/day (6.7 mg/kg of d-alpha-tocopherol in the form of tocofersolan). The total daily dose is limited to 6.7 ml solution per day (335 mg of d-alpha-tocopherol) for patients weighing 50 kg or more according to current clinical practice in the management of cystic fibrosis. In other words, in this indication, the maximum daily dose of propylparaben administered is 6 mg, equivalent to 0.12 mg/kg/day (6.7 ml of Vedrop with 0.09% of propylparaben for a child of 50 kg).
The recommended total daily dose in paediatric patients suffering from chronic cholestasis (usually very young, mostly between 0 and 3 years of age), 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. The maximum daily dose of propylparaben is 4.5 mg equivalent to 0.3 mg/kg/day (5.1 ml Vedrop for a child of 15 kg).
Secondly, the treatment duration with Vedrop is limited. Indeed, children with congenital chronic cholestasis or hereditary chronic cholestasis are diagnosed very early after birth. They rapidly go through porto-enteral derivation surgery (Kasai procedure) in order to rebuild the bile duct. If surgery fails (around 50% of cases), liver transplantation is performed as soon as possible (usually long before one year of age). The administration of vitamin E as Vedrop will only occur when the biliary duct is not successfully restored, meaning that longer administration of this medicinal product is restricted to children in whom the Kasai procedure has failed and who have not yet received a liver transplantation. Therefore, the duration of the treatment is around 6 months in this population.
For children with cystic fibrosis, Vedrop is indicated between 0 and 6 years of age because it is a liquid formulation. At 7 years old, children can usually swallow and have capsules of vitamin E. So the total duration can last up to 6 years.
Finally, there is no available approved oral solution of water-soluble vitamin E in the EU. In other words, there is no alternative treatment to Vedrop.

In conclusion, in the applicant`s opinion exposure to propylparaben contained in Vedrop should not be considered as a cause for concern since it will be a limited exposure (low daily intake and limited duration of treatment). Furthermore, there is the lack of therapeutic alternative. Finally, the applicant highlights that the EMEA/CHMP Paediatric Working Party identified pegylated vitamin E for the treatment of vitamin E deficiency in chronic cholestasis as one of the needs for research and development of medicinal products for children.

Ground for re-examination 2: The composition of the clinical trial batches has not been sufficiently characterised in terms of active species and impurities, and it was not established whether the impurities had been adequately identified and qualified

Applicant`s position

The active species and impurities were not part of the specifications set in Eastman's DMF, the active ingredient manufacturer. As requested during the previous evaluation, the composition in active species of the clinical batches was asked to Eastman by Orphan Europe.
The composition of the two tocofersolan batches used in the Vedrop clinical batches of the Orphan Europe clinical trials were eventually obtained the day before the oral explanation held on 15th December 2008.
The content in active species as monoester, diester, free PEG and impurities were indicated and the availability of this information was orally presented to the CHMP during the oral explanation held in January 2009. Eastman also gave the composition of the tocofersolan batches intended for marketing. The chain length of PEG was confirmed by Eastman (n=22 to 24) with a molecular mass of 950-1050.
All these batches are consistent regarding the analytical results obtained on the active species and impurities and compliant with the specifications of the European Food Safety Authorities (EFSA) report on TPGS.

Regarding the impurities and according to the recent results obtained, Orphan Europe is able to lower the specifications of 7 out of the 11 known impurities below the ICH qualification level of 0.15%

(impurities 2-8-10-12-13-14 and 15 mentioned in the specifications of the active substance in Ground 3).
Two other specifications of impurities (impurities 6 and 9, Propionate ester of TPGS monoester and Ethyl ester of tocopheryl succinate) were also lowered below the specifications of the EFSA report from 1.5% to 1.0%.
Regarding the two last impurities (impurities 4 and 3 PEG ester of succinic acid ester of TPGS and succinic acid ester of TPGS monoester), specifications were maintained, respectively at 0.25% and 2%. Moreover, a toxicological expert, Dr D.Marzin (Institut Pasteur de Lille) assessed the impurities of tocofersolan (those mentioned in the EFSA report) and according to their structure and their metabolism, concluded that none of the impurities of the EFSA report has a toxicological concern at the specification level of the EFSA report.

The EFSA limits were established for a daily dose of tocofersolan of about 3 g for a 50 kg child i.e. about 2 to 3 fold the maximum daily dose of 1.2 g of tocofersolan proposed by Orphan Europe. This means that the maximum daily dose of tocofersolan is 0.024 g/kg/day below the NOAEL of 1g/kg/day.

The impurities that are mentioned are oxidized form of tocopherol, ester succinic acid of TPGS, propionate ester of TPGS that could be mainly hydrolysed by esterases in plasma into succinic acid, tocopherol or its derivatives (which are endogenous products), and PEG 1000 at a concentration with no toxicological concern.

Ground for re-examination 3: The specification of the active substance and finished product should be revised and updated batch analysis data for the active substance and finished product should have been resubmitted according to the revised specifications

Applicant`s position

The revised sets of specifications are available for the active substance and for the finished product according to the tests and limits discussed in the Day 180 List of Outstanding issues responses. Furthermore, all the methods mentioned have been validated.

Regarding the active substance, the base was the Eastman's ASMF. Some other tests were added in accordance with the requirements of the CHMP during the assessment procedure and the data communicated by Eastman to Orphan Europe the day before the oral explanation held on 15th December.
Then, tests as assay of active species (monoester, diester), free PEG, sulfated ashes, water content, succinic acid and 11 other impurities were added.
Those impurities with results on batches were communicated by Eastman the day before the oral explanation and mentioned only orally to the CHMP.
Those impurities which specifications were set based on Eastman's specifications were lowered in a way to be the more possible in accordance with the ICH Q3A guideline, concerning the qualification threshold of 0.15%.
As mentioned in the previous response, 8 impurities out of 12 were compliant with this specification, 2 other were lowered below the Eastman's specifications (impurities 6 and 9) and 2 other were maintained at the same specification (impurities 4 and 3). None of these impurities present a toxicological concern.
Regarding the finished product, the assay of the tocofersolan, of tocopherol and the products involved in the composition of tocofersolan (monoester of TPGS, diester of TPGS) are tested. The specifications of the preservatives at a lower limit of 95% ensure a good efficacy of the antimicrobial system. Osmolality is controlled. The impurities have been lowered to acceptable levels.

Ground for re-examination 4: The demonstration of PK and clinical efficacy in patients with cystic fibrosis was insufficient

Applicant`s position

In cystic fibrosis (CF), though alternative formulations exist on various European markets the situation remains heterogeneous and in most markets no drinkable water-soluble formulation of vitamin E is available. Consequently, either liposoluble formulations, or tablets or capsules, or if possible a drinkable suspension are used (e.g. under a Named Patient program –"ATU" – in France). This latter preparation is used because there is a clear unmet medical need in the CF population of young children who cannot easily swallow capsules or tablets. However, such programme, i.e. provision of drug under Named Patient Use should be limited in time. Alternatively, preparations of the vitamin together with other oligo-elements are made available through Internet purchasing system. In the applicant`s opinion this does not constitute a controlled and adequate way of marketing products, lobbying initiatives from providers settled as off-shore companies towards CF-patients' associations are undertaken because of the unmet medical need.

Bioequivalence was tested only in healthy volunteers (HV). Data in children with CF or with chronic cholestasis (CC) were only complementary and should not be regarded as bioequivalence tests.

Pharmacokinetics (PK) calculations to test bioequivalence in HV were appropriate to compare products of different powerfulness. By similarity to calculations in HV, plasma concentrations and AUC were divided by the dose, and appropriate statistical tests (Anova and non parametric) carried out to evaluate the difference between the two formulations in respective children populations. This was recently accepted for publication in a peer reviewed journal of pharmacology. This cannot constitute a methodological drawback specifically in CF children. Moreover PK data either in CF or in CC were not presented as efficacy data.

Ground for re-examination 5: There was insufficient evidence that the formulation of the investigational product was the same as Vedrop intended for marketing

Applicant`s position
Clinical studies submitted in support of the CC indication were performed 15-20 years ago and "bridging" data was requested. The Applicant has made every effort to retrieve and explain the non-availability of bridging data between Vedrop and the TPGS formulations used in studies considered as "pivotal" for the demonstration of its biological and clinical efficacy.
No proof could be provided that the quality of the investigational product was the same as Vedrop. Conversely, it is likely to be different as the initial formulation of the investigational product was made in a hospital pharmacy with no information of stability of the product or storage conditions.
Comparisons of past oral vitamin E tolerance test results and those obtained in the applicant's own sponsored study (BIOEQPED 2006) show indirect evidence that the biological results were similar in both studies. Personally-owned data from R.J. Sokol were also provided to highlight the PK similarities between various formulations that he had used during the clinical investigation of TPGS.
Information on biological indexes under Vedrop in the CC population as data from the Named Patient Use program was provided. As compared to TPGS used in the "pivotal" studies, they objectivised similar results with these different preparations, constituting indirect bridging data.
In conclusion, direct bridging data remain inaccessible as the quality of the initial product is unknown; there is no stock of this product and even the producing Companies no longer exist.

Report from the Ad-hoc Expert meeting on Vedrop re-examination

Following the request from the applicant, as agreed by the CHMP, an Ad-hoc Expert meeting has been convened on 12 May 2009 to provide comments on the grounds for negative opinion and advice on the list of questions raised by the CHMP and adopted during the April 2009 CHMP meeting.

The recommendations from the Ad-hoc expert group on these CHMP questions were:

- The expert group was asked to comment on whether the inclusion of propylparaben in the proposed paediatric formulation at the level proposed has been sufficiently justified and is acceptable. The expert group was also asked to comment if administration at a maximum daily dose of 6 mg of propylparaben is acceptable in children of all age groups.

The majority of experts were of the opinion that the propylparaben level is adequately justified, and that it may be considered acceptable in the light of the clinical need for the product in the small target population. It was also specified that Vedrop posology corresponds with a 5.36 mg PP maximum daily dose for a 50 kg patient in CF, and a 0.272 mg/kg/day propylparaben in the indication for CC.
The propylparaben level is higher than normally used, but as they see it there are no public health safety reasons to refuse the use of this specific product based on currently available data. When clear recommendations become available based on future toxicology data, the list of all propylparaben containing products may have to be reviewed in its entirety at that point in time.
However because of the lack of adequate juvenile study especially assessing the risk of testicular toxicity of propylparaben there is a potential safety concern for this specific product that will be used long term in neonates. It was not considered appropriate or feasible to ask for clinical follow up of fertility but the need for a juvenile study in neonatal animals (e.g. as a post-marketing commitment as part of the RMP) was suggested in view of the high propylparaben level for use in the low-age population.
In conclusion, the expert group considered that the propylparaben content in Vedrop is acceptable provided a non clinical study in juvenile animals is performed. A protocol would have to be submitted and the proposed age range of the studied animals justified to address the concern in the lower age range population. This study could be performed post approval as a post-marketing commitment.

- The expert group was asked to comment on whether the composition of the clinical trial batches has been sufficiently characterised in terms of active species and impurities, whether the impurities had been adequately identified and qualified and whether there was sufficient evidence that the formulation of the investigational product was the same as Vedrop intended for marketing.

It was noted that impurities have been adequately identified and qualified; therefore from the quality point of view there are no concerns.
From the toxicology point of view there are also no concerns regarding these impurities.
It was agreed that the limits of the active moieties should be tightened around the results of the clinical batches and this issue should be addressed before a decision on the licence is taken.

- The expert group is asked to comment on whether the PK data provided and the clinical efficacy demonstrated in patients with cystic fibrosis is sufficient

According to the experts the PK data provided are not adequate; concerns raised were that the measured levels of Vitamin E in plasma in pretreated patients (at baseline) showed a tendency to decrease over time when on treatment with Vedrop; although not a formal comparison, the plasma levels achieved with Vedrop were much lower than with the Cambridge product; in the absence of an untreated control (subjects on a Vitamin E-containing diet) the meaningfulness of the increase in plasma levels under Vedrop treatment were not entirely clear; patient numbers studied are low, and variability is high which significantly reduce the robustness of the study results.

The experts agreed that clinical efficacy in patients with cystic fibrosis has not been demonstrated since no assessment of possible clinically relevant outcome (e.g. nerve function) was available. Furthermore, it was considered, that for CF in general there may not be a general unmet medical need (even considering countries where the Cambridge formulation is not available), since in CF the improvements in adequate substitution with pancreatic enzymes have improved the situation, adequate nutrition was of prominent importance, and a general deficiency and need for substitution of fat-soluble vitamins, including Vitamin E, in all CF patients is questionable.

In conclusion the beneficial effect of Vedrop in CF patients has not been demonstrated.

After the expert meeting the applicant decided to withdraw the indication for cystic fibrosis patients and submitted revised Product information, RMP and revised specifications for the active substance and finished product

CHMP position on the Grounds for re-examination

CHMP position on Ground for re-examination no 1 (Propylparaben)

The antimicrobial preservative system used in Vedrop combines three preservatives selected for their well known antimicrobial and antifungal efficacy in order for the product to meet the requirement of the Ph.Eur. for preservative efficacy. The combination of propylparaben / methylparaben is widely used as being known to be the most effective antimicrobial system against moulds and bacteria. Despite propylparaben not being used in food it can be said that propylparaben is widely used in medicines, including products used in the paediatric population.
Vedrop posology corresponds with a 5.36 mg propylparaben maximum daily dose for a 50 kg patient in CF, and a 0.272 mg/kg/day propylparaben in the indication for CC. On this basis CHMP considers that a refusal of the MA on the basis of propylparaben content is not justified.

The propylparaben level is higher than normally used, but is certainly not the highest (when considering daily intake). Moreover, there are no public health safety reasons to refuse the use of this specific product based on currently available data.

Taking into account the lack of adequate juvenile study especially assessing the risk of testicular toxicity of propylparaben there is a potential safety concern for this specific product that will be used long term in neonates. Therefore, it was not considered appropriate or feasible to ask for clinical follow up of fertility but the need for a juvenile study in neonatal animals was stressed in view of the high propylparaben level for use in the low-age population. In this context, the applicant committed to participate in the consortium of companies working with the AFSSAPS, to assess the potential risk of propylparaben on the reproductive system of the neonatal rat.

CHMP was of the opinion that the propylparaben level is adequately justified, and that it may be considered acceptable in the light of the clinical need for the product in the small target population.

CHMP position on ground for re-examination no 2 (active species and impurities)

It was agreed that the limits for impurities proposed by the applicant are marginally outside the ICH qualification limits. Furthermore, a non-clinical expert report dated January 2009 from Daniel Merzin (Institut Pasteur de Lille, France) has been submitted. This report did not highlight any concerns regarding the initial higher impurity limits (apart from succinic acid ester of TPGS monoester which has now been increased from 1.5% (level of evaluation) to 2%. Moreover, a document from the European Food and Safety Agency (EFSA) states that "the use of TPGS in foods for special medical purposes is not a safety concern at the anticipated exposure level 51.7-64.5 mg/Kg/bw/day but is contraindicated in children with severe impairment of kidney function"
It can be concluded that the aspects of identification and qualification of impurities are adequately resolved.

CHMP position on ground for re-examination no 3 (revised specifications of the active substance and finished product and updated batch analysis data according to the revised specifications)

It was noted that the active substance testing at different stages have been harmonised and assay limits tightened around clinical trial results.
The Specifications of the active substance and finished product have been revised accordingly. Furthermore, the Applicant has agreed to submit the updated batch analysis data (active substance and finished product) as a FUM.

CHMP position on ground for re-examination no 4 (PK data and demonstration of clinical efficacy in patients with cystic fibrosis insufficient)

The results of PK studies in HV and patients with CF showed that the absorption of the pegylated d α tocopherol (tocofersolan) is not better than that of the α dl tocopherol (Cambridge reference), when equal doses in IUs (100 IU) were compared.

The results of an open six months maintenance study in paediatric patients with CF, in which their previous vitamin E treatment was switched to Vedrop, are open to criticism. The trial was uncontrolled; 5 various vitamin E preparations were used as prior treatment, the dose of tocofersolan was 6,7 mg/kg/day but in the "first phase" of the study it was individualized (2,4 mg/kg/day – 21,4 mg/kg/day).
The results at three and six month post-switch show a slight downward trend with mean vitamin E levels of ≈ 25, 24.5, 23 μmol/L at baseline, three months and six months respectively. Further time points could clarify whether this trend was real or a chance finding.
In any case the results suggest, that switching patients from other vitamin E formulations to Vedrop at least at the recommended dose (6,7 mg/kg/day) in patients with CF may result in worse vitamin E supplementation than when using other available products.

In conclusion, the CHMP agreed with the experts` recommendation that the beneficial effect of Vedrop has not been demonstrated in CF patients.

CHMP position on Ground for re-examination no 5 (insufficient evidence that the formulation of the investigational product was the same as Vedrop intended for marketing)

Direct bridging data between Vedrop and the TPGS formulations used in studies considered as "pivotal" for the demonstration of its biological and clinical efficacy is not available. The formulations used in the early scientific evaluation of the biology of vitamin E were of an extemporaneous or magisterial nature and a link to them cannot be expected. The Applicant has argued that similar biological results were obtained in the studies with both formulations, i.e. essentially 'indirect' bridging data.
When the totality of the available data is considered, sufficient information is known about the efficacy of this product and its mechanism of action to recommend it for approval in the absence of more specific bridging data between developmental formulations.

Overall conclusion on grounds for re-examination and updated benefit/risk assessment

Quality

Taking into consideration the initial data submitted and the additional clarification presented by the Applicant with the detailed grounds of re-examination it can be concluded that the Information on development, manufacture, control of the active substance and the finished product have been presented in a satisfactory manner and justified in accordance with relevant CHMP and ICH guidelines. The results of tests carried out indicate satisfactory consistency and uniformity of the finished product. Therefore, this medicinal product should have a satisfactory and uniform performance in the clinic. The previous major outstanding issues regarding the quality of the active substance and finished product have been resolved. It was noticed that the Applicant has revised the specification of the active substance and finished product. Moreover, an updated batch analysis data for the active substance and finished product will be submitted as a FUM according to the revised specifications.
The Applicant has provided the relevant information regarding the composition of the clinical trial batches in terms of the quantities of active species present and with regard to impurities present.
The impurities presented in the active substance have been adequately identified and qualified; from the quality and toxicology point of view there are no concerns.
It was noted that the limits of the active moieties were tightened around the results of the clinical batches. All concerns regarding the uncertainty of the similarity between clinical trial batches and the finished product intended for commercialisation have been clarified.
CHMP decided that the propylparaben level is adequately justified, and that it may be considered acceptable in the light of the clinical need for the product in the small target population. Furthermore, it was noticed that there are other medicines, which are already on the EU market that have a higher daily intake of this particular preservative. However, a non clinical study in juvenile animals (neonates) with propylparaben should be performed. In this context, the Applicant committed to participate in the consortium of companies working with the AFSSAPS, to assess the potential risk of propylparaben on the reproductive system of the neonatal rat.

In conclusion it can be confirmed that the quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. At the time of the CHMP opinion, there some minor unresolved quality issues, which do not have any impact on the benefit/risk ratio of the medicinal product. These will be addressed as part of the follow-up measures to be addressed post-authorisation.

Efficacy

Tocofersolan has been shown to be effective in correcting blood vitamin E levels in patients presenting with lipid malabsorption due to chronic cholestasis. From the historical data submitted, tocofersolan may be effective in correcting or preventing neurological symptoms in patients with congenital chronic cholestasis. The extent of regression of neurological symptoms depends on the age of the patients and the duration of malabsorption. Tocofersolan seems effective in preventing neurological complications when given early to patients, preferably before the age of 3 years.
Plasma vitamin E levels should be monitored and the dose adjusted accordingly if necessary (see SPC 4.2 Posology and administration).

The demonstration of efficacy, both clinically and biochemically (pharmacokinetics), in patients with cystic fibrosis is insufficient.

Safety

Experience concerning the clinical safety of tocofersolan is mainly based on published papers in the literature (in 27 healthy volunteers and 116 patients) and on the Applicant's sponsored studies (in 12 healthy volunteers and 42 patients).

Tocofersolan is taken up by cells as the intact molecule, hydrolyzed intra-cellularly and the alpha-tocopherol moiety then appears in chylomicrons in the lymph in a manner identical to vitamin E absorbed from the diet as shown *in vitro*. The other constituent of Vedrop, Polyethylene Glycol 1000, does not contribute to the pharmacological action of Vedrop. It only acts as a vector of vitamin E to its intestinal absorption sites (*i.e.* the apical membrane of the enterocytes) in cases where physiological lipo-solubilizing agents are missing because of an underlying disease. Nephrotoxicity is an established adverse effect of glycols, particularly small glycol molecules, e.g. ethylene and diethylene glycol or low-molecular-weight PEG. Results from animal and human studies appear not to substantiate this risk with regard to the high-molecular-weight PEG 1000. An appropriate precautionary statement was included in the product information (SPC section 4.4 Special warnings and precautions for use)

Overall, adverse effects seen with tocofersolan therapy appear to be not serious, are mostly related to the gastrointestinal tract (diarrhoea), and are often dose-related. Although vitamin E and tocofersolan have been used as supplements in many patients over many years, data from controlled trials are sparse. Due to limited data and lack of systematic controlled studies, no definite conclusions can be drawn regarding drug-drug interactions or other interactions. However, available evidence indicates that tocofersolan, due to inhibition of P-Glycoprotein transporter, may enhance intestinal absorption of other concomitant fat-soluble vitamins (A, D, E, K) or that of highly lipophilic medicinal products (see SPC section 4.5 Interactions with other medicinal products and other forms of interaction).

Vedrop contains propylparaben (0.08 %). As information on the preclinical toxicity of propylparaben on the reproductive system is lacking, a preclinical study in neonatal animals is needed in view of the high propylparaben level for use in the low-age population. In this context, the Applicant committed to participate in the consortium of companies working with the AFSSAPS, to assess the potential risk of Propylparaben on the reproductive system of the neonatal rat.

Risk Management Plan

The MAA submitted a risk management plan.

Table 7
Summary of the risk management plan

Safety concerns	Proposed pharmacovigilance activities	Proposed risk minimization activities
Potential risks		
Drug interactions	Routine pharmacovigilance	SPC section 4.5 contains the following statement: *"Due to inhibition of P-Glycoprotein transporter, tocofersolan may also enhance intestinal absorption of other concomitant fat-soluble vitamins (A, D, E, K) or that of highly lipophilic medicinal products (such as steroids, antibiotics, antihistamines, cyclosporine, tacrolimus). Therefore, monitoring should be performed and, when necessary, doses should be adjusted."*
Missing information		
Mid-term safety in patients with congenital or hereditary CC	Routine pharmacovigilance To set up a patient registry in order to collect data on demographics of patients, on the use of Vedrop and on the safety profile	-
Exposure during pregnancy	Routine pharmacovigilance	SPC section 4.6 contains the following statement: *"For tocofersolan no clinical data on exposed pregnancies are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or post-natal development (see section 5.3). Caution should be exercised when prescribing to pregnant women."*
Exposure in patients with renal or hepatic impairment	Routine pharmacovigilance	SPC section 4.4 contains the following statement: *"Due to the potential for renal toxicity of polyethylene glycols, Vedrop should be administered with caution and under close monitoring of the renal function in patient with renal impairment e.g. dehydrated patients."* *"As data on patients with hepatic impairment are limited, Vedrop should be administered with caution and under close monitoring of the hepatic functions in such patients."*
Preclinical toxicity of propylparaben contained in Vedrop, on the reproductive system	Preclinical study Monitoring of endocrine status of the patients in the frame of the patient registry	-
Potential for off-label use in patients with CF	Routine Pharmacovigilance Analysis of the data in this subpopulation in each PSUR	-

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

- User consultation

The user testing of the PL was performed and judged as acceptable.

Risk-benefit assessment

Please also refer to section 3.6 for the initial risk-benefit discussion. Since then the Applicant has withdrawn the application for the indication cystic fibrosis.

During the re-examination procedure the risk-benefit of Vedrop in congenital chronic cholestasis or hereditary chronic cholestasis was confirmed to be positive. The CHMP was of the opinion that the propylparaben level is adequately justified, and is acceptable in the light of the clinical need for the product in the small target population. Therefore, considering the unmet medical need of the product in young children with congenital chronic cholestasis or hereditary chronic cholestasis, this indication can be accepted with the conditions laid down in the SPC, i.e. monitoring of vitamin E levels (SPC 4.2), a warning for drug-drug interactions and a precautionary statement regarding potential for renal toxicity due to PEG (SPC 4.4).
Based on the limited amount of preclinical and clinical data available (due to the rarity of the disease), this indication can be approved under exceptional circumstances. In this respect, as requested by the CHMP, the applicant has committed to provide further data post-authorisation, as specific obligations, which will form the basis of an annual re-assessment of the benefit/risk profile of Vedrop:
- Non-clinical: The applicant commits on the principle to participate to the consortium of companies working with the AFSSAPS to assess the potential risk of propylparaben on the reproductive system of the neonatal rat.
- Clinical: In the frame of the RMP, the applicant will set up a registry in patients with congenital chronic cholestasis or hereditary chronic cholestasis.

An updated risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.

- no additional risk minimisation activities were required beyond those included in the product information.

Recommendation following re-examination

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Vedrop in the treatment of vitamin E deficiency due to digestive malabsorption in paediatric patients suffering from congenital chronic cholestasis or hereditary chronic cholestasis was favourable and therefore recommended the granting of the marketing authorisation under exceptional circumstances.