SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.
See section 4.8 for how to report adverse reactions.

1 NAME OF THE MEDICINAL PRODUCT

Vazkepa 998 mg soft capsules

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 998 mg of icosapent ethyl.

Excipients with known effect

Each capsule contains 30 mg maltitol (E965 ii), 83 mg sorbitol (E420 ii) and soya lecithin.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Soft capsule (capsule)

Oblong soft capsule, 25 x 10 mm, printed with “IPE” in white ink, with a light yellow to amber shell containing a colourless to pale yellow liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Vazkepa is indicated to reduce the risk of cardiovascular events in adult statin-treated patients at high cardiovascular risk with elevated triglycerides (≥150 mg/dL [≥ 1.7 mmol/l]) and

- established cardiovascular disease, or
- diabetes, and at least one other cardiovascular risk factor.

For study details including cardiovascular risk factors and results with respect toeffects on cardiovascular events see section 5.1.

4.2 Posology and method of administration

Posology

The recommended daily oral dose is 4 capsules taken as two 998 mg capsules twice daily.

If a dose is missed, patients should take it as soon as they remember. However, if one daily dose is missed, the next dose should not be doubled.

Elderly (≥ 65 years)

No dose adjustment is necessary based on age (see section 5.2).

Renal impairment

No dose reduction is recommended (see also section 5.2).

Hepatic impairment

No dose reduction is recommended (see also sections 4.4 and 5.2).

Paediatric population

There is no relevant use of icosapent ethyl in children aged <18 years of age in reducing the risk of cardiovascular events in statin-treated patients at high cardiovascular risk with elevated triglycerides and other risk factors for cardiovascular disease.

Method of administration

Oral use.

Vazkepa should be taken with or following a meal.

To ensure the full intended dose is received, patients should be advised to swallow the capsules whole and not to break, crush, dissolve, or chew them.

4.3 Contraindications

Hypersensitivity to the active substance, soya or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Allergies to fish and/or shellfish

Icosapent ethyl is obtained from the oil of fish. It is not known whether patients with allergies to fish and/or shellfish are at increased risk of an allergic reaction to icosapent ethyl. Icosapent ethyl should be used with caution in patients with known hypersensitivity to fish and/or shellfish.

Hepatic impairment

In patients with hepatic impairment, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) concentrations should be monitored as clinically indicated before the start of treatment and at appropriate intervals during treatment.

Atrial fibrillation or flutter

Icosapent ethyl was associated with an increased risk of atrial fibrillation or flutter requiring hospitalisation in a double-blind placebo-controlled trial. The incidence of atrial fibrillation was greater in patients with a previous history of atrial fibrillation or flutter (see section 4.8). Patients, particularly those with a relevant medical history, should be monitored for clinical evidence of atrial fibrillation or atrial flutter (e.g., dyspnoea, palpitations, syncope/dizziness, chest discomfort, change in blood pressure, or irregular pulse). Electrocardiographic evaluation should be performed when clinically indicated.

Bleeding

Treatment with icosapent ethyl has been associated with an increased incidence of bleeding. Patients taking icosapent ethyl along with antithrombotic agents, i.e., antiplatelet agents, including acetylsalicylic acid, and/or anticoagulants, may be at increased risk of bleeding and should be monitored periodically (see section 4.8).

Excipients content

Sorbitol (E420 ii)

This medicinal product contains 83 mg of sorbitol in each capsule. The additive effect of concomitantly administered medicinal products containing sorbitol (or fructose) and dietary intake of sorbitol (or fructose) should be taken into account.

The content of sorbitol in medicinal products for oral use may affect the bioavailability of other medicinal products for oral use administered concomitantly.

Patients with hereditary fructose intolerance (HFI) should not take this medicinal product.

Maltitol (E965 ii)

This medicinal product contains 30 mg of maltitol in each capsule.

Patients with rare hereditary problems of fructose intolerance should not take this medicinal product.

Soya lecithin

This medicinal product contains soya lecithin. Patients who are allergic to soya or peanut should not use this medicinal product.

4.5 Interaction with other medicinal products and other forms of interaction

Icosapent ethyl was studied at the dose level of four 998 mg capsules/day with the following medicinal products which are typical substrates of cytochrome P450 enzymes: omeprazole, rosiglitazone, warfarin and atorvastatin. No interactions were observed.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are a limited amount of data from the use of icosapent ethyl in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of icosapent ethyl during pregnancy unless the benefit of use outweighs the potential risk to the foetus.

Breast-feeding

It is not known whether icosapent ethyl is excreted in human milk. Studies from the literature have shown that the active metabolite eicosapentaenoic acid (EPA) is excreted in human milk at levels which correlated to maternal diet. Available toxicological data in rats have shown excretion of icosapent ethyl in milk (see section 5.3).

A risk to the suckling child cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from icosapent ethyl therapy considering the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no data on fertility in humans from the use of icosapent ethyl. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3).

4.7 Effects on ability to drive and use machines

On the basis of its pharmacodynamic profile and clinical study adverse reaction data, icosapent ethyl is expected to have no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions associated with icosapent ethyl werebleeding (11.8%), peripheral oedema (7.8%), atrial fibrillation (5.8%), constipation (5.4%), musculoskeletal pain (4.3%), gout (4.3%)

and rash (3.0%).Tabulated list of adverse reactions

Adverse reactions are classified according to frequency and system organ class. Reporting frequencies for adverse reactions have been estimated from a long-term cardiovascular outcomes study in which subjects were observed for a median follow- up duration of 4.9 years. Frequency categories are defined according to the following conventions: 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) and not known (cannot be estimated from the available data).

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Table 1 lists adverse reactions

Table 1 Adverse reactions

MedDRA Sytem organ class	**Adverse reaction**	**Frequency**
Immune system disorders	Hypersensitivity Pharyngeal swelling	Uncommon Not known
Metabolism and nutrition disorders	Gout	Common
Nervous system disorders	Dysgeusia[1]	Uncommon
Cardiac disorders	Atrial fibrillation or flutter[2]	Common
Vascular disorders	Bleeding[2]	Very common
Gastrointestinal disorders	Constipation[2]	Common
	Eructation	Common
Skin and subcutaneous tissue disorders	Rash	Common
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	Common
General disorders and administration site conditions	Peripheral oedema	Common

1 Dysguesia describes the “verbatim” term: Fishy taste 2 See section

Description of selected adverse reactions

Description of selected adverse reactions

Bleeding

Bleeding occurred in 11.8% of subjects receiving icosapent ethyl in a placebo- controlled cardiovascular outcomes trial compared with 9.9% in subjects receiving placebo. Serious bleeding events were reported more frequently in subjects receiving icosapent ethyl than in those receiving placebo when administered in combination with concomitant antithrombotic medication (3.4% vs. 2.6%), but occurred at the same rate (0.2%) in subjects not taking concomitant anticoagulant/antiplatelet medication (see section 4.4).

The bleeding events most frequently observed with icosapent ethyl were gastrointestinal bleeding (3.1%), contusion (2.5%), haematuria (1.9%), and epistaxis (1.5%).

Atrial fibrillation/flutter

Atrial fibrillation or atrial flutter occurred in 5.8% of subjects receiving icosapent ethyl in a placebo-controlled cardiovascular outcomes trial compared with 4.5% in subjects receiving placebo. Atrial fibrillation or atrial flutter requiring hospitalisation for 24 hours or more occurred in 3% of subjects treated with icosapent ethyl compared with 2% in subjects receiving placebo. Atrial fibrillation and atrial flutter were reported more frequently in subjects with a previous history of atrial fibrillation or atrial flutter receiving icosapent ethyl than in those receiving placebo (12.5% vs. 6.3%) (see section 4.4).

Constipation

Constipation occurred in 5.4% of subjects receiving icosapent ethyl in a placebo- controlled cardiovascular outcomes trial compared with 3.6% of subjects receiving placebo. Serious constipation was less common for icosapent ethyl (0.1%) and placebo (0.2%). The relative incidence of constipation in this study may have been confounded by a residual laxative effect for placebo, which comprised a subtherapeutic dose of light mineral oil (4 mL).

The following adverse reactions have been identified from global post-marketing use of icosapent ethyl. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish causal relationship to drug exposure: blood triglycerides increased, arthralgia, diarrhoea, abdominal discomfort, and pain in the extremities.

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:- Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

There is no specific treatment for icosapent ethyl overdose. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Lipid modifying agents, Other lipid modifying agents, ATC code: C10AX06

Mechanism of action

Icosapent ethyl is a stable ethyl ester of the omega-3 fatty acid, eicosapentaenoic acid (EPA). The mechanisms of action contributing to reduction of cardiovascular events with icosapent ethyl are not completely understood. The mechanisms are likely multi- factorial including improved lipoprotein profile with reduction of triglyceride-rich lipoproteins, anti-inflammatory, and antioxidant effects, reduction of macrophage accumulation, improved endothelial function, increased fibrous cap thickness/stability, and antiplatelet effects. Each of these mechanisms can beneficially alter the development, progression, and stabilisation of atherosclerotic plaque, as well as the implications of plaque rupture, and preclinical and clinical studies support such benefits with EPA. Systemic and localised anti-inflammatory effects of EPA may result from displacement of pro-inflammatory arachidonic acid (AA), directing catabolism away from eicosanoids (2-series prostaglandins and thromboxanes, and 4- series leukotrienes) to non- or anti-inflammatory mediators. However, the direct clinical meaning of individual findings is not clear.

Pharmacodynamic effects

Icosapent ethyl improves the lipoprotein profile by suppressing cholesterol-, fatty acid- and triglyceride (TG)-synthesising enzymes, increasing fatty acid β-oxidation, and reducing microsomal triglyceride transfer (MTP) protein, resulting in decreased hepatic TG and very low-density lipoprotein (VLDL) synthesis and release. Icosapent ethyl also increases expression of lipoprotein lipase leading to increased TG removal from circulating VLDL and chylomicron particles. In patients with elevated TG levels, icosapent ethyl lowers TG, VLDL, remnant lipoprotein cholesterol, and levels of inflammatory markers such as C-reactive protein. However, TG reduction appears to provide only a minor contribution to the reduction in risk of cardiovascular events with icosapent ethyl.

Clinical efficacy and safety

REDUCE-IT was a multinational, double-blind, randomised, placebo-controlled, event-driven trial in 8,179 (4,089 icosapent ethyl, 4,090 placebo) statin-treated adult patients enrolled with low-density lipoprotein cholesterol (LDL-C) >1.03 mmol/L (40 mg/dL) and ≤2.59 mmol/L (100 mg/dL) and moderately elevated triglyceride (TG) levels (≥1.53 mmol/L and <5.64 mmol/L [≥135 mg/dL and <500 mg/dL] as measured during patient screening, i.e. qualifying visits pre-enrolment)

and either established cardiovascular disease (70.7%) or diabetes and other risk factors for cardiovascular disease (29.3%). Patients with established cardiovascular disease were defined as being at least 45 years of age and having a documented history of coronaryartery disease, cerebrovascular or carotid disease, or peripheral artery disease. Patients in the other risk group were defined as being at least 50 years of age with diabetes requiring medical treatment and at least one additional risk factor i.e., hypertension or on an antihypertensive medicinal product; age at least 55 years (men) or at least 65 years (women); low high-density lipoprotein cholesterol levels; smoking; raised high-sensitivity C-reactive protein levels; renal impairment; micro or macroalbuminuria; retinopathy; or reduced ankle brachial index. Patients were randomly assigned 1:1 to receive either icosapent ethyl or placebo (as 4 capsules daily). The median follow-up duration was 4.9 years. Overall, 99.8% of patients were followed for vital status until the end of the trial or death.

The baseline characteristics were balanced between the groups, median age at baseline was 64 years (range: 44 years to 92 years), with 46% being at least 65 years old; 28.8% were women. The trial population was 90.2% White, 5.5% Asian, 4.2% identified as Hispanic ethnicity, and 1.9% were Black. Regarding prior diagnoses of cardiovascular disease, 46.7% had prior myocardial infarction, 9.2% had symptomatic peripheral arterial disease, and 6.1% prior unknown stroke or transient ischemic attack (TIA). Selected additional baseline risk factors included hypertension (86.6%), diabetes mellitus (0.7% type 1; 57.8% type 2), eGFR <60 mL/min per 1.73 m^2 (22.2%), congestive heart failure (17.7%), and current daily cigarette smoking (15.2%). Most patients were taking moderate-intensity (63%) or high- intensity (31%) statin therapy at baseline. Most patients at baseline were taking at least one other cardiovascular medicinal product including antiplatelet and/or antithrombotic agents (85.5%), beta blockers (70.7%), antihypertensives (95.2%), angiotensin converting enzyme (ACE) inhibitors (51.9%), or angiotensin receptor blockers (ARB; 26.9%); 77.5% were taking an ACE inhibitor or ARB. The protocol excluded patients taking PCSK9 inhibitors. On stable background lipid-lowering therapy, the median [Q1, Q3] LDL-C at baseline was 1.9 [1.6, 2.3] mmol/L (75.0 [62.0, 89.0] mg/dL); the mean (SD) was 2.0 (0.5) mmol/L (76.2 [20.3] mg/dL). On stable background lipid-lowering therapy, the median [Q1, Q3] fasting TG was 2.4 [2.0, 3.1] mmol/L (216.0 [176.0, 272.5] mg/dL); the mean (SD) was 2.6 (0.9) mmol/L (233.2 [80.1] mg/dL).

Icosapent ethyl significantly reduced the risk for the primary composite endpoint (time to first occurrence of cardiovascular death, myocardial infarction, stroke, coronary revascularisation, or hospitalisation for unstable angina; $p<0.0001$) and the key secondary composite endpoint (time to first occurrence of cardiovascular death, myocardial infarction, or stroke; $p<0.0001$). The results of the primary and secondary efficacy endpoints are shown in Table 2. The Kaplan-Meier estimates of the cumulative incidence of the key secondary composite endpoint over time are shownin Figure 1.

Table 2 Effect of icosapent ethyl on time to first occurrence of cardiovascular events in patients with elevated triglyceride levels and cardiovascular disease or diabetes and other risk factors in REDUCE-IT

	Icosapent ethyl	**Placebo**	**Icosapent ethyl vs Placebo**
	N = 4,089 n (%)	**N = 4,090 n (%)**	**Hazard Ratio (95% CI)**
Primary composite endpoint			
Cardiovascular death, myocardial infarction, stroke, coronary revascularisation, hospitalisation for unstable angina (5-point MACE)	705 (17.2)	901 (22.0)	0.75 (0.68, 0.83)
Key secondary composite endpoint			
Cardiovascular death, myocardial infarction, stroke (3-point MACE)	459 (11.2)	606 (14.8)	0.74 (0.65, 0.83)

Other secondary endpoints			
	Icosapent ethyl	**Placebo**	**Icosapent ethyl vs Placebo**
	N = 4,089 n (%)	**N = 4,090 n (%)**	**Hazard Ratio (95% CI)**
Cardiovascular death[1]	174 (4.3)	213 (5.2)	0.80 (0.66, 0.98)
Death by any cause[2]	274 (6.7)	310 (7.6)	0.87 (0.74, 1.02)
Fatal or non-fatal myocardial infarction	250 (6.1)	355 (8.7)	0.69 (0.58, 0.81)
Fatal or non-fatal stroke	98 (2.4)	134 (3.3)	0.72 (0.55, 0.93)
Emergent or urgent coronary revascularisation	216 (5.3)	321 (7.8)	0.65 (0.55, 0.78)
Coronary revascularisation[3]	376 (9.2)	544 (13.3)	0.66 (0.58, 0.76)
Hospitalisation for unstable angina[4]	108 (2.6)	157 (3.8)	0.68 (0.53, 0.87)

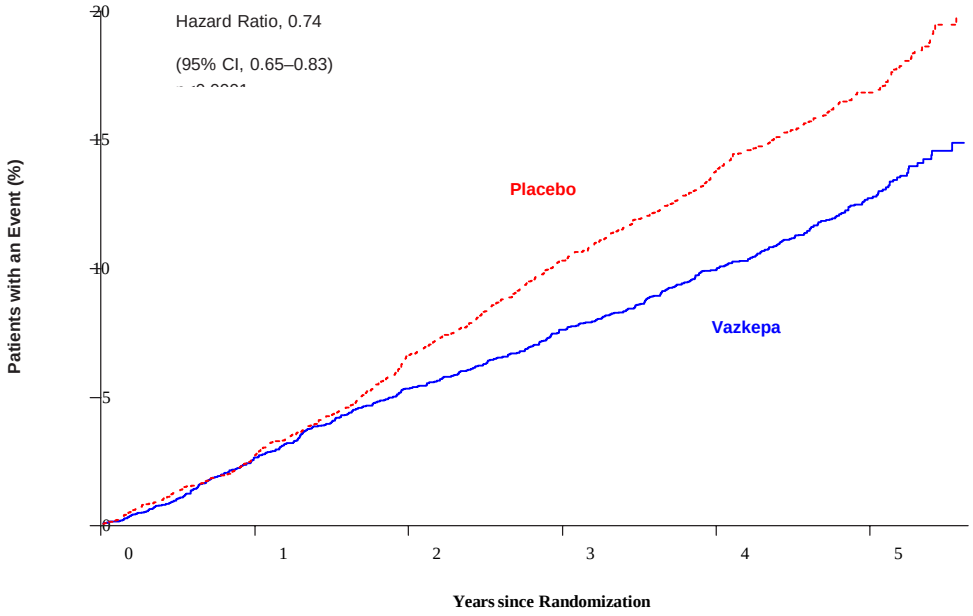
[1] Cardiovascular death includes adjudicated cardiovascular deaths and deaths of undetermined causality.

[2] Death by any cause, or total mortality, is not a component of either the primary composite endpoint or key secondary composite endpoint.

[3] The predefined composite secondary endpoint included emergent or urgent revascularisation ($p<0.0001$); coronary revascularisations is the composite of all revascularisation and was predefined as a tertiary endpoint.

[4] Determined to be caused by myocardial ischemia by invasive/non-invasive testing and requiring emergent hospitalisation.

Figure 1 Kaplan-Meier estimated incidence of key secondary composite endpoint in REDUCE-IT



No. at Risk						
Placebo	4090	3837	3500	3002	2542	1487
Vazkepa	4089	3861	3565	3115	2681	1562

Key secondary composite endpoint consisted of cardiovascular death, myocardial infarction, or stroke (3-point MACE)

Abbreviations: CI confidence interval

The median TG and LDL-C baseline values were similar between the icosapent ethyl group and placebo group. The median change in TG from baseline to Year 1 was -
0.4 mmol/L (-39 mg/dL, -18%) in the icosapent ethyl group and 0.1 mmol/L (5 mg/dL, 2%) in the placebo group. The median change in LDL-C from baseline to Year 1 was 0.1 mmol/L (2 mg/dL, 3%) in the icosapent ethyl group and 0.2 mmol/L (7 mg/dL, 10%) in the placebo group. Prespecified analyses of the effect of icosapent ethyl on cardiovascular outcomes in the REDUCE-IT trial showed little to no correlation between either TG or LDL-C response and cardiovascular effect based on baseline or on-study achieved TG or LDL-C levels. See section 5.1 mechanism of action for more information.

Paediatric population

The licensing authority has waived the obligation to submit the results of studies with icosapent ethyl in all subsets of the paediatric population for the treatment of hypertriglyceridemia and to reduce the risk cardiovascular events (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

After oral administration, icosapent ethyl is de-esterified during the absorption process and the active metabolite EPA is absorbed in the small intestine and enters the systemic circulation mainly via the thoracic duct lymphatic system. Peak plasma concentrations of EPA were reached approximately 5 hours following oral doses of icosapent ethyl.

Icosapent ethyl was administered with or following a meal in all clinical studies; no food effect studies were performed (see section 4.2).

Distribution

The mean volume of distribution at steady-state of EPA is approximately 88 liters. The majority of EPA circulating in plasma is incorporated in phospholipids, triglycerides and cholesteryl esters, and <1% is present as the unesterified fatty acid. Greater than 99% of unesterified EPA is bound to plasma proteins.

Biotransformation and elimination

EPA is mainly metabolised by the liver via beta-oxidation similar to dietary fatty acids. Beta oxidation splits the long carbon chain of EPA into acetyl Coenzyme A, which is converted into energy via the Krebs cycle. Cytochrome P450-mediated metabolism is a minor pathway of elimination of EPA. The total plasma clearance of EPA at steady-state is 684 mL/hr. The plasma elimination half-life ($t_{1/2}$) of EPA is approximately 89 hours. Icosapent ethyl does not undergo renal excretion.

Pharmacokinetic/pharmacodynamic relationship(s)

Triglycerides level/reduction in hypertriglyceridemia

A linear relationship between EPA levels in plasma or red blood cells (RBCs) and TG reduction was observed in two Phase III studies.

Cardiovascular risk reduction

Analyses of the primary (5-point) and key secondary (3-point) MACE endpoints suggest that on-treatment lipoprotein changes had limited influence on cardiovascular risk reductions, while on-treatment steady-state serum EPA levels accounted for the majority of the relative risk reduction observed in REDUCE-IT. Baseline serum EPA level was 26 μg/mL; compared to patients with an on-treatment steady-state serum EPA level below 100 μg/mL, patients with on-treatment EPA levels ≥175 μg/mL had a >50% reduced risk of a cardiovascular event.

Renal and hepatic impairment

The pharmacokinetics of icosapent ethyl has not been studied in patients with renal or hepatic impairment. Patients did not require routine dose adjustment due to hepatic or renal impairment in a well-controlled cardiovascular outcomes study of icosapent ethyl.

Other special populations

Elderly (≥ 65 years)

The pharmacokinetics of icosapent ethyl has not been studied in elderly patients. Elderly patients did not require routine dose adjustment in well-controlled clinical studies of icosapent ethyl.

Paediatric population

The pharmacokinetics of icosapent ethyl has not been studied in paediatric subjects.

5.3 Preclinical safety data

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

At the highest dose levels in reproductive and developmental studies, no adverse effects were observed in rats or rabbits at approximately 6 to 8 times the human equivalent dose based on body surface area comparison. In a rat embryo-foetal study, no adverse effects were observed at exposures 6.9 fold higher than the clinical exposure (based on AUC).

Animal studies indicate that icosapent ethyl crosses the placenta and is found in foetal plasma.

Animal studies indicate that icosapent ethyl is excreted in milk.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule fill

all-rac-alpha-tocopherol

Capsule shell

Gelatin

Glycerol

Liquid maltitol (E965 ii)

Liquid sorbitol (non-crystallising) (E420 ii)

Purified water

Soya lecithin

Printing ink

Titanium dioxide

Propylene glycol

Hypromellose

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

5 years.

6.4 Special precautions for storage

Store below 30 °C.

Bottle: keep the bottle tightly closed in order to protect from moisture.

Blister: store in the original package in order to protect from moisture.

6.5 Nature and contents of container

High density polyethylene (HDPE) bottles with a child-resistant polypropylene heatinduction sealed closure containing 120 soft capsules. Pack size of one bottle or three bottles per carton.

PVC/PCTFE/Al perforated unit dose blisters containing 4x2 soft capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

Amarin Pharmaceuticals Ireland Limited

88 Harcourt Street

Dublin 2, D02DK18

Ireland

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 51241/0002

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

20/04/2021

10 DATE OF REVISION OF THE TEXT

28/11/2023