1. NAME OF THE MEDICINAL PRODUCT

Evkeeza 150 mg/ml

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of concentrate for solution for infusion contains 150 mg of evinacumab.

One vial of 2.3 ml of concentrate contains 345 mg of evinacumab.
One vial of 8 ml of concentrate contains 1,200 mg of evinacumab.

Evinacumab is produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion (sterile concentrate)

Clear to slightly opalescent, colourless to pale yellow sterile solution with a pH of 6.0 and an osmolality of approximately 500 mmol/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Evkeeza is indicated as an adjunct to diet and other low-density lipoprotein-cholesterol (LDL-C) lowering therapies for the treatment of adult and adolescent patients aged 12 years and older with homozygous familial hypercholesterolaemia (HoFH).

4.2 Posology and method of administration

Before treatment initiation of evinacumab the patient should be on an optimal LDL-C lowering regimen.

Treatment with evinacumab should be initiated and monitored by a physician experienced in the treatment of lipid disorders.

Posology

The recommended dose is 15 mg/kg administered by intravenous infusion over 60 minutes once monthly (every 4 weeks).

If a dose is missed, it should be administered as soon as possible. Thereafter, treatment with evinacumab should be scheduled monthly from the date of the last dose.

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.

Elderly
No dosage adjustment is required for elderly patients (see sections 5.1 and 5.2).

Renal impairment
No dose adjustment is required in patients with renal impairment (see section 5.2).

Hepatic impairment
No dose adjustment is required in patients with hepatic impairment (see section 5.2).

Paediatric population
No dose adjustment is required for paediatric patients aged 12 to 17 years (see sections 4.8, 5.1 and 5.2). Evkeeza is not indicated in children aged less than 12 years.

Method of administration

Evkeeza is for intravenous infusion use only.

Administration
- If refrigerated, allow the solution to come to room temperature (up to 25 ºC) prior to administration.
- Evinacumab should be administered over 60 minutes by intravenous infusion through an intravenous line containing a sterile, in-line or add-on 0.2-micron to 5-micron filter. Do not administer evinacumab as an intravenous push or bolus.
- Do not mix other medicinal products with evinacumab or administer concomitantly via the same infusion line.

The rate of infusion may be slowed, interrupted, or discontinued if the patient develops any signs of adverse reactions, including infusion-associated symptoms.

For instructions on dilution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity and infusion reactions

Hypersensitivity reactions, including anaphylaxis, and infusion reactions have been reported with evinacumab (see section 4.8). If signs or symptoms of serious hypersensitivity or serious infusion reactions occur, discontinue treatment with evinacumab, treat according to the standard-of-care, and monitor until signs and symptoms resolve.

Excipients

This medicinal product contains 30 mg of proline in each ml. Proline may be harmful for patients with hyperprolinaemia type I or type II.

This medicinal product contains 1 mg of polysorbate 80 in each ml. Polysorbates may cause allergic reactions.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. No interacting mechanisms between evinacumab and other lipid-lowering medications have been observed.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should use effective contraception during treatment with evinacumab and for at least 5 months after the last dose of evinacumab.

Pregnancy

There is a limited amount of data from the use of evinacumab in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Human IgG antibodies are known to cross the placenta barrier; therefore, evinacumab has the potential to be transmitted from the mother to the developing foetus. Evinacumab may cause foetal harm when administered to a pregnant woman and it is not recommended during pregnancy and in women of childbearing potential not using effective contraception unless the expected benefit to the patient outweighs the potential risk to the foetus.

Breast-feeding

It is unknown whether evinacumab is excreted in human milk. Human IgGs are known to be excreted in breast milk during the first few days after birth, which decrease to low concentrations soon afterwards; consequently, a risk to the breast-fed infant cannot be excluded during this short period. Afterwards, Evkeeza could be used during breast-feeding if clinically needed.

Fertility

No human data on the effect of evinacumab on fertility are available. Animal studies do not indicate harmful effects with respect to male and female fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Evkeeza may have a minor influence on the ability to cycle, drive and use machines. Dizziness and asthenia may occur following administration of Evkeeza (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

The most frequently occurring adverse reactions are nasopharyngitis (13.7%), influenza like illness (7.7%), dizziness (6.0%), back pain (5.1%) and nausea (5.1%). The most serious adverse reaction is anaphylaxis (0.9%).

Tabulated list of adverse reactions

Table 1 lists the incidence of adverse reactions in the pooled controlled clinical trials of evinacumab therapy involving 117 patients with HoFH and persistent hypercholesterolaemia. Adverse reactions are listed by system organ class (SOC) and by frequency. Frequencies are defined as: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000); not known (cannot be estimated from available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 1: Adverse reactions

MedDRA System organ class	Preferred term	Frequency categories
Infections and infestations	Nasopharyngitis	Very Common
	Upper respiratory tract infection	Common
Immune system disorders	Anaphylaxis	Uncommon
Nervous system disorders	Dizziness	Common
Respiratory, thoracic and mediastinal disorders	Rhinorrhoea	Common
Gastrointestinal disorders	Nausea	Common
	Abdominal pain	Common
	Constipation	Common
Musculoskeletal and connective tissue disorders	Back pain	Common
	Pain in extremity	Common
General disorders and administration site conditions		
	Influenza like illness	Common
	Asthenia	Common
	Infusion related reaction	Common
	Infusion site reactions	Common

Description of selected adverse reactions

Hypersensitivity reactions
Anaphylaxis was reported in 1 (0.9%) patient treated with evinacumab (see section 4.4).

Infusion reactions
Infusion reactions (e.g., infusion site pruritus) were reported in 9 (7.7%) patients treated with evinacumab and in 2 (3.7%) patients treated with placebo.

Paediatric population

The safety profile observed in 13 adolescent patients with HoFH aged 12 to 17 years treated with evinacumab 15 mg/kg IV every 4 weeks was consistent with the safety profile of adult patients with HoFH.

Evkeeza is not indicated in children aged less than 12 years.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse reactions should be reported to the Ministry of Health according to the National Regulation by using an online form: https://sideeffects.health.gov.il/

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other lipid modifying agents, ATC code: C10AX17

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 role in the regulation of lipid metabolism by inhibiting lipoprotein lipase (LPL) and endothelial lipase (EL).

Evinacumab blockade of ANGPTL3 lowers TG and HDL-C by releasing LPL and EL activities from ANGPTL3 inhibition, respectively. Evinacumab reduces LDL-C independent of the presence of LDL receptor (LDLR) by promoting very low-density lipoprotein (VLDL) processing and VLDL remnants clearance upstream of LDL formation through EL-dependent mechanism.

Clinical efficacy and safety

Homozygous familial hypercholesterolaemia (HoFH)

Study ELIPSE-HoFH

This was a multicentre, double-blind, randomised, placebo-controlled trial evaluating the efficacy and safety of evinacumab 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 randomised to receive evinacumab 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. statins, ezetimibe, PCSK9 inhibitor antibodies, lomitapide, and lipoprotein apheresis). The diagnosis of HoFH was determined by genetic testing or by the presence of the following clinical criteria: history of an untreated TC > 500 mg/dl (13 mmol/l) together with either xanthoma before 10 years of age or evidence of TC > 250 mg/dl (6.47 mmol/l) in both parents. Patients regardless of mutation status were included in the trial. Patients were defined as having null/null or negative/negative variants if the variations resulted in little to no residual LDLR function; null/null variants were defined as having < 15% LDLR function based on in vitro assays and negative/negative variants were defined as having premature termination codons, splice site variations, frame shifts, insertion/deletions or copy number variations. In this trial, 32.3% (21 of 65) of patients had null/null variants and 18.5% (12 of 65) of patients had negative/negative variants.

The mean LDL-C at baseline was 255.1 mg/dl (6.61 mmol/l) and in the subset of patients with null/null variants was 311.5 mg/dl (8.07 mmol/l) and with negative/negative variants was 289.4 mg/dl (7.50 mmol/l). At baseline, 93.8% of patients were on statins, 75.4% on ezetimibe, 76.9% on a PCSK9 inhibitor antibodies, 21.5% on lomitapide, and 33.8% were receiving lipoprotein apheresis. The mean age at baseline was 42 years (range 12 to 75) with 12.3% ≥65 years old; 53.8% women, 73.8% White, 15.4% Asian, 3.1% Black and 7.7% Other or not reported.

The primary efficacy endpoint was percent change in LDL-C from baseline to Week 24. At Week 24, the LS mean treatment difference between evinacumab and placebo in mean percent change in LDL-C from baseline, was -49.0% (95% CI: -65.0% to -33.1%; p < 0.0001). For efficacy results see Table 2.

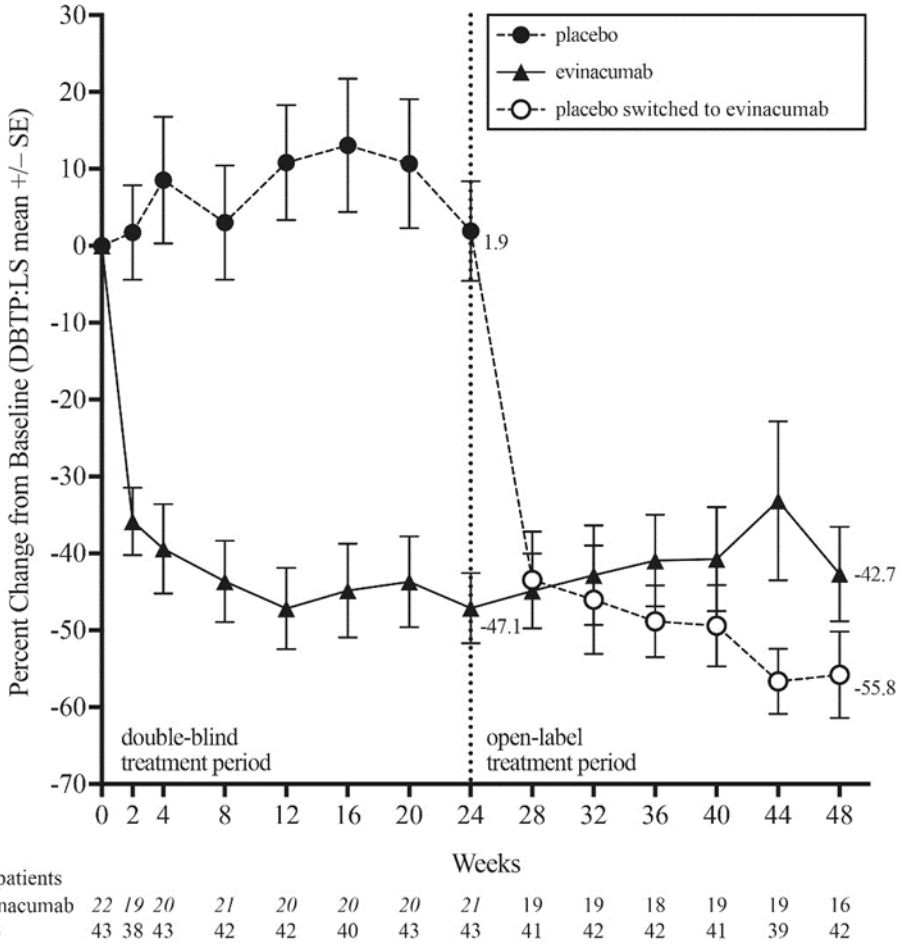
Table 2: Effect of evinacumab on lipid parameters in patients with HoFH in study ELIPSE-HoFH

	Baseline (mean), mmol/l (N = 65)	LS mean percent change or change from baseline at Week 24		Difference from placebo (95% CI)	P-value
		evinacumab (N = 43)	placebo (N = 22)		
LDL-C (percent change)	6.6	-47.1%	+1.9%	-49% (-65.0 to -33.1)	< 0.0001
LDL-C (absolute change) (mmol/l)	6.6	-3.5	-0.1	-3.4 (-4.5 to -2.3)	< 0.0001
ApoB (g/l)	1.7	-41.4%	-4.5%	-36.9% (-48.6 to -25.2)	< 0.0001
Non-HDL-C	7.2	-49.7%	+2.0%	-51.7% (-64.8 to -38.5)	< 0.0001
TC	8.3	-47.4%	+1.0%	-48.4% (-58.7 to -38.1)	< 0.0001
TG	1.4	-55.0%	-4.6%	-50.4% (-65.6 to -35.2)	< 0.0001[a]
HDL-C[b]	1.2	-29.6%	+0.8%	-	-

[a]nominal p-value since TG is not a key secondary endpoint
[b]Mean percent change at Week 24 results are presented based on the actual treatment received in safety population (evinacumab, n=44; placebo, n=20); there is no formal statistical testing in safety population

After the double-blind treatment period, 64 of the 65 randomised patients who entered the open-label treatment period received evinacumab. The mean percent change in LDL-C from baseline to Week 48 ranged from -42.7% to -55.8%. Figure 1 shows the LDL-C mean percent change from baseline for the double-blind and observed mean percent change for the open-label treatment periods across patients who were on evinacumab or placebo during the double-blind treatment period.

Figure 1: Calculated LDL-C LS mean percent change from baseline over time through Week 24, and observed mean percent change from Week 28 through Week 48 in study ELIPSE-HoFH



At Week 24, the observed reduction in LDL-C with evinacumab was similar across predefined subgroups, including age, sex, null/null or negative/negative variants, concomitant treatment with lipoprotein apheresis, and concomitant background lipid-lowering medications (statins, ezetimibe, PCSK9 inhibitor antibodies, and lomitapide). The effect of evinacumab on cardiovascular morbidity and mortality has not been determined.

Study ELIPSE-OLE

In a multicentre, open-label extension study 81 patients with HoFH showed a 43% decrease in LDL-C at 24 weeks of exposure following evinacumab treatment 15 mg/kg IV every 4 weeks on top of other lipid-lowering therapies (e.g., statins, ezetimibe, PCSK9 inhibitor antibodies, lomitapide, and lipoprotein apheresis). Patients regardless of mutation status were included in the trial, including patients with null/null or negative/negative variants.

Paediatric population

In ELIPSE-HoFH, 1 adolescent patient received 15 mg/kg IV of evinacumab every 4 weeks and 1 adolescent patient received placebo, as an adjunct to other lipid-lowering therapies (e.g., statins, ezetimibe, PCSK9 inhibitor antibodies and lipoprotein apheresis). Both adolescent patients had null/null variants in the LDLR. At Week 24, the percent change in LDL-C with evinacumab was - 73.3% and with placebo +60%.

In ELIPSE-OLE, 13 adolescent patients received 15 mg/kg IV of evinacumab every 4 weeks as an adjunct to other lipid-lowering therapies (e.g., statins, ezetimibe, PCSK9 inhibitor antibodies and lipoprotein apheresis). Two patients entered after completing the ELIPSE-HoFH study and 11 patients were evinacumab-naïve. The mean baseline LDL-C in these adolescent patients was 310.3 mg/dl (8.04 mmol). The mean age was 14 years (range: 12 to 17 years), with 61.5% males and 38.5% females. At baseline, all patients were on a statin, 69.2% on ezetimibe, 46.2% on PCSK9 inhibitor, and 61.5% were receiving lipoprotein apheresis. Four (30.8%) patients had null/null variants and 4 (30.8%) patients had negative/negative variants for LDLR mutations. At Week 24, the percent change in LDL-C with evinacumab was -52.4% (n=9).

5.2 Pharmacokinetic properties

Absorption

Evinacumab is administered intravenously to patients with HoFH. Based on population PK modelling, at the end of infusion at steady-state, C_{max} is 689 ± 157 mg/l following a dose of 15 mg/kg every 4 weeks. The accumulation ratio is 2. Mean steady-state trough concentration is 241 ± 96.5 mg/l.

Distribution

The total volume of distribution estimated by population PK analysis in a typical individual weighing 74.1 kg was approximately 4.8 L and scales with body weight, indicating that evinacumab is distributed primarily in the vascular system.

Biotransformation

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.

After the last steady-state dose of 15 mg/kg IV every 4 weeks, the median time for evinacumab concentrations to decrease below the lower limit of detection (78 ng/ml) is 19 weeks.

Linearity/non-linearity

Due to nonlinear 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.

Pharmacokinetic/pharmacodynamic relationship(s)

The pharmacodynamic effect of evinacumab in lowering LDL-C is indirect and mediated through the binding to ANGPTL3. Concentration of total ANGPTL3 increases from baseline upon administration of evinacumab and the increases plateau when target saturation is approached. When target is saturated, further increase in evinacumab concentrations is not expected to result in a further LDL-C reduction.

Special populations

A population PK analysis conducted on data from 183 healthy subjects and 95 patients with HoFH, suggests that the following factors have no clinically significant effect on the exposure of evinacumab: age (12 to 75 years), gender, body weight (42 to 152 kg), race. Apheresis did not appear to substantially influence the pharmacokinetics of evinacumab.

Paediatric population
There were 2 patients aged 12 to 17 years with HoFH receiving evinacumab at 15 mg/kg IV every 4 weeks, steady-state trough and end-of-infusion concentrations were within the range observed in adult patients.

Evkeeza is not indicated in children aged less than 12.

Renal impairment
Evinacumab is not expected to undergo significant renal elimination. 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.

Hepatic impairment
Evinacumab is not expected to undergo significant hepatic elimination. No data are available in patients with hepatic impairment.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology and repeated dose toxicity.

Carcinogenicity and mutagenicity

Carcinogenicity and genotoxicity studies have not been conducted with evinacumab. Monoclonal antibodies are not expected to alter DNA or chromosomes.

Reproductive toxicology

No effects on surrogate markers of fertility in male and female reproductive organs were observed in a 6-month chronic toxicology study with sexually mature cynomolgus monkeys. In animal reproduction studies, evinacumab was administered subcutaneously to pregnant rabbits every 3 days from gestation day 7 until gestation day 19 during organogenesis. Maternal toxicity (premature neonatal death, foetal loss and/or premature delivery) was observed at all doses and foetal findings (soft tissues and skeletal malformations) were observed at all but the lowest dose (1 mg/kg). Mean systemic exposure measured during the gestation period in rabbits was below that measured at maximum recommended human dose (MRHD) of 15 mg/kg every 4 weeks. Because the lipid profile of rabbits differs significantly from that of humans, particularly during pregnancy, the clinical relevance of these results is uncertain.

There were no effects on embryo-foetal development when rats were subcutaneously administered evinacumab every 3 days from gestation day 6 to gestation day 18 during organogenesis. Mean systemic exposure measured during the gestation period in rats was below that measured at MRHD of 15 mg/kg every 4 weeks.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Water for injections
L-Proline
L-Arginine hydrochloride
L-Histidine hydrochloride monohydrate
Polysorbate 80
L-Histidine

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened vial

The expiry date of the product is indicated on the packaging materials.

After dilution

From a microbiological point of view, the product should be used immediately. If not used immediately, it is the responsibility of the user to follow the in-use storage times and conditions prior to use.

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

- under refrigeration at 2 ºC to 8 ºC 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 ºC for no more than 6 hours from the time of infusion preparation to the end of the infusion.

6.4 Special precautions for storage

Unopened vial

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

For storage conditions after dilution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

2.3 ml of concentrate in a 3 ml clear Type 1 glass vial with a grey chlorobutyl stopper with coating and a seal cap with a flip-off button containing 345 mg of evinacumab.
Pack size of 1 vial.

8 ml of concentrate in a 20 ml clear Type 1 glass vial, with a grey chlorobutyl stopper with coating and a seal cap with a flip-off button containing 1,200 mg of evinacumab.
Pack size of 1 vial.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Preparation of solution

Evkeeza is supplied as a single use vial only. During preparation and reconstitution a strictly aseptic technique should be used.

- Visually inspect the medicinal product for cloudiness, discolouration or particulate matter prior to administration.
- Discard the vial if the solution is cloudy or discoloured or contains particulate matter.
- Do not shake the vial.
- Withdraw the required volume of evinacumab from the vial(s) based on patient's body weight and transfer into an intravenous infusion bag containing sodium chloride 9 mg/ml (0.9%) or dextrose 50 mg/ml (5%) for infusion. Mix the diluted solution by gentle inversion.
- The final concentration of the diluted solution should be between 0.5 mg/ml to 20 mg/ml.
- Do not freeze or shake the solution.
- Discard any unused portion left in the vial.

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

7. MANUFACTURER

Ultragenyx Germany GmbH
Rahel-Hirsch-Str. 10
10557 Berlin
Germany

8. REGISTRATION HOLDER

Truemed Ltd.,
10 Beni Gaon St., Poleg Industrial Park,
P.O.B 8105, Netanya 4250499

9. REGISTRATION NUMBER

177-05-37833-00

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