Date: 6 February 2023
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

VAZKEPA

International non-proprietary name: icosapent ethyl
Pharmaceutical form: soft capsule
Dosage strength(s): 998 mg
Route(s) of administration: oral
Marketing Authorisation Holder: Amarin Switzerland GmbH
Marketing Authorisation No.: 68354
Decision and Decision date: approved on 22 November 2022

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
FDA	Food and Drug Administration (USA)
GLP	Good Laboratory Practice
HDL-C	High-density lipoprotein cholesterol
HDPE	High Density Polyethylene
HPLC	High performance liquid chromatography
HTG	Hypertriglyceridaemia
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International nonproprietary name
ITT	Intention-to-treat
LDL	Low-density lipoprotein
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PCTFE	Polychlorotrifluoroethylene
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric Study Plan (US-FDA)
PVC	Polyvinyl chloride
RMP	Risk Management Plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance icosapent ethyl of the medicinal product mentioned above.

2.2 Indication and Dosage

2.2.1 Requested Indication

Vazkepa is used to reduce the risk of cardiovascular events in statin-treated adult patients at high cardiovascular risk with elevated triglyceride levels (≥ 150 mg/dL) as well as:

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

For study details including cardiovascular risk factors and for outcomes related to cardiovascular events, see "Properties/Effects".

2.2.2 Approved Indication

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 to effects on cardiovascular events see “Properties/Effects”.

2.2.3 Requested Dosage

Summary of the applied standard dosage:

The recommended daily dose for oral use is four capsules, with two capsules of 998 mg taken twice daily.
Vazkepa should be taken with or after a meal. To ensure that the full intended dose is taken, patients should be advised to swallow the capsules whole and not to break, crush, dissolve or chew them.

2.2.4 Approved Dosage

(see appendix)

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2.3 Regulatory History (Milestones)

Application	28 April 2021
Formal control completed	27 May 2021
List of Questions (LoQ)	24 September 2021
Answers to LoQ	19 December 2021
Predecision	18 March 2022
Answers to Predecision	16 May 2022
Labelling corrections	11 August 2022
Answers to Labelling corrections	25 August 2022
Final Decision	22 November 2022
Decision	approval

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3 Medical Context

Hyperlipidaemia is a diverse group of disorders characterised by an excess of different lipid entities (i.e. triglycerides, cholesterol and phospholipids) in the blood. Hypertriglyceridaemia (HTG) refers to the high levels of triglycerides in the bloodstream. High triglycerides levels are often associated with low HDL-C (high-density lipoprotein cholesterol) and high levels of small dense LDL (low-density lipoprotein) particles. HTG is associated with atherogenesis and a risk for acute cardiovascular events that continue despite statin treatment.
HTG has been shown to be an independent risk factor for cardiovascular diseases. Since current international guidelines and recommendations recognise that triglyceride goals are not always achievable with current lipid-lowering therapies, there remains an unmet medical need to provide additional triglyceride therapies for patients with HTG.

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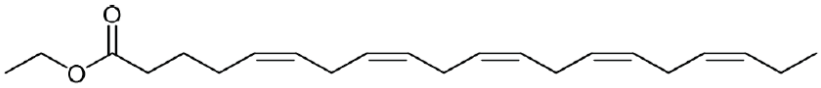
4 Quality Aspects

4.1 Drug Substance

INN:	Icosapent ethyl
Chemical name:	Ethyl (5Z,8Z,11Z,14Z,17Z)-5,8,11,14,17-icosapentaenoate
Molecular formula:	$C_{22}H_{34}O_2$
Molecular mass:	330.51 g/mol



Icosapent ethyl is blended with small amounts of all-rac-alpha-tocopherol (Vitamin E) as an anti-oxidant.

Physico-chemical properties:
Clear, colourless to faint yellow viscous liquid, practically insoluble in water, very soluble in many organic solvents.

Synthesis:
The drug substance is obtained from marine (mainly fish) oil. The original marine oil is gained in triglyceride form from marine species; in early manufacturing steps, trans-esterification is performed, followed by a series of purification steps. Depending on the respective drug substance manufacturer, different chromatographic techniques are adopted to isolate icosapent ethyl from the complex Omega-3 fatty acid ethyl ester mixture. Once the required assay of icosapent ethyl is reached, the final step consists of addition of alpha-tocopherol as an anti-oxidant. The manufacturing processes have been adequately described and the processes are controlled with appropriate in-process controls and tests for isolated intermediates.

Specification:
In order to ensure a consistent quality of the drug substance, the specifications include all relevant test parameters as recommended by the relevant ICH guidelines. The analytical methods are adequately described and the non-compendial methods are fully validated in accordance with the ICH guidelines.

Stability:
Appropriate stability data have been presented. Based on the results, satisfactory re-test periods have been established when stored in tight packaging (in-lined or coated drums) under inert atmosphere.

4.2 Drug Product

Description and composition:
Vazkepa drug product is a soft capsule containing 998 mg of icosapent ethyl (and all-rac-alpha-tocopherol as an anti-oxidant). The soft gelatin capsule is oblong, 25 x 10 mm, light yellow to amber-coloured, containing a colourless to pale yellow liquid and imprinted with ‘IPE’ in white ink. All excipients used in the drug product are widely used in pharmaceutical preparations for oral solid dosage forms and meet the standards defined in the current Ph. Eur. While the absolute composition of the capsule material is dependent on the respective manufacturer due to slightly different capsule thicknesses, after drying, the relative composition is identical.

Pharmaceutical development:
A soft gelatin capsule was chosen as the dosage form due to the liquid nature of the drug substance and its low aqueous solubility, while the composition of the capsule material has been optimised to minimise oxygen permeability.

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Manufacture:
Vazkepa capsules are manufactured in a two-step process. The gelatin mass is prepared separately and then introduced into the encapsulation process, followed by drying, polishing and sizing.

Specification:
Adequate tests and acceptance criteria for release and shelf-life have been established for the control of the finished product. The specifications include relevant physicochemical characteristics, identification of the drug substance as well as assay and purity tests.

Container Closure System:
The container closure system for the commercial market presentation is an HDPE bottle with a child-resistant polypropylene closure (including a heat induction seal). Each bottle contains 120-capsules for a one-month supply based on a dose of 4 capsules/day. The container closure system for the 8-count physician sample presentation is in a PVC/PCTFE film with aluminium foil backing for blisters.

Stability:
Appropriate stability data have been generated for both packaging configurations and according to the relevant international guidelines. The storage recommendations are “Do not store above 30 °C”, and to keep the bottle tightly closed and the blister in its original packaging to protect the content from humidity.

4.3 Quality Conclusions

Satisfactory and consistent quality of the drug substance and drug product has been demonstrated.

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5 Nonclinical Aspects

Regarding the marketing authorisation application for Vazkepa (icosapent ethyl), the Nonclinical Assessment Division conducted an abridged evaluation, which was based on the assessment report from the EMA CHMP (dated 28 January 2021) provided by the applicant. In addition, the publicly available FDA pharmacology review (dated 5 June 2012) was considered.
Overall, the submitted nonclinical documentation is considered appropriate to support the approval of Vazkepa in the proposed indication. The pharmaco-toxicological profile has been sufficiently characterised. There were no safety issues identified in the nonclinical studies that would be of concern for human use.
As a post-approval commitment for the EMA, a hERG assay with eicosapentaenoic acid (EPA) was performed. Since EPA did not inhibit hERG up to the highest tested concentration, the outcome does not change the favourable evaluation of the EMA CHMP. The safety margins are considered sufficient.
All nonclinical data that are relevant for safety are adequately mentioned in the information for healthcare professionals.

6 Clinical and Clinical Pharmacology Aspects

The evaluation of the clinical and clinical pharmacology data of this application has been carried out in reliance on previous regulatory decisions by the EMA. The available assessment report and respective product information from the EMA were used as a basis for the clinical and clinical pharmacology evaluation.

7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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8 Appendix

Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to VAZKEPA was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ 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 new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

VAZKEPA®

Composition

Active substances

Icosapent ethyl.

Excipients

Capsule fill: all-rac-alpha-tocopherol (E307).

Capsule shell: Gelatin, glycerol (E422), liquid maltitol (E965 ii) with max. 30 mg maltitol per capsule, liquid sorbitol 70% (non-crystallising) (E420 ii) with max. 83 mg sorbitol per capsule, triglycerides, medium-chain, purified water, soya lecithin (E322).
Printing ink: Titanium dioxide (E171), propylene glycol (E1520), hypromellose (E464).

Pharmaceutical form and active substance quantity per unit

Soft 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.

Each capsule contains 998 mg of icosapent ethyl.

Indications/Uses

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 to effects on cardiovascular events see «Properties/effects».

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Dosage/Administration

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

Patients with hepatic disorders

No dose reduction is recommended (see also «Warnings and precautions» and «Pharmacokinetics»).

Patients with renal disorders

No dose reduction is recommended (see also «Pharmacokinetics»).

Elderly patients

No dose adjustment is necessary based on age (see «Pharmacokinetics»).

Children and adolescents

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.

Delayed administration

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.

Mode 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.

Contraindications

Hypersensitivity to the active substance, soya or to any of the excipients listed under «Composition».

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Warnings and precautions

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 «Undesirable effects»). 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 «Undesirable effects»).

Other ingredients

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.

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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.

Interactions

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.

Increased bleeding risk

Patients taking concomitant antithrombotic agents should be monitored as treatment with icosapent ethyl has been associated with an increased incidence of bleeding (see “Warnings and precautions”).

Pregnancy, 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 «Preclinical data»). 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.

Lactation

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.

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.

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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 «Preclinical data»).

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.

Undesirable effects

Summary of the safety profile

The most frequently reported adverse reactions associated with icosapent ethyl were bleeding (11.8%), peripheral oedema (7.8%), atrial fibrillation (5.8%), constipation (5.4%), musculoskeletal pain (4.3%), gout (4.3%) and rash (3.0%).

List of adverse reactions

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.
The adverse reactions are arranged according to MedDRA system organ classes and the conventional frequencies as follows: "very common" (≥1/10); "common" (≥1/100, <1/10); "uncommon" (≥1/1,000, <1/100); "rare" (≥1/10,000, <1/ 1,000); "very rare" (<1/10,000); “not known (cannot be estimated from the available data).

Immune system disorders
Uncommon: Hypersensitivity.
Not known: Pharyngeal swelling.

Metabolism and nutrition disorders
Common: Gout.

Nervous system disorders
Uncommon: Dysgeusia (describes the “verbatim” term: Fishy taste).

Cardiac disorders
Common: Atrial fibrillation or flutter.

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Vascular disorders

Very common: Bleeding (11.8%).

Gastrointestinal disorders

Common: Constipation, eructation.

Skin and subcutaneous tissue disorders

Common: Rash.

Musculoskeletal and connective tissue disorders

Common: Musculoskeletal pain.

General disorders and administration site conditions

Common: Peripheral oedema.

Description of specific adverse reactions and additional information

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 «Warnings and precautions»).

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 «Warnings and precautions»).

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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 suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

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.

Properties/Effects

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.

Pharmacodynamics

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

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 coronary artery 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.

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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 endpoint are shown in Table 1. The Kaplan-Meier estimates of the cumulative incidence of the primary composite endpoint over time are shown in Figure 1.

Table 1: 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)

Regarding the secondary endpoint of 3-point MACE (cardiovascular death, myocardial infarction, or stroke), patients treated with icosapent ethyl had a relative risk reduction of 26% (95% CI 0.65, 0.83, p<0.0001). Death by any cause (not a component of primary or secondary endpoints) reported a 13%

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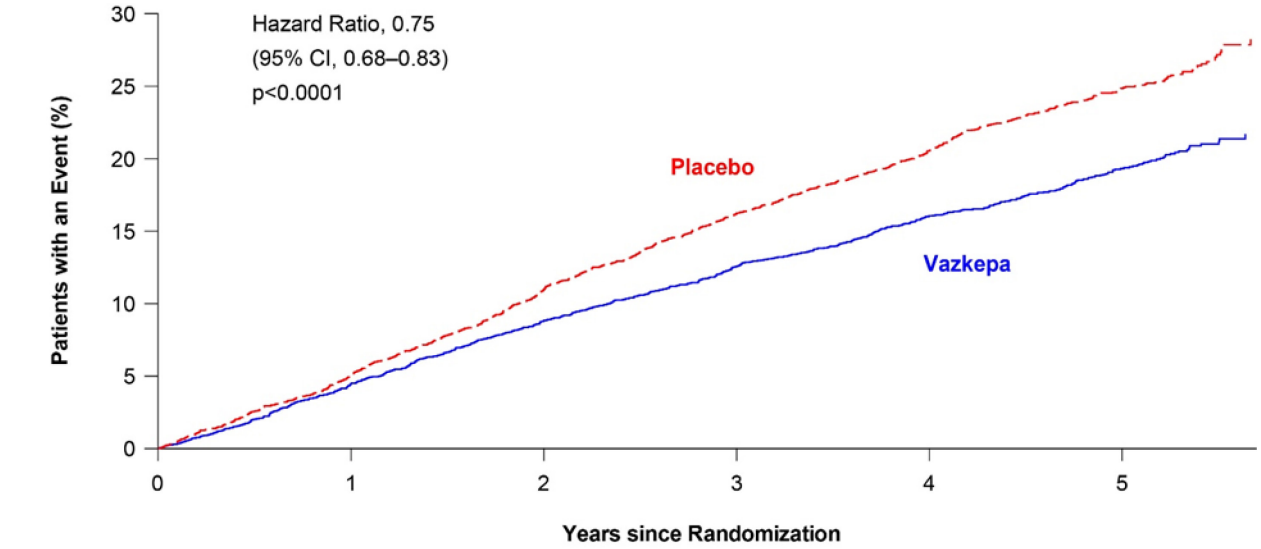
risk reduction (95% CI 0.74, 1.02). All other secondary endpoints achieved a risk reduction of between 20-35%.

Figure 1: Kaplan-Meier estimated cumulative incidence of primary composite endpoint in REDUCE-IT



No. at Risk						
Placebo	4090	3743	3327	2807	2347	1358
Vazkepa	4089	3787	3431	2951	2503	1430

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 «Mechanism of action» for more information.

Paediatrics

Swissmedic 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 «Dosage/administration» for information on paediatric use).

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Pharmacokinetics

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 «Dosage/administration»).

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.

Metabolism

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 cancer cycle. Cytochrome P450-mediated metabolism is a minor pathway of elimination of EPA.

Elimination

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.

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Kinetics in specific patient groups

Hepatic impairment and renal 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.

Elderly patients

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.

Children and adolescents

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

Preclinical 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.

Other information

Incompatibilities

Not applicable.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

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Special precautions for storage

Do not store above 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.

Keep out of the reach of children.

Authorisation number

68354 (Swissmedic).

Packs

Pack with 1 bottle containing 120 soft capsules. [B]

Blister pack containing 4x2 capsules in perforated daily dose blisters. [B]

Marketing authorisation holder

Amarin Switzerland GmbH, Zug

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August 2022