Pr Vascepa®
(icosapent ethyl)

Product Monograph

HLS Therapeutics®

PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

Pr VASCEPA®

Icosapent ethyl capsules

1 g, for oral use

Lipid-regulating agent

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TABLE OF CONTENTS

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

VASCEPA® (icosapent ethyl) is indicated to reduce the risk of cardiovascular events (cardiovascular death, non-fatal myocardial infarction, non-fatal stroke, coronary revascularization or hospitalization for unstable angina) in statin-treated patients with elevated triglycerides, who are at high risk of cardiovascular events due to:

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

1.1 Pediatrics

Pediatrics (<18 years): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (≥65 years): Evidence from clinical studies and experience suggests that use in the geriatric population is not associated with differences in safety or effectiveness, but greater sensitivity of some older individuals cannot be ruled out.

2 CONTRAINDICATIONS

VASCEPA is contraindicated in patients who are hypersensitive to VASCEPA or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

3 DOSAGE AND ADMINISTRATION

3.1 Recommended Dose and Dosage Adjustment

The dose of VASCEPA is 4 grams per day, taken as two 1 g capsules twice a day with food.

3.2 Administration

Patients should be advised to swallow VASCEPA capsules whole. Do not break open, crush, dissolve, or chew VASCEPA.

3.3 Missed Dose

If a dose is missed, patients should take it as soon as they remember. However, if they miss one day of VASCEPA, they should not double the dose when they take their next dose.

4 OVERDOSAGE

There is no specific treatment for VASCEPA overdose. In the event of an overdose, the patient should be treated symptomatically and supportive measures instituted as required. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance VASCEPA clearance.

For management of a suspected drug overdose, contact your regional poison control centre.

5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 – Dosage Form, Strengths and Composition

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	1 g amber-colored, oblong, soft-gelatin capsules imprinted with VASCEPA.	gelatin, glycerin, hypromellose, maltitol, propylene glycol, purified water, sorbitol, titanium dioxide, and tocopherol

The 1 g dosage strength is available in 8 count blisters and bottles of 120 capsules.

6 WARNINGS AND PRECAUTIONS

General

Icosapent ethyl is not the same as, and should not be substituted with, or combined with other products that contain omega-3 fatty acids. Patients should be questioned about which natural health products or dietary supplements they may be taking, and cautioned not to take other omega-3 fatty acid products while they are taking VASCEPA, without first consulting their attending physician.

Bleeding

Treatment with VASCEPA has been associated with an increased incidence of bleeding (see ADVERSE REACTIONS, Bleeding). Patients taking VASCEPA along with antithrombotic agents, i.e., anti-platelet agents, including aspirin, and/or anticoagulants, may be at increased risk of bleeding. Monitor these patients appropriately.

Carcinogenesis and Mutagenesis

No carcinogenicity or mutagenicity data in humans are available (see NON-CLINICAL TOXICOLOGY, Carcinogenicity and Genotoxicity).

Immune System

It is not known whether patients with allergies to fish and/or shellfish are at increased risk of an allergic reaction to VASCEPA, which is a fish-derived product. VASCEPA should be used with caution in patients with known hypersensitivity to fish and/or shellfish.

Monitoring and Laboratory Tests

In patients with hepatic impairment, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels should be monitored periodically during therapy with VASCEPA.

Sexual Health

Fertility: No fertility data in humans are available. No significant effect on fertility was observed in rats receiving eicosapentaenoic acid ethyl ester orally (see NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology).

6.1 Special Populations

6.1.1 Pregnant Women

There are no adequate and well-controlled studies that evaluated the use of VASCEPA in pregnant women. In animal reproduction studies in pregnant rats, oral administration of icosapent ethyl or eicosapentaenoic acid (EPA) ethyl ester during organogenesis resulted in fetal visceral or skeletal abnormalities, increased incidence of absent optic nerves, and unilateral testes atrophy even at doses below an equivalent to the clinical dose of 4 g/day based on a comparison of body surface area, for a 60 kg human (see NON-CLINICAL TOXICOLOGY, Reproductive and Developmental Toxicology). 14C-labelled ethyl-EPA given orally to pregnant dams was shown to transfer to the fetus, especially in early gestation (gestation day 12) during which peak concentrations in fetuses and placentas reached 1.9- and 3.6-times the concentration in maternal plasma, respectively, at 24 hours post-administration.

Therefore, the use of VASCEPA is not recommended during pregnancy.

6.1.2 Breast-feeding

There is no information regarding the presence of VASCEPA in human milk, the effects on the breastfed infant, or the effects on milk production. However, studies with other omega-3-acid ethyl esters have demonstrated excretion in human milk, therefore VASCEPA may also be excreted in human milk. An animal study in lactating rats given one dose of ^{14}C-labelled ethyl-EPA by oral gavage demonstrated that EPA levels were 6 to 14 times higher in milk than in plasma at their maximum, 24 hours post-administration. After 96 hours (4 days), the concentration of EPA measured in milk was still 20% of the peak values.

The use of VASCEPA in nursing women is not recommended (see NON-CLINICAL

TOXICOLOGY, Reproductive and Developmental Toxicology).

6.1.3 Pediatrics

Pediatrics (<18 years): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

6.1.4 Geriatrics

Geriatrics (≥65 years): Of the total number of patients in well-controlled clinical studies of VASCEPA, 45% were 65 years of age and over. Effectiveness was consistently observed between these patients and younger patients. No overall differences in safety were observed between age groups.

7 ADVERSE REACTIONS

7.1 Adverse Drug Reaction Overview

The safety of VASCEPA was evaluated in 8,179 patients in the REDUCE-IT cardiovascular outcomes trial, with 4,089 receiving VASCEPA and 4,090 patients receiving placebo. The median duration was 4.9 years. The overall adverse event rates were similar in patients treated with VASCEPA (82%), compared to placebo (81%), while the incidence of serious adverse events was the same in patients treated with VASCEPA (31%) and placebo (31%). The rate of adverse events leading to discontinuation of study drug was also the same in patients treated with VASCEPA (8%) and placebo (8%). The most common adverse reaction with VASCEPA reported in ≥5% of patients and significantly greater than placebo was peripheral edema.

7.2 Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

<u>Adverse Reactions in the REDUCE-IT trial</u>

In this double-blind, randomized, placebo-controlled cardiovascular outcomes trial, 4,089 patients were randomized to VASCEPA, and 4,090 to placebo (see CLINICAL TRIALS, Prevention of Cardiovascular Events). The median age of enrolled patients was 64 years (range: 44 to 92 years), and 46% were 65 years of age or older. Twenty-nine percent (29%) were female, 90.2% were White, 5.5% were Asian, and 4.2% identified as Hispanic ethnicity, and 1.9% were Black. Patients were exposed to VASCEPA or placebo for a median of 4.3 years; with 87% of patients for ≥12 months, 77% for ≥24 months, 65% for ≥36 months, 54% for ≥48 months, 29% for ≥60 months.

Table 2 - Adverse Reactions Occurring at Incidence ≥5% and Significantly Greater than Placebo in REDUCE-IT

System Organ Class Preferred Term	**VASCEPA (N=4089) n (%)**	**Placebo (N=4090) n (%)**
General disorders and administration site conditions		
peripheral edema	267 (6.5)	203 (5.0)
constipation	221 (5.4)	149 (3.6)
atrial fibrillation	215 (5.3)	159 (3.9)

Cardiovascular

Atrial Fibrillation: In the REDUCE-IT trial, adjudicated events of atrial fibrillation/atrial flutter were observed more frequently in the VASCEPA group than in the placebo group, at 3.1% and 2.1%, respectively (p=0.004), The incidence of unadjudicated atrial fibrillation/atrial flutter adverse events was also significantly higher in the VASCEPA group than in the placebo group, at 5.8% and 4.5% of patients, respectively (p=0.008).

Hematologic

Bleeding: In the REDUCE-IT trial, a significantly higher incidence of bleeding events was observed with VASCEPA than with placebo, at 11.8% and 9.9% of patients, respectively (p=0.006). Serious adverse bleeding events were observed in 2.7% of patients exposed to VASCEPA, and 2.1% to placebo, (p=0.06). There were no significant differences between the VASCEPA-treated group and the placebo group in the rates of adjudicated hemorrhagic stroke, at 0.3% and 0.2% (p=0.54), or serious gastrointestinal bleeding, at 1.5% and 1.1%, respectively (p=0.15).

Less Common Clinical Trial Adverse Reactions

The following less common adverse reactions at <5% in the VASCEPA group and at least 1% greater than in the placebo group are presented below.

Metabolism and nutrition disorders: gout

Musculoskeletal and connective tissue disorders: musculoskeletal pain

7.3 Post-Market Adverse Reactions

The following adverse reactions have been identified from global post-marketing use of VASCEPA. 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: arthralgia, diarrhea, abdominal discomfort, and pain in the extremities.

8 DRUG INTERACTIONS

8.1 Overview

VASCEPA was associated with an increased risk of bleeding in the pivotal REDUCE-IT trial. The incidence of bleeding was greater in patients receiving concomitant antithrombotic medications, such as aspirin, clopidogrel, or warfarin (see WARNINGS AND PRECAUTIONS, Bleeding, and ADVERSE REACTIONS, Bleeding).

8.2 Drug-Drug Interactions

VASCEPA was studied at the 4 g/day dose level with the following medications which are typical substrates of cytochrome P450 enzymes, and no drug-drug interactions were observed:

- *Omeprazole:* In a drug-drug interaction study with 28 healthy adult subjects, VASCEPA 4 g/day at steady-state did not significantly change the steady-state AUCT or Cmax of omeprazole when co-administered at 40 mg/day to steady-state.

- *Rosiglitazone:* In a drug-drug interaction study with 28 healthy adult subjects, VASCEPA 4 g/day at steady-state did not significantly change the single dose AUC or Cmax of rosiglitazone at 8 mg.

- *Warfarin:* In a drug-drug interaction study with 25 healthy adult subjects, VASCEPA 4 g/day at steady-state did not significantly change the single dose AUC or Cmax of R- and S- warfarin or the anti-coagulation pharmacodynamics of warfarin when co-administered as racemic warfarin at 25 mg.

- *Atorvastatin:* In a drug-drug interaction study of 26 healthy adult subjects, VASCEPA 4 g/day at steady-state did not significantly change the steady-state AUCT or Cmax of atorvastatin, 2-hydroxyatorvastatin, or 4-hydroxyatorvastatin when co-administered with atorvastatin 80 mg/day to steady-state.

8.3 Drug-Food Interactions

VASCEPA was administered with or following a meal in all clinical studies; no food effect studies were performed.

9 ACTION AND CLINICAL PHARMACOLOGY

9.1 Mechanism of Action

The mechanisms of action contributing to reduction of cardiovascular events with VASCEPA (icosapent ethyl) are not completely understood but are likely multi-factorial.

9.2 Pharmacokinetics

Absorption: After oral administration, VASCEPA is de-esterified during the absorption process and the active metabolite icosapentaenoic acid is absorbed in the small intestine and enters the

systemic circulation mainly via the thoracic duct lymphatic system. Peak plasma concentrations of icosapentaenoic acid were reached approximately 5 hours following oral doses of VASCEPA.

Distribution: The mean volume of distribution at steady-state of icosapentaenoic acid is approximately 88 litres. The majority of icosapentaenoic acid 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 icosapentaenoic acid is bound to plasma proteins.

Metabolism: Icosapentaenoic acid is mainly metabolized by the liver via beta-oxidation similar to dietary fatty acids. Beta oxidation splits the long carbon chain of icosapentaenoic acid into acetyl Coenzyme A, which is converted into energy via the Krebs cycle.

Elimination: Cytochrome P450-mediated metabolism is a minor pathway of elimination of icosapentaenoic acid. The total plasma clearance of icosapentaenoic acid at steady state is 684 mL/hr. The plasma elimination half-life (t1/2) of icosapentaenoic acid is approximately 89 hours. VASCEPA does not undergo renal excretion.

Special Populations and Conditions

Pediatrics: The pharmacokinetics of VASCEPA has not been studied in pediatric patients.

Sex: When administered VASCEPA in clinical trials, plasma total icosapentaenoic acid concentrations did not differ significantly between men and women

Hepatic Insufficiency: VASCEPA has not been studied in patients with hepatic impairment.

Renal Insufficiency: VASCEPA has not been studied in patients with renal impairment.

10 STORAGE, STABILITY AND DISPOSAL

Store at room temperature (20° to 25°C). Keep out of reach of children.

Safely throw away medicine that is out of date or no longer needed.

PART II: SCIENTIFIC INFORMATION

11 PHARMACEUTICAL INFORMATION

Drug Substance

Each VASCEPA® capsule contains 1 gram of icosapent ethyl (in a 1 g capsule).

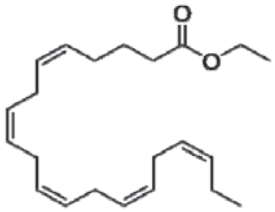
Proper name: icosapent ethyl

Chemical name: ethyl all-cis-5,8,11,14,17-icosapentaenoate

Molecular formula: $C_{22}H_{34}O_2$

Molecular Mass: 330.512 g/mol

Structural formula:



Physicochemical properties: icosapent ethyl (IPE) is a clear, colourless to pale yellow liquid, insoluble in water, soluble in ethanol

12 CLINICAL TRIALS

12.1 Prevention of Cardiovascular Events

12.1.1 Study Demographics and Trial Design

The REDUCE-IT study was a double-blind, randomized, placebo-controlled trial in 8,179 statin-treated adult patients with elevated serum triglyceride (TG) levels (≥1.5 mmol/L and <5.6 mmol/L) who were also at high risk for atherothrombotic events. Patients either had established cardiovascular disease (CVD) (70.7%), define as the secondary prevention cohort, or were at high risk for CVD (29.3%), defined as primary prevention cohort. Patients with established cardiovascular disease were at least 45 years of age and having a documented history of coronary artery disease, cerebrovascular or carotid disease, or peripheral artery disease. Patients with other risk factors for cardiovascular disease were at least 50 years of age and had diabetes and at least one additional major cardiovascular risk factor. Patients were randomly assigned 1:1 to receive either VASCEPA at 4 grams daily, given as two 1 gram capsules twice a day with food, or placebo. 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.

At baseline, the median age was 64 years (range: 44 years to 92 years), with 46% being at least 65 years old, and 28.8% women. The trial population was 90.2% White, 5.5% Asian, 1.9% Black, and 4.2% were identified as of Hispanic ethnicity.

Patients enrolled in the trial included 46.7% who had prior myocardial infarction, 9.2% who had symptomatic peripheral arterial disease, and 6.2% who had prior ischemic stroke, and 4.6% who had prior transient ischemic attack (TIA). Additional baseline risk factors included hypertension (86.6%), diabetes mellitus (58.5%), eGFR <60 mL/min/1.73m^2 (22.2%), congestive heart failure (17.7%), and current daily cigarette smoking (15.2%). Most patients at baseline were taking at least one other cardiovascular medication including anti-hypertensives (95%), anti-platelet agents (79.4%), beta blockers (70.7%), angiotensin-converting enzyme (ACE) inhibitors (51.9%), and angiotensin receptor blockers (ARB) (27.0%), with 77.5% taking either an ACE inhibitor or ARB.

At baseline, while on stable background lipid-lowering therapy, the median LDL-C was 1.9 mmol/L, while the median fasting serum TG was 2.4 mmol/L. Baseline TG levels ranged from 0.92 to 15.8 mmol/L.

12.1.2 Study Results

The primary composite endpoint (time to first occurrence of cardiovascular death, myocardial infarction, stroke, coronary revascularization, or hospitalization for unstable angina) occurred at an event rate of 4.3 per 100 patient-years in patients treated with VASCEPA, compared to 5.7 per 100 patient-years in patients treated with placebo ($p<0.0001$), while the key secondary composite endpoint (time to first occurrence of cardiovascular death, myocardial infarction, or stroke) occurred at an event rate of 2.7 per 100 patient-years in patients treated with VASCEPA, compared to 3.7 per 100 patient-years in patients treated with placebo ($p<0.0001$).

The results of the primary and secondary efficacy endpoints are shown in Table 3 below, while the Kaplan-Meier estimates of the cumulative incidence of the primary and key secondary composite endpoints over time are shown in Figure 1 and Figure 2 below.

Table 3. Effect of VASCEPA on Time to First Occurrence of Cardiovascular Events in Patients with Established CVD or at High Risk for CVD and Elevated Triglyceride Levels in REDUCE-IT

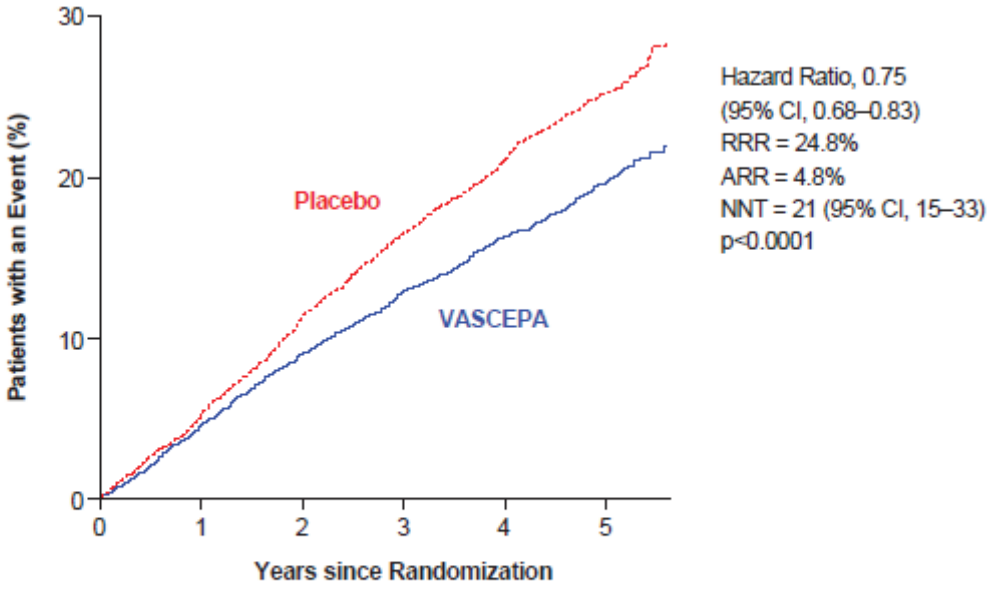
	VASCEPA		Placebo		VASCEPA vs Placebo
	N = 4089 n (%)	Incidence Rate (per 100 patient years)	N = 4090 n (%)	Incidence Rate (per 100 patient years)	Hazard Ratio (95% CI)
Primary composite endpoint					
Cardiovascular death, myocardial infarction, stroke, coronary revascularization, hospitalization for unstable angina (5-point MACE)	705 (17.2)	4.3	901 (22.0)	5.7	0.75 (0.68, 0.83)
Key secondary composite endpoints					
Cardiovascular death, myocardial infarction, stroke (3-point MACE)	459 (11.2)	2.7	606 (14.8)	3.7	0.74 (0.65, 0.83)
Other secondary endpoints					
Cardiovascular death[1]	174 (4.3)	1.0	213 (5.2)	1.2	0.80 (0.66, 0.98)
Non-fatal myocardial infarction	237 (5.8)	1.4	332 (8.1)	2.0	0.70 (0.59, 0.82)
Non-fatal stroke	85 (2.1)	0.5	118 (2.9)	0.7	0.71 (0.54, 0.94)
Coronary revascularization	376 (9.2)	2.3	544 (13.3)	3.4	0.66 (0.58, 0.76)
Hospitalization for unstable angina[2]	108 (2.6)	0.6	157 (3.8)	0.9	0.68 (0.53, 0.87)
All-cause mortality[3]	274 (6.7)	1.6	310 (7.6)	1.8	0.87 (0.74, 1.02)

[1] CV Death includes adjudicated cardiovascular deaths and deaths of undetermined causality

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

[3] All-cause mortality is not a component of either the primary composite endpoint or key secondary endpoint

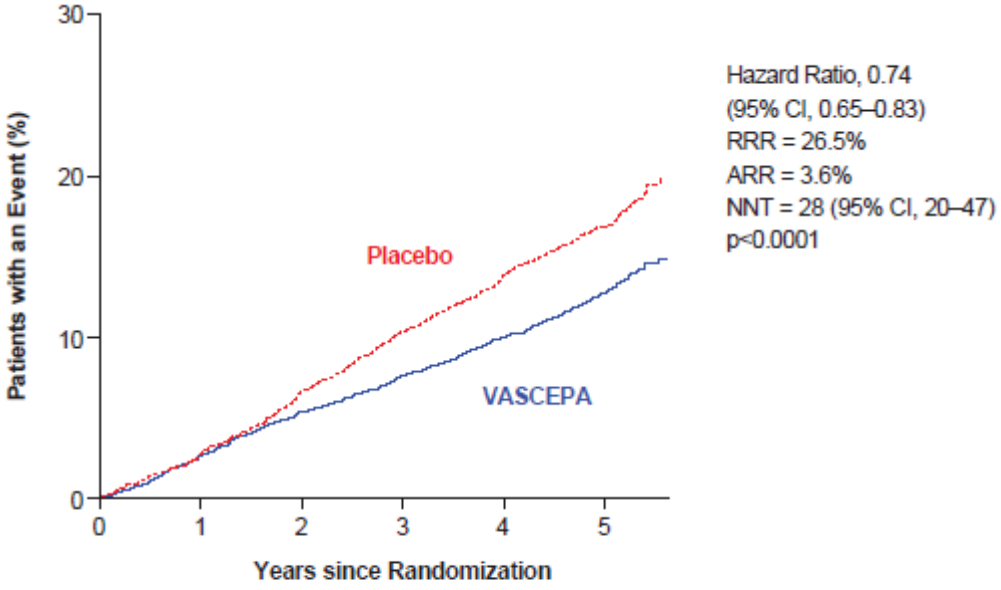
Figure 1. Kaplan-Meier Estimated Cumulative Incidence of Primary Composite Endpoint in REDUCE-IT



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

RRR = relative risk reduction; ARR= absolute relative risk; NNT= number needed to treat

Figure 2. Kaplan-Meier Estimated Incidence of Key Secondary Composite Endpoint in REDUCE-IT



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

RRR = relative risk reduction; ARR= absolute relative risk; NNT= number needed to treat

The median difference between VASCEPA and placebo in TG from baseline to Month 4 was -20.1% (p<0.001), and from baseline to Month 12 was -19.7% (p<0.001), in favour of VASCEPA. At Month 12, the median TG was 2.0 mmol/L in the VASCEPA group, with 35.9% of patients with available measurements having TG <1.7 mmol/L and 61.3% having a TG <2.3 mmol/L. Prespecified analyses of the effect of VASCEPA on cardiovascular outcomes in the REDUCE-IT trial failed to demonstrate a correlation between triglyceride response and cardiovascular effect based on baseline triglyceride levels or on-treatment change in triglyceride levels.

The median difference between VASCEPA and placebo in LDL-C from baseline to Month 12 was -6.6% (p<0.001), in favour of VASCEPA. At Month 12, the median LDL-C was 2.0 mmol/L in the VASCEPA group, with 35.5% with available measurements of patients having LDL-C <1.8 mmol/L and 79.9% having LDL-C <2.6 mmol/L.

13 NON-CLINICAL TOXICOLOGY

General Toxicology

In a 39-week dog study, icosapent ethyl was administered to beagle dogs at doses of 0.3, 1 or 2 g/kg/day. Expected pharmacological changes in plasma lipid concentrations (lower total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides) were observed at all dose levels. At doses ≥1 g/kg/day, there were increases in alkaline phosphatase and aspartate aminotransferase levels. Vacuolar degeneration of the adrenal glands followed a dose-related pattern. The NOAEL is 0.3 g/kg/day (2.5 times the 4 g/day clinical dose based on a body surface area comparison, for a 60 kg human).

Carcinogenicity

In a 2-year rat carcinogenicity study with oral gavage doses of 0.09, 0.27, and 0.91 g/kg/day icosapent ethyl, a significant treatment-related increase in mortality was observed in females. Anterior lobe pituitary adenoma was the most frequent cause of death in females treated with the highest dose who died prematurely. There was a statistically significant dose-related increase in hemangiomas of the mesenteric lymph node, the site of drug absorption, in males and females. Incidence in mid-dose females was higher than in controls at an exposure 2.7 times the exposure at the clinical dose of 4 g/day (based on AUC), whereas incidence in treated males was higher than in controls only at the highest dose level, at which exposure is 6.8 times the clinical dose of 4 g/day. Overall incidence of hemangiomas and hemangiosarcomas in all vascular tissues did not increase with treatment.

In a 6-month carcinogenicity study in Tg.rasH2 transgenic mice with oral gavage doses of 0.5, 1, 2, and 4.6 g/kg/day icosapent ethyl, drug-related incidences of benign squamous cell papilloma in the skin and subcutis of the tail were observed in high dose male mice. The papillomas were considered to develop secondary to chronic irritation of the proximal tail associated with fecal excretion of oil and therefore not clinically relevant. Drug-related neoplasms were not observed in female mice.

Genotoxicity

Icosapent ethyl was not mutagenic with or without metabolic activation in the bacterial mutagenesis (Ames) assay. A chromosomal aberration assay in Chinese Hamster Ovary cells was positive for clastogenicity with and without metabolic activation, but icosapent ethyl did not induce micronuclei *in vivo* in mice.

Reproductive and Developmental Toxicology

Only one full study report compliant with Good Laboratory Practices was submitted. In that study, icosapent ethyl was given by oral gavage to female rats from gestation day 6 to 16 at doses of 0.3, 1.0 or 2.0 g/kg/day. Minor abnormalities included 13th reduced ribs, additional liver lobes, and testes medially displaced or not fully descended in the treated groups, including at the lowest dose of 0.3 g/kg/day equivalent to 0.7 times the recommended dose of 4 g/day of icosapent ethyl in a 60 kg human based on body surface area comparisons.

Concerning fertility in male and female rats, oral gavage of EPA ethyl ester at doses of 0.3, 1.0 or 3.0 g/kg/day for 9 weeks (males) or 2 weeks (females) pre-mating was not associated with significant reduction of copulation or fertility rates. Increased anogenital distance was observed in high-dose female pups, and skeletal variations (cervical rib, dumbbell shape of the vertebral body) were more common in the offspring from the treatment groups than in controls. In two follow-up studies, offspring exposed to EPA ethyl ester in utero had lower fertility rates even at the low dose, lower copulation rates when mated together, and/or lower implantation rate.

In two supporting studies, EPA ethyl ester given at doses of 0.3, 1.0 or 3.0 g/kg/day by oral gavage to rats either in early (day 7 to 17) or late gestation and nursing period (day 17 to post-natal day 20) led to different effects in offspring. Offspring exposed early in gestation had higher incidences of minor abnormalities (such as unilateral testes atrophy, absent optic nerves, early incisor eruption, incomplete or abnormal ossification of various skeletal bones, increased incidence of cervical ribs and of poorly ossified sternebra, and lower rates of opening of the foramen transversarium of the 7th cervical vertebra). Offspring exposed later in gestation and before weaning did not present with malformations. In both studies, adverse effects were seen in offspring at the lowest dose tested of 0.3 g/kg/day, which is approximately equivalent to 0.7 times the recommended dose of 4 g per day of icosapent ethyl in a 60 kg human.

Likewise, in a supportive study where EPA ethyl ester was given by oral gavage at doses of 0.1, 0.3, or 1.0 g/kg/day to rabbits during gestation days 6 to 18, the high dose (1.0 g/kg/day) led to an increase in fetal death correlated with higher maternal toxicity (weight loss and reduced food consumption). Higher rates of skeletal variations (13th rib) were seen in the mid- and high-dose groups. The mid-dose is equivalent to 1.5 times the recommended dose of icosapent ethyl in a 60 kg human.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

PrVASCEPA®
Icosapent ethyl capsules

Read this carefully before you start taking **VASCEPA** and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about **VASCEPA**.

What is VASCEPA used for?
VASCEPA is used to lower your risk of:

- dying from heart disease
- having a heart attack or stroke
- having certain types of heart surgery or
- having to be hospitalized for unstable angina (a condition in which your heart does not get enough blood flow and oxygen)

It is used in adults who have high levels of triglycerides (a type of fat found in your blood), are currently taking cholesterol-lowering medications called statins and who are at a high risk of experiencing heart related problems due to:

- an existing heart condition, or
- diabetes and at least one other heart-related problem

How does VASCEPA work?
VASCEPA contains a type of omega-3-fatty acid from fish oil called eicosapentaenoic acid (EPA). Exactly how VASCEPA works is not known. It does help lower the amount of triglycerides made by your body.

What are the ingredients in VASCEPA?
Medicinal ingredients: icosapent ethyl
Non-medicinal ingredients: gelatin, glycerin, hypromellose, maltitol, propylene glycol, purified water, sorbitol, titanium dioxide, and tocopherol

VASCEPA comes in the following dosage forms:
Capsule: 1 g

Do not use VASCEPA if:

- If you are allergic to icosapent ethyl or any of the other ingredients in VASCEPA (see Non-medicinal ingredients above).

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take VASCEPA. Talk about any health conditions or problems you may have, including if you:

- are allergic to fish or shellfish. It is not known if people who are allergic to fish or shellfish are also allergic to VASCEPA.

- are taking other omega-3 fatty acid products. **Do not** take other omega-3 fatty acid products while you are taking VASCEPA.
- are taking medicines to reduce the formation of blood clots (anticoagulants, or anti-platelet medications, including aspirin). If so, you may be at increased risk of bleeding. Your doctor should monitor you if you are taking VASCEPA with these types of medications.
- have liver problems. Your doctor may perform blood tests to monitor you.
- if you are pregnant or planning to become pregnant. It is not known if VASCEPA will harm your unborn baby. You should not take VASCEPA while pregnant.
- If you are breastfeeding or planning to breastfeed. VASCEPA may pass into your breast milk and may harm your baby. You should not take VASCEPA if you are breastfeeding.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with VASCEPA:
- other omega-3 fatty acids
- medicines to reduce the formation of blood clots (anticoagulants, anti-platelet medications, including aspirin)

How to take VASCEPA:
- Take it with your meals
- Swallow capsules whole. Do not break, crush, dissolve, or chew the capsules before swallowing.

Usual adult dose: Take 2 capsules twice a day.

Overdose:

If you think you have taken too much VASCEPA, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:
- If you miss a dose, take it as soon as you remember
- If you miss taking VASCEPA for one day, do not double your dose when you take your next dose.

What are possible side effects from using VASCEPA?

These are not all the possible side effects you may feel when taking VASCEPA. If you experience any side effects not listed here, contact your healthcare professional.

Side effects include:
- constipation

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON			
Swelling of hands, feet, ankles, and lower legs	✔		
Irregular heart rhythm, palpitations			✔
Unusual bleeding			✔

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html)
- for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store at room temperature (20° to 25°C) in the original container. Keep out of reach and sight of children.

If you want more information about VASCEPA:
- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (https://health-products.canada.ca/dpd-bdpp/index-eng.jsp); the manufacturer's website https://www.vascepa.ca, or by calling 1-833-266-3423.

This leaflet was prepared by HLS Therapeutics Inc.

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Pr Vascepa®
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