IPAR

Public Assessment Report for a
Medicinal Product for Human Use

Scientific Discussion

Metaperex 400 IU soft capsules
Rrr alpha-tocoferol
PA1748/005/001

The Public Assessment Report reflects the scientific conclusion reached by the Health Products Regulatory Authority (HPRA) at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation for a specific medicinal product for human use. It is made available by the HPRA for information to the public, after deletion of commercially sensitive information. The legal basis for its creation and availability is contained in Article 21 of Directive 2001/83/EC, as amended. It is a concise document which highlights the main parts of the documentation submitted by the applicant and the scientific evaluation carried out by the HPRA leading to the approval of the medicinal product for marketing in Ireland.

CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the HPRA has granted a marketing authorisation for Metaperex 400 IU soft capsules, from Kora Corporation Ltd t/a Kora Healthcare on 20th January 2023 for

- Vitamin E deficiency in patients diagnosed with ataxia with vitamin E deficiency (AVED).

This decentralised application concerns Metaparex 280mg (400 IU) soft capsules which contains rrr-alpha-tocopherol. It is made as per Article 28(3) of Directives 2001/83/EC in accordance with Article 10(a) Well Established Use (WEU).

With Ireland as the Reference Member State in this Decentralized Procedure, Kora Healthcare is applying for Marketing Authorisation in Belgium, The Netherlands and the United Kingdom as Northern Ireland.

The Summary of Product Characteristics for (SmPC) for this medicinal product is available on the HPRA's website at www.hpra.ie

Name of the product	Metaperex 400 IU soft capsules
Name(s) of the active substance(s) (INN)	rrr- alpha-tocoferol
Pharmacotherapeutic classification (ATC code)	A11HA03
Pharmaceutical form and strength(s)	280 mg Capsule, soft
Marketing Authorisation Number(s) in Ireland (PA)	PA1748/005/001
Marketing Authorisation Holder	Kora Corporation Ltd t/a Kora Healthcare
MRP/DCP No.	IE/H/1189/001/DC
Reference Member State	IE
Concerned Member State	BE NL XL

II. QUALITY ASPECTS

II.1. Introduction

This application is for Metaperex 400 IU soft capsules.

II.2 Drug substance

The active substance is RRR-α-Tocopherol an established active substance described in the European Pharmacopoeia, and is manufactured in accordance with the principles of Good Manufacturing Practice (GMP)

The active substance specification is considered adequate to control the quality and meets current pharmacopoeial requirements. Batch analytical data demonstrating compliance with this specification has been provided.

II.3 Medicinal product

P.1 Composition

Each capsule contains 280 mg of RRR-α-Tocopherol (equivalent to 400 IU of Vitamin E)

The excipients in the medicinal product are listed in section 6.1 of the SmPC.
A visual description of the product is included in section 3 of the SmPC.

P.2 Pharmaceutical Development

The product is an established pharmaceutical form, and its development is adequately described in accordance with the relevant European guidelines.

P.3 Manufacture of the Product

The product is manufactured in accordance with the principles of good manufacturing practice (GMP) at suitably qualified manufacturing sites.

The manufacturing process has been validated according to relevant European/ICH guidelines and the process is considered to be sufficiently validated.

P.4 Control of Other Substances (Excipients)

All ingredients comply with Ph. Eur. or are adequately controlled by the manufacturer's specifications.

P.5 Control of Finished Product

The Finished Product Specification is based on the pharmacopoeial monograph for the dosage form, and the tests and control limits are considered appropriate for this type of product.

The analytical methods used are described in sufficient detail and are supported by validation data.

Batch analytical data for a number of batches from the proposed production site(s) have been provided and demonstrate the ability of the manufacturer to produce batches of finished product of consistent quality.

P.6 Packaging material

The approved packaging for this product is described in section 6.5 of the SmPC.

Evidence has been provided that the packaging complies with Ph. Eur./EU legislation for use with foodstuffs requirements.

P.7 Stability of the Finished Product

Stability data on the finished product in the proposed packaging have been provided in accordance with EU guidelines and support the shelf-life and storage conditions listed in sections 6.3 and 6.4 of the SmPC.

II.4 Discussion on Chemical, Pharmaceutical and Biological Aspects

The important quality characteristics of the product are well-defined and controlled. Satisfactory chemical and pharmaceutical documentation has been provided, assuring consistent quality of Metaperex 400 IU soft capsules.

III. NON-CLINICAL ASPECTS

III.1 Introduction

The active substance alpha-tocopherol has been available on the European market for more than 10 years and is a well-known active substance. No new preclinical data have been supplied with this application and none are necessary. A non-clinical overview summarising relevant non-clinical studies has been included in the dossier; this is acceptable for this type of application.

III.2 Pharmacology

The pharmacology of vitamin E is well known and well described in the literature. Its primary mechanism of action is as an antioxidant. The safety profile of vitamin E has been demonstrated through clinical use. The information provided is considered acceptable for an application under Article 10(a) of Directive 2001/83/EC (well-established use).

III.3 Pharmacokinetics

Tocopherols are absorbed in the medial small intestine and are bound to lipoproteins in the blood. α-tocopherol is widely distributed in the body. It undergoes oxidation to carboxyethylhydroxychromanol via a process mediated by cytochrome P450s,

though the full process is poorly understood. Intermediate and short chain metabolites are excreted via urine, mostly as glucoside conjugates, while faeces contain mainly long chain metabolites. α-tocopherol has been identified as an inducer of CYP3A4.

III.4 Toxicology

Bibliographic data are inconclusive with respect to the carcinogenicity of α-tocopherol, but this is acceptable considering the extensive clinical experience with this active substance. The potential increased risk of prostate cancer in men associated with long-term use of vitamin E supplements is reflected in the SmPC. Non-clinical bibliographic data are also inconclusive with respect to the reproductive toxicity of vitamin E and use of this product is not recommended in pregnancy or breastfeeding.

III.5 Ecotoxicity/environmental risk assessment

According to the "Guideline on the environmental risk assessment of medicinal products for human use" (EMEA/CHMP/SWP/4447/00), vitamins due to their nature are unlikely to result in a significant risk to the environment. Therefore, further studies on the environmental risk of Metaperex 400 IU soft capsules are not required.

III.6 Discussion on the non-clinical aspects

Alpha-tocopherol is a widely used, well-known active substance. An abridged dossier was submitted in accordance with Article 10a of Council Directive 2001/83/EEC as amended. The applicant has not provided additional nonclinical studies and further studies are not required. The non-clinical evidence in support of this application is based on relevant published scientific literature which is appropriate. Non-clinical findings are adequately represented in the appropriate sections of the SmPC.

IV. CLINICAL ASPECTS

IV.1 Introduction

For generic applications (Article 10.1, 10.3, 10.4, 10.c),the following statements can be used:

The active substance alpha-tocopherol has been available on the European market for more than 10 years and is a well-known active substance with established efficacy and tolerability.

For this well-established use application, the applicant has submitted no new bioequivalence studies. In place of this the applicant submitted references to literature and assessments of comparability of Metaparex to other approved alpha tocopherol products.

IV.2 Pharmacokinetics

Absorption

α-Tocopherol is absorbed via the lymphatic pathway and transported in association with chylomicrons (Bjørneboe, 1990). Because of difficulties in estimating the actual α-tocopherol absorption, relative bio-availabilities between various vitamin E forms have been investigated and shown to be useful for identifying α-tocopherol regulatory mechanisms [(Burton, 1998); (Traber, 1990); (Traber, 2015)]. Other than various causes of fat malabsorption that lead to poor α-tocopherol absorption and vitamin E deficiency, there is little information with regard to the effect of physiologic factors on vitamin E bioavailability. In addition, little information is available concerning the effects of age on vitamin E bioavailability (Traber, 2015).

While the efficiency of vitamin E absorption is low in humans, the precise rate of absorption is not known with certainty (IOM, 2000). That the absorption of a-tocopherol is incomplete is suggested by many studies in animals and a small number of studies in man. This appears to be true for all the fat soluble vitamins (Kelleher, 1970).

Following plasma vitamin E saturation, the plasma uptake of newly absorbed a-tocopherol is diminished (Lodge, 2005). Vitamin E is 20% to 50% absorbed by intestinal epithelial cells in the small intestine (Pubchem, 2020). However, it has been reported that in the gastro-intestinal system the absorption rate of vitamin E varies inter-individually between 20%-80% (Bjørneboe, 1990) (Rigotti, 2007) (Schmölz, 2016). In early studies vitamin E absorption was estimated to be 51 to 86 percent, measured as fecal radioactivity following ingestion of α-tocopherol (Kelleher, 1970), (MacMahon, 1970). Vitamin E absorption from the intestinal lumen is dependent upon biliary and pancreatic secretions, micelle formation, uptake

into enterocytes, and chylomicron secretion. Defects at any step lead to impaired absorption. Chylomicron secretion is required for vitamin E absorption and was suggested to be the most important factor for efficient vitamin E absorption (IOM, 2000).
All of the various vitamin E forms, including α- and γ-tocopherols, RRR- and SRR-α-tocopherols, or RRR- and all racα-tocopherols, showed similar apparent efficiencies of intestinal absorption and subsequent secretion in chylomicrons (IOM, 2000).
The plasma and red blood cell pharmacokinetics and bioavailability of the natural source (RRR, d) and all racemic (all rac, dl) stereoisomers of alpha-tocopherol were studied in 12 men in a double-blind randomized crossover study. Subjects were administered two 400-mg soft-gelatin capsules of either RRR or all rac alpha-tocopherol. Plasma alpha-tocopherol concentrations were determined by high-performance liquid chromatography at various time intervals for up to 96 hours post administration. Pharmacokinetic modelling of the data showed that alpha-tocopherol was absorbed after a 2 to 4 hour lag time and maximum plasma concentration occurred from 12 to 14 hours post administration. There were no significant differences in the Ka, t1/2 a, beta, or t1/2 beta between RRR and all rac. Mean plasma alpha-tocopherol concentrations were greater for RRR than all rac
from 10 to 96 hours post administration and significantly greater at 24 hours ($P < .05$). The red blood cell alpha-tocopherol concentration from the RRR preparation was significantly greater than from the all rac preparation from 24 to 96 hours post administration with peak plasma concentration for RRR (4.8 micrograms/mL) significantly greater than for all rac (4.0 micrograms/mL, $P < .05$). The RRR area under the concentration curve from time 0 to time 96 (AUC 0-96) for both plasma and red blood cells were significantly greater than the all rac AUC 0-96 ($P < .05$) indicating a greater bioavailability of RRR versus all rac alpha-tocopherol. This difference in overall bioavailability was apparently not due to a single pharmacokinetic component (Ferslew, 1993). Vitamin E is absorbed together with lipids and thus has to be taken with a meal containing a sufficient amount of fat to guarantee optimal bioavailability (Brigelius-Flohé, 2002).

Distribution
Distribution of vitamin E to tissues via the lymphatic system occurs as a lipoprotein complex. High concentrations of vitamin E are found in the adrenals, pituitary, testes, and thrombocytes (Pubchem, 2020). During chylomicron catabolism, some vitamin E is distributed to all of the circulating lipoproteins (IOM, 2000). Chylomicron remnants, containing newly absorbed vitamin E, are taken up by the liver. Vitamin E is secreted from the liver in very low density lipoproteins (VLDLs), as demonstrated in animals and in in vivo experiments (IOM, 2000).
Plasma vitamin E concentrations depend upon the secretion of vitamin E from the liver, and only one form of vitamin E, α-tocopherol, is preferentially re-secreted by the liver. Thus, the liver, not the intestine, discriminates between tocopherols and is responsible for the preferential plasma enrichment with α-tocopherol, α-tocopherol transfer gene is a likely candidate for this discriminatory function (IOM, 2000).

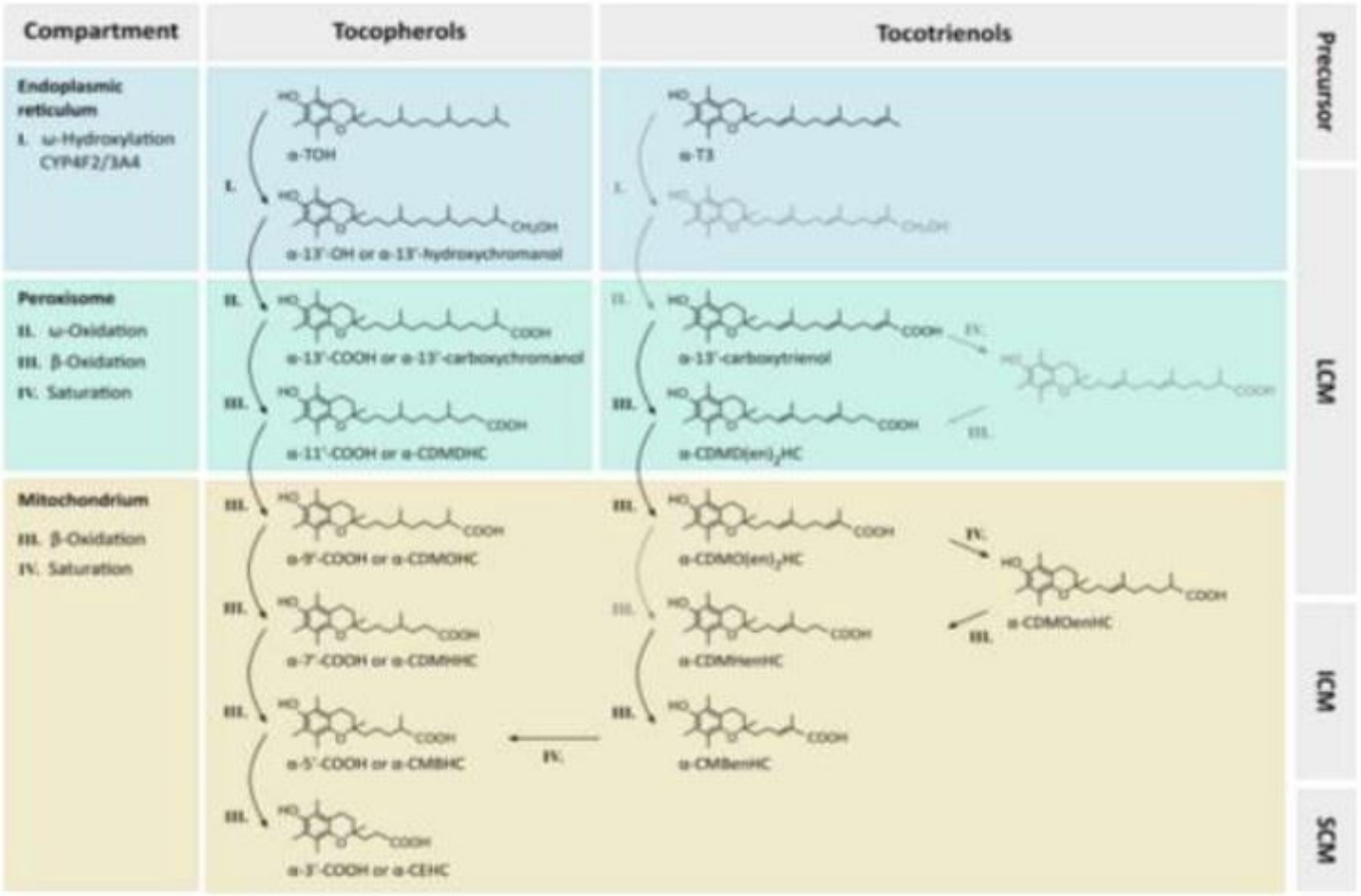
Elimination
Vitamin E is stored unmodified in tissues (principally the liver and adipose tissue) and excreted via the faeces. Excess vitamin E is converted to a lactone, esterified to glucuronic acid, and subsequently excreted in the urine (Pubchem, 2020).
A kinetic model of vitamin E transport in human plasma has been developed using data from studies with deuterium-labeled stereoisomers of α-tocopherol (RRR and SRR). RRR-a-Tocopherol rapidly leaves the plasma but is incorporated into VLDLs and resecreted back into the plasma. The result of this process is the apparent slow disappearance of RRR-a-tocopherol from the plasma (Traber, Traber
MG, Ramakrishnan R, Kayden HJ. Human plasma vitamin E kinetics demonstrate rapid recycling of plasma RRR-alpha-tocopherol. Proc Natl Acad Sci U S A. 1994;91(21):10005-10008, 1994). The apparent half-life of RRR-α-tocopherol in normal subjects was approximately 48 hours, consistent with the "slow" disappearance of RRR-α-tocopherol from the plasma, whereas the half-life for SRR-α-tocopherol was approximately 13 hours (IOM, 2000).

In the study carried out by Kelleher et al., a small quantity of the administered of α-tocopherol (almost always less than 6%) was excreted in the urine (Kelleher, 1970). Similar results have been obtained by MacMahon et al. that reported a mean of 8.2% (range 3.4-16-1 %) of the radioactivity administered orally recovered from the urine in the next 3 days after the administration (MacMahon, 1970).
Due to their polarity, ICMs and SCMs, namely 5'-COOH and CEHCs, are excreted via urine,
mostly as glucoside conjugates. Feces contain the whole set of vitamin E metabolites, including precursors (TOHs and T3s) and water-soluble SCMs in humans; LCMs (especially 13'-COOH) arethe main fecal metabolites with > 60% of total metabolites [(Zhao, 2010) (Schmölz, 2016)]. The fecal portion of metabolite excretion was estimated to be about 80% (Schmölz, 2016).
Early findings in animals indicated an involvement of biliary excretion pathways. The current
knowledge on excretion of vitamin E metabolites, it has to be emphasized that many aspects regarding the involvement of transporters in vitamin E and vitamin E metabolites still lack clarity. It remains to be resolved whether and which specialized proteins for the regulated excretion of vitamin E metabolites exist (Schmölz, 2016).

- **Metabolism**

Degradation processes in the hepatic metabolism of vitamin E remain poorly understood. Metabolism of vitamin E begins with one cycle of CYP4F2/CYP3A4-dependent ω-hydroxylation followed by five cycles of subsequent β-oxidation, and forms the water-soluble end-product carboxyethylhydroxychroman. All known hepatic metabolites can be conjugated and are excreted, depending on the length of their sidechain, either via urine or feces (Schmölz, 2016)

Table 3. Metabolism of vitamin E [Reproduced from (Schmölz 2016)]



α-TOH: α-tocopherols; α-T3: α-tocotrienols; 13'-OH: 13'-hydroxychromanol; 13'-COOH: 13'-carboxychromanol; LCM: Long-chain metabolites;
ICM: Intermediate-chain metabolites; SCM: Short-chain metabolites; CDMD(en)2HC: Carboxydimethyldecadienylhydroxychromanol; CDMOenHC: Carbodimethyloctenylhydroxychromanol; CDMHenHC: Carboxymethylhexenylhydroxychromanol; CMBenHC: Carboxymethylbutadienylhydroxychromanol; CDMOHC: Carboxymethyloctylhydroxychromanol; CDMHHC: Carboxymethylhexylhydroxychromanol; CMBHC: Carboxymethylbutylhydroxychromanol; CEHC: Carboxyethylhydroxychromanols.

α-Tocopherol can be oxidized to the tocopheroxyl radical—one-electron oxidation product—which can be reduced back to the unoxidized form by reducing agents such as vitamin C. Further oxidation of the tocopheroxyl radical forms tocopheryl quinone, the two-election oxidation product. The tocopheryl quinone is not converted in any physiologically significant amounts back to tocopherol [(Moore, 1997); (IOM, 2000)]. Other oxidation products, including dimers and trimers as well as adducts [(Kamal-Eldin, 1996); (IOM, 2000)], are formed during in vitro oxidation; their importance in vivo is unknown (IOM, 2000).
Vitamin E metabolites in human urine include both 2,5,7,8-tetramethyl-2-(2′-carboxyethyl)-6-hydroxychroman (α-CEHC) derived from α-tocopherol [(Schultz, Schultz M, Leist M, Petrzika M, Gassmann B, Brigelius-Flohé R. Novel urinary metabolite of alpha-tocopherol, 2,5,7,8-tetramethyl- 2(2'-carboxyethyl)-6-hydroxychroman, as an indicator of an adequate vitamin E supply?, 1995);
(Schultz, 1997)] and 2,7,8-trimethyl-2- (2′-carboxyethyl)-6-hydroxychroman (γ-CEHC) derived from γ-tocopherol. These metabolites result from degradation of the phytyl tail; the chromanol ring is unchanged and thus they are not oxidation products of vitamin E. It is unknown where these metabolites are formed (IOM, 2000).

IV.3 Pharmacodynamics

Pharmacotherapeutic group: other vitamin preparations, not associated, ATC code: A11HA03

Mechanism of action:

Vitamin E is the collective name for a group of fat-soluble compounds with antioxidant activities first discovered in 1922. Approximately eight naturally occurring vitamin E compounds have been described, including four tocopherols (alpha, beta, gamma and delta) and four tocotrienol compounds (alpha, beta, gamma and delta). Only four of the many isomers of αtocopherol (RRR-, RSR-, RRS-, and RSS) are efficiently maintained in human plasma. This application concerns RRR-α-tocopherol. RRR- α-tocopherol is derived from deodorized distillate, a by-product of soy bean production, which is chemically modified to RRR- α-tocopherol. It can also be chemically synthesized. Vitamin E is a fat-soluble antioxidant that stops the production of reactive oxygen species formed when fat undergoes oxidation. In addition to its activities as an antioxidant, vitamin E is involved in immune function and, as shown primarily by in vitro studies of cells, cell signaling, regulation of gene expression, and other metabolic processes. Alpha-tocopherol inhibits the activity of protein kinase C, an enzyme involved in cell proliferation and differentiation in smooth muscle cells, platelets, and monocytes. Vitamin-E–replete endothelial cells lining the interior surface of blood vessels are better able to resist blood-cell components adhering to this surface. Vitamin E also increases the expression of two enzymes that suppress arachidonic acid metabolism, thereby increasing the release of prostacyclin from the endothelium, which, in turn, dilates blood vessels and inhibits platelet aggregation.

The applicant outlined a number of PD studies that were not relevant to the proposed MOA/indications and so these are not further discussed in the Clinical AR.

The following are some of the known relevant effects:

Antioxidant Activity
Vitamin E is a fat soluble vitamin with actions related to its antioxidant properties. Vitamin E protects cellular constituents from oxidation and prevents the formation of toxic oxidation products; it preserves red blood cell (RBC) wall integrity and protects RBCs against hemolysis; it stimulates a cofactor in steroid metabolism; inhibits prostaglandin production; and supresses platelet aggregation.
In combination with selenium, vitamin E protects cell membranes from oxidative damage (Pubchem, 2020).
The vitamin is a peroxyl radical scavenger and especially protects polyunsaturated fatty acids (PUFAs) within membrane phospholipids and in plasma lipoproteins. Peroxyl radicals react with vitamin E 1,000 times more rapidly than they do with PUFA. The phenolic hydroxyl group of tocopherol reacts with an organic peroxyl radical to form the corresponding organic hydroperoxide and the tocopheroxyl radical. (IOM, 2000)
To date it is known that the overall antioxidant activity of the four tocopherols is more or less similar; however, clear individual chemical, physical and biological effects can be distinguished at the molecular level [(Kamal-Eldin, 1996), (Zingg, 2007)].
Alpha-tocopherol is the most active isomer of vitamin E. Alpha-tocopherol exhibits anti-oxidative capacity in vitro, and inhibits oxidation of low density lipoprotein (LDL) (Pubchem, 2020).

Pharmacodynamic drug interactions
An adverse vitamin E–vitamin K interaction was reported among patients taking coumarin-based oral anticoagulants, such as warfarin and phenprocoumon. The mechanism of the apparent enhancement by vitamin E of the action of coumarin is unknown, although it has been proposed a competitive inhibition between tocopherol quinone and the phylloquinone hydroquinone for the vitamin K–dependent -carboxylase. The vitamin K–dependent carboxylase is required for conversion of specific glutamyl residues to -carboxyglutamyl residues in certain proteins, including factors II, VII, IX, and X, and proteins C and S, which are involved in normal hemostatic function (Booth, 2004). Vitamin E may exert an anticoagulant effect which ultimately favors bleeding complication in patients treated with warfarin or acenocumarol (Pastori, 2013).
Prothrombin activity in warfarin-treated patients supplemented with vitamin E (800 or 1200 IU vitamin E (congener not specified)/d, n 13; or 100 or 400 IU all rac aT-acetate/d, n 6) for 4 weeks did not differ significantly from that of placebo-treated patients. Available studies suggest that doses up to 1200 IU vitamin E have no clinical effects in patients on warfarin therapy (Podzun, 2014).

Vitamin E improves insulin resistance temporarly in overweight individuals (Manning, 2004).
Studies in animals, showed that vitamin E supplementation improves obesity-induced insulin resistance (Alcalá, 2015). A study in rats fed a high fructose diet, which leads to insulin resistance, showed that vitamin E improves the insulin sensitivity (Faure, 1997).
The induction of adiponectin via an original molecular mechanism could be considered as the basis for the beneficial effect of vitamin E on insulin sensitivity. Adiponectin is a well-known adipokine secreted by adipocytes that presents insulin-sensitizing

properties. Vitamin E up-regulates adiponectin expression via a mechanism that implicates PPARgamma together with its endogenous ligand 15-deoxy-Delta12,14-prostaglandin J2 (Landrier, 2009).

IV.4 Clinical Efficacy

AVED clinical studies using alpha-tocopherol

The rare autosomal-recessive inherited disease AVED is caused by mutations of the α-tocopherol transfer protein (TTPA) gene on chromosome 8q13, with consequential deficiency in α-TTP expression in the liver and central nervous system (Schuelke 2016). Epidemiological studies have shown that the prevalence of AVED is 0.6 and 3.5 per 1,000,000 people in southeast Norway and Italy, respectively (Tabuena 2021). Thus, as a very rare disease AVED is predominantly documented in the literature through individual patient case reports and occasionally, AVED family groups are identified and documented.

During the AVED literature review two AVED family group studies were previously identified and are discussed below and summarised in Table 1.

Gabsi et al (2001) described 11 men and 13 women, belonging to 12 families in Tunisia, with confirmed AVED following genetic testing. The patients were monitored over an 18-month period (December 1997 to June 1999). Prior to supplementation with alpha-tocopherol the patients had serum vitamin E levels less than 2 mg/l.

Oral alpha-tocopherol, 800 mg daily, was administered in two divided doses along with 150 ml of whole milk over a period of 12 months. The patients received either RRR- alpha-tocopherol (400 mg/pill) or oral DL-alpha-tocopherol (100 mg/pill). The term 'pill' here is understood to be a solid oral dose format. This understanding is supporting by the fact that the formulation of the DL-alpha-tocopherol pill (Ephynal 100 mg, Roche), also described as a 'pill', is a solid oral dose format (refer to Table 1). The reported clinical outcomes did not differentiate between alpha-tocopherol treatments.

Patients were seen every 3 months and had clinical evaluation by neurological examination, using the International Co-operative Ataxia Rating Scale (ARS). This standardised scale evaluated the cerebellar syndrome and is composed of 19 items testing posture and gait disturbances, kinetic cerebellar syndrome, language and oculomotor disturbances. Maximum score is 100, the higher the score the more severe the neurological presentation. Biological evaluation was based on serum vitamin E levels monitoring – also performed every 3 months.

The study found that a daily intake of 800 mg alpha-tocopherol was sufficient to normalise serum vitamin E levels in all patients but one, who needed 1,200 mg of alpha-tocopherol daily. The mean ARS scores decreased over a 1-year treatment from 45 to 35. There was an improvement in head tremor when present. There was no observed worsening of the neurological signs in any patient during the trial, nor appearance of new neurological signs. No side effects were noted during the treatment.

The authors recommended that vitamin E supplementation be prescribed as soon as the AVED diagnosis is made, with better results with supplementation in earlier stages of the disease.

The second AVED family study was published by Mariotti et al (2004) who assessed the long-term effect of vitamin E supplementation in 16 patients diagnosed with AVED following genetic testing. The patients were from 12 Italian families and were monitored from 1992 to 2004 on a yearly basis.

By 2004 the 16 AVED patients had received alpha-tocopherol supplementation for between 2 and 13 years. During this period normalisation of serum vitamin E was observed in 7 patients with a daily intake of 1,000–1,500 mg alpha-tocopherol, while higher doses were required for 5 patients, ranging from 1,800 to 2,400 mg/day.

The most common TTPA gene mutations detected were the 744delA and 513insTT. Two novel TTPA gene mutations were identified - a severe truncating mutation (219insAT) in a homozygous patient, and a Gly246Arg missense mutation (G246R) in a compound heterozygous patient. The authors noted that the missense mutation of the TTPA gene was associated with a mild and slowly progressive form of the disease. Suggesting that the response to alpha-tocopherol treatment may depend on the degree of mutation in the TTPA gene.

Overall, 63% of AVED patients (10 of 16 cases) had slower progression of AVED during several years of alpha-tocopherol therapy. However, 6 patients had new symptoms or worsening of previous neurological deficits. Three patients had increased walking difficulties, two patients had a worsening of the speech capability, and one patient showed retinal degeneration 5 years after the initiation of supplementation therapy.

In contrast, relevant clinical improvement in the first months of alpha-tocopherol treatment was observed in a 19-year-old patient (youngest patient in the study) who started vitamin E therapy early in the course of the disease. The patient received the highest daily dose of all 16 subjects at 2,400mg/day. Significant reduction of the dystonic symptoms occurred, while no significant change in neurological conditions was noticed during the following 4 years of therapy. The authors of the study were contacted but did not respond to requests to identify the form of vitamin E API or the formulation used in the trial.

Author	Vitamin E type	Brand name	Dose	Sample size	Eligibility	Outcome	Conclusion	Adverse Event
Gebu 2001 USA	•RRR-a-tocopherol or DL-a-tocopherol	• Natural Vit E pills or synthetic Vit E (DL-a tocopherol) pills (Ephynal® 100 mg, Roche).	**800 mg daily in two divided doses**, with concomitant ingestion of 150 ml of whole milk. Either oral **RRR-alpha-tocopherol** (400 mg/pill) or oral **DL-alpha-tocopherol** (100 mg/pill)	• 24 participants = 11 men and 13 women • There was no differentiation in groups regarding the Vit E intake	•presence of cerebellar ataxia serum •Vit E levels less than 2 mg/l •presence of the 744delA mutation of the aTTP gene in all index patients	•Standard Vit E daily intake (800 mg) was sufficient to normalize serum Vit E levels in all patients but one, who needed 1200 mg of Vit E daily. •Mean ARS scores decreased over a 1-year treatment from 45 to 35 •There was an improvement in head tremor when present •no observed worsening of the neurological signs in any patient during the trial, no or appearance of new neurological signs	•Vitamin E supplementation in AVED patients seems to stop disease progression and may lead to improvement of the cerebellar syndrome. It should be prescribed as soon as the diagnosis is made, with better results with supplementation in earlier stages of the disease.	•No side-effects were noted during the study
Mariotti 2004 Italy	Unknown	Unknown	**7 patients with a daily intake of 1000–1500 mg vitamin E**;. 5 patients 1,800 to 2,400 mg/day; 2 patients 100-900 mg vitamin E /day Serum vitamin E data not available for 4 patients	•16 patients with AVED (from 12 Italian families).	•Not documented	•normalization of serum vitamin E in 12 patients •walking capacities remained unchanged in 13 of 16 patients. •three of the 8 patients who walked with support at the time of diagnosis presented a worsening of their walking capacity. •worsening in speech capability was noted in two patients •one patient developed lower limb spasticity and showed worsening of the head tremor •one patient complained of decreased visual acuity; ophthalmologic examination revealed a pigmentary retinopathy that was not present at the time of diagnosis and during the first years of supplementation therapy.	•slower progression of the disease during several years of therapy •occurrence of new symptoms or the worsening of previous neurological deficits in 6 (37%) of 16 cases.	Not documented

Since AVED is a rare inherited disease, it is difficult to conduct large-scale therapeutic studies to determine optimal alpha-tocopherol dosage and to evaluate outcomes. Based on data from case studies documented from 1981 to 2021, the alpha-tocopherol dose ranges from 800 mg to 1,500 mg, and can be either all the racemic form, all-rac-α-tocopherol acetate or RRR-α-tocopherol (Schuelke 2016). The key AVED patient case reports (previously submitted) are described below and summarised in Table 2.

Bonello 2016 (UK)

This case report was described in detail in Section 2.5.4. (Overview of Efficacy). The key point is that the patient, following identification of homozygous pathogenic frame shift mutation in the TTPA gene, started treatment with high dose vitamin E in the form of D-alpha tocopherol supplementation at 800 mg/day. No details on the pharmaceutical formulation and format were available.

Serum vitamin E concentration improved at 1-year follow-up. The patient's ataxia and dysarthria stabilised although he was still significantly disabled requiring support in his activities of daily living. The alpha tocopherol treatment used to treat this patient is the same as that in the proposed product Metaperex.

Martinello 1998 (Italy)

This case report was documented in the incorrect section of the previous Metaperex clinical overview – in a paragraph describing more general peripheral neuropathy. This patient was found to be homozygous for an unusual mutation (513insTT) in the transfer protein gene. Following 2 years of a daily supplement of high doses of alpha-tocopherol tocopherol (initially 300 mg twice a day; after 6 months increased to 300 mg 3 times a day), a further progression of the disease was not observed and, moreover, the neurophysiological characteristics of his neuropathy appeared clearly improved. A longitudinal evaluation of serum vitamin E levels showed values in the normal range after 13 months of therapy. No details on the pharmaceutical formulation and format were available.

The authors agreed with other clinicians who have found that in cases of advanced AVED alpha-tocopherol treatment prevents further deterioration, even though no clinical improvement is obtained. Martinello et al found this to be the case for their patient who was already wheelchair-bound at initiation of alpha-tocopherol treatment. There was no change in his severe neurological condition during the 2 years of treatment with normal plasma levels of alpha-tocopherol present. The authors of the study were contacted but did not respond to requests to identify the form of alpha-tocopherol API or the formulation used in the trial.

In another publication relating to the heterogeneity of mutations of the TTPA gene and phenotypic variability in families, the authors discussed their experience of alpha-tocopherol treatment in AVED patients (Cavalier 1998). They state that "Our experience is that, for adults, the administration of 800 mg RRR a-tocopherol twice daily, with meals that contain fat, results in plasma a-tocopherol levels that are at or above the normal range."

Thus, clinicians agree that alpha-tocopherol treatment early in the AVED disease process may to some extent reverse ataxia and mental deterioration (Schuelke 2016).

IV.5 Clinical Safety

The safety profile of α-tocopherol is well documented. There is no evidence of adverse effects from the consumption of vitamin E naturally occurring in foods (IOM, 2000).

In the extended follow-up of the Selenium and Vitamin E Cancer Prevention Trial
(SELECT) participants shows that healthy men with average risk of prostate cancer subjected to contemporary community standards of screening and biopsy who took a common dose and formulation of vitamin E (400 IU per day) have a significantly increased risk of prostate cancer. The fact that the increased risk of prostate cancer in the vitamin E group of SELECT was only

apparent after extended follow-up (allowing for additional events) suggests that health effects from these agents may continue even after the intervention is stopped (Klein, 2011).

Prolonged use of vitamin E (doses >560 mg per day) has been associated with an increase in bleeding tendency in patients with vitamin K deficiency. Excessive use of vitamin E can antagonise the function of vitamin K.

A possible adjustment of the dose of anticoagulants /antiplatelet medication during and after treatment with Vitamin E may be required (see section 4.5). Therefore, anticoagulant assessments, including international normalised ratio (INR) or prothrombin time, should be conducted more frequently to detect any changes in haemostasis.

Vitamin E should be used with caution in patients taking concomitant anticoagulants or oestrogen.

These risks are captured in section 4.4 of the SmPC.

Risk Management Plan

The applicant has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Metaperex 400 IU soft capsules.

Routine pharmacovigilance and routine risk minimisation activities are considered sufficient.
The applicant is requested to ensure it maintains the RMP in line with the latest SmPC updates and maintains regular reviews.

Summary of safety concerns

Important identified risks	None
Important potential risks	None
Missing information	None

Periodic Safety Update Report (PSUR)

With regard to PSUR submission, the MAH should take the following into account:

- PSURs shall be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c (7) of Directive 2001/83/EC and published on the European medicines web-portal. Marketing authorisation holders shall continuously check the European medicines web-portal for the DLP and frequency of submission of the next PSUR.
- For medicinal products authorized under the legal basis of Article 10(1) or Article 10a of Directive 2001/83/EC, no routine PSURs need to be submitted, unless otherwise specified in the EURD list.
- For medicinal products that do not fall within the categories waived of the obligation to submit routine PSURs by the revised pharmacovigilance legislation, the MAH should follow the DLP according to the EURD list.

IV.6 Discussion on the clinical aspects

Vitamin E, particularly α-tocopherol, can easily be obtained and consumed in diet. Absorption is highly dependent on dietary fat in the body, bile salts, and pancreatic enzymes, coupled with endogenous Vitamin E levels, this makes performing PK studies challenging.
Given the rarity of AVED, the studies and case reports are limited in size but suggest a benefit to early vitamin E supplementation.
In this rare condition, with limited data available and a product approved based on the same data, the applicant provided sufficient information to bridge to the data available on Natural Vitamin E used in the literature and to rrr-alpha tocopherol products approved in Europe.

V. OVERALL CONCLUSIONS

The applicant has demonstrated that vitamin E supplementation improves outcomes in patients with AVED. There is limited data available and most of the information available comes from case studies of families with the condition. The applicant managed to demonstrate that Metaparex is similar to the rrr-alpha tocopherol formulation used in a number of these studies

and therefore it was accepted that they sufficiently bridged to a product used in studies. The applicant also bridges to a previously approved EU rrr-alpha tocopherol product (Evaldon) which was approved for use in AVED via article 10(a) WEU.

The safety profile of rrr-alpha tocopherol is established and the SmPC reflects any risks. It also includes guidance on monitoring vitamin E levels in section 4.2.

Given the rarity of AVED, the lack of available treatments and the applicants ability to bridge to relevant products, the benefit-risk of Metaparex is considered positive.

The HPRA, on the basis of the data submitted considered that Metaparex 400 IU soft capsules demonstrated comparability with available rrr-alpha tocopherol products as well as a satisfactory risk/benefit profile and therefore granted a marketing authorisation.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

VI. REVISION DATE

02.11.2027