PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]**EVKEEZA**®

Evinacumab for injection

150 mg/mL concentrate for solution for infusion

Other lipid modifying agents, C10AX17

Established Pharmacologic Class: Angiopoietin-like Protein 3 (ANGPTL3) Inhibitor

Ultragenyx Pharmaceutical Inc.
60 Leveroni Court
Novato, CA 94949

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Innomar Strategies, Inc.
3470 Superior Court
Oakville, ON, L6L 0C4
Canada

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RECENT MAJOR LABEL CHANGES

Not applicable.

TABLE OF CONTENTS

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

EVKEEZA® (evinacumab for injection) is indicated as an adjunct to diet and other low-density lipoprotein cholesterol (LDL-C) lowering therapies for the treatment of adult and pediatric patients aged 5 years and older with homozygous familial hypercholesterolemia (HoFH).

The effects of Evkeeza on cardiovascular morbidity and mortality have not been determined.

1.1 Pediatrics

Pediatrics (5 years to 17 years): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of Evkeeza in pediatric patients aged 5 years to 17 years have been established. Therefore, Health Canada has authorized an indication for pediatric use (see 8 ADVERSE REACTIONS and 14 CLINICAL TRIALS).

Pediatrics (< 5 years): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for use in patients < 5 years of age.

1.2 Geriatrics

No dose adjustment is required for elderly patients (≥ 65 years of age) (see 10.3 Pharmacokinetics and 14 CLINICAL TRIALS).

2 CONTRAINDICATIONS

Evkeeza is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient or component of the container. For a complete listing, see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION, AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

4.2 Recommended Dose and Dosage Adjustment

- The recommended dose for Evkeeza is 15 mg/kg administered by intravenous (IV) infusion over 60 minutes every 4 weeks.
- Evkeeza should be administered by a health professional only.
- The rate of infusion may be slowed, interrupted, or discontinued if the patient develops any signs of adverse reactions, including infusion-associated symptoms.
- Evkeeza can be administered without regard to lipoprotein apheresis.

4.3 Preparation

Evkeeza is supplied as single-use only and does not contain a preservative; aseptic technique must be observed.

- Visually inspect the drug product for cloudiness, discolouration, or particulate matter prior to administration.

- Evkeeza is a clear to slightly opalescent, colourless to pale yellow solution.
- Discard the vial if the solution is cloudy or discoloured or contains particulate matter.
- Do not shake the vial.
- Withdraw the required volume from the vial(s) of Evkeeza and transfer into an IV infusion bag containing sodium chloride 9 mg/mL (0.9%) or dextrose 50 mg/mL (5%) for infusion. Mix diluted solution by gentle inversion.
- The final concentration of the diluted solution should be between 0.5 mg/mL and 20 mg/mL.
- Do not freeze or shake the solution.
- Discard any unused portion left in the vial.
- Once infusion is prepared, the diluted solution should be administered immediately (see 11 STORAGE, STABILITY, AND DISPOSAL).

4.4 Administration

- If refrigerated, allow the solution to come to room temperature (up to 25°C) prior to administration.
- Evkeeza is for intravenous (IV) infusion only. It should be administered over 60 minutes through an IV line containing a sterile, inline or add-on 0.2 micron to 5 micron filter. Do not administer Evkeeza as an IV push or bolus.
- Do not mix other medicinal products with Evkeeza or administer concomitantly via the same infusion line.
- Once the infusion is prepared, the diluted solution should be administered immediately (see 11 STORAGE, STABILITY, AND DISPOSAL).
- The rate of infusion may be slowed, interrupted, or discontinued if the patient develops any signs of adverse reactions, including infusion-associated symptoms.
- Dispose of any unused medicinal product or waste material in accordance with local requirements.

4.5 Missed Dose

If a dose of Evkeeza is missed, administer as soon as possible. Thereafter, Evkeeza should be scheduled every 4 weeks from the date of the last dose.

5 OVERDOSAGE

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

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

6 DOSAGE FORMS, STRENGTHS, COMPOSITION, AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the

batch/lot number of the product supplied.

Table 1: Dosage Forms, Strengths, Composition, and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-Medicinal Ingredients
Intravenous infusion	150 mg/mL concentrate for solution for infusion	L-arginine hydrochloride L-histidine L-histidine monohydrochloride monohydrate L-proline Polysorbate 80 Water for injection

Evkeeza is a clear to slightly opalescent, colourless to pale yellow sterile solution supplied in 345 mg/2.3 mL (150 mg/mL) and 1,200 mg/8 mL (150 mg/mL) single-use vials with a pH of 6.0 and an osmolality of approximately 500 mmol/kg.

7 WARNINGS AND PRECAUTIONS

Immune

Hypersensitivity and Infusion Reactions

Hypersensitivity reactions, including anaphylaxis and infusion reactions (e.g., infusion site pruritus), have been reported with Evkeeza. If signs or symptoms of serious hypersensitivity reactions occur, discontinue treatment with Evkeeza, treat according to the standard of care, and monitor until signs and symptoms resolve (see 2 CONTRAINDICATIONS).

Reproductive Health: Female and Male Potential

Women of childbearing potential should use effective contraception during treatment with Evkeeza and for at least 5 months after the last dose of Evkeeza (see 7.1.1 Pregnant Women).

Fertility

No human data on the effect of Evkeeza on fertility are available.

Teratogenic Risk

Human IgG antibodies are known to cross the placenta barrier; therefore, Evkeeza has the potential to be transmitted from the mother to the developing fetus. Evkeeza may cause fetal harm when administered to a pregnant woman and it is not recommended during pregnancy and in women of childbearing potential not using effective contraception.

7.1 Special Populations

7.1.1 Pregnant Women

There is a limited amount of data from the use of Evkeeza in pregnant women.

Evkeeza may cause fetal harm when administered to a pregnant woman based on studies in animals demonstrating teratogenicity and maternal toxicity at maternal exposures below the human exposure at the maximum recommended human dose (MRHD) of 15 mg/kg every 4 weeks (see 16 NON-CLINICAL TOXICOLOGY). Human IgG antibodies are known to cross the placenta barrier; therefore, Evkeeza has the potential to be transmitted from the mother to the developing fetus. Animal studies have shown the presence of evinacumab in fetal sera, indicating that evinacumab crosses the placental barrier (see 16 NON-CLINICAL TOXICOLOGY).

Evkeeza is not recommended during pregnancy and in women of childbearing potential not using effective contraception. Before initiating treatment with Evkeeza in women of childbearing potential, determine pregnancy status. Women of childbearing potential should use effective contraception during treatment with Evkeeza and for at least 5 months after the last dose of Evkeeza.

7.1.2 Breastfeeding

There is no information regarding the presence of Evkeeza in human milk, the effects on the breastfed infant, or the effects on milk production. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for Evkeeza and any potential adverse effects on the breastfed infant from Evkeeza or from the underlying maternal condition. Human IgG is present in human milk.

7.1.3 Pediatrics

The safety and efficacy of Evkeeza in pediatric patients aged 5 years to 17 years have been established (see 8 ADVERSE REACTIONS and 14 CLINICAL TRIALS). The safety and efficacy of Evkeeza in pediatric patients aged less than 5 years have not been established.

7.1.4 Geriatrics

Clinical studies of Evkeeza did not include sufficient numbers of patients 65 years of age and older to determine whether the observed efficacy is different from younger adult patients. In placebo-controlled studies, 20 patients treated with Evkeeza were ≥ 65 years of age and 1 patient treated with Evkeeza was ≥ 75 years of age. No overall differences in safety were observed between these patients and younger patients.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

The most common adverse reactions to Evkeeza were nasopharyngitis (13.7% vs. 13.0% in placebo), influenza-like illness (7.7% vs. 5.6% in placebo), dizziness (6.0% vs. 0% in placebo), back pain (5.1% vs.

3.7% in placebo), and nausea (5.1% vs. 1.9% in placebo). Fatigue (15%) was identified as an adverse reaction to Evkeeza for pediatric patients aged ≥ 5 to 11 years only.

Anaphylaxis was reported in 1 (0.9%) patient treated with Evkeeza. Infusion reactions (e.g., infusion site pruritus) were reported in 9 (7.7%) patients treated with Evkeeza and in 2 (3.7%) patients treated with placebo. Infusion reactions led to discontinuation of treatment in 2 (1.7%) patients treated with Evkeeza.

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials; therefore, 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 may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

8.2.1 Clinical Trial Adverse Reactions – Adult and Pediatric Patients (12 to 17 years old) with HoFH

Summary of the Safety Profile

Overall, 138 adult and pediatric (12 to 17 years old) patients with HoFH have been treated with an IV dose of Evkeeza in either placebo-controlled or ongoing open-label clinical trials. In these trials, 138 patients were treated with Evkeeza 15 mg/kg Q4W for at least 24 weeks, 120 patients were treated for at least 52 weeks, and 78 patients were treated for at least 104 weeks.

The safety data are based on pooled results from two, 24-week, randomized, double-blind, placebo controlled-trials. There was a total of 117 patients with HoFH and persistent hypercholesterolemia randomized (1 patient not dosed), of whom 81 patients received Evkeeza 15 mg/kg IV every 4 weeks and 35 patients received Evkeeza 5 mg/kg IV every 4 weeks. The age range was 12 to 76 years. Sixty-five (65) patients had HoFH.

Tabulated Summary of Adverse Reactions

Table 2 lists the incidence of adverse reactions reported in the pooled placebo-controlled clinical trials of Evkeeza therapy involving 117 patients. Adverse drug reactions are listed by frequency.

The placebo-controlled studies pool provides an integration of 24 weeks of data from the double-blind treatment phase of the Phase 3 study in patients with HoFH (Study R1500-CL-1629) and the Phase 2 study in patients with persistent hypercholesterolemia (Study R1500-CL-1643).

Table 2 : Adverse Drug Reactions in HoFH Patients Treated with Evkeeza in Placebo-Controlled Trials (All Treatment-Emergent Adverse Events Reported with a ≥ 3% Frequency in the All Evkeeza IV Doses Group and at a ≥ 1% Higher Frequency than in the Placebo IV Q4W Group)

System Order Class Preferred Term	All Evkeeza IV Doses[a] n = 117 (%)	Placebo IV Q4W n = 54 (%)
Gastrointestinal Disorders		
Nausea	5	2
Abdominal pain	3	2
Constipation	3	0
General Disorders and Administration Site Conditions		
Influenza like illness	8	6
Asthenia	3	0
Infusion site pruritus	2	0
Immune System Disorders		
Anaphylaxis	1	0
Infections and Infestations		
Nasopharyngitis	14	13
Upper respiratory tract infection	3	0
Musculoskeletal and Connective Tissue Disorders		
Back pain	5	4
Pain in extremity	5	0
Nervous System Disorders		
Dizziness	6	0
Respiratory, Thoracic, and Mediastinal Disorders		
Rhinorrhea	3	0

IV = intravenous; Q4W = every 4 weeks

[a] All Evkeeza intravenous doses include 5 mg/kg IV Q4W data from Study R1500-CL-1643 plus 15 mg/kg IV Q4W from the double-blind treatment period of both Study R1500-CL-1643 and Study R1500-CL-1629.

The safety profile observed in 14 adolescent patients with HoFH aged 12 to 17 years treated with Evkeeza 15 mg/kg IV every 4 weeks was consistent with the safety profile of adult patients with HoFH.

Description of Selected Adverse Reactions

Hypersensitivity Reactions

Anaphylaxis was reported in 1 (0.9%) patient treated with Evkeeza.

Infusion Reactions

Infusion reactions (infusion site pruritus, pyrexia, muscular weakness, nausea, and nasal congestion) were reported in 9 (7.7%) patients treated with Evkeeza and in 2 (3.7%) patients treated with placebo. Infusion reactions led to discontinuation of treatment in 2 (1.7%) patients treated with Evkeeza.

8.2.2 Clinical Trial Adverse Reactions – Pediatric Patients (> 5 to 11 Years Old) with HoFH

The safety of Evkeeza was assessed in 20 pediatric patients (≥ 5 to 11 years of age) with HoFH in an open-label trial with a median treatment duration of 50 weeks (see 14 CLINICAL TRIALS). The safety profile of Evkeeza observed in these patients was consistent with the safety profile observed in adults and adolescent patients aged 12 years and older, with the additional adverse reaction of fatigue. Fatigue was reported in 3 (15%) pediatric patients.

8.3 Less Common Clinical Trial Adverse Reactions

Transient, mild to moderate decreases in diastolic blood pressure and increases in heart rate occurred in clinical trials during Evkeeza infusion but did not require intervention and resolved post-infusion.

8.3.1 Less Common Clinical Trial Adverse Reactions – Pediatrics

Not applicable.

8.5 Post-Market Adverse Reactions

No new adverse drug reactions or adverse reactions have been identified during post-marketing experience.

9 DRUG INTERACTIONS

9.2 Drug Interactions Overview

Drug interaction studies have not been conducted with Evkeeza. No drug-drug interaction mechanisms between Evkeeza and other lipid-lowering medications are known. In the clinical trial, the concentrations of statins (atorvastatin, rosuvastatin, simvastatin) were not meaningfully altered in patients taking statins prior to and following administration of Evkeeza. Concentrations of Evkeeza were comparable in patients with HoFH taking or not taking background lipid-lowering therapy.

9.3 Drug-Behavioural Interactions

Interactions with behaviour have not been established.

9.4 Drug-Drug Interactions

Interactions with other drugs have not been established.

9.5 Drug-Food Interactions

Interactions with food have not been established.

9.6 Drug-Herb Interactions

Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

Interactions with drug-laboratory products have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

Evinacumab is a recombinant human monoclonal antibody, which specifically binds to and inhibits ANGPTL3. ANGPTL3 is a member of the angiopoietin-like protein family that is expressed primarily in the liver and plays a prominent role in the regulation of lipid metabolism by inhibiting lipoprotein lipase (LPL) and endothelial lipase (EL). Evinacumab inhibition of ANGPTL3 leads to reduction in LDL-C, high-density lipoprotein cholesterol (HDL-C), and triglyceride (TG) concentrations. Evinacumab reduces LDL-C independent of the presence of the LDL receptor (LDL-R) by promoting very low-density lipoprotein (VLDL) processing and clearance upstream of LDL formation. Evinacumab blockade of ANGPTL3 lowers TG and HDLC by rescuing LPL and EL activities, respectively.

10.2 Pharmacodynamics

Administration of evinacumab in HoFH patients resulted in reductions in LDL-C, TC, HDL-C, apolipoprotein B, and TG.

10.3 Pharmacokinetics

Absorption

Based on population pharmacokinetic (PK) modelling, the end of infusion at steady-state C_{max} is 718 ± 183 mg/L in adult HoFH patients following a dose of 15 mg/kg every 4 weeks. Steady-state is reached after 4 doses and the accumulation ratio is 2 based on AUC. Mean steady-state C_{trough} is 266 ± 120 mg/L in adult HoFH patients. Due to non-linear clearance, a slightly greater than dose proportional increase was observed, with a 4.3-fold increase in area under the concentration-time curve at steady-state ($AUC_{tau.ss}$) for a 3-fold increase in dose from 5 mg/kg to 15 mg/kg IV every 4 weeks.

Table 3: Summary of Population PK Model-Derived Empirical Bayes Estimates and Post-hoc Exposure Predictions for Evinacumab in Children (age 5 to 11 years), Adolescents (age 12 to 17 years), and Adults (≥ 18 years) with HoFH Receiving Evinacumab 15 mg/kg IV Q4W

PK Parameter	Age Group	N	Mean (SD)	Median (5^{th}, 95^{th})
Linear CL (L/day)	Children	20	0.066 (0.025)	0.057 (0.038, 0.098)
	Adolescents	3	0.082 (0.006)	0.079 (0.078, 0.087)
	Adults	84	0.094 (0.038)	0.086 (0.051, 0.156)
V_{ss} (L)	Children	20	3.83 (0.993)	3.73 (2.39, 5.02)
	Adolescents	3	3.54 (1.38)	3.99 (2.19, 4.58)
	Adults	84	4.71 (1.22)	4.42 (3.24, 7.33)
$C_{trough,ss}$ (mg/L)	Children	20	174 (74.1)	185 (44.7, 276)
	Adolescents	3	182 (81.5)	138 (132, 262)
	Adults	84	266 (120)	234 (115, 508)
$C_{max,ss}$ (mg/L)	Children	20	444 (111)	470 (285, 587)
	Adolescents	3	635 (179)	668 (464, 782)
	Adults	84	718 (183)	691 (473, 1031)
$AUC_{tau,ss}$ (mg×day/L)	Children	20	7187 (2419)	7584 (3140, 10160)
	Adolescents	3	8611 (2431)	8515 (6458, 10831)
	Adults	84	11222 (3887)	10546 (6568, 18749)

$AUC_{tau,ss}$ = area under the concentration time curve for a dosing interval (tau) at steady state; CL = Clearance; $C_{max,ss}$ = maximum concentration at steady state; $C_{trough,ss}$ = minimum concentration at steady state; HoFH = homozygous familial hypercholesterolemia; IV = intravenous; N = number of patients; PK = pharmacokinetic; SD = standard deviation; V_{ss} = steady state volume of distribution; Q4W = every 4 weeks

Distribution

The total steady-state volume of distribution estimated by population PK analysis was approximately 4.7 L in adult patients.

Metabolism

Specific metabolism studies were not conducted because evinacumab is a protein. As a human monoclonal IgG4 antibody, evinacumab is expected to be degraded into small peptides and amino acids via catabolic pathways in the same manner as endogenous IgG.

Elimination

Evinacumab elimination is mediated by parallel linear and nonlinear pathways. At higher concentrations, evinacumab elimination is primarily through a non-saturable proteolytic pathway, while at lower concentrations, the non-linear saturable ANGPTL3 target mediated elimination predominates. Elimination half-life is a function of evinacumab concentrations in serum and is not a constant.

Following cessation of dosing once steady-state was reached, the population PK predicted median time for evinacumab concentrations to decrease below the lower limit of assay detection (78 ng/mL) is approximately 20 weeks.

Special Populations and Conditions

A population PK analysis conducted on data from 183 healthy subjects and 107 patients with HoFH, suggests that the following factors have no clinically significant effect on the exposure of evinacumab: age (5 to 75 years), gender, body weight (20 to 152 kg), or race (White, Asian, Black, and Other) and no dose adjustment is required based on these demographics. Apheresis did not appear to substantially influence the pharmacokinetics of evinacumab.

Pediatrics: There were 3 patients aged 12 to 17 years with HoFH receiving evinacumab at 15 mg/kg IV every 4 weeks. Steady-state C_{max} and C_{trough} trough concentrations were generally within the range observed in adult patients based on population PK analysis (see Table 3).

For the 20 patients aged ≥ 5 to 11 years with HoFH receiving evinacumab at 15 mg/kg IV every 4 weeks, steady-state C_{max} and C_{trough} concentrations were approximately 35% lower than those predicted in adult patients based on population PK analysis (see Table 3).

The pharmacokinetics of evinacumab in pediatric patients less than 5 years of age with HoFH have not been established. Health Canada has not authorized an indication for use in patients < 5 years of age.

Hepatic Insufficiency: No data are available in patients with hepatic impairment.

Renal Insufficiency: Observed trough concentrations at steady state were comparable between patients with mild or moderate renal impairment and patients with normal renal function. No data are available in patients with severe renal impairment.

11 STORAGE, STABILITY, AND DISPOSAL

Storage

Unopened Vial

- Store in a refrigerator (2°C to 8°C).
- Store in the original carton to protect from light.
- Do not freeze.
- Do not shake.

After opening

Once opened, the medicinal product should be diluted and infused immediately.

After dilution

If the diluted solution is not administered immediately, it may be stored:

- under refrigeration at 2°C to 8°C for no more than 24 hours from the time of infusion preparation to the end of the infusion

or

- at room temperature up to 25°C for no more than 6 hours from the time of infusion preparation to the end of the infusion

Disposal

Dispose of any unused medicinal product or waste material in accordance with local requirements.

12 SPECIAL HANDLING INSTRUCTIONS

Not applicable.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Evinacumab for injection

Chemical name: Immunoglobulin G4, anti-(human protein angptl3 (angiopoietin-like 3)) (human monoclonal REGN1500 heavy chain), disulfide with human monoclonal REGN1500 light chain, dimer.

Molecular formula and molecular mass: Based on the primary structure (in the absence of N-linked glycosylation), evinacumab possesses a molecular weight of 146.08 kDa ($C_{6480}H_{9992}N_{1716}O_{2042}S_{46}$), taking into account the formation of 16 disulfide bonds. The complementarity-determining regions (CDRs) within the heavy and light chain variable domains combine to form the binding sites of evinacumab to its target, which is angiopoietin-like3 (ANGPTL3).

Evinacumab is a recombinant human monoclonal antibody produced by recombinant DNA technology in Chinese hamster ovary (CHO) cell suspension culture. Evinacumab is purified to produce a final concentrated pool; excipients are added to the concentrated evinacumab pool to produce formulated drug substance (FDS).

Product Characteristics

Evinacumab concentrate for solution for infusion is a clear to slightly opalescent, colourless to pale yellow liquid that is essentially free from visible particles. Evkeeza, the evinacumab drug product (DP), is an aqueous buffered solution nominally containing 150 mg/mL of evinacumab, 70 mM L-arginine-HCl, 10 mM L-histidine, 3% (w/v) L-proline, and 0.1% (w/v) polysorbate 80. There are two DP presentations: a 345 mg vial (2.7 mL fill volume with a 2.3 mL withdrawable volume in a 3 mL glass vial) and a 1,200 mg vial (9.0 mL fill volume with an 8.0 mL withdrawable volume in a 20 mL glass vial).

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Homozygous Familial Hypercholesterolemia

Table 4: Summary of Patient Demographics for Clinical Trials in Homozygous Familial Hypercholesterolemia (HoFH)

Study No.	Study Design	Dosage, Route of Administration, and Duration	Patients (N)	Age (Range)	Sex
Study R1500-CL-1629 (ELIPSE-HoFH)	Multicentre, double-blind, randomized, placebo-controlled	15 mg/kg, intravenously every 4 weeks, 24 weeks	43 (2 adolescents)	35 patients were ≥ 12 years to < 65 years; 8 patients were ≥ 65 years	19 Males; 24 Females
		placebo	22		
		24-week open-label treatment period	65		
Study R1500-CL-1719 (ELIPSE-OLE)	Ongoing multicentre, open-label extension study	15 mg/kg, intravenously every 4 weeks, 24 weeks	116[a] (14 adolescents)	≥ 12 years of age	59 Males ; 57 Females (adolescents : 9 Males ; 5 Females)
Study R1500-CL-17100	Multicentre, three-part, single-arm, open-label	Part A: single dose; 15 mg/kg intravenously	Part A: 6	≥ 5 to 11 years of age	8 Males; 12 Females
		Part B: 15 mg/kg intravenously every 4 weeks	Part B: 14		
		Part C[b]: 15 mg/kg intravenously every 4 weeks	Part C: 20		

[a] Indicates the total number of patients enrolled as of the data cut-off date of 25 April 2022.

[b] Part C was an extension study from Part A and Part B evaluating the long-term safety in 20 pediatric patients with HoFH. It consists of a 48-week treatment period and a 24-week follow-up period (on-going). Patients in Part C entered directly from Part A or Part B.

Study R1500-CL-1629 (ELIPSE-HoFH)

This was a multicentre, double-blind, randomized, placebo-controlled trial evaluating the efficacy and safety of Evkeeza compared to placebo in 65 patients with HoFH. The trial consisted of a 24-week double-blind treatment period and a 24-week open-label treatment period. In the double-blind treatment period, 43 patients were randomized to receive Evkeeza 15 mg/kg IV every 4 weeks and 22 patients to receive placebo. Patients were on a background of other lipid lowering therapies (e.g., a

combination of statins, ezetimibe, PCSK9 inhibitor antibodies, lomitapide, and/or lipoprotein apheresis). The diagnosis of HoFH was determined by genetic testing or by the presence of the following clinical criteria: history of an untreated total cholesterol (TC) > 12.93 mmol/L (500 mg/dL) together with either xanthoma before 10 years of age or evidence of TC > 6.47 mmol/L (250 mg/dL) in both parents. Patients regardless of mutation status were included in the trial. A total of 51% of patients included in the study had either limited LDL receptor function, defined by < 15% receptor function by in vitro assays, or minimal to no LDL-R function predicted by mutation analysis.

The mean LDL-C at baseline was 6.61 mmol/L (255.1 mg/dL). At baseline, 94% of patients were on statins, 75% on ezetimibe, 77% on a PCSK9 inhibitor antibody, 22% on lomitapide, and 34% were receiving lipoprotein apheresis. The mean age at baseline was 42 years (range 12 to 75) with 12% ≥ 65 years old; 54% women, 74% White, 15% Asian, 3% Black and 8% Other or not reported.

The primary efficacy endpoint was percent change in LDL-C from baseline to Week 24. Key secondary endpoints included the absolute change in LDL-C from baseline to Week 24, and the percent changes in ApoB, non-HDL-C, and TC from baseline to Week 24. For efficacy results, see Table 5. Other endpoints included the percent changes in triglyceride (TG) and high-density lipoprotein (HDL) from baseline to Week 24.

Table 5: Effect of Evkeeza on Lipid Parameters in Patients with HoFH in Study R1500-CL-1629 (ELIPSE-HoFH)

	Baseline (mean), mmol/L (mg/dL) (N = 65)	LS Mean Percent Change or Change from Baseline at Week 24		Difference from Placebo (95% CI)	P-value
		Evkeeza (N = 43)	Placebo (N = 22)		
LDL—C (percent change)	6.6 (255.1)	-47%	+1.9%	-49% (-65 to -33)	< 0.0001
LDL-C (absolute change) (mmol/L) (mg/dL)	6.6 (255.1)	-3.5 (-134.7)	-0.1 (-2.6)	-132.1 (-175.3 to -88.9) [-3.4 (-4.5 to -2.3)]	< 0.0001
ApoB (g/L)	171.4 (1.7)	-41%	-4.5%	-37% (-49 to -25)	< 0.0001
Non HDL—C	7.2 (277.8)	-50%	+2.0%	-52% (-65 to -39)	< 0.0001
TC	8.3 (322.3)	-47%	+1.0%	-48% (-59 to -38)	< 0.0001

ApoB = apolipoprotein B; CI = confidence interval; HDL-C = high-density lipoprotein cholesterol; HoFH = homozygous familial hypercholesterolemia, ITT = intent-to-treat, LDL-C = low-density lipoprotein cholesterol; LS = least squares; N = number of randomized patients; TC = total cholesterol

After the double-blind treatment period, 64 of the 65 randomized patients who entered the open-label treatment period received Evkeeza (15 mg/kg IV every 4 weeks). Of the patients with baseline and post-baseline LDL-C values, the mean percent change in calculated LDL-C from baseline to Week 48 ranged from -43% to -56% (n = 58).

Study R1500-CL-1719 (ELIPSE-OLE)

In an ongoing multicentre, open-label extension study in 116 patients with HoFH, data available from 86 patients at 24 weeks of exposure following Evkeeza treatment 15 mg/kg IV every 4 weeks as an adjunct to other lipid lowering therapies (a combination of statins, ezetimibe, a PCSK9 inhibitor antibody and/or lomitapide) showed a 44% decrease in calculated LDL-C from baseline after 24 weeks (n = 86).

Patients who entered after completing Study R1500-CL-1629 (ELIPSE-HoFH) showed a 50% decrease in LDL-C compared to baseline after 24 weeks (n = 60), 44% at 48 weeks (n = 56), and 40% at 96 weeks (n = 48). Patients were included in the trial regardless of mutation status.

Pediatric Patients (12 to 17 years of age) with HoFH

In Study R1500-CL-1629 (ELIPSE-HoFH), 1 adolescent patient received 15 mg/kg IV of Evkeeza every 4 weeks and 1 adolescent patient received placebo, as an adjunct to other lipid-lowering therapies (e.g., a combination of statins, ezetimibe, a PCSK9 inhibitor antibody, and/or lipoprotein apheresis). At

Week 24, the percent change from baseline in calculated LDL-C with Evkeeza was -73% (n = 1) and was +60% with placebo (n = 1).

In Study R1500-CL-1719 (ELIPSE-OLE), 14 adolescent patients received 15 mg/kg IV of Evkeeza every 4 weeks as an adjunct to other lipid-lowering therapies (e.g., a combination of statins, ezetimibe, a PCSK9 inhibitor antibody, and/or lipoprotein apheresis). Two patients entered after completing the R1500-CL-1629 (ELIPSE-HoFH) study and 12 patients were Evkeeza-naïve. The mean baseline LDL-C in these adolescent patients was 7.88 mmol/L (300.4 mg/dL). The mean age was 14.4 years (range: 12 to 17 years), with 64% males and 36% females. At baseline, all patients were on a statin, 71% on ezetimibe, 43% on PCSK9 inhibitor, and 64% were receiving lipoprotein apheresis. Of the patients with a baseline and a post-baseline LDL-C value at Week 24, the mean percent change compared to baseline in calculated LDL-C with Evkeeza was -55% (n = 12).

Pediatric Patients (5 to 11 years of age) with HoFH

Study R1500-CL-17100 was a multicentre, three-part, single-arm, open-label study evaluating the efficacy, safety, and tolerability of Evkeeza in pediatric patients (≥ 5 to 11 years of age) with HoFH. The study included three parts: Part A, Part B, and Part C. Part A was a single-dose, open-label study to assess the safety, pharmacokinetics, and pharmacodynamics of Evkeeza 15 mg/kg IV in 6 patients with HoFH followed by a 16-week observational period to determine the dose for the rest of the study. Part B was a single-arm, 24-week, open-label treatment period evaluating the efficacy and safety of Evkeeza 15 mg/kg IV every 4 weeks in 14 patients with HoFH. Part C was an extension study from Part A and Part B evaluating the long-term safety of Evkeeza 15 mg/kg IV every 4 weeks in 20 patients with HoFH. It consisted of a 48-week treatment period and a 24-week follow-up period (on-going). Patients in Part C entered directly from Part A or Part B.

Patients were on any combination of lipid-lowering therapies, including maximally tolerated statins, ezetimibe, lomitapide, and/or lipoprotein apheresis. The diagnosis of HoFH was determined by genetic testing or by the presence of the following clinical criteria: history of an untreated total cholesterol (TC) > 13 mmol/L (> 500 mg/dL) and TG < 7.8 mmol/L (< 300 mg/dL) AND either tendinous xanthoma before 10 years of age or evidence of TC >6.47 mmol/L (> 250 mg/dL) in both parents; LDL-C > 3.36 mmol/L (> 130 mg/dL); body weight ≥ 15 kg. At baseline, 90% of patients were on statins, 95% on ezetimibe and 60% were receiving lipoprotein apheresis.

The mean age at baseline was 9.0 years (range ≥ 5 to < 12); 40% males and 60% females; 70% White, 5% Black, 10% Asian, 5% American Indian or Alaska Native, and 10% Other. Mean body weight was 37.9 kg, and body mass index (BMI) was 18.8 kg/m^2. Overall, for patients in Part A and Part B, the mean LDL-C at baseline was 7.8 mmol/L (301.9 mg/dL).

In Part B, the primary efficacy endpoint was percent change in calculated LDL-C from baseline to Week 24. At Week 24, the mean percent change in calculated LDL-C from baseline was −48% (95% confidence interval: −69% to −28%)(n = 14).

14.3 Immunogenicity

Immunogenicity data are highly dependent on the sensitivity and specificity of the assay as well as other factors. Additionally, the observed incidence of antibody positivity in an assay may be influenced by several factors, including sample handling, timing of sample collection, concomitant medications, and

underlying disease. For these reasons, comparison of the incidence of antibodies to evinacumab with the incidence of antibodies to other products may be misleading. A low incidence of treatment-emergent anti-drug antibodies (ADA), which were generally low titer, were detected in evinacumab studies.

In the 24-week, placebo-controlled pool, no patients developed treatment-emergent antibodies to evinacumab.

In an open-label study in pediatric patients (≥ 5 to 11 years old), the incidence of treatment-emergent antibody was 5% (1 of 20 evinacumab-treated patients), which was low titer. In this patient, there were no clinically meaningful effects on safety, efficacy, or evinacumab concentrations.

In an open-label study in adults and adolescents (≥ 12 years of age), the incidence of treatment-emergent antibody was 1.7% (2/116 evinacumab-treated patients), which were low titer. In these patients, there were no clinically meaningful effects on safety, efficacy, or evinacumab concentrations.

15 MICROBIOLOGY

No microbiological information is required for this drug product.

16 NON-CLINICAL TOXICOLOGY

In all studies and species tested and following both intravenous and subcutaneous administration, evinacumab induced decreases in circulating triglyceride concentrations at most dose levels tested, including in pregnant and juvenile animals. Decreases in circulating total cholesterol, HDL cholesterol, and/or LDL cholesterol concentrations were also observed, depending on the species and study. These effects were consistent with the expected pharmacological activity of evinacumab in animals.

General Toxicology

Repeat-dose toxicity of evinacumab was assessed in a 13-week study in rats and a 26-week study in sexually mature cynomolgus monkeys. Animals were administered evinacumab by subcutaneous injection at doses of 10, 30, or 100 mg/kg body weight once weekly or by intravenous injection at a dose of 100 mg/kg body weight once weekly. There were no adverse findings at subcutaneous or intravenous doses up to 100 mg/kg body weight (no-observed-adverse-effect level [NOAEL]), including no effects on respiratory, central nervous system, and cardiovascular functions in cynomolgus monkeys. Exposures at the NOAELs for the intravenous route were 4.6-fold and 14.6-fold greater in rats and cynomolgus monkeys, respectively, than the human exposure at the MRHD of 15 mg/kg every 4 weeks, based on AUC.

Carcinogenicity

Carcinogenicity studies have not been conducted with evinacumab.

Genotoxicity

Genotoxicity studies have not been conducted with evinacumab.

Reproductive and Developmental Toxicity

In a stand-alone fertility study conducted in male rabbits, male animals were administered evinacumab at doses of 100 or 300 mg/kg body weight once every 5 days by intravenous injection from prior to mating, through mating, and post-mating (total of 16 doses). Corresponding exposures were 11.2-fold and 30.0-fold the human exposure at the MRHD of 15 mg/kg every 4 weeks based on AUC, respectively. Evinacumab administration did not impair male fertility and had no adverse effects on sperm parameters (sperm count, density, and motility) or on fetal development. However, an ADA response was observed in a few animals of each dose group, resulting in moribundity that required early euthanasia. Adverse kidney effects (mesangioproliferative glomerulonephritis and interstitial nephritis) were also observed at both doses in surviving males. Thus, while the NOAEL for effects on male fertility in rabbits was 300 mg/kg body weight (highest dose tested) by intravenous injection, the NOAEL for general toxicity in male rabbits could not be determined.

Surrogate markers of fertility were assessed in the 26-week repeat-dose toxicity study conducted in sexually mature cynomolgus monkeys described above. No adverse effects were observed on total sperm count, sperm density, sperm motility, sperm morphology, and estrous cyclicity. In addition, there were no adverse evinacumab-related anatomic pathology or histopathology findings in reproductive tissues.

Effects of evinacumab on development were assessed in the studies below. In all studies, maternal exposure at all doses during gestation and the lactation period were below the human exposure at the MRHD of 15 mg/kg body weight every 4 weeks.

Effects of evinacumab on embryo-fetal development were assessed in rabbits following maternal administration. Evinacumab was administered subcutaneously to pregnant rabbits at doses of 1, 5, 10, or 30 mg/kg body weight every 3 days during the period of organogenesis (gestation day [GD] 7 to 19). Evinacumab administration was associated with teratogenicity (fetal malformations) at doses ≥ 5 mg/kg body weight. Fetal malformations were observed in the head, brain, skull, and paws at high incidence rates. These malformations consisted of domed head correlating with dilation of the lateral and third ventricles of the brain, cleft palate correlating with incompletely ossified palates, and flexed paws. Other malformations consisted of small tongue, scoliosis, open eyelid, gastroschisis, protrusion of the liver and small intestines through abdominal opening, and various skeletal malformations involving the vertebrae and paws. Reductions in litter size and the number of live fetuses and increases in post-implantation loss and resorptions were also observed at doses ≥ 10 mg/kg body weight, and reduced fetal weight was observed at doses ≥ 5 mg/kg body weight. In addition, maternal toxicity (maternal death, abortion, and premature delivery, as well as clinical signs and weight loss) was observed at all doses. The NOAEL for maternal toxicity in rabbits could not be identified, and the NOAEL for embryo-fetal toxicity in rabbits was 1 mg/kg body weight every 3 days by subcutaneous injection.

Effects of evinacumab on embryo-fetal development were also assessed in rats. Evinacumab was administered subcutaneously to pregnant rats at doses of 5, 10, 30, or 100 mg/kg body weight every 3 days during the period of organogenesis (GD 6 to 18). There were no adverse effects on embryofetal development in rats. However, maternal toxicity was observed in rats at a dose of 100 mg/kg body weight and consisted of maternal death and abortion. The NOAEL for maternal toxicity in rats was 30 mg/kg body weight every 3 days by subcutaneous injection, while the NOAEL for embryo-fetal toxicity in rats was 100 mg/kg body weight every 3 days by subcutaneous injection (the highest dose tested).

In a combined female fertility and pre-and post-natal development study conducted in rats, female rats were administered evinacumab by subcutaneous injection at doses of 30 or 100 mg/kg body weight every 3 days from prior to mating, through mating, and throughout gestation and lactation. The F1 generation was not administered evinacumab. No maternal toxicity or adverse effects on fertility were observed in F0 females. There were also no adverse effects on post-natal development in offspring, including no adverse effects on neurobehavioural endpoints, sexual maturation, and reproduction. A pharmacological effect (decreases in blood triglyceride, total cholesterol, HDL cholesterol, and LDL concentrations) was observed in offspring at both dose levels, but was without adverse effects. Thus, the NOAEL for the effects of evinacumab on female fertility and pre- and post-natal development following maternal exposure in rats is 100 mg/kg body weight every 3 days (highest dose tested) by subcutaneous injection.

Evinacumab was detected in the sera of rabbit and rat fetuses and in rabbit offspring, indicating that evinacumab crosses the placental barrier and may be excreted in milk.

Juvenile Toxicity

Effects of evinacumab in juvenile animals following repeat dosing were assessed in juvenile rat and rabbit studies. Rats were administered evinacumab by subcutaneous injection at doses of 30 or 100 mg/kg body weight once weekly or by intravenous injection at a dose of 100 mg/kg body weight once weekly (corresponding exposures were approximately 1.2-fold, 4.5-fold, and 6.1-fold, respectively, the human pediatric exposures at the MRHD of 15 mg/kg every 4 weeks based on AUC). Rabbits were administered evinacumab by intravenous injection at doses of 30, 100, or 300 mg/kg body weight once every 5 days (corresponding exposures were approximately 3.1-fold, 13.0-fold, and 29.8-fold, respectively, the human pediatric exposures at the MRHD of 15 mg/kg every 4 weeks based on AUC). There were no adverse findings in rats, including on sexual maturation and neurobehavioural endpoints. However, in rabbits, an increase in mortalities was observed at 300 mg/kg body weight. No other adverse effects were observed in rabbits, including on sexual maturation, neurobehavioural endpoints, and reproduction.

PATIENT MEDICATION INFORMATION

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PrEVKEEZA®

Evinacumab for Injection Concentrate for Solution for Infusion

Read this carefully before you start taking Evkeeza 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 Evkeeza.

What is Evkeeza used for?

Evkeeza is used to treat adults and children aged 5 years and older with very high cholesterol caused by a condition called homozygous familial hypercholesterolaemia (HoFH). Evkeeza is used with a low-fat diet and other medicines to bring down cholesterol levels. Homozygous familial hypercholesterolaemia runs in families and it is usually passed down by both father and mother. People with this condition have extremely high levels of LDL-cholesterol ('bad cholesterol') from birth. Such high levels can lead to heart attacks, heart valve disease, or other problems at an early age.

How does Evkeeza work?

Evinacumab, the active substance in Evkeeza, attaches to a protein in the body called ANGPTL3 and blocks its effects. ANGPTL3 is involved in controlling cholesterol levels. When evinacumab blocks the effects of ANGPLT3, the level of LDL-cholesterol in the blood is reduced and problems caused by high LDL-cholesterol levels may also be reduced.

What are the ingredients in Evkeeza?

Medicinal ingredients: evinacumab

Non-medicinal ingredients: L-arginine hydrochloride, L-histidine, L-histidine monohydrochloride monohydrate, L-proline, polysorbate 80, and Water for Injection, USP

Evkeeza comes in the following dosage forms:

Concentrate for solution for infusion: 345 mg/2.3 mL (150 mg/mL) and 1,200 mg/8 mL (150 mg/mL). Evkeeza is supplied as one single-use vial per carton.

Do not use Evkeeza if:

- You are allergic to evinacumab or to any of the ingredients in this medicine.

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

- Allergic reactions (hypersensitivity), including a severe reaction known as anaphylaxis. Symptoms may include swelling of the lips, tongue, or throat that make it difficult to swallow or breathe, and may also include wheezing, feeling dizzy, or fainting. If you notice any of these symptoms, tell your healthcare professional right away.
- If you are pregnant, think you might be pregnant, or plan to become pregnant, ask your healthcare professional for advice before taking Evkeeza. Evkeeza may harm your unborn baby. Tell your healthcare professional if you become pregnant while using Evkeeza. **For people who are able to become pregnant:**
    - Your healthcare professional may do a pregnancy test before you start treatment with Evkeeza.
    - You should use an effective method of birth control during treatment and for at least 5 months after the last dose of Evkeeza. Talk to your healthcare professional about birth control methods that you can use during this time.
- If you are breastfeeding or plan to breastfeed, ask your healthcare professional for advice before you are given Evkeeza. It is not known if Evkeeza passes into your breast milk. You and your healthcare professional should decide if you will receive Evkeeza or breastfeed.

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

- Studies to test how Evkeeza interacts with other drugs have not been done.

How to take Evkeeza:

- Evkeeza will be given to you by a healthcare professional.
- Your healthcare professional will withdraw the required amount of Evkeeza from the vial and transfer it into an IV infusion bag. The IV bag contains either a salt solution equivalent to 9 mg/mL (0.9%) or sugar solution equivalent to 50 mg/mL (5%) for infusion. Diluted solution is then mixed by gentle inversion.
- The final concentration of the diluted solution should be between 0.5 mg/mL and 20 mg/mL.

Usual dose

- The usual dose for Evkeeza is 15 mg/kg administered at room temperature by intravenous (IV) infusion over 60 minutes every 4 weeks.
- If you miss any infusion appointments, call your healthcare professional as soon as possible to reschedule.
- Your healthcare professional may slow down your infusion rate, temporarily stop, or permanently stop treatment with Evkeeza if you have certain side effects.

- Your healthcare professional may prescribe other cholesterol-lowering medicines to use with Evkeeza. Use the other prescribed medicines exactly as your healthcare professional tells you to.

Overdose:

It is unlikely that you will receive too much Evkeeza as you will be closely monitored by healthcare professionals during your infusion. However, if you think you, or a person you are caring for, have taken too much Evkeeza, 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 of Evkeeza, call your healthcare professional as soon as possible to reschedule.

What are the possible side effects from using Evkeeza?

These are not all the possible side effects you may have when taking Evkeeza. If you experience any side effects not listed here, tell your healthcare professional.

- Abdominal pain
- Back pain
- Constipation
- Decreased energy
- Dizziness
- Flu symptoms
- Itchiness at the site of the injection
- Nausea
- Pain in legs or arms
- Runny nose
- Fatigue (for patients aged 5-11 years old)
- Sore throat or sinus infection

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	
UNCOMMON			
• Anaphylaxis (symptoms may include swelling of the lips, tongue, or throat that make it difficult to swallow or breathe, and may also include wheezing, feeling dizzy, or fainting)			X

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

The storage details are as follows:

Unopened Vial

- Store the Evkeeza vial in a refrigerator (2°C to 8°C).
- Store in the original carton to protect from light.
- Do not freeze.
- Do not shake.

After opening

Once opened, Evkeeza should be diluted and used immediately.

After dilution
If the diluted solution is not used immediately, it may be stored:

- in the refrigerator at 2°C to 8°C for no more than 24 hours from the time of infusion preparation to the end of the infusion

or

- at room temperature up to 25°C for no more than 6 hours from the time of infusion preparation to the end of the infusion

Keep out of reach and sight of children.

If you want more information about Evkeeza:

- 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://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html), the manufacturer's website (https://www.ultragenyx.com), or by calling 1-833-388-5872.

This leaflet was prepared by Ultragenyx Pharmaceutical Inc.

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