

## VEDROP® SUMMARY OF PRODUCT CHARACTERISTICS

### 1. NAME OF THE MEDICINAL PRODUCT

Vedrop 50 mg/ml oral solution

### 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 50 mg of d-alpha-tocopherol, in the form of tocopherolsol, corresponding to 74.5 IU of tocopherol.

#### Excipients:

Each ml contains 3 mg sodium methyl parahydroxybenzoate (E219), 0.90 mg sodium propyl parahydroxybenzoate (E217), 0.03 mmoles of potassium and 0.14 mmoles of sodium.

For a full list of excipients, see section 6.1.

### 3. PHARMACEUTICAL FORM

Oral solution.

Slightly viscous, pale yellow solution.

### 4. CLINICAL PARTICULARS

#### 4.1 Therapeutic indications

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

#### 4.2 Posology and method of administration

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

Bioavailability of vitamin E from Vedrop differs from that of other medicinal products. The dose should be prescribed in mg of d-alpha-tocopherol in the form of tocopherolsol. Plasma vitamin E level should be monitored monthly for at least the first few months of therapy, thereafter at regular intervals and the dose adjusted accordingly if necessary.

#### Posology

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

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

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

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

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

Weight (kg)	Vedrop volume (ml)
3	1.0
4	1.4
5	1.7
6	2.0
7	2.4
8	2.7
9	3.1
10	3.4
15	5.1

#### Method of administration

Vedrop is administered orally with or without water. The 1-ml or 2-ml oral syringes included in the container are designed to assist in measuring out the exact dose in accordance with the prescribed posology.

#### **4.3 Contraindications**

Hypersensitivity to the active substance or to any of the excipients.

Vedrop must not be used in prematures.

#### **4.4 Special warnings and precautions for use**

As large doses of vitamin E have been reported to increase bleeding tendency in vitamin-K deficient patients or those taking oral anti-vitamins K treatment, it is therefore recommended to monitor the prothrombin time and international normalised ratio (INR). A possible adjustment of the dose of oral anticoagulant during and after treatment with Vedrop may be necessary.

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.

Renal function and serum osmolarity should be evaluated and monitored under treatment with Vedrop.

Vedrop contains sodium methyl parahydroxybenzoate (E219) and sodium propyl parahydroxybenzoate (E217) which may cause allergic reactions (possibly delayed).

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium-free'. And it also contains potassium, less than 1 mmol (39 mg) per dose, i.e. essentially 'potassium-free'.

#### **4.5 Interactions with other medicinal products and other forms of interaction**

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.

#### 4.6 Pregnancy and lactation

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.

It is unknown whether tocofersolan is excreted in human breast milk. The excretion of tocofersolan in milk has not been studied in animals. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Vedrop should be made taking into account the benefit of breast-feeding to the child and the benefit of tocofersolan therapy to the woman.

#### 4.7 Effects on ability to drive and use machines

No studies on the potential effects on the ability to drive and use machines have been performed.

#### 4.8 Undesirable effects

Reported adverse reactions are listed below, by system organ class and by frequency.

Frequencies are defined as: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ), very rare ( $< 1/10,000$ ).

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System organ class	Adverse drug reactions
Gastrointestinal disorders	<i>Common:</i> diarrhoea
Skin and subcutaneous tissue disorders	<i>Uncommon:</i> alopecia, pruritus, rash
General disorders and administration site conditions	<i>Uncommon:</i> asthenia, headache
Investigations	<i>Uncommon:</i> serum sodium abnormal, serum potassium abnormal, transaminases increase

#### 4.9 Overdose

Large vitamin E doses may cause diarrhoea, abdominal pain, and other gastrointestinal disturbances. No case of overdose with tocofersolan has been reported.

### 5. PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other plain vitamin preparations; ATC code: A11HA08

Vitamin E is the principal lipo-soluble antioxidant in the organism. It acts as a free radical chain breaking molecule, stopping the peroxidation of polyunsaturated fatty acids and it is involved in maintaining the stability and integrity of cell membranes.

This medicinal product has been authorised under “Exceptional Circumstances”.

This means that due to the rarity of the disease it has not been possible to obtain complete information on this medicinal product.

The European Medicines Agency (EMA) will review any new information which may become available every year and this SPC will be updated as necessary.

## 5.2 Pharmacokinetic properties

The active substance d-alpha-tocopherol-polyethylene glycol 1000 succinate (tocofersolan) is a pro-drug; the active metabolite is the d-alpha-tocopherol. At low concentrations, tocofersolan forms micelles which enhance absorption of non-polar lipids such as fat-soluble vitamins. Its critical micellar concentration is low (0.04 to 0.06 mmol/l).

The hydrolysis of tocofersolan occurs in the gut lumen. Taken up by cells, the alpha-tocopherol moiety appears in chylomicrons in the lymph in a manner identical to vitamin E absorbed from the diet. Cellular uptake does not require receptors, binding proteins or metabolic processes and does not occur by pinocytosis. Absorption of deuterated tocofersolan showed a normal pattern in lipoproteins: alpha-tocopherol peaked first in chylomicrons, then in very low-density lipoproteins (VLDL) and finally in low-density lipoproteins (LDL) and high-density lipoproteins (HDL), and the disappearance portions of the curves paralleled those in control subjects.

Located principally on cell membranes, within mitochondria and microsomes, vitamin E is ubiquitously distributed (red blood cells, brain, muscle, liver, platelets) and fat tissues are its major reservoir.

A study in 12 healthy volunteers compared tocofersolan with a water-miscible reference vitamin E after a single oral loading dose of 1200 IU. The relative bioavailability of tocofersolan tended to be higher ( $F_{rel}$  of  $1.01 \pm 1.74$ ) with  $AUC_{0-t}$  of  $0.383 \pm 0.203 \mu M \cdot h/mg$ ,  $C_{max}$  of  $0.013 \pm 0.006$ ,  $t_{max}$  of 6.0 h (6.0 – 24.0), and  $t_{1/2}$  of 29.7 h (16.0 – 59.5).

In a similar study tocofersolan showed a higher bioavailability than a water-miscible reference vitamin E in paediatric patients with chronic cholestasis (n=6), absorption was significantly higher on both plasma concentration maximum increase (p=0.008) and AUC (p=0.0026).

Vitamin E is mainly eliminated in the bile (75%) and stools, either as free tocopherol or as oxidized forms. Urine represents a minor elimination route of vitamin E (as glucuro-conjugate).

## 5.3 Preclinical safety data

Non-clinical data in the literature reveal no special hazard for humans based on conventional studies of repeated dose toxicity, genotoxicity and toxicity to reproduction.

# 6. PHARMACEUTICAL PARTICULARS

## 6.1 List of excipients

Potassium sorbate  
Sodium methyl parahydroxybenzoate (E219)  
Sodium propyl parahydroxybenzoate (E217)  
Glycerol  
Disodium phosphate dodecahydrate  
Concentrated hydrochloric acid  
Purified water

## **6.2 Incompatibilities**

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

## **6.3 Shelf life**

2 years.

After first opening the bottle: 1 month.

## **6.4 Special precautions for storage**

Keep the bottle tightly closed.

## **6.5 Nature and contents of container**

Type III brown glass bottle with screw cap of HDPE and LDPE seal. Oral syringes with housing of LDPE and piston of polystyrol. Each bottle contains 10 ml, 20 ml or 60 ml of oral solution.

Boxes containing:

- one 10 ml bottle and one 1 ml oral syringe
- one 20 ml bottle and one 1 ml oral syringe
- one 60 ml and one 2 ml oral syringe

Not all pack sizes may be marketed.

## **6.6 Special precautions for disposal and other handling**

Doses for administration should be extracted from the bottle using the oral syringes which are provided in the pack.

The 1 ml oral syringe is graduated from 0.05 to 1 ml in steps of 0.05 ml, and the 2 ml oral syringe from 0.1 to 2 ml in steps of 0.1 ml.

As Vedrop contains 50 mg/ml, one graduation of the 1 ml oral syringe corresponds to 2.5 mg of d-alpha-tocopherol in the form of tocofersolan and one graduation of the 2-ml oral syringe corresponds to 5 mg of d-alpha-tocopherol in the form of tocofersolan.

## **7. MARKETING AUTHORISATION HOLDER**

Orphan Europe S.A.R.L.  
Immeuble "le Wilson"  
70 avenue du Général de Gaulle  
92800 Puteaux  
France

## **8. MARKETING AUTHORISATION NUMBER(S)**

## **9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

## **10. DATE OF REVISION OF THE TEXT**

Detailed information on this product is available on the website of the European Medicines Agency (EMA) <http://www.emea.europa.eu>

