ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

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

1. NAME OF THE MEDICINAL PRODUCT

Evkeeza 150 mg/ml concentrate for solution for infusion

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 paediatric patients aged 6 months 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 body weight (bw) 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 6 months to 17 years (see sections 4.8, 5.1 and 5.2). The safety and efficacy of Evkeeza in children aged less than 6 months have not been established. No data are available.

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, fatigue 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 clinical trials of evinacumab therapy involving 137 treated patients (117 adult and adolescent patients with HoFH and persistent hypercholesterolaemia from pooled controlled clinical trials and 20 paediatric patients aged >5 to 11 years with HoFH from Study R1500-CL-17100). 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	Fatigue*	Very Common
	Influenza like illness	Common
	Asthenia	Common
	Infusion related reaction	Common
	Infusion site reactions	Common

* See section Paediatric population, below.

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 14 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.

The safety of evinacumab was assessed in 20 paediatric patients aged ≥ 5 to 11 years. The safety profile of evinacumab observed in these patients was consistent with the safety profile observed in adult and adolescent patients aged 12 years and older, with the additional adverse reaction of fatigue. Fatigue was reported in 3 (15%) patients (See section 5.1).

Data are available for 5 patients aged ≥1 to 5 years old treated with evinacumab via compassionate use. The treatment duration was between 12 weeks and 90 weeks. Based on safety data received, no new safety concern has been identified (see section 5.1).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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.

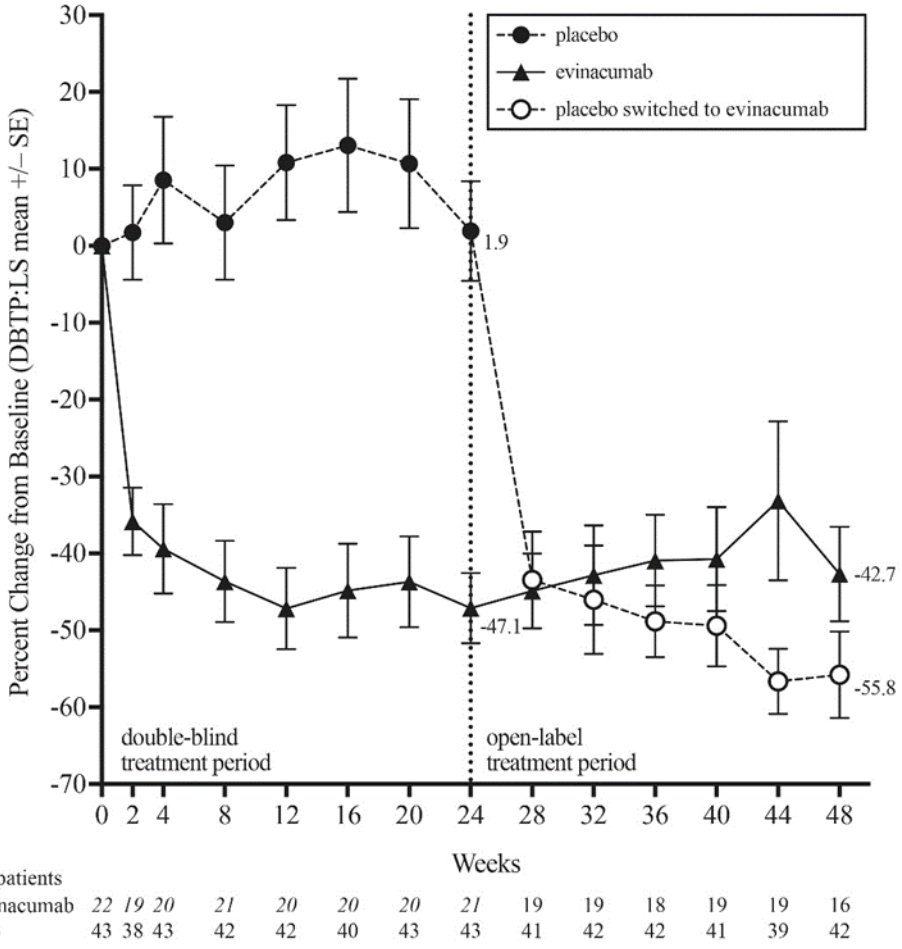
Table 2: Effect of evinacumab on lipid parameters in patients with HoFH in study ELIPSE-HoFH

	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

This was a multicentre, open-label extension study in 116 patients with HoFH. Data available from 86 patients at 24 weeks showed a 43.6% decrease in LDL-C 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). Reductions from baseline in LDL-C were consistent at 48 and 96 weeks; the mean percent change from baseline in calculated LDL-C at 48 weeks (n=95) was -43.9% and at 96 weeks (n=63) was -37.2%. Patients regardless of mutation status were included in the trial, including patients with null/null or negative/negative variants.

Paediatric population

ELIPSE-HoFH

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%.

ELIPSE-OLE

In ELIPSE-OLE, 14 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 12 patients were evinacumab-naïve. The mean baseline LDL-C in these adolescent patients was 300.4 mg/dl (7.88 mmol). The mean age was 14.4 years (range: 12 to 17 years), with 64.3% males and 35.7% females. At baseline, all patients were on a statin, 71.4% on ezetimibe, 42.9% on PCSK9 inhibitor, and 64.3% were receiving lipoprotein apheresis. Four (28.6%) patients had null/null variants and 4 (28.6%) patients had negative/negative variants for LDLR mutations. At Week 24, the percent change in LDL-C with evinacumab was -55.4% (n=12).

Study R1500-CL-17100

This was a multicenter, three-part, single-arm, open-label study evaluating the efficacy, safety, and tolerability of evinacumab in paediatric patients aged ≥ 5 to 11 years 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, PK, and PD of evinacumab 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 evinacumab 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 evinacumab 15 mg/kg IV every 4 weeks in 20 patients with HoFH. It consists of a 48-week treatment period and a 24-week follow-up period (ongoing). 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 lipoprotein apheresis.

The diagnosis of HoFH was determined by genetic testing or by the presence of the following clinical criteria: history of untreated total cholesterol (TC) > 13 mmol/l (> 500 mg/dl) and TG < 7.8 mmol/l (< 690 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.

Overall, for patients in Part A and Part B, the mean LDL-C at baseline was 7.8 mmol/l (301.9 mg/dl). At baseline, 90% of patients were on statins, 95% were 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.

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 −48.3% (95% confidence interval: −68.8% to −27.8%). For efficacy results, see Table 3.

Table 3: Lipid parameters in paediatric patients (≥ 5 to 11 years) with HoFH on other lipid-lowering therapies at week 24

	LDL-C	ApoB	Non-HDL-C	TC	Lp(a)
Baseline (mean) (N = 14)	6.8 mmol/l (263.7 mg/dl)	168.2 mg/dl (1.682 g/l)	7.3 mmol/l (282.2 mg/dl)	8.1 mmol/l (315.5 mg/dl)	158.6 nmol/L
Percent change from baseline (95% CI)	-48.3 (-68.8 to -27.8)	-41.3 (-58.9 to -23.8)	-48.9 (-68.1 to -29.7)	-49.1 (-64.9 to -33.2)	-37.3 (-42.2 to -32.3)

At week 24, the reduction in LDL-C with evinacumab was similar across baseline characteristics, including age, sex, limited LDL-R activity, concomitant treatment with lipoprotein apheresis, and concomitant background lipid-lowering medications (statins, ezetimibe, and lomitapide).

Other investigations

The efficacy of evinacumab for paediatric patients aged 6 months to less than 5 years has been predicted based on integrated PK/PD modelling and simulations (see section 5.2). Paediatric patients aged 6 months to less than 5 years receiving evinacumab 15 mg/kg every 4 weeks are predicted to experience a similar or higher magnitude of percent change in LDL-C at week 24 compared to adults while plateauing at higher absolute LDL-C concentrations at week 24.

In addition, data are available for 5 patients aged ≥1 to 5 years old with HoFH who received evinacumab via compassionate use. The prescribed dose was 15 mg/kg evinacumab every 4 weeks, the same as that used in older children and adults. Administration of evinacumab showed a clinically meaningful reduction of LDL-C consistent with that observed in patients ≥ 5 years old in clinical studies. The benefits included a reduction in LDL-C of 37.1% at week 90 in one of the patients in whom plasmapheresis frequency was reduced during the treatment period, and reductions of 43.1% at week 72, 66.3% at week 62, 77.3% at week 16, and 75.0% at week 12 respectively in the other patients. Xanthomas completely resolved in the patient in whom plasmapheresis frequency was reduced, after approximately 1 year of treatment with evinacumab.

This medicine has been authorised under 'exceptional circumstances'. This means that due to the rarity of the disease it has not been possible to obtain complete information on this medicinal product. The European Medicines Agency will review any new information which may become available every year and this SmPC will be updated as necessary.

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, mean ± SD C_{max} is 681 ± 185 mg/l in adult patients following a dose of 15 mg/kg every 4 weeks. The accumulation ratio is approximately 2. The mean ± SD steady-state trough concentration is 230 ± 81.3 mg/l in adult patients.

Distribution

The steady-state volume of distribution estimated by population PK analysis in a typical individual weighing 72 kg was approximately 4.9 L in adult patients, 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 approximately 21 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 adult participants and 139 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 (19.7 to 152 kg), race. Apheresis did not appear to substantially influence the pharmacokinetics of evinacumab.

Paediatric population
There were 14 patients aged 12 to 17 years with HoFH receiving evinacumab at 15 mg/kg IV every 4 weeks, steady-state trough and maximum concentrations were generally within the range of those in adult patients. The mean steady-state C_{max} was 566 ± 206 mg/l in patients aged 12 to < 18 years with HoFH.

For the 20 patients aged 5 to 11 years with HoFH receiving evinacumab at 15 mg/kg IV every 4 weeks, the mean (SD) steady-state trough evinacumab concentration based on population PK analyses was 160 ± 57.6 mg/l and the mean (SD) steady-state C_{max} was 419 ± 99.4 mg/l in patients aged 5 to 11 years with HoFH.

The pharmacokinetics of evinacumab in paediatric patients less than 5 years of age with HoFH were predicted from a model-based extrapolation analysis. This analysis used population PK modelling and simulations based on previously observed data in older children, adolescents, and adults, together with assumptions on the biological development and pathophysiological circumstances in younger children with HoFH. The predicted mean steady-state trough concentrations and mean accumulation ratios in patients 6 months to less than 5 years were lower but within the ranges predicted for patients aged 5 years and older. The predicted mean steady-state maximum concentration was 499±185 mg/L for patients aged 6 months to less than 2 years and 513±179 mg/L for patients aged 2 to less than 5 years.

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 including juvenile toxicity studies 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

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

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

4 years

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.
    - For patients weighing 45 kg and above, the IV infusion bag should contain a maximum volume of 250 ml of 9 mg/ml (0.9%) sodium chloride, or 50 mg/ml (5%) dextrose.
    - For patients weighing between 26 kg and 44 kg, the IV infusion bag should contain a maximum volume of 150 ml of 9 mg/ml (0.9%) sodium chloride, or 50 mg/ml (5%) dextrose.

    - For patients weighing between 3 kg and 25 kg, the IV infusion bag should contain a maximum volume of 5 ml/kg. The corresponding volume for patients weighing between 3 kg and 25 kg should range from 15 ml to 125 ml of 9 mg/ml (0.9%) sodium chloride, or 50 mg/ml (5%) dextrose administered at a maximum rate of 5 ml/kg/hour.
- 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. MARKETING AUTHORISATION HOLDER

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

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1551/001
EU/1/21/1551/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 June 2021

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

ANNEX II

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

Regeneron Pharmaceuticals, Inc.
81 Columbia Turnpike
Rensselaer, NY 12144
United States

Name and address of the manufacturer(s) responsible for batch release

Ultragenyx Netherlands B. V.
Evert van de Beekstraat 1, Unit 104
1118 CL Schiphol
Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicine's web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

Description	Due date
Non-interventional post-authorisation safety study (PASS): In order to evaluate the long term safety outcomes in patients with Homozygous Familial Hypercholesterolemia (HoFH) who are treated with evinacumab as well as the frequency and outcomes of pregnancy in female patients with HoFH treated with evinacumab and to evaluate the atherosclerosis process over time in patients with HoFH who are treated with evinacumab and undergo cardiac imaging, the MAH should conduct and submit the results of a study based on data from a registry in patients with HoFH.	Annual study reports will be submitted with the annual reassessment.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Evkeeza 150 mg/ml concentrate for solution for infusion
evinacumab

2. STATEMENT OF ACTIVE SUBSTANCE(S)

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.

3. LIST OF EXCIPIENTS

Excipients: proline, arginine hydrochloride, histidine, histidine hydrochloride monohydrate, polysorbate 80 and water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Concentrate for solution for infusion
345 mg/2.3 ml
1 200 mg/8 ml
1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use.
Read the package leaflet before use.
For single use only.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Store in the original carton to protect from light.

Do not freeze.
Do not shake.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1551/001
EU/1/21/1551/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Evkeeza 150 mg/ml sterile concentrate
evinacumab
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

345 mg/2.3 ml
1 200 mg/8 ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Evkeeza 150 mg/ml concentrate for solution for infusion
evinacumab

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine - because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or nurse.
- If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Evkeeza is and what it is used for

What Evkeeza is
Evkeeza contains the active substance evinacumab. It is a type of medicine called a 'monoclonal antibody'. Monoclonal antibodies are proteins that attach to other substances in the body.

What Evkeeza is used for
Evkeeza is used to treat adults and children aged 6 months and older with very high cholesterol caused by a condition called 'homozygous familial hypercholesterolaemia'. 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 the production of cholesterol, and blocking its effect reduces the production of cholesterol. In this way, Evkeeza can lower blood levels of LDL-cholesterol and so prevent problems caused by high LDL-cholesterol levels.

2. What you need to know before you are given Evkeeza

You should not be given Evkeeza if:
- you are allergic to evinacumab or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions

Talk to your doctor or nurse before you are given Evkeeza.

Look out for serious side effects
Evkeeza can cause serious allergic reactions.
- Tell your doctor or nurse immediately if you get any symptoms of a severe allergic reaction. The symptoms are listed in "Serious side effects" in section 4.

Children
Evkeeza is not recommended for children below the age of 6 months because there is not yet enough information on its use in this group of patients.

Other medicines and Evkeeza
Tell your doctor if you are taking, have recently taken or might take any other medicines.

Pregnancy and contraception
If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.
- Evkeeza may harm your unborn baby.
- Tell your doctor immediately if you become pregnant while you are being treated with Evkeeza.

If you are able to become pregnant, you should use effective contraception to avoid becoming pregnant.
- use effective contraception while you are being treated with Evkeeza and
- use effective contraception for at least 5 months after the last dose of Evkeeza.

Talk to your doctor about the best contraception method for you during this time.

Breast-feeding
- If you are breast-feeding or plan to breast-feed, ask your doctor for advice before you are given this medicine.
- It is not known if Evkeeza passes into the breast milk.

Driving and using machines
It is possible that Evkeeza could make you feel dizzy and tired and may affect your ability to ride a bike, drive, or use any tools or machines. If you think you are affected, do not ride a bike, drive, or use machines and tools, and tell your doctor (see section 4).

Evkeeza contains proline
This medicine contains 30 mg of proline in each ml. Proline may be harmful for patients with hyperprolinaemia, a rare genetic disorder in which proline builds up in the body. If you (or your child) have hyperprolinaemia, do not use this medicine unless your doctor has recommended it.

Evkeeza contains polysorbate 80
This medicine contains 1 mg of polysorbate 80 in each ml. Polysorbates may cause allergic reactions. Tell your doctor if you (or your child) have any known allergies.

3. How Evkeeza is given

How much Evkeeza is given
Your doctor will work out how much of the medicine to give you. The amount will depend on your body weight.
- The recommended dose is 15 milligrams for every kilogram you weigh.
- You will be given the medicine around once a month.

How Evkeeza is given
Evkeeza is usually given by a doctor or nurse. It is given as a drip into a vein ('intravenous infusion') over 60 minutes.

If you miss your dose of Evkeeza
If you have missed an appointment to receive Evkeeza, talk to your doctor or nurse as soon as possible.

If you have any further questions on the use of this medicine, ask your doctor or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Severe allergic reactions (uncommon: may affect up to 1 in 100 people)
Tell your doctor or nurse immediately if you get any of the following symptoms of a severe allergic reaction (anaphylactic reaction). The drip will be stopped immediately and you may need to take other medicines to control the reaction:
- swelling – mainly of the lips, tongue or throat, which makes it difficult to swallow or breathe
- breathing problems or wheezing
- feeling dizzy or fainting
- rash, hives
- itching.

Other side effects
Tell your doctor or nurse if you notice any of the following side effects:

Very common (may affect more than 1 in 10 people)
- symptoms of the common cold, such as runny nose (nasopharyngitis).

Common (may affect up to 1 in 10 people)
- feeling dizzy
- sore throat or sinus infection (upper respiratory tract infection)
- feeling sick (nausea)
- stomach pain
- constipation
- back pain
- pain in your hands or feet (pain in extremity)
- symptoms of flu
- feeling tired or weary (asthenia)
- infusion reaction, such as itching where the drip is given.

Additional side effects in children aged 5 to 11 years

Very common (may affect more than 1 in 10 people)
- feeling tired (fatigue).

Reporting of side effects
If you get any side effects, talk to your doctor or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Evkeeza

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and vial after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2 ºC to 8 ºC).
Do not freeze. Do not shake.
Store in the original carton to protect from light.
Do not use this medicine if you notice it is cloudy, discoloured or contains particulate matter.

Do not store any unused portion of the infusion solution for re-use. Any unused portion of the infusion solution should not be re-used and should be disposed in accordance with local requirements.

6. Contents of the pack and other information

What Evkeeza contains
- The active substance is evinacumab.

Each 1 ml of concentrate for solution for infusion contains 150 mg of evinacumab.

Each vial contains either 345 mg of evinacumab in 2.3 ml of concentrate or 1 200 mg of evinacumab in 8 ml of concentrate.

- The other ingredients are proline, arginine hydrochloride, histidine hydrochloride monohydrate, polysorbate 80, histidine and water for injections.

What Evkeeza looks like and contents of the pack
Evkeeza concentrate for solution for infusion is a clear to slightly opalescent, colourless to pale yellow solution.

It is available in packs containing either 1 glass vial of 2.3 ml of concentrate or 1 glass vial of 8 ml of concentrate.

Marketing Authorisation Holder
Ultragenyx Germany GmbH
Rahel-Hirsch-Str. 10
10557 Berlin
Germany

Manufacturer
Ultragenyx Netherlands B. V.
Evert van de Beekstraat 1, Unit 104
1118 CL Schiphol
Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

BE, BG, CZ, DK, DE, EE, ES, HR, IE, IS, IT, CY, LI, LV, LT, LU, HU, MT, NL, NO, AT, PL, PT, RO, SI, SK, FI, SE
Ultragenyx Germany GmbH, DE
Tel/Tél/Тел./Tlf/Puh/Sími : + 49 30 20179810

EL
Medison Pharma Greece Single Member Societe Anonyme, EL
Τηλ: +30 210 0100 188

FR
Ultragenyx France SAS, FR

Tél: + 33 1 85 65 37 61 ou 0800 91 79 24 (numéro vert)

This leaflet was last revised in <month year>.
This medicine has been authorised under 'exceptional circumstances'. This means that due to the rarity of the disease it has not been possible to obtain complete information on this medicinal product. The European Medicines Agency will review any new information which may become available every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu/

The following information is intended for healthcare professionals only:

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.

Instructions for use

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.
    - For patients weighing 45 kg and above, the IV infusion bag should contain a maximum volume of 250 ml of 9 mg/ml (0.9%) sodium chloride, or 50 mg/ml (5%) dextrose.
    - For patients weighing between 26 kg and 44 kg, the IV infusion bag should contain a maximum volume of 150 ml of 9 mg/ml (0.9%) sodium chloride, or 50 mg/ml (5%) dextrose.
    - For patients weighing between 3 kg and 25 kg, the IV infusion bag should contain a maximum volume of 5 ml/kg. The corresponding volume for patients weighing between 3 kg and 25 kg should range from 15 ml to 125 ml of 9 mg/ml (0.9%) sodium chloride, or 50 mg/ml (5%) dextrose administered at a maximum rate of 5 ml/kg/hour.
- 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.

After dilution
Once prepared, administer the diluted solution immediately. 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.

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.