

15 December 2016 EMA/140771/2017 Committee for Medicinal Products for Human Use (CHMP)

# Assessment Report on extension of Marketing Authorisation

Repatha

International non-proprietary name: evolocumab

Procedure No. EMEA/H/C/003766/X/0002

# **Note**

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.



# **Table of contents**

1. Background information on the procedure	6
1.1. Submission of the dossier	6
1.2. Steps taken for the assessment of the product	7
2. Scientific discussion	7
2.1. Introduction	
2.2. Quality aspects	
2.2.1. Introduction	
2.2.2. Active Substance	9
2.2.3. Finished Medicinal Product	9
2.2.4. Discussion on chemical, pharmaceutical and biological aspects	13
2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects	
2.2.6. Recommendations for future quality development	14
2.3. Non-clinical aspects	14
2.3.1. Ecotoxicity/environmental risk assessment	14
2.3.2. Conclusion on the non-clinical aspects	14
2.4. Clinical aspects	15
2.4.1. Introduction	15
2.4.2. Pharmacokinetics	15
2.4.3. Conclusions on clinical pharmacology	17
2.5. Clinical efficacy	17
2.5.1. Conclusions on the clinical efficacy	18
2.6. Clinical safety	18
2.6.1. Conclusions on the clinical safety	
2.7. Risk Management Plan	
2.8. Pharmacovigilance	22
2.9. Product information	22
2.9.1. User consultation	22
2.9.2. Additional monitoring	23
3. Benefit-Risk Balance	23
4. Recommendations	24

# List of abbreviations

AE adverse event

Al/pen prefilled autoinjector/pen

AMD automated mini doser (formerly referred to as LVI [larger volume injector] and 3.5 mL personal injector)

ApoA1 apolipoprotein A1

ApoB apolipoprotein B

ApoB Apolipoprotein B

AUC Area under the curve

AUC area under the concentration time curve

AUCinf area under the concentration-time curve from time 0 to infinity

AUClast area under the concentration time curve from time 0 to the last quantifiable concentration

AUCx-y area under the concentration-time curve from time x to time y

AUECx-y area under the effect curve from time x to time y

BA bioavailability

BE bioequivalence

CAS completer analysis set

CHD coronary heart disease

CHMP Committee for Medicinal Products for Human Use

**CHO Chinese Hamster Ovary** 

CI confidence interval

CK creatine kinase

CL clearance

CL/F estimated mean apparent clearance

Cmax Maximum concentration

Cmax maximum concentration

CMC Chemistry, Manufacturing, and Controls

CrCL creatinine clearance

CTCAE Common Terminology Criteria for Adverse Events

EC50 area under the concentration-time curve from week 8 to week 12 required to achieve half-maximal

response

Eff effect magnitude

ELISA Enzyme-linked immunosorbent assay

ELISA enzyme-linked immunosorbent assay

EPD Embryo-foetal and Postnatal Development

EvoMab evolocumab (AMG 145)

F bioavailability

FAS full analysis set

FcRn neonatal Fc receptor

FH familial hypercholesterolemia

**GLP Good Laboratory Practice** 

**GOF Gain of Function** 

HDL C high density lipoprotein cholesterol

HDL-c High Density Lipoprotein cholesterol

IDL C intermediate density lipoprotein cholesterol

IP investigational product

**IV** Intravenous

IV intravenous(ly)

Ka absorption rate constant

Km concentration of half maximal nonlinear clearance

LDL C low density lipoprotein cholesterol

LDL low density lipoprotein

LDL-c High Density Lipoprotein cholesterol

LDLR High Density Lipoprotein receptor

LDLR low density lipoprotein receptor

LLOQ lower limit of quantification

LOF Loss of Function

LOF loss of function

Lp(a) lipoprotein(a)

LS least squares

mAb Monoclonal antibody

non HDL C non high density lipoprotein cholesterol

OLE open label extension

PCSK9 proprotein convertase subtilisin/kexin type 9

PD pharmacodynamic(s)

PFS prefilled syringe

PK / PD Pharmacokinetics / Pharmacodynamics

PK pharmacokinetic(s)

Q2W Once every two weeks

QD once daily

QM Once monthly

QTcF QT interval using Fridericia's correction

QW Once weekly

RBC red blood cells

RES reticuloendothelial system

SC Subcutaneous

SD standard deviation

SE standard error

SoC standard of care

SOC system organ class

Statin hydroxymethylglutaryl coenzyme A (HMG CoA) reductase inhibitor

TC total cholesterol

TCR Tissue Cross Reactivity

TDAR T-cell dependent antibody response

TG Triglycerides

Tmax Time at maximum concentration

tmax time to maximum concentration

ULN upper limit of normal

VLDL C very low density lipoprotein cholesterol

VLDL-c Very low density lipoprotein cholesterol

VLDLR Very low density lipoprotein receptor

# 1. Background information on the procedure

# 1.1. Submission of the dossier

The Marketing Authorisation Holder (MAH) Amgen Europe B.V. submitted on 8 October 2015 an extension of the Marketing Authorisation.

The MAH applied for the addition a new strength of 420 mg solution for injection in cartridge, for subcutaneous administration by an automated mini-doser device.

Repatha is approved in the following indications:

#### Hypercholesterolaemia and mixed dyslipidaemia

Repatha is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non familial) or mixed dyslipidaemia, as an adjunct to diet:

- in combination with a statin or statin with other lipid lowering therapies in patients unable to reach LDL C goals with the maximum tolerated dose of a statin or,
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

#### Homozygous familial hypercholesterolaemia

Repatha is indicated in adults and adolescents aged 12 years and over with homozygous familial hypercholesterolaemia in combination with other lipid-lowering therapies.

The effect of Repatha on cardiovascular morbidity and mortality has not yet been determined.

The indications for the new strength are the same.

#### The legal basis for this application refers to:

Article 19 of Commission Regulation (EC) No 1234/2008 and Annex I of Regulation (EC) No 1234/2008, (2) point (c) - Extensions of marketing authorisations.

# Information on Paediatric requirements

Not applicable.

#### Information relating to orphan market exclusivity

## Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

#### Scientific Advice

The applicant did not seek scientific advice at the CHMP in relation to this line extension application.

# 1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was Johann Lodewijk Hillege

- The application was received by the EMA on 08 October 2015.
- The procedure started on 29 October 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 22 January 2016. The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on 26 January 2016.
- During the PRAC meeting on 11 February 2016, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the meeting on 25 February 2016, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 1 March 2016.
- The MAH submitted the responses to the CHMP consolidated List of Questions on 24 March 2016.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 2 May 2016. The PRAC Rapporteur's Assessment Report on the applicant's responses to the List of Questions was circulated to all PRAC members on 3 May 2016.
- During the PRAC meeting on 13 May 2016, the PRAC agreed on the PRAC Assessment Overview and Advice to CHMP.
- During the CHMP meeting on 26 May 2016, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The MAH submitted the responses to the CHMP List of Outstanding Issues on 17 November 2016.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 7 December 2016.
- During the meeting on 15 December 2016, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for an extension of the marketing authorisation for Repatha.

# 2. Scientific discussion

#### 2.1. Introduction

A large body of epidemiological evidence exists demonstrating a strong positive correlation and causal relationship between serum low density lipoprotein cholesterol (LDL-C), and the risk of coronary heart disease (CHD). Other clinical manifestations of atherosclerosis also appear linked to plasma LDL-C levels such as cerebrovascular disease (i.e. stroke) or peripheral vascular disease. In addition, clinical trials have shown that LDL lowering therapy with HMG-Co A reductase inhibitors (and possibly ezetimibe) reduces risk for CHD. The relationship between LDL-C levels and CHD risk is present over a broad range of LDL levels. Epidemiologic data indicate a continuous increasing risk from very low to "normal" and high levels of LDL-C. A

list of interventions to achieve LDL-C control in patients with elevated LDL-C and with high cardiovascular risk are available, such as statins and other lipid-lowering therapies. Often however these are not sufficiently effective or their use is limited by toxicity. There is an undisputed medical need for new effective and well tolerated treatments of lipid disorders. The primary goal of treating lipid disorders is to prevent cardiovascular morbidity and mortality associated with disturbed lipid levels and ideally this effect should be demonstrated pre-approval. Nevertheless, for medicinal products acting on LDL-C, at least a detrimental effect on mortality and morbidity should be excluded prior to registration. Until relevant clinical trial data are available, it is specifically mentioned in Section 4.1 of the SmPC that beneficial effects on mortality and morbidity have not been evaluated.

Recycling of the hepatic cell surface LDLR plays a critical role in the maintenance of cellular and whole body cholesterol balance by regulating plasma LDL-C levels. It has been shown that PCSK9 plays an important role in the recycling and regulation of LDLR (Horton et al., 2007; Brown and Goldstein, 2006). PCSK9 is a member of the subtilisin family of serine proteases and is expressed predominantly in the liver, kidney, and intestine (Zaid et al., 2008). Following secretion, it causes post-translational decrease in the expression of hepatic cell surface LDLR by binding it and targeting the LDLR for lysosomal destruction. The reduction in hepatic LDLR leads to increased levels of circulating LDL-C. Thus, PCSK9 may represent a target for inhibition by novel therapeutics in the indications of (1) primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia and (2) HoFH.

Evolocumab is a first in class fully human monoclonal immunoglobulin G2 directed against human proprotein convertase subtilisin/kexin type 9 (PCSK9). Evolocumab binds selectively to PCSK9 and inhibits circulating PCSK9 from binding to the LDLR on the liver cell surface, thus preventing PCSK9-mediated LDLR degradation. The inhibition of PCSK9 by evolocumab leads to increased LDLR expression and subsequent decreased circulating concentrations of LDL-C. In addition to LDL-C, inhibition of PCSK9 by evolocumab was also suggested to reduce total cholesterol, apolipoprotein B (ApoB), non-high-density lipoprotein cholesterol (non-HDL-C), very-low density lipoprotein cholesterol (VLDL-C), triglycerides and lipoprotein(a) (Lp[a]), total cholesterol/HDL C, ApoB/apolipoprotein A1 (ApoA1), and increase HDL-C and ApoA1.

The following two indications of Repatha are currently authorised in the European Union (from 17 July 2015):

## Hypercholesterolaemia and mixed dyslipidaemia

Repatha is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non-familial) or mixed dyslipidaemia, as an adjunct to diet:

- in combination with a statin or statin with other lipid lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or,
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

# Homozygous familial hypercholesterolaemia

Repatha is indicated in adults and adolescents aged 12 years and over with homozygous familial hypercholesterolaemia in combination with other lipid-lowering therapies.

The effect of Repatha on cardiovascular morbidity and mortality has not yet been determined.

Evolocumab is currently registered as prefilled syringe (PFS) or prefilled autoinjector/pen (AI/pen) intended for subcutaneous (SC) administration. The dose is either 140 mg every 2 weeks (Q2W) or 420 mg once monthly (QM).

With this line extension a new strength with a lower concentration of the active ingredient (120 mg/mL) will be added: a 120 mg/mL formulation supplied in a prefilled cartridge (3.5 mL= 420 mg evolocumab) assembly, which is co-packaged with an automated device referred to as an automated mini-doser (AMD). This new strength can be used to administer a dose of 420 mg with one injection instead of using 3 prefilled syringes/prefilled autoinjectors.

# 2.2. Quality aspects

#### 2.2.1. Introduction

The currently approved evolocumab finished product is supplied as a 140 mg/mL formulation in a sterile, single use, preservative free solution for delivery by subcutaneous injection. The finished product is supplied in either a prefilled syringe (PFS) or a prefilled auto-injector pen (SureClick), which is a disposable, handheld, mechanical (spring-based) injection device that is provided ready to use and pre-assembled with the same PFS.

This line extension concerns a 420 mg formulation supplied in a prefilled cartridge assembly, which is co-packaged with an automated device referred to as automated mini-doser (AMD). The prefilled cartridge assembly is loaded into the AMD prior to use. The AMD is a compact, sterile single use, disposable, electro-mechanical (battery powered, microprocessor controlled) on body injection device. The AMD is designed to subcutaneously administer the 3.5 ml dose in 9 minutes.

Changes introduced with this line extension are:

- 420 mg formulation in 3.5 mL (120 mg/mL) in addition to 140 mg in 1 mL formulation (no change to the excipients);
- New automated delivery device (AMD);
- Crystal Zenith (CZ) resin cartridge;
- Additional finished product filling site (Patheon, Italy).

The recommended dose of Repatha is either 140 mg every two weeks or 420 mg once monthly; both doses are clinically equivalent.

Pack sizes of one cartridge/AMD or multipack of three (3x1) cartridges/AMD are proposed.

# 2.2.2. Active Substance

The entire Repatha CTD 3.2.S Module related to the existing presentations (EU/1/15/1016/001-005) remains unchanged.

# 2.2.3. Finished Medicinal Product

#### **Description of the product and Pharmaceutical Development**

With the exception of the concentration of the active ingredient, the composition of the 420 mg formulation is equivalent to the approved 140 mg/mL. The prefilled cartridge contains 3.5 mL (deliverable volume) of 120 mg/mL evolocumab in proline, acetate, polysorbate 80, and water for injection. Dose per container is 420 mg.

#### Formulation development

The rationale for lower protein concentration (120 mg/mL) compared to the approved presentations was to lower viscosity in order to achieving a convenient injection time. Data collected from the evolocumab glass PFS matrix study demonstrated robustness of the target formulation. Testing conditions for the prefilled CZ cartridge matrix study were determined by design of experiment methodology with limited test formulations covering only the high and low of the range of each of the components assessed. The parameters evaluated included pH, protein concentration, acetate, proline, and polysorbate 80 concentrations. At the conditions studied (2°C to 8°C and 25°C), the formulations tested exhibited similar degradation patterns, indicating that changes in the components around the drug product formulation target do not have an impact on stability.

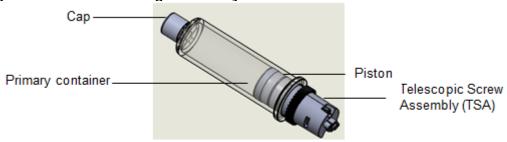
A lower concentration of the active ingredient (120 mg/mL) was chosen for the CZ cartridge in order to lower viscosity and achieve a convenient injection time.

Container closure system development

#### a) Cartridge

The primary container closure consists of a 5 mL CZ cartridge with a chlorobutyl elastomeric septum, a chlorobutyl elastomeric piston and a Telescopic Screw Assembly (TSA) that is threaded into the piston. The cartridge and septum are secured together using a cap (Figure 1).

Figure 1: Prefilled Cartridge Assembly



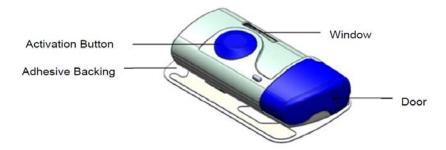
The TSA transfers rotational movement of the AMD motor into linear movement of the piston and hence functions like a syringe plunger rod.

The CZ resin is a polyolefin formulation that is non-compendial since the resin contains a novel additive, proprietary to the manufacturer and partial hexane solubility precludes one of the polyolefine compendial tests. Both the septum and piston are laminated with a fluoropolymer film on the product contact surface.

# b) Automated mini-doser (AMD) (Figure 2)

The AMD is made from polycarbonate, polybutylene terephthalate, polyxymethylene and silicone with a stainless steel 29 gauge needle. The administration device contains silver oxide-zinc batteries and includes an adhesive patch made from polyester tape with an acrylate adhesive.

Figure 2: Automated Minidoser (AMD)



The prefilled cartridge is co-packaged with the AMD. The prefilled cartridge assembly is loaded into the AMD immediately prior to use. The AMD is designed for use only with the provided 3.5 mL prefilled cartridge.

The safety and suitability of the primary packaging components was demonstrated, including extractable and biological reactivity testing. Data were also provided from extractable testing using model solvents and an assessment of leachables data after long-term stability. Information on the composition and properties of the non-compendial CZ resin was provided.

Compatibility with the AMD was investigated by comparing product quality before and after extrusion through the cartridge to identify any potential impact from shear stress after extrusion.

Furthermore a biological risk assessment of the AMD was performed to test fluid pathway and skin contacting components of the AMD for biocompatibility. Fluid path parts were evaluated for cytotoxicity and acute systemic toxicity. Additionally, the intentional skin contact parts of the AMD, including the cover, base and door, were evaluated for *in vitro* cytotoxicity, *in vivo* sensitisation, and *in situ* irritation, to applicable ISO standards.

The prefilled cartridge maintains container closure integrity from microbial contamination over shelf life and after transportation, and assembly with the TSA and subsequent co-packaging with the AMD did not compromise the container closure integrity of the cartridge.

# Manufacturing process development

Data on a sufficient number of batches of 120 mg/ml prefilled cartridges (CZ cartridges) have been presented.

Prefilled cartridge (Patheon) and loaded AMD (Patheon) finished product were comparable, as demonstrated by the lot release, characterisation, and stressed stability data presented and therefore suitable for clinical and commercial use.

## Manufacture of the product and process controls

The 420 mg finished product manufacturing process at Patheon includes preparation of formulation buffer and polysorbate solution, drug substance thaw (statically or dynamically), finished product formulation, bioburden reduction filtration, filtered formulated finished product hold, sterile filtration, aseptic filling and piston placement, inspection, and storage at 2-8 °C. The formula ingredients and amounts for the formulation buffers and the polysorbate 80 solution buffer are provided. After mixing is complete samples are withdrawn for in-process testing (protein concentration, pH, osmolality, endotoxins, pre-hold bioburden). The formulated finished product is filtered through a 0.22  $\mu$ m PVDF filter and may be stored as per a validated hold time study. The formulated finished product is sterile filtered through a 0.22  $\mu$ m PVDF filter and filled into cartridges. In-process tests are in place for pre-filtration bioburden, filter integrity, deliverable volume (fill weight), piston

position, polysorbate 80 concentration. Acceptable ranges, where appropriate, were provided for operational parameters.

The batch formula was provided. Reprocessing of any finished product formulation or filling steps is currently not allowed. Appropriate procedures are in place to assure the sterility of the final product.

The process validation of the 220 mg prefilled cartridge utilises a lifecycle approach, which involves a series of activities from the process design through commercial production to establish that the process is under control and is capable of consistently producing product that meet pre-established quality attributes. Process validation was performed using pre-defined acceptance criteria. Three consecutive 420 mg prefilled cartridge lots were produced at Patheon using 5 mL cartridges for a 3.5 mL deliverable volume. The process validation was performed following a batch size bracket approach, which included testing the extremes of the batch size range. In addition, the longest fill lot was included in the bracket to demonstrate lot homogeneity. All 420 mg prefilled cartridge validation data met acceptance criteria demonstrating consistency and reliability of the evolocumab 420 mg formulation and cartridge filling processes at Patheon.

Finished product filled in cartridge is shipped to a different, contracted facility for TSA assembly, co-packaging and labelling. The sterile AMD is received pre-packaged in a preformed blister tray from the device manufacturer. A labelled cartridge assembly is placed into the AMD blister tray and placed into the dispensing pack. Transport validation has demonstrated maintenance of product quality throughout shipping.

#### **Product specification**

The release and end-of-shelf-life specifications proposed are the same as the approved specifications for the Repatha PFS and auto-injector/pen presentation (except the protein concentration). Controls cover identity, purity, potency and other general tests. As no differences are expected, alignment of the specifications is accepted. It can be accepted that the small difference in concentration will not affect the outcome of the tests or the stability.

Only the proposed stability specification for the cation exchange high-performance liquid chromatography (CEX-HPLC) Basic Peak proposed for the AMD is slightly different from the specification registered for the PFS/auto-injector pen.

In addition to the release tests for the 420 mg prefilled cartridge finished product, the loaded AMD is gravimetrically tested for deliverable volume.

#### Functionality of the AMD

The functionality of the AMD is tested by the supplier. The accepted quality limits (AQL) of the AMD have been justified. It was confirmed that the viscosity of the placebo-filled cartridge used for functionality testing is equivalent with evolocumab 420 mg. After loading of the cartridge and activation of the AMD the 3.5 mL dose will be delivered within 9 minutes ( $\pm 1$  minute) with a continuous flowrate which is assured by the design of the software and the device.

The specifications of the 420 mg AMD finished product were presented and are considered acceptable.

#### Stability of the product

Finished product stability studies were performed as per ICH Q1A and Q5C guidelines. Stability studies were conducted at the recommended storage condition of 5 °C to support expiry and at elevated temperatures to support limited room temperature storage (controlled, 25 °C or less) and to support potential temperature deviations during handling and transportation. The finished product is sensitive to light, but shown to be stable during temperature cycling studies.

The stability program for the AMD includes additionally assessment of functionality for all lots studied. Other issues related to functionality of the device (injection time, buzzers, lights, leaking) are not addressed in a stability test. It is confirmed that the applicant is responsible for the stability studies regarding functionality of the device. The approach is sufficiently explained and is deemed suitable for its purpose.

Stability data compiled to date for the 420 mg AMD include primary, validation and supporting lots. When stored at the recommended and accelerated storage conditions of 5 °C, 25 °C, and 30 °C the test results remain within the proposed stability specification acceptance criteria through the latest time points tested. There is no indication that the stability is different from evolocumab filled in PFS or auto-injector/pen.

Overall the stability data support the 24 month shelf life at 5°C. If removed from the refrigerator, Repatha may be stored at room temperature (up to 25°C) in the original carton and must be used within one month.

### Adventitious agents

The information previously provided for Repatha (PFS and/or auto-injector/pen) on adventitious agents is applicable and considered sufficient. No material of animal origin is used in the manufacturing process of evolocumab.

## 2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The information provided to support this line extension is comprehensive and of appropriate quality. It provides an adequate description of development of the cartridge and the automated delivery device (AMD) as well as the manufacture and control of the finished product. Compatibility of the cartridge as well as comparability with the registered PFS presentation has been demonstrated.

A Major Objection was raised during the review regarding the need for CE marking for the AMD in accordance with Article 1(3) of the Council Directive 93/42/EEC that states:"...If, however, such a device is placed on the market in such a way that the device and the medicinal product form a single integral product which is intended exclusively for use in the given combination and which is not reusable, that single product shall be governed by Directive 2001/83/EC". Therefore, at the moment of the placing on the market, the three following cumulative conditions should be satisfied:

- The device and the medicinal product form a single integral product;
- Intended exclusively for use in the given combination;
- · Which is not reusable.

While in the present case the second condition (Intended exclusively for use in the given combination) and third condition (Which is not reusable) are considered satisfied, for the first condition the patient is clearly required to assemble the cartridge and the AMD before administration and consequently the AMD and the cartridge

containing the medicinal product did not a form "single integral product". Therefore the CHMP required that the AMD is CE marked. As a consequence, the applicant provided a CE mark for the AMD and the issue was considered resolved.

With the exception of the CE mark, no other major issues were raised during initial assessment of the dossier. A limited number of other concerns were identified and have been satisfactorily addressed. In particular, the applicant provided a detailed explanation regarding the AMD how a continuous flow rate is assured by the software and device design as well as the routine device lot testing. A continuous flow rate has been convincingly shown for three AMD lots. As a consequence, CHMP agreed that an additional release test for the AMD on this specific aspect is not needed.

The stability data for the AMD presentation are limited but support the claimed shelf life.

A post approval change management protocol (PACMP) was submitted for the addition of Amgen Manufacturing Limited building 1 (AML-1) located in Juncos, Puerto Rico, as an alternative manufacturing facility for the formulation and aseptic filling of evolocumab 420 mg prefilled cartridges. AML-1 is currently approved for formulation and filling of evolocumab 140 mg prefilled syringes (EMEA/H/C/003766/IB/0003). The PACMP is acceptable and the implementing Type IB variation is awaited.

# 2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

From a quality point of view the line extension is approvable when Repatha is used in accordance with the SmPC and package leaflet.

## 2.2.6. Recommendations for future quality development

Not applicable.

## 2.3. Non-clinical aspects

No new nonclinical studies were submitted with this application. This was considered acceptable. Since there is no overall increase in the daily dosage of evolocumab, the nonclinical studies previously submitted in the initial marketing authorization application are relevant to the line extension application and no further nonclinical studies were considered necessary.

## 2.3.1. Ecotoxicity/environmental risk assessment

No ERA have been done, which is agreed seen the nature of the product. Evolocumab is a protein composed of normal amino acids and readily biodegradable. Therefore it does not pose a risk for the environment.

## 2.3.2. Conclusion on the non-clinical aspects

The CHMP considered that from a non-clinical point of view the line extension for Repatha 420 mg solution for injection in cartridge was acceptable.

# 2.4. Clinical aspects

## 2.4.1. Introduction

No new clinical studies were submitted to support this line extension.

In the initial MAA evolocumab was evaluated in approximately 6800 subjects in 26 clinical studies presented herein representing 124 weeks of evolocumab treatment to support the two requested indications: 1) hypercholesterolaemia and mixed dyslipidaemia and 2) homozygous familial hypercholesterolaemia. Within the 26 studies in the evolocumab clinical program, 8 studies were primarily clinical pharmacology studies and the remaining 18 studies provided supportive data on the pharmacokinetic and pharmacodynamic properties of evolocumab.

The evidence supporting the lipid lowering indications for evolocumab included key data from 16 phase 2 and phase 3 evolocumab studies: 15 studies enrolled subjects with primary hyperlipidemia (heterozygous familial and nonfamilial) and mixed dyslipidemia and 2 studies enrolled HoFH subjects. From these studies, one study enrolled severe FH subjects (both HoFH and non HoFH) and supported both indications. Two additional randomized, device controlled, home use studies were also conducted.

Comparative **bioavailability between different devices** of administration was investigated in **study 20110168**. This study was submitted within the initial MAA and showed that the 420 mg dose administered with the automatic minidoser (AMD) was bioequivalent with the 3 Al/pens (1 mL each, 140 mg/mL).

#### 2.4.2. Pharmacokinetics

## Study 20110168

This study investigated comparative bioavailability between different devices of administration. It was a phase 1 open-label, randomized, parallel study in healthy volunteers to compare the pharmacokinetics of evolocumab when delivered subcutaneously (SC) via AMD (test article) versus 3 prefilled AI/pens (reference article).

Subjects were randomized equally into 1 of 2 parallel treatments. Treatment A was a 420 mg total dose of evolocumab via 3 prefilled AI/pens and treatment B was a 420 mg dose of evolocumab using a single AMD. Subjects were followed through study day 85 for safety, tolerability, pharmacokinetic, and pharmacodynamic assessments. A 12-week study period was chosen in order to characterize area under the drug concentration-time curve (AUC) from time 0 to the time of the last quantifiable concentration (AUClast) after a 420 mg dose.

Inclusion criteria for this study included, but were not limited to, healthy female subjects of non-reproductive potential and healthy male subjects  $\geq$  18 and  $\leq$  55 years of age who had a LDL level > 70 mg/dL and < 190 mg/dL and body mass index between 18 and 32 kg/m², inclusive, at the time of screening.

A total of 265 subjects (n = 130 for the AMD and n = 135 for the AI/pen) who received a full dose of IP and had a pharmacokinetic parameter estimated were included in the primary pharmacokinetic analysis set.

The purpose of the study was:

#### **Primary**

to demonstrate pharmacokinetic equivalence of the 3.5 mL personal injector (also referred to as automated mini-doser [AMD] in this report) (test article) to 3 prefilled autoinjector/pens (AI/pens) (reference article)

## Secondary

- to evaluate single-dose safety, tolerability, and additional pharmacokinetic parameters of AMG 145 administered by 3.5 mL personal injector and 3 prefilled AI/pens
- to compare low-density lipoprotein cholesterol (LDL-C) responses after administration with a 3.5 mL personal injector and 3 AI/pens
- to assess complete delivery of 3.5 mL personal injector and 3 AI/pens.

#### Table PK1 Evolocumab pharmacokinetic parameter after s.c. administration of evolocumab at 420 mg using an Automated Mini-doser (Test) Versus 3 Autoinjector/Pens (Reference)

Evolocumab 420 mg AMD (Test)				Evolocuma	(Reference)	
Descriptive	t <sub>max</sub>	C <sub>max</sub>	AUC <sub>last</sub>	t <sub>max</sub>	C <sub>max</sub>	AUC <sub>last</sub>
Statistics	(day)	(µg/mL)	(day•µg/mL)	(day)	(µg/mL)	(day•µg/mL)
N	130	130	118	135	135	122
Mean	NR	59.0	924	NR	53.7	870
SD	NR	17.2	346	NR	16.8	309
Min	2.0	8.63	162	1.9	14.8	190
Median	4.0	56.6	841	4.0	51.2	815
Max	9.9	103	2150	10	108	2010
CV%	NR	29.2	37.5	NR	31.3	35.5

Al/Pen = autoinjector/pen; AMD = automated mini-doser; AUC<sub>last</sub> = AUC from time zero to time of last quantifiable concentration; C<sub>max</sub> = Maximum observed drug concentration; CV = coefficient of variation; SD = standard deviation; t<sub>max</sub> = Time to reach C<sub>max</sub>

Table PK2 Statistical evaluation of pharmacokinetic parameter of evolocumab after s.c. administration of evolocumab at 420 mg using an Automated Mini-doser (Test) versus 3 Autoinjector/Pens (Reference)

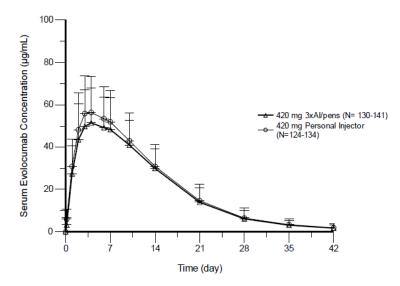
		AMD (Test) (N = 130)			(			Ratio of Test/Reference <sub>3</sub>	
Parameter(unit)	n	LSMean	90% CI	n	LSMean	90% CI	LSMean	90% CI	
AUClast	118	862.62	(815.31, 912.68)	122	817.55	(773.43, 864.18)	1.06	(0.96, 1.14)	
(day*ug/mL)									
Cmax (ug/mL)	130	56.19	(53.59, 58.93)	135	51.07	(48.74, 53.51)	1.10	(1.03, 1.18)	

CI = Confidence Interval.

LS Mean = least squares geometric mean from the SAS PROC MIXED procedure are based on natural log scale data converted back to the original scale.

AMD = automated mini-doser

Mean (SD) unbound evolocumab concentration-time curves after s.c. administration Figure PK3 of 420 mg using an Automated Mini-doser (Test) versus 3 Autoinjector/Pens (Reference)



The AMD and AI/pen devices were bioequivalent based on the 90% CI for the ratio (AMD to AI/pen) for both  $C_{max}$  and AUC<sub>last</sub>. Changes in UC LDL-C and PCSK9 indicated a similar pharmacodynamic response for each drug product presentation. Complete delivery of evolocumab was obtained for 93.1% of the AMDs used and 98.9% of the AI/pens used.

Study 20110168 showed that the 420 mg dose administered with the AMD presentation at 120 mg/mL with a 3.5 mL fill was pharmacokinetically equivalent to the reference presentation of 3 AI/pens (1 mL each, 140 mg/mL).

Although not directly compared, the pharmacokinetic comparability of a 420 mg dose administered using 3 PFS injections or 1 AMD injection can be also inferred from the pharmacokinetic equivalence of a single PFS or AI injection of evolocumab 140 mg in Study 20120133 and the pharmacokinetic equivalence of 3 AI/pen injections or 1 AMD injection of evolocumab 420 mg.

#### 2.4.3. Conclusions on clinical pharmacology

Comparative bioavailability between different devices of administration was investigated in study 20110168, assessed within the IMA procedure. This study showed that the 420 mg dose administered in currently assessed presentation as solution for injection in cartridge (containing 420 mg of evolocumab in 3.5 mL of solution [120 mg/mL]) used with automatic mini-doser (AMD) was bioequivalent with the 3 autoinjector/pens ([AI/pens]; containing 140 mg of evolocumab in 1 mL of solution each, [140 mg/mL]).

The CHMP considered that the 420 mg dose administered with the new proposed presentation (solution for injection in cartridge used with AMD) was equivalent to the authorised reference presentation of 3 AI/pens. Therefore the addition of the new strength Repatha, 420 mg solution for injection in cartridge with AMD was considered acceptable from clinical pharmacology point of view.

# 2.5. Clinical efficacy

No new clinical studies were submitted to support this line extension. The efficacy of a dose of 420 mg evolocumab has been demonstrated during initial marketing authorisation.

For primary hypercholesterolaemia and mixed dyslipidaemia in adults the recommended dose of Repatha is either 140 mg every two weeks or 420 mg once monthly. Both doses are clinically equivalent. For homozygous familial hypercholesterolaemia in adults and adolescents aged 12 years and over the initial recommended dose is 420 mg once monthly. After 12 weeks of treatment, dose frequency can be up-titrated to 420 mg once every 2 weeks if a clinically meaningful response is not achieved. Patients on apheresis may initiate treatment with 420 mg every two weeks to correspond with their apheresis schedule.

# 2.5.1. Conclusions on the clinical efficacy

No new clinical studies were submitted within current application. This was considered acceptable as the use of Repatha 420 mg dose was authorised within initial marketing authorisation (IMA) procedure for use once monthly or every 2 weeks. It was recommended to deliver this dose using three pre-filled syringes/pre-filled pens administered consecutively within 30 minutes. With current application it was agreed that this 420 mg dose once monthly or every 2 weeks could be also delivered using a single cartridge with automated mini-doser (AMD) device.

The CHMP considered the line extension to add new strength, Repatha 420 mg solution for injection in cartridge with AMD, to be acceptable from clinical efficacy point of view.

# 2.6. Clinical safety

The safety of evolocumab in the 420 mg dose has been demonstrated during initial marketing authorisation.

An additional Clinical Device Safety Summary was submitted for the AMD presentation which summarizes complaints and adverse device effects as reported for 3 completed clinical trials and an ongoing clinical trial with a data cut-off of 01 July 2014. The completed clinical trials to which is referred to were already assessed during the initial marketing authorisation application.

Table 1: Summary of Clinical Studies with AMD Devices Used in the Evolocumab Program

Study	Brief Description	Device(s) Used			
Clinical Pharmacology Studies (Phase1)					
20120135	Drug delivery performance of the 3.5 mL personal injector (AMD) using placebo buffer				
20110168	PK/PD equivalence of AI/pen vs. AMD AI/pen, AMD				
Efficacy and Safety Studies for Hyperlipidemia and Mixed Dyslipidemia					
20120138 (ongoing)	Controlled, Long-term Study (Phase 3)  Long-term, controlled, open-label extension; AI/pen self-administration (OSLER-2)				
20120356 Device Home-Use Study with Self Administration (Phase 3) Clinical home use of evolocumab with AI/Pen vs. AMD		AI/pen, AMD			

Al/pen = autoinjector/pen; AMD = automated mini-doser; PD = Pharmacodynamic; PK = Pharmacokinetic. All studies are completed unless indicated as ongoing. The data cut-off for ongoing studies is 1 July 2014.

Additionally cumulative complaints and adverse device effects data for the evolocumab 420 mg automated mini-doser (AMD) have been provided with a data cut-off date of 17 January 2016 (coinciding with the most recent PSUR data lock point). The updated data came from the only ongoing trial to use the AMD, Study 20120138.

#### Adverse events

## <u>Device Related Adverse Events</u>

Data from clinical studies demonstrate that all 3 subcutaneous (SC) presentations (ie, prefilled syringe [PFS], autoinjector/pen [AI/pen] and automated mini-doser [AMD]) evaluated during the evolocumab clinical development program exhibited **device related adverse events that were uncommon, mostly grade 1**, and generally limited to injection site reactions.

The AI/pen was used in the controlled blinded phase 3 studies. Across the controlled blinded phase 3 device studies, fewer than 3% of subjects reported a device related adverse event. The overall incidence of device related adverse events across treatment groups were 1.5% in evolocumab 140 mg Q2W; 2.8% in evolocumab 420 mg QM, 0.8% in placebo Q2W, and 2.6% in placebo QM. The large **majority** of device-related adverse events were **related to the injection site** (ie, injection site bruising, injection site erythema, and injection site pain). Most device related adverse events were grade 1 in severity. Furthermore, there were no serious or unexpected device related adverse events reported in clinical studies of evolocumab.

In the year 1 standard of care (SoC) - controlled period, thirty seven (1.9%) subjects reported device related adverse events in the evolocumab plus SoC group. All 37 subjects were in the evolocumab group because subjects assigned to SoC alone did not receive any placebo injections. Most device related adverse events were grade 1 in severity.

During the year 2+ open label extension period, 17 subjects received evolocumab via AI/pen in study 20120138, and no device related adverse events were reported.

Two phase 3, evolocumab clinical home-use studies (20120348 and 20120356) assessed the effective administration of evolocumab by subjects or caregivers in the home use setting (self-administration) using the 3 different SC presentations (PFS, AI/pen, and AMD) and showed consistent results with the safety profile across the evolocumab program.

A total of 23 new device failures were reported with a total of 3678 new injection attempts with the AMD device since the original submission data **cut-off of 01 July 2014**. This information, combined with a low number of device related adverse events (all non-serious and CTCAE grade 1 or grade 2 in severity), supports the safety profile of the AMD.

Updated total number of complaints and device related adverse events with a data cut-off of 17 January 2016

The updated total number of complaints and device related adverse events with a data **cut-off of 17 January 2016**, derived from the ongoing extension study (20120138) was provided and indicated that there were no serious or unanticipated clinical effects or harms associated with the use of the AMD device.

A total of 251 total complaint issues were reported out of a total of 4506 AMD injections (181 new complaints out of 3978 new device injection attempts since the previous cut-off). As described by the applicant, the total

number of complaint issues represents complaints not associated with device failures, those associated with device failures, and those currently under further root cause investigation.

#### Non-device issues

Of the 251 AMD device complaints, 158 were non-device issues, of which the majority were associated with use errors. The highest percentages of errors were due to "device door not fully closed" (61 errors) and "activation button pressed prior to application" (21 errors). The CHMP considered 158 of non-device issues out of 4506 device injection attempts (3.5%) relatively low and therefore acceptable. Additionally, the applicant has **updated the Instructions for Use** documentation resulting in a subsequent reduced rate of use errors observed in the extension Study 20120138, suggesting an even lower percentage of non-device issues in the future. However, these findings may be biased, since the applicant has not made a distinction between attempts and subsequent non-device issues observed in new or experienced users of the AMD. Furthermore, the CHMP considered these non-device issue of less importance compared to device failures since it was clear that in most of these use errors evolocumab had not been administered at all and, consequently, a new AMD device has to be used.

#### Device failures

Since the data cut-off date of July 2014, there has been 23 new confirmed device failures reported in the ongoing extension study despite an increase of 3678 injection attempts. According to the applicant, the performance was attributed to the recent design changes. Overall, the updated data showed a device failure of 1.7% which was considered relatively low and therefore reassuring. As already stated above, the most likely clinical consequences of a device failure are underdosing. The CHMP acknowledged that a single underdosing event will not lead to an immediate safety risk to the patient. Additionally, consecutive suspected underdosing events could also be easily confirmed by LDL-C analysis. Additionally, in the Instructions for Use it is advised that when a patients has persistence of repeat device failures this should be discussed with the healthcare professional.

Furthermore, since the cut-off date of July no unexpected or serious device related adverse has been observed. The incidence of device related adverse events was low, grade 1 or grade 2 and generally limited to injection site reactions.

It was agreed with the MAH that neither unanticipated clinical effects nor harms were associated with the use of the new AMD device. Device related adverse events were uncommon, mostly not severe, and generally limited to injection site reactions (injection site bruising, injection site erythema, and injection site pain). There was a slightly higher incidence in device related adverse events in the QM regimen compared to the Q2W, which may be due to the differences injection frequency (1 injection for 140 mg Q2W and 3 injections for QM per treatment time point). However, there were no apparent differences in incidence in device related adverse events between subjects receiving evolocumab compared with those receiving placebo regardless of the device used.

It was not specified whether the complaints and adverse device effects reported during the completed phase 3 clinical trial (Study 2010356) and the ongoing clinical trial (Study 20120138) occurred under clinical site supervision in the clinic or without supervision in a home-use setting. Due to the low number of device-related adverse events and imbalance between home-use injections and in-clinic injections, no firm conclusions can be made regarding whether the device complaints occurred more often in a home-use setting than in the clinic. However, considering that the percentage of complaints is relatively low despite that the number of home-use injections is greater than the number of in clinic injections this can be accepted.

Based on the evidence and considerations discussed above, the CHMP considered the inclusion of "Device Failure" as an important risk in the EU-RMP not warranted.

# 2.6.1. Conclusions on the clinical safety

The updated total number of complaints and device related adverse events with a data cut-off of 17 January 2016, derived from the ongoing extension study (20120138) was provided and indicated that there were no serious or unanticipated clinical effects or harms associated with the use of the AMD device.

The safety of evolocumab in the 420 mg dose has been demonstrated during initial marketing authorisation (IMA) application. The safety of this dose delivered as solution for injection in a cartridge to be used with the automated mini-doser (AMD), has been sufficiently demonstrated. Therefore, from a clinical safety point of view, the CHMP considered that the line extension for Repatha 420 mg solution for injection in cartridge was acceptable.

# 2.7. Risk Management Plan

An updated RMP version 1.3 was provided in support of the application. The MAH has updated the RMP with information regarding the automated mini-doser (AMD) device and made some editorial changes to ensure that the content reflects the recent approval of Repatha.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 1.3 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 1.3 with the following content:

## Safety concerns

**Table 2: Summary of Safety Concerns** 

Important identified risks	None
Important potential Risks	<ul><li>Hypersensitivity</li><li>immunogenicity</li></ul>
Missing information	- use in pregnant/lactating women
	- use in paediatric patients
	- use in elderly patients ≥ 75 years old
	- use in patients with severe renal impairment
	- (eGFR < 30 mL/min/1.73m2)
	- use in patients with severe hepatic impairment (Child-Pugh class C)
	- use in patients with Hepatitis-C
	- use in patients with type 1 diabetes

-	use in patients with HIV
-	long-term use including effects of LDL-C $<$ 40 mg/dL or $<$ 1.03 mmol/L

## Pharmacovigilance plan

There are no changes to the pharmacovigilance plan.

The PRAC, having considered the updated data submitted, was of the opinion that no changes to the existing pharmacovigilance plan are warranted.

#### Risk minimisation measures

There were no changes to the risk minimisation measures proposed.

The PRAC, having considered the updated data submitted, was of the opinion that no changes to the existing risk minimisation measures are warranted.

# 2.8. Pharmacovigilance

# Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

#### 2.9. Product information

#### 2.9.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed within the current application on the basis of a bridging report making reference to Repatha initial MAA.

The applicant considered that the results from the original patient consultation were applicable for the addition of the cartridge on the basis that: (1) the pharmaceutical form remained unchanged (solution for injection), (2) the route of administrations remained unchanged (subcutaneous use), (3) the design and layout of the package leaflet remained consistent with the approved package leaflet, (4) the risks and safety information described in the parent package leaflet remained unchanged, (5) the clinical benefits described in the parent package leaflet remained unchanged, (6) administration instructions followed the same content, allowing for changes in the proposed pharmaceutical presentation.

The CHMP agreed the information in the PL is the same, but the specific instructions for use of Repatha single use automated mini-doser and cartridge are significantly longer and contain additional steps compared (e.g. loading of the cartridge and troubleshooting) to the prefilled pen or syringe. The device has received a CE mark, and the instructions for use (IFU) were considered a critical part of the product information to ensure the correct administration of the medicinal substance. Therefore the applicant performed a user testing on the instructions for use for Repatha single use AMD and cartridge. The report submitted by the applicant has been found acceptable.

# 2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Repatha (evolocumab) is included in the additional monitoring list as it contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU and it is a biological product that is not covered by the previous category and authorised after 1 January 2011.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

## 3. Benefit-Risk Balance

#### Benefits

Evolocumab is a **first in class** fully human monoclonal immunoglobulin G2 directed against human proprotein convertase subtilisin/kexin type 9 (PCSK9), which inhibits circulating PCSK9 from binding to the LDLR on the liver cell surface, thus preventing PCSK9-mediated LDLR degradation. This leads to LDL-C reduction.

Evolocumab is authorised in treatment of patients with hypercholesterolaemia or mixed dyslipidaemia and in patients with homozygous familial hypercholesterolaemia. The effect of evolocumab on cardiovascular morbidity and mortality has not yet been determined. Efficacy has been demonstrated based on the reduction in LDL-C level, an established surrogate marker for cardiovascular disease. The effect of Repatha on cardiovascular morbidity and mortality is investigated in long-term ongoing clinical trials.

**No new clinical studies were submitted** within current application. The use of Repatha 420 mg dose was authorised within initial marketing authorisation (IMA) procedure where it was agreed that the dose 420 mg once monthly or every 2 weeks should be delivered using three pre-filled syringes or pre-filled pens administered consecutively within 30 minutes. With current application it was proposed to add new strength, Repatha 420 mg. This would permit that 420 mg dose once monthly or every 2 weeks could be delivered as single injection using cartridge with automated mini-doser (AMD) device.

Comparative bioavailability between different ways of administration was investigated in study 20110168, assessed within the IMA procedure. This study showed that the 420 mg dose administered in currently assessed presentation as solution for injection in cartridge (containing 420 mg of evolocumab in 3.5 mL of solution [120 mg/mL]) used with AMD was bioequivalent with the 3 autoinjector/pens ([AI/pens]; containing 140 mg of evolocumab in 1 mL of solution each, [140 mg/mL]).

#### Risks

The safety of evolocumab in the 420 mg dose has been demonstrated during IMA procedure where it was concluded that **evolocumab displayed an acceptable safety profile** with a comparable or slightly higher incidence of adverse events to that of the comparator therapy (placebo or standard of care), with very limited patients discontinuing treatment or showing serious adverse events. In addition, evolocumab treatment did not cause any major effects on known safety problems associated with existing lipid lowering therapies such as liver disorders, renal disorders, diabetes and musculoskeletal disorders.

No new clinical studies were provided within current application. **Cumulative complaints and adverse device effects data for the evolocumab 420 mg automated mini-doser (AMD)** were provided with a data cut-off date of 17 January 2016 (coinciding with the most recent PSUR data lock point); the updated data came from the only ongoing trial to use the AMD, Study 20120138.

#### Benefit-risk balance

The CHMP considered that the benefit-risk balance for the line extension Repatha 420mg solution for injection in cartridge (containing 420 mg of evolocumab in 3.5 mL of solution) to be positive.

# 4. Recommendations

#### **Outcome**

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Repatha 420 mg Solution for injection is favourable in the following indication:

#### Hypercholesterolaemia and mixed dyslipidaemia

Repatha is indicated in adults with primary hypercholesterolaemia (heterozygous familial and non familial) or mixed dyslipidaemia, as an adjunct to diet:

- in combination with a statin or statin with other lipid lowering therapies in patients unable to reach LDL C goals with the maximum tolerated dose of a statin or,
- alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

#### Homozygous familial hypercholesterolaemia

Repatha is indicated in adults and adolescents aged 12 years and over with homozygous familial hypercholesterolaemia in combination with other lipid-lowering therapies.

The effect of Repatha on cardiovascular morbidity and mortality has not yet been determined.

The CHMP therefore recommends the extension(s) of the marketing authorisation for Repatha subject to the following conditions:

### Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

### Conditions and requirements of the Marketing Authorisation

### Periodic Safety Update Reports

The requirements for submission of periodic safety update reports 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 medicines web-portal.

# Conditions or restrictions with regard to the safe and effective use of the medicinal product

# Risk Management Plan (RMP)

The 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.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

These conditions fully reflect the advice received from the PRAC.