Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Metaperex 400 IU soft capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

Excipient with known effect: refined soya-bean oil (146 mg per capsule)
For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Capsule, soft
Yellow-brown coloured, clear oval shaped soft gelatine capsules with a clear yellow-brown oily liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Metaperex 400 IU soft capsules is indicated in the following conditions for adults:

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

4.2 Posology and method of administration

Dosage should be adjusted to the type of disorder and the patient's clinical condition.

One international unit (IU) of vitamin E equals the biologic activity of 1 mg of all rac-α-tocopheryl acetate (dl-α-tocopheryl acetate).

For adults diagnosed with AVED the following doses should be administered:

- 800 IU (560 mg) vitamin E per day (2 capsules) divided into 2 doses.

Diagnosis of vitamin E deficiency should be documented and based on:

- measuring the plasma α-tocopherol level (level < 5µg/mL or <11.6 µmol/L indicates vitamin E deficiency) and/or
- ratio of plasma α-tocopherol to plasma lipid level (in adults; < 0.8 mg/g total lipid).

Plasma vitamin E level should be monitored monthly initially, to ensure levels return to the normal range, thereafter at 6-month intervals and the dose adjusted accordingly if necessary.

Method of administration

For oral use.

Vitamin E is absorbed with lipids, therefore advise patients to take vitamin E during or after a meal to ensure optimal absorption.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Metaperex 400 IU soft capsules contains soya-bean oil. If you are allergic to peanut or soya, do not use this medicinal product.
- Vitamin K deficiency (increased risk of bleeding)

4.4 Special warnings and precautions for use

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.

In a long term study of dietary supplementation, Vitamin E (400 IU daily) was found to significantly increase the risk of prostate cancer among healthy men.

There is limited data on the use of vitamin E in patients with renal impairment. Based on the available data, the dose of vitamin E should be assessed for each patient with renal impairment depending on their clinical circumstances.

4.5 Interaction with other medicinal products and other forms of interaction

Haemostasis
Vitamin E may have antagonist activity with respect to vitamin K. K, and so may increase the tendancy to bleeding.
High doses of vitamin E may increase the risk of bleeding in patients taking concomitant:
- anticoagulants (e.g., warfarin or phenprocoumon)
- inhibitors of platelet aggregation (e.g., acetylsalicylic acid, clopidogrel, ticlopidine, dipyridamole, eptifibatide, tirofiban and abciximab) or
- thrombolytics (e.g. recombinant tissue plasminogen activator).

Vitamin E should not be administered concomitantly with Ibrutinib as it may enhance the antiplatelet effect of Ibrutinib.
Tipranavir, used in the treatment of HIV-1 infection, is associated with an increased risk of bleeding and fatal and non-fatal intracranial haemorrhages and these risks may be increased with high dose vitamin E.
Vitamin E may increase the risk of thrombosis in patients taking oestrogens.

Sequestrants
Sequestrants bind to vitamin E and reduce absorption. Any of these agents should be administered more than two hours before or after vitamin E.

Colestyramine and colestipol reduce gastrointestinal absorption of vitamin E.

Orlistat may impair absorption of fat-soluble vitamins, including vitamin E.

Concomitant use of iron-containing medicines reduces activity of vitamin E, therefore a few hours interval should be maintained between taking both medications.

Metabolic Interactions
High-dose vitamin E, either alone or in combination with other antioxidants, may alter the pharmacokinetics of ciclosporin and decrease its serum concentration.
Anticonvulsants (e.g., phenobarbital, phenytoin and carbamazepine), as inducers of P450 enzymes, may lower plasma vitamin E levels.
Vitamin E increases the absorption, utilisation and storage of vitamin A.

Vitamin E may be present in significant quantities as an excipient, for example Selumetinib contains D-alpha-tocopheryl and should not be taken with vitamin E (Selumetinib 10 mg capsule contains 32 mg vitamin E; 25 mg capsule contains 36 mg vitamin E).

Vitamin E has been shown to induce the expression of the cytochrome P450 enzyme CYP3A4. This enzyme is responsible for the reduced physiological effects of vitamin K and for the reduction in ciclosporin levels.

4.6 Fertility, pregnancy and lactation

Pregnancy
There is limited data on the use of vitamin E in pregnant women. Doses of vitamin E above the recommended daily allowance should not be used in women during pregnancy. Therefore Metaperex should not be used in pregnancy.

Breastfeeding
There is insufficient information on the effects of vitamin E in newborns and infants.Vitamin E passes into breast milk. Doses of vitamin E above the recommended daily allowance of 28.5 IU (19 mg) should not be used in nursing mothers. Therefore Metaperex should not be used during breastfeeding.

Fertility
No data available.

4.7 Effects on ability to drive and use machines

Vitamin E has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

General
Following extended periods of high doses of vitamin E (800 – 1,200 mg daily)
(anti-platelet activity and associated with it, bleeding).

Undesirable effects are listed according to their frequencies as follows:
Very common: (≥ 1/10)
Common: (≥ 1/100 to < 1/10)
Uncommon: (≥ 1/1,000 to < 1/100)
Rare: (≥ 1/10,000 to < 1/1,000)
Very rare (< 1/10,000)
Not known: (frequency cannot be estimated from the available data)

Safety information is based on data from Eudravigilance for vitamin E (tocopherol) and clinical trials. None of the available data allows an assessment of the frequency of undesired effects.

Doses higher than 1,000 mg daily may cause the following undesirable effects:

MedDRA System Organ Class	Undesirable Effects	Frequency
General disorders and administration site conditions	Unusual tiredness or weakness	Not known
Gastrointestinal disorders	Nausea, diarrhoea, flatulence, abdominal pain and oral pain	Not known
Nervous systems disorders	Headaches and dizziness	Not known
Skin and subcutaneous tissue disorders	Rash	Not known
Eye disorders	Blurred vision	Not known
Immune system disorders	Anaphylaxis, urticaria, allergic oedema, erythema and blisters	Not known
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Not known

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance; Website: www.hpra.ie.

4.9 Overdose

Chronic hypervitaminosis E is unknown. The symptoms and signs of vitamin E overdose are nonspecific. Transient gastrointestinal disorders such as nausea, diarrhoea, flatulence have been reported with daily doses above 700 mg. Other symptoms may include tiredness, asthenia, headache, blurred vision and dermatitis. If an overdose is suspected, vitamin E treatment should be stopped. If necessary, general supportive measures should be taken. Consideration should be given to specific treatment, such as giving vitamin K to patients who are actively bleeding or have a severe haemorrhage.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vitamins; Other plain vitamin preparations; tocopherol (vit E); ATC code: A11HA03

Mechanism of action

Vitamin E is an essential nutritional element and is the only lipid-soluble, chain-breaking antioxidant that prevents the propagation of free-radical reactions. Not all of the physiological effects of vitamin E are known. Alpha-tocopherol is the most active isomer of vitamin E. Vitamin E protects polyunsaturated fatty acids (PUFAs) within biological membrane and in plasma lipoproteins. Peroxyl radicals react with vitamin E 1,000 times more rapidly than they do with PUFA. Vitamin E protects red blood cells against hemolysis; it stimulates a cofactor in steroid metabolism; inhibits prostaglandin production; and supresses platelet aggregation.

Clinical efficacy and safety

AVED patients are deficient in vitamin E, which manifests as increased irritability, sleeping disorders, increased red blood cells sensitivity to chemical agents, which as a result may lead to their haemolysis. In vitamin E deficiencies tissue cholesterol level increases, tissues' susceptibility to oxidative actions increases, platelets' susceptibility to aggregation increases and also prostacycline synthesis decreases. Vitamin E deficiency may occur in patients with impaired fats absorption disorders. Administration of vitamin E results in considerable improvements in symptoms.

5.2 Pharmacokinetic properties

Absorption
Vitamin E is absorbed from the gastrointestinal tract via the same mechanisms as liposoluble substances, therefore its absorption is optimal in the presence of lipids. Vitamin E absorption from the intestinal lumen is dependent upon biliary and pancreatic secretions, micelle formation, uptake into enterocytes, and chylomicron secretion. Vitamin E is 20% to 50% absorbed by intestinal epithelial cells in the small intestine, however the rate of absorption can vary inter-individually between 20% to 80%.
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. 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. Plasma vitamin E concentrations depend upon the secretion of vitamin E from the liver.
Biotransformation
Vitamin E is stored unmodified in tissues (principally the liver and adipose tissue). Metabolism of vitamin E begins with CYP4F2/CYP3A4-dependent ω-hydroxylation followed β-oxidation, and forms the water-soluble end-product carboxyethylhydroxychroman.
Elimination
All known vitamin E hepatic metabolites can be conjugated and are excreted either via urine or faeces. Approximately 80% of vitamin E metabolites are excreted in the feces. Excess vitamin E is converted to a lactone, esterified to glucuronic acid, and subsequently excreted in the urine.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on available toxicity studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Refined soya-bean oil.
Components of capsule: gelatin, glycerol

6.2 Incompatibilities

Not applicable

6.3 Shelf life

4 years

6.4 Special precautions for storage

Do not store above 25 °C

6.5 Nature and contents of container

The soft capsules are contained in PVC-PVDC blister packs welded to a sheet of aluminium lacquered with PVDC.

Pack size: 60 soft capsules

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Kora Corporation Limited trading as Kora Healthcare
20 Harcourt Street
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8 MARKETING AUTHORISATION NUMBER

PA1748/005/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of First Authorisation: 20th January 2023

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