Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

Evkeeza 150 mg/ml concentrate for solution for infusion

(evinacumab)

PLGB 47793/0003

Ultragenyx Germany GmbH

LAY SUMMARY

Evkeeza 150 mg/ml concentrate for solution for infusion (evinacumab)

This is a summary of the Public Assessment Report (PAR) for Evkeeza 150 mg/ml concentrate for solution for infusion. It explains how this product was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product.

This product will be referred to as Evkeeza in this lay summary for ease of reading.

For practical information about using Evkeeza, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Evkeeza and what is it used for?
This product has been authorised by MHRA for Great Britain (GB; consisting of England, Scotland and Wales). In coming to its decision, MHRA has relied on a European Commission (EC) decisions on 17 June 2021 and 13 April 2022 (C(2021)4567(final); EMEA/H/C/005449/0000 and C(2022)2528(final); EMA/H/C/005449/T/0003, respectively), in accordance with the advice from the Committee for Medicinal Products for Human Use (CHMP). This is known as the EC Decision Reliance Procedure.

This application is a full-dossier application. This means that the results of pharmaceutical, non-clinical and clinical tests have been submitted to show that this medicine is suitable for treating the specified indication.

Evkeeza is used to treat adults and children aged 12 years 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?
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.

Evinacumab, 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.

How is Evkeeza used?
The pharmaceutical form of this medicine is a concentrate for solution for infusion (sterile concentrate).

How much Evkeeza is given
The patient's doctor will work out how much of the medicine to give their patient. The amount will depend on the patient's weight.
• The recommended dose is 15 milligrams for every kilogram the patient weighs.
• The patient 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.

For further information on how Evkeeza is used, refer to the PIL and Summary of Product Characteristics (SmPC) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

This medicine can only be obtained with a prescription.

The patient should ask the administering healthcare practitioner if they have any questions concerning their medicine.

What benefits of Evkeeza have been shown in studies?
A main study showed that Evkeeza effectively reduced LDL cholesterol levels in adults and adolescents aged 12 years and older with homozygous familial hypercholesterolaemia. The participants received Evkeeza or placebo (a 'dummy treatment') while also taking other cholesterol-lowering therapies.

The main study involved 65 patients who received either Evkeeza or placebo once every four weeks. After 24 weeks, the average LDL cholesterol levels in the blood of patients receiving Evkeeza had reduced by around 47% (almost half) from the start of the treatment, compared with about a 2% increase in patients receiving placebo. The improvement in LDL cholesterol levels with Evkeeza was maintained when treatment was given for 24 additional weeks.

What are the possible side effects of Evkeeza?
For the full list of all side effects reported with this medicine, see Section 4 of the PIL or the SmPC available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

Why was Evkeeza approved?
Two studies showed that adding Evkeeza to other cholesterol-lowering treatments effectively reduced LDL cholesterol levels in the blood of patients with homozygous familial hypercholesterolaemia. However, the long-term benefits for the heart and circulatory system still need to be studied.

Side effects with Evkeeza were acceptable, and most patients could receive prolonged treatment (at least one year) without needing to stop.

Therefore, the MHRA decided that the benefits are greater than the risks and recommended that this medicine can be approved for use.

Evkeeza has been authorised under "exceptional circumstances". This means that because of the rarity of this disease it has been impossible to get complete information on this medicine. Any new information on Evkeeza will be reviewed every year and this report will be updated as necessary.

Evkeeza has been authorised with the condition to perform further studies to minimise the risk. See section below "What measures are being taken to ensure the safe and effective use of Evkeeza?"

What measures are being taken to ensure the safe and effective use of Evkeeza?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Evkeeza. The RMP details the important risks of Evkeeza, how these risks can be minimised, any uncertainties about Evkeeza (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Evkeeza:

Summary of safety concerns	
Important identified risks	None
Important potential risks	Embryofoetal toxicity
Missing information	Safety of long-term use (eg, >2 years) Use in pregnant or breast-feeding women

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Evkeeza are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

In addition to the safety information provided in the Evkeeza product information, the Marketing Authorisation Holder (MAH) has committed to additional pharmacovigilance activities through the provision of safety data derived from a long-term safety study to address the potential risk of embryofoetal toxicity.

An RMP and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

Other information about Evkeeza
A Marketing Authorisation was granted in GB on 26 August 2022.

The full PAR for Evkeeza follows this summary.

This summary was last updated in December 2022.

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I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the application for Evkeeza 150 mg/ml concentrate for solution for infusion (PLGB 47793/0003) could be approved.

The product is approved for the following indication:

- 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).

The active substance, 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.

This product has been authorised by MHRA for Great Britain (GB; consisting of England, Scotland and Wales). In coming to its decision, MHRA has relied on European Commission (EC) decisions on 17 June 2021 and 13 April 2022 (C(2021) 4567(final); EMEA/H/C/005449/0000 and C(2022)2528(final); EMA/H/C/005449/T/0003, respectively), in accordance with the advice from the Committee for Medicinal Products for Human Use (CHMP).

For the scientific discussion of the quality, non-clinical and clinical assessment conducted by the European Medicines Agency (EMA), please refer to the European Public Assessment Report, available on the EMA website.

This application was approved under Regulation 50 of the Human Medicines Regulation 2012, as amended (previously Article 8.3 of Directive 2001/83/EC, as amended).

In line with the legal requirements for children's medicines, the application included a licensing authority decision on the agreement of a paediatric investigation plan (PIP) MHRA-100521-PIP01-22-M01.

At the time of the submission of the application the PIP was not yet completed as some measures were deferred.

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product at all sites responsible for the manufacture, assembly and batch release of this product.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

A Marketing Authorisation was granted in GB on 26 August 2022.

II. PRODUCT INFORMATION

SUMMARY OF PRODUCT CHARACTERITICS (SmPC)

The SmPC is in line with current guidelines and is satisfactory.

PATIENT INFORMATION LEAFLET (PIL)

The PIL is in line with current guidelines and is satisfactory.

LABEL

The labelling is in line with current guidelines and is satisfactory.

III. QUALITY ASPECTS

The MHRA considered that the quality data submitted for this application is satisfactory.

The grant of a Marketing Authorisation is recommended.

IV. NON-CLINICAL ASPECTS

The MHRA considered that the non-clinical data submitted for this application is satisfactory.

The grant of a Marketing Authorisation is recommended.

V. CLINICAL ASPECTS

The MHRA considered that the clinical data submitted for this application is satisfactory.

The grant of a Marketing Authorisation is recommended.

VI. RISK MANAGEMENT PLAN (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. In addition to routine pharmacovigilance and risk minimisation measures, the following additional pharmacovigilance measures have been proposed:

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Embryofoetal toxicity	**Routine risk minimisation measures**: – SmPC Sections 4.6 and 5.3 – PL Section 2 Recommendation that women of childbearing potential should use effective contraception during treatment with evinacumab and for at least 5 months after the last dose is included in the SmPC Section 4.6 and PL Section 2. – SmPC Section 4.2 Legal status: Evinacumab is subject to restricted medical prescription. Treatment with Evinacumab should be initiated and monitored by a physician experienced in the treatment of lipid disorders. **Additional risk minimisation measures**: None	**Routine pharmacovigilance activities beyond signal detection and adverse reactions reporting:** None **Additional pharmacovigilance activity:** – Long-term safety study
Safety of long-term use (eg, >2 years)	**Routine risk minimisation measures**: Restricted medical prescription **Additional risk minimisation measures**: None	**Routine pharmacovigilance activities beyond signal detection and adverse reactions reporting:** None **Additional pharmacovigilance activity:** – Long-term safety study

Safety Concern	Risk Minimisation Measures	Pharmacovigilance Activities
Use in pregnant and breast-feeding women	**Routine risk minimisation measures**: – SmPC Sections 4.6 and 5.3 – PL Section 2 Recommendation that women of childbearing potential should use effective contraception during treatment with evinacumab and for at least 5 months after the last dose is included in the SmPC Section 4.6 and PL Section 2. 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, evinacumab could be used during breast-feeding if clinically needed is included in SmPC Section 4.6 and PL Section 2 as recommendation on use of evinacumab for breast-feeding women. – SmPC Section 4.2 Legal status: Evinacumab is subject to restricted medical prescription. Treatment with Evinacumab should be initiated and monitored by a physician experienced in the treatment of lipid disorders. **Additional risk minimisation measures**: None	**Routine pharmacovigilance activities beyond signal detection and adverse reactions reporting:** None **Additional pharmacovigilance activity:** Long-term safety study (note that pregnancy information will be evaluated in the proposed long-term safety study to address the potential risk of embryofoetal toxicity)

PL=package leaflet; SmPC=summary of product characteristics.

This is acceptable.

VII. USER CONSULTATION

A full colour mock-up of the PIL has been provided with the application, in accordance with legal requirements.

The PIL has been evaluated via a user consultation study in accordance with legal requirements. The results show that the PIL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VIII. OVERALL CONCLUSION, BENEFIT/RISK AND RECOMMENDATION

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The benefit/risk balance is, therefore, considered to be positive.

As comprehensive data on the product are not available, Evkeeza 150 mg/ml concentrate for solution for infusion has been authorised under "exceptional circumstances". The Marketing Authorisation Holder shall complete, within the stated timeframe, the following measures:

Description	Due date
1. Category 2 PASS - Evaluation of the Long-Term Effects of Evinacumab Treatment in Patients with Homozygous Familial Hypercholesterolemia (HoFH)	30/06/2029

The SmPC, PIL and labelling are satisfactory.

In accordance with legal requirements, the current approved GB versions of the SmPC and PIL for this product are available on the MHRA website.

Representative copies of the labels at the time of GB licensing are provided below.


Ultragenyx Germany GmbH
Rahel-Hirsch-Str. 10
10557 Berlin
Germany/Deutschland/
Duitsland
EU/1/21/1551/001
IRELAND/UNITED KINGDOM
POM
Great Britain:
PLGB 47793/0003
DEUTSCHLAND
Verschreibungspflichtig
Wirkstoff: Evinacumab
Gentechnisch hergestellt aus Zelllinien des Chinesischen Hamsterovars (CHO-K1)
PZN - 18113590
ÖSTERREICH
Rezept- und apothekenpflichtig
NEDERLAND
Uitsluitend recept
10020601
Evkeeza 150 mg/ml
concentrate for solution for infusion
Konzentrat zur Herstellung einer Infusionslösung
concentraat voor oplossing voor infusie
evinacumab/Evinacumab
345 mg/2,3 ml
Intravenous use
Intravenöse Anwendung
Intraveneus gebruik
For single use only
Nur zum einmaligen Gebrauch
Uitsluitend voor eenmalig gebruik
1 vial/Durchstechflasche/injectieflacon
ultragenyx
NL Elke ml concentraat voor oplossing voor infusie bevat 150 mg evinacumab.
Eén injectieflacon van 2,3 ml concentraat bevat 345 mg evinacumab.
Hulpstoffen: proline, argininehydrochloride, histidine, histidinehydrochloridemonohydraat, polysorbaat 80 en water voor injecties.
Lees voor het gebruik de bijsluiter.
Buiten het zicht en bereik van kinderen houden.
Bewaren in de koelkast.
Bewaren in de oorspronkelijke doos ter bescherming tegen licht.
Niet in de vriezer bewaren.
Niet schudden.
DE Jeder ml Konzentrat zur Herstellung einer Infusionslösung enthält 150 mg Evinacumab.
Eine Durchstechflasche mit 2,3 ml Konzentrat enthält 345 mg Evinacumab.
Sonstige Bestandteile: Prolin, Arginin-Hydrochlorid, Histidin, Histidin-Hydrochlorid-Monohydrat, Polysorbat 80 und Wasser für Injektionszwecke.
Packungsbeilage beachten.
Arzneimittel für Kinder unzugänglich aufbewahren.
Im Kühlschrank lagern.
Im Originalkarton aufbewahren, um den Inhalt vor Licht zu schützen. Nicht einfrieren. Nicht schütteln.
FPO
694420
EN 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.
Excipients: proline, arginine hydrochloride, histidine, histidine hydrochloride monohydrate, polysorbate 80 and water for injections.
Read the package leaflet before use.
Keep out of the sight and reach of children.
Store in a refrigerator. Store in the original carton to protect from light. Do not freeze.
Do not shake.
Lot/EXP
Variable Data to be printed here
Evkeeza 150 mg/ml
concentrate for solution for infusion
Konzentrat zur Herstellung einer Infusionslösung
concentraat voor oplossing voor infusie
evinacumab/Evinacumab
345 mg/2,3 ml

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Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations, where significant changes are made, are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the Marketing Authorisation are recorded in the current SmPC and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**

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