Final Study Report

Title	Registry of pediatric patients treated with Vedrop® (tocofersolan) in Europe for vitamin E deficiency due to digestive malabsorption in congenital or hereditary chronic cholestasis
Date	April 07th, 2017
Active substance	d-alpha-tocopherol-polyethylene glycol 1000 succinate (tocofersolan) ATC code: A11HA08
Medicinal product	Vedrop®
Marketing Authorisation Holder	Orphan Europe SARL
Objective	To collect data on the demographics of patients, on the use of Vedrop® and on its efficacy and safety profiles
Countries	France, the Netherlands, Germany, Sweden and Spain
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Synopsis

Title

Registry of pediatric patients treated with Vedrop® (tocofersolan) in Europe for vitamin E deficiency due to digestive malabsorption in congenital or hereditary chronic cholestasis.

Keywords

Cholestasis, vitamin E, vitamin E deficiency, tocofersolan, Vedrop®, fat malabsorption, biliary atresia, transient neonatal cholestasis, Alagille syndrome.

Rationale and background

To compensate for the limited clinical data that supported the initial marketing authorization of Vedrop®, Orphan Europe set up a Registry of patients with vitamin E deficiency due to malabsorption in congenital chronic cholestasis or hereditary chronic cholestasis, and treated with Vedrop®. The goal was to include at least 500 patients.

The number of patients having exceeded 500, and the fact that the results have not impacted the benefit/risk ratio of Vedrop®, the present report on the Registry is intended to be final.

Objectives

The objectives of the registry were to collect data of patients treated with tocofersolan (Vedrop®) in terms of patient demography, Vedrop® use, and Vedrop® safety/efficacy profiles.

Study design

The registry recovered demographic and treatment data, evaluated efficacy by assessing the plasmatic levels of vitamin E and safety by recovering adverse events. Data collection was performed both prospectively and retrospectively when relevant data was available.

Setting

Period of recruitment: March 2010 to February 2017. Treatment duration: not limited. Treatment stop: at the discretion of the treating physician. An active safety monitoring was undertaken by a CRO. The study took place in 11 centers in 5 European countries.

Subjects and study size

A total of 508 patients (safety population) were included in the Registry. Most patients (391) were treated after Registry start in March 2010 and up to 28 February 2017. A total of 117 patients were treated between September 2007 (Marketing Authorisation Application) and July 2009 (MA grant). These 117 patients were analysed retrospectively.

Efficacy Population: 391 patients for whom at least one measure of plasmatic vitamin E level is available at baseline and during follow up. Safety Population: 508 patients, i.e., all patients treated. Eight patients discontinued without follow-up.

Variables and data sources

Laboratory tests for tocopherolemia (vitamin E), total cholesterolemia (TC), and total triglyceridemia (TG), as well as commonly used markers of renal and hepatological functions were collected and analysed. No tests

were enforced and all data was obtained from laboratory and clinical tests performed for the benefit of the patient and in accordance with the local site practice.

Results

Baseline

Patient from France accounted for the majority of patients (59%), whereas patients from Germany and Netherlands accounted for around 12% of patients each, and Spain and Sweden for around 8% each. Males and females were equally represented (Females: 49%). Most patients had biliary atresia (46%), Alagille and transient neonatal cholestasis represented around 12% of patients each, whereas patients with Progressive familial intrahepatic cholestasis (PFIC) represented 9% of all patients. Other pathologies included metabolic diseases, and cystic fibrosis. The median age was less than 5.5 months in all pathologies, except for PFIC and other hepatic causes. The vitamin E deficiency appeared to be less important in cystic fibrosis patients when compared to the other patients. When the ratio vitamin E/TC+TG was considered, the cystic fibrosis patients appeared to be even less deficient in vitamin E when compared to other patients.

Exposure

Overall patients were treated with a median dose of 0.32 ml/kg/day in accordance with the recommended dose of 0.34 ml/kg/day. Although in most pathologies the median doses received were around 0.3 ml/kg/day, that was lower in cystic fibrosis (0.14 ml/kg/day), which is in accordance with their lower degree of vitamin E deficiency and of cholestasis.

Safety

A total of 3 adverse drug reactions with Vedrop® have been reported: 2 cases of vomiting and one case of abdominal pain. One serious adverse event of portal hypertension was estimated as related to Vedrop® by the physician but was subsequently considered by the Sponsor to be unrelated to Vedrop® and due to the underlying disease. No case of alopecia, asthenia, rash, enterocolitis, and no abnormal behaviour such as aggressiveness and or psychiatric disorder was reported.

Efficacy

Treatment with Vedrop® increased over 2-fold the plasmatic levels of vitamin E. When the ratio vitamin E/TC+TG was considered, Vedrop® was efficient in increasing this ratio over baseline values for all pathologies except in cystic fibrosis and in patients with other extrahepatic causes. This is consistent with the fact that such diseases have non-exclusive hepatobiliary etiologies.

Conclusion

Vedrop® was shown to be safe and efficient in restoring vitamin E levels in its claimed indications. Since the Sponsor complied with the request to include at least 500 patients and since the benefit/risk ratio of Vedrop® has remained unchanged since initial marketing Authorisation, the present report is intended to be final for this Registry.

Marketing Authorisation Holder

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