



23 June 2016
EMA/CHMP/748108/2013, Rev. 3
Committee for Medicinal Products for Human Use (CHMP)

Guideline on clinical investigation of medicinal products in the treatment of lipid disorders

Adopted by CHMP	July 2004
Date for coming into effect	January 2005
Adopted by CHMP for release for consultation (Draft Guideline Rev. 1)	18 November 2010
Start of public consultation	30 November 2010
End of consultation (deadline for comments)	31 May 2011
Agreed by Cardiovascular Working Party (Draft Guideline Rev. 1 + Rev. 2)	28 November 2012
Adopted by CHMP for release for consultation (Draft Guideline Rev. 1 + Rev. 2)	3 December 2012
Start of public consultation	15 December 2012
End of consultation (deadline for comments)	15 March 2013
Adopted by Cardiovascular Working Party	27 November 2013
Adopted by CHMP	19 December 2013
Date for coming into effect	01 June 2014
Agreed by Cardiovascular Working Party	11 May 2016
Adopted by CHMP	23 June 2016
Date for coming into effect	1 January 2017

Keywords	<i>lipid lowering agents, cholesterol, hypercholesterolemia, statins</i>
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Cover Note to the June 2016 update of the Guideline

This Guideline replaces the '*Guideline on clinical investigation of medicinal products in the treatment of lipid disorders (EMA/CHMP/748108/2013)*'. The changes follow the adoption of the CHMP '*Reflection paper (RP) on assessment of cardiovascular safety profile of medicinal products (EMA/CHMP/50549/2015)*' and were aligned with simultaneously adopted modifications to the CHMP '*Guideline on Clinical investigation on medicinal products in the treatment of hypertension (EMA/CHMP/29947/2013/Rev. 4)*' and the '*CHMP Guideline on clinical evaluation of medicinal products used in weight management (EMA/CHMP/311805/2014)*'. Hence the CHMP considered that the Concept Paper and the public consultation phases are not needed as they took place in the context of implementation of the RP where already reference is made to this guideline. This justification is provided in line with the '*Procedure for European Union Guidelines and Related documents within the pharmaceutical legislative framework (EMEA/P/24143/2004 Rev. 1 corr)*'.

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Executive summary

This document is the revised version of the 'Note for guidance on clinical investigation of medicinal products in the treatment of lipid disorders (CHMP/EWP/3020/03)'. It is intended to provide guidance for the evaluation of drugs in the treatment of lipid disorders and details the main regulatory requirements that are expected to be followed in the development of a lipid modifying medicinal product. In particular, the sections concerning the recommended endpoints and long term safety data, including morbidity and mortality data, have been updated. Furthermore the document was updated following finalisation of the *Reflection paper on assessment of cardiovascular safety profile of medicinal products (EMA/CHMP/50549/2015)*. Latterly, there is an attempt to use imaging modalities as surrogate markers of outcome benefit with lipid modifying agents in many trials. This section of the guideline has also been revised in order to provide a discussion of regulatory aspects of these markers.

1. Introduction (background)

Lipid disorders may manifest in different ways, leading to changes in plasma lipoproteins levels and/or function. Lipid disorders are commonly classified according to the prevailing laboratory abnormality, but this classification does not accurately represent the different genetic and metabolic defects, or clinical syndromes. Blood lipid levels may be affected by other clinical conditions such as diabetes mellitus, thyroid disorders or nephrotic syndrome; in such cases, the lipid levels should be reassessed once the underlying disease has been controlled or treated.

Lipid disorders most often imply hypercholesterolemia. A large body of epidemiological evidence now 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 reduces risk for CHD. The relationship between LDL-C levels and CHD risk is present over a broad range of LDL levels. The dividing line between "normocholesterolemia" and "hypercholesterolemia" is arbitrary and in fact may be non-existent. Epidemiologic data indicate a continuous increasing risk from very low to "normal" and high levels of LDL-C.

Treatment decisions are based not only on the level of LDL-C, but on the overall, multifactorial level of cardiovascular risk. Modifications of LDL-C goals are discerned on the basis of:

- Presence of clinical forms of atherosclerosis (CHD, ischemic stroke or peripheral vascular disease)
- Diabetes mellitus
- chronic kidney disease
- Integrated global risk scoring models (e.g. SCORE)
- Monogenic dyslipidaemia (e.g. familial hypercholesterolemia)

Concomitantly other lipid disorders may be present, in particular hypertriglyceridemia ("mixed hyperlipidemia"). In addition, lipid disorders may also implicate isolated or prevalent hypertriglyceridemia and/or low high density lipoprotein cholesterol (HDL-C). Although elevated triglycerides (TG) are noted as a risk factor, the evidence on the benefits of lowering elevated TG levels is still modest when LDL-C and HDL-C changes are corrected for. The treatment strategy for

elevated TG depends on the causes of the elevation and its severity. Low HDL -C level, whether or not in conjunction with elevated LDL-C or TG levels, has also been shown to be a risk factor for cardiovascular disease (CVD). Low HDL-C warrants clinical attention although the goal of therapy needs further specification due to lack of direct evidence that raising HDL-C is associated with CVD prevention. More recently other lipoproteins e.g. lipoprotein Lp(a) and apolipoprotein Apo(B), have also been investigated as possible risk factors for CHD. However, their role is not clearly defined at the present time.

2. Scope

The guideline provides advice to applicants on the main regulatory requirements that are expected to be followed in the development of a medicinal product for treatment of lipid disorders associated with increased cardiovascular risk encountered in adult patients (i.e. lipid modifying agents). Lipid disorders in paediatric patients are addressed in a separate addendum.

3. Legal basis and relevant guidelines

This guideline should be read in conjunction with the introduction and general principles and Annex I to Directive 2001/83 as amended and with the following guidelines:

- Note for Guidance on General Considerations for Clinical Trials (CHMP/ICH/291/95, ICH E8)
- Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95, ICH E6)
- Note for Guidance on Dose Response Information to support Drug Registration (CPMP/ICH/378/95, ICH E4)
- Note for Guidance on Statistical Principles for Clinical Trials (CPMP/ICH/363/96, ICH E9)
- Note for Guidance on Choice of Control Group for Clinical Trials (CPMP/ICH/364/96, ICH E10)
- Guideline on the choice of the Non-inferiority margin (EMA/CPMP/EWP/2158/99)
- Points to Consider on Switching between Superiority and Non-inferiority (CPMP/EWP/482/99)
- Note for Guidance on the Investigation of Drug Interactions (CPMP/EWP/560/95)
- Note for Guidance on Population Exposure: The extent of population exposure to assess clinical safety (CPMP/ICH/375/95 adopted November 1994)
- ICH E7: Studies in support of special populations: geriatrics
- Points to consider on multiplicity issues in clinical trials (CPMP/EWP/908/99)
- Paediatric addendum to CHMP guideline on clinical investigation of medicinal products in the treatment of lipid disorders (EMA/CHMP/494506/2012)
- Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus (CPMP/EWP/1080/00 Rev. 1)
- Guideline on the evaluation of medicinal products for cardiovascular disease prevention EMA/CHMP/EWP/311890/2007
- Guideline on clinical investigation of medicinal products in the treatment of hypertension (EMA/CHMP/29947/2013/Rev. 4).

- Reflection paper on assessment of cardiovascular safety profile of medicinal products (EMA/CHMP/50549/2015)

In addition, all pertinent elements outlined in current and future EU and ICH guidelines and regulations should also be taken into account.

4. Evaluation of efficacy

Efficacy may be evaluated using a number of parameters ranging from modification of lipid levels to demonstration of effect on clinical outcomes.

4.1. Efficacy endpoints

4.1.1. Morbidity and mortality

The primary goal of treating lipid disorders is to prevent cardiovascular morbidity and mortality associated with disturbed lipid levels. HMG-CoA reductase inhibitors have accrued considerable evidence demonstrating reduction of cardiovascular events (including stroke) and overall mortality in patients with cardiovascular risk factors, irrespective of their LDL-C levels. Such robust evidence is not consistently seen with other lipid modifying agents.

The requirement of clinical studies showing beneficial outcome on morbidity and mortality during registration largely depends on the mechanism of action and the pharmacological class of the medicinal product and the target population. Such studies are not foreseen for the registration of a new HMG-CoA reductase inhibitor. Until clinical trial data are available, it should be specifically mentioned in the Summary of product characteristics (SmPC) that beneficial effects on mortality and morbidity have not been evaluated.

For medicinal products modifying lipid parameters other than LDL-C, demonstration of a positive clinical outcome in terms of morbidity and mortality is required.

4.1.2. Lipid levels

A relative reduction in LDL-C level is acceptable as a primary efficacy endpoint in patients with primary hypercholesterolemia, provided that claims in the label are restricted to a lipid lowering effect.

In principle, an isolated effect on TG or HDL-cholesterol is not expected to be the sole basis for the demonstration of the efficacy of a new lipid-modifying agent, but should be seen in conjunction with the effect on non-HDL cholesterol and the underlying pharmacological mechanisms of actions (see section 4.2.2).

There is limited experience with clinical studies investigating medicinal products which qualitatively modify dyslipidaemias. Scientific advice could be requested to specifically address such developments.

4.1.3. Vascular damage (target organ damage)

Target organ damage of heart, brain, kidneys and, in particular, blood vessels is presumably and plausibly associated with morbidity and mortality. Vascular damage is an integral part of atherosclerosis. Imaging modalities such as IMT (intima media thickness) measurement, IVUS (intravascular ultrasound), and MRI (magnetic resonance imaging), have evolved over the past few years as indicators of vascular (or target organ) damage and atherosclerotic burden. Amongst various modalities available, cIMT (carotid IMT) and IVUS may have sufficient validity and weight of evidence

for use in phases of drug development including dose finding studies as markers of atherosclerotic process. However they lack the evidence base to suggest that small changes in these parameters influence outcome (that is, to be considered as surrogate markers).

Therefore, in the developmental phase (phase II or phase III), the possible parameters for evaluation could include reduction in IMT with treatment, changes in plaque volume or burden, changes in plaque composition and reduction in number of plaques at a variety of sites. Irrespective of the method used, its validity and reliability need to be specifically documented particularly at each specific site including its correlation with clinical endpoints such as either all-cause mortality or cardiovascular (CV mortality). In this context, data generated from two different vascular beds by two different techniques is considered more robust in estimating the overall atherosclerotic burden. Demonstration of regression of atherosclerotic burden is the preferred parameter of effect rather than lack of progression as the endpoint. While evidence may be generated from a single study of adequate sample size that evaluates imaging outcomes in the short term and CV outcome in the long term as part of validation using an embedded design, ideally, validation and confirmation should come from two independent studies. When two independent studies are used, directional concordance of effect of intervention, for example, with use of lipid modifying agents is expected. In such cases, care should be taken to ensure that the baseline characteristics of subjects or patients recruited are consistent between studies. In long term studies, ethical considerations governing the use of placebo should be taken into account.

At the present time, in adults, it is difficult to envisage an indication solely based on use of these imaging markers as their independent contribution to the risk stratification, or as a risk marker when adjusted for conventional risk factors, remains to be established. Therefore, the parameters evaluated by these modalities should correlate with clinically relevant outcomes. When such markers are included in the clinical trials or an attempt is made to base the indication on these parameters, the onus rests with the company to demonstrate the necessary link between the marker, clinical event and the influence of the therapeutic intervention on imaging measures in the chosen patient population.

4.2. Methods to assess efficacy

4.2.1. Evaluation of morbidity and mortality

To show a beneficial effect on CV morbidity and mortality, the preferred primary endpoint should be a composite of major cardiovascular events (CV or all-cause death, non-fatal myocardial infarction and non-fatal stroke) adjudicated by a blinded, independent committee. If cardiovascular instead of all-cause mortality is chosen, effects on non-cardiovascular mortality should also be taken into account.

The inclusion of other events, such as transient ischemic attack, silent MI, unstable angina pectoris or therapeutic interventions (need for PCI) is used in some trials to increase statistical efficiency. The inclusion of such softer endpoints, which are less objectively defined can complicate interpretation of the results, and is accordingly not encouraged. If included, clinically relevant justifications should be provided. The use of standard definitions as proposed in the appropriate clinical guidelines or regulatory guidance documents are encouraged.

4.2.2. Measurement of lipid levels

Lipid-altering effects of lipid-modifying agents should be documented as the pre-/post- treatment change in lipid levels. All measurements should be performed under standardised, fasting conditions following a dietary lead-in period with or without wash-out of appropriate duration, depending on the pharmacological action of the administered standard therapy and as justified by the sponsor.

In patients with primary hypercholesterolemia reduction in LDL-C is the primary endpoint to support the indication of hypercholesterolemia or mixed hyperlipidaemia. As a secondary endpoint these effects can also be assessed with respect to response criteria according to internationally accepted standards, such as those formulated by the European Atherosclerosis Society (EAS) or National Cholesterol Education Program (NCEP). Changes in TG, and HDL-C should also be studied as secondary parameters as they are becoming increasingly used to assist treatment recommendations. Estimation of non-HDL-C can also serve as a valid secondary endpoint in certain conditions, e.g. hypertriglyceridaemia with diabetes.

Other lipid parameters, such as apolipoprotein A1 (apo A1), apolipoprotein B (apo B), or the balance between apo B and apo A1 (or apoB/apoA1 ratio), and lipoprotein (a), can be considered secondary efficacy measures only if considered relevant to the primary outcome. In diabetic subjects pre/post treatment change in glycaemic control should be documented, as this may affect lipid levels.

It is also recognized that not only quantitative lipid abnormalities exist, but qualitative abnormalities as well, such as small and dense or oxidized, that may become prime targets for new forms of lipid modifying agents.

4.2.3. Assessment of vascular damage (target organ damage)

An imaging surrogate biomarker for atherosclerosis might be intended to measure the change in thickness of the IMT either in carotid artery or in the coronary arteries, measure changes in plaque volume/burden including the number of plaques or measure changes in plaque composition. Importantly, the surrogate marker should be reproducible and correlate with an accepted clinical outcome measure. Several methodologies as detailed above (cIMT, IVUS, MRI or other) could be used in the detection of these imaging surrogate markers. For any marker or methodology (cIMT or IVUS), it is important that the investigative staff receive comprehensive training and those reading the images are blinded to treatment and sequence. Image acquisition and analysis should be carried out by experienced technicians to a high, reliable quality. It is important to ensure that measurement methodology, the sites of measurement, the operator and the ultrasound machine are optimal at all trial sites. A centralised laboratory measurement is recommended and inter-observer variability should be discussed in the study report. This should be minimised and the impact of such variability should be discussed in any regulatory submission. Based on the current level of evidence, two methodologies are considered relevant for discussion.

cIMT

For cIMT, images of right as well as left common carotid arteries (CCA), carotid bulb and internal carotid arteries (ICA) need to be obtained. The pre/post intervention difference in IMT needs to be defined a priori and adequately justified (such as 0.05 mm/year or other appropriate value) along with the clinical relevance. It is recommended that the change in mean maximum IMT be the primary measurement across 12 pre-selected carotid arterial segments over time (18 - 24 months; as a study of shorter duration will neither be conclusive nor helpful). If fewer segments are chosen based on other considerations, they will need to be adequately justified including consensus reports and evidence base. It is also recognised that mean IMT has been considered as a relevant parameter by some groups, but the evidence base to support this will need to be included in any justification. The following secondary measurements could be considered: absolute change from baseline of the combined cIMT (CCA, carotid bulb and ICA of both right and left carotid arteries) after 24 months, the difference in slope of the far-wall mean IMT (both common carotid arteries), the change in mean and/or maximum far wall IMT, the rate of progression measured as linear slope on annual ultrasound examinations and the average of the maximum cIMT of the far wall of up to 6 arterial segments.

IVUS

In order to demonstrate changes with IVUS using a pullback method, a minimum of 20% luminal narrowing of the relevant coronary artery at baseline is required. It is recognised that IVUS is invasive, but efforts should be made to include at least two measurements at relevant time points in the same arterial segment (e.g. baseline and end of treatment period) under similar conditions. Use of IVUS in conjunction with cIMT in the same study should be considered. For IVUS, percent plaque volume (change from baseline) is recommended as the primary measurement. Alternatively, total plaque burden or total atheroma volume is the other preferred measurement. In each instance, justification that the chosen value is of clinical significance will be required. In addition, the impact on the lumen diameter needs to be established. Other measures that could be considered include normalised total plaque volume (percent change) and plaque volume in most diseased 10mm³ segment (change from baseline in mm and percent change).

5. Selection of patients

For the evaluation of the effects of a new agent for treatment of lipid disorders, the study population will generally depend on the type of lipid disorders for which the drug is intended. Studies for the evaluation of efficacy or safety of a new lipid-modifying agent are mainly performed in patients with primary hypercholesterolemia and mixed hyperlipidemia with moderate to very highly elevated LDL-C levels. Both genders should be adequately represented in the studied population. Children and adolescents below 18 years are addressed in the paediatric addendum to the guideline. The number of subjects 75 years and older included in (pivotal) trials should be sufficient to assess both efficacy and safety in this group.

For the evaluation of clinical outcomes, patients should be chosen with a well characterised risk level and either homogeneous or stratified based on risk level, thus permitting a straightforward extrapolation of the results. Patients with clinical and/or other manifestations of atherosclerosis and/or type 2 diabetes mellitus should be represented in adequate numbers that will permit sub-group analysis and also evaluation of consistency with the overall results of the study. These studies may include patients with borderline high or even "normal" cholesterol levels.

When specifically claimed, patients with familial hypercholesterolemia (heterozygous and homozygous) should normally be studied in separate clinical trials, based on their cholesterol levels and clinical genetic characteristics.

6. Strategy and design of clinical trials

Studies involving the first administration of medicinal products for lipid disorders to man do not differ essentially from those dealing with other cardiovascular medicinal products.

In all studies a dietary lead-in period is obligatory before randomization. Inclusion criteria and the reliability of the methods used to establish the diagnosis should be justified, taking into account such factors as the target population and assay accuracy. For patients administered similar or other lipid-modifying therapies, these should be withdrawn at the start of this period when monotherapy is studied, requiring an adequate wash-out. Dietary supplements should be recorded and remain unchanged throughout the trial duration.

6.1. Pharmacodynamics

Pharmacodynamic studies should include evaluation of mechanism of action, tolerability, duration of action, and relevant clinical or haemodynamic parameters. Investigation of off target effects for example blood pressure, immunological reactions or complement activation may be necessary. When off target effects are noted in early, they will need specific attention during subsequent phase 2 or 3 studies. Further studies will depend on the mechanism of action of the drug and toxicology data, such as pre-clinical evidence of cataract and occurrence of signs and symptoms of myopathy.

6.2. Pharmacokinetics

Data should be in accordance with EC requirements. Special attention should be paid to pharmacokinetic interactions with concomitant medications used commonly in these populations. In certain cases specific studies in subpopulations may be required to evaluate variations due to genetic polymorphisms relating to both efficacy and safety. Special attention will be needed for drugs with long half-life on the accumulation potential and overall exposure (see also section 7 for impact on safety).

6.3. Therapeutic studies

6.3.1. Therapeutic exploratory studies

Dose-response studies should be randomized, placebo-controlled and double-blinded and at least 3 dosages should be studied to establish the clinically useful dose-range as well as the optimal dose. The parallel group design with randomization to several fixed dose groups is the general rule for the major dose-response studies. Distinction should be made between the separate lipid modifying effects of the different dosages. Dose schedules should be clearly defined for older patients and high-risk patients. Duration of these studies may vary from 4 weeks to 3 months.

6.3.2. Therapeutic confirmatory studies.

6.3.2.1. Demonstration of lipid-modifying effects as monotherapy

Given the efficacy and safety of particular drugs (mainly statins), placebo controlled trials investigating products for monotherapy are no longer acceptable in large groups of patients and high risk subjects. Patients who are considered intolerant to statins due to adverse events should be studied separately, or as a pre-specified alternative treatment group within a clinical trial. There is no consensus definition for statin intolerance, but there should be documented evidence of intolerance due to emerging AEs to 2 different statins (administered in doses required to achieve the target LDL-C level).

Comparative studies with accepted therapy are expected for evaluating the efficacy and safety of newer lipid-modifying drugs. The appropriate comparator(s) should be selected based on the pharmacological class, type of lipid modifying effects and the claimed indication. When comparison is made within the same pharmacological class, specific attention should be paid to dosing based on relative potency. General considerations should be applied when establishing a clinically relevant difference or a non-inferiority margin. Three arm studies including (short term) placebo may be valuable depending on the magnitude of response in the initial therapeutic studies. The dose schedule selected for pivotal studies on lipid altering effects must be justified on the basis of the dose finding studies in the target population. Duration will depend on their expected outcome but should last at least a minimum of 3 months (for known mechanisms of action) and preferably up to 12 months (for others), depending on dose titration and the time to achieve maximal response. The dose should be

increased according to dosing rules expressed in the protocol, and at each dose level the duration of treatment should be long enough to estimate the effect of the respective dose prior to further dose adaptation.

6.3.2.2. Demonstration of lipid modifying effects in combination with other lipid-modifying agents

Combination of lipid-modifying agents should be specifically studied in comparison to placebo in patients with inadequate response to any of the components of the combination separately. The adequacy of the response needs to be defined in terms of the desired lipid modifying effect and will depend on current standards. In case the new drug is only intended to be administered in combination with an existing drug, the target population is expected to be patients not adequately controlled with a standard dose of the marketed drug in monotherapy. Specifically, in cases of LDL-C elevations, patients should be on a maximum-tolerated statin dose, before adding a second lipid-modifying agent. In principle, combination strategies are not expected to be licensed as first line therapy on the basis of their effect on LDL-cholesterol and other lipid parameters, in particular TG and HDL-C alone, unless the applicant is able to justify the benefit of such strategy in terms of morbidity and mortality.

6.3.2.3. Demonstration of benefits in clinical outcome

Any claims of a beneficial effect on the clinical outcome, in particular cardiovascular outcome, should be supported by long-term, controlled, parallel and double-blind clinical studies. Either superiority or a non-inferiority approach can be adopted. When using the non-inferiority approach, establishing assay sensitivity is of paramount importance. If there is no established therapy for the specific target population, a placebo-controlled study aiming to demonstrate superiority, might be acceptable.

7. Safety aspects

Efforts should be made to comprehensively assess any potential adverse reactions that are characteristic of the class of drug being investigated. All adverse events occurring during the course of clinical trials should be fully documented with separate analysis of adverse drug events/reactions, dropouts, deaths while on therapy and clinical laboratory results. In the clinical studies, an overall plan for the detection and evaluation of potential adverse events, including justification of the size and duration of the studies with respect to the possibility of detecting safety signals, should be prospectively designed early during the clinical development, optimally by the time of phase II studies. This program should take into consideration key elements of the safety pharmacology, as well as key toxicological findings from non-clinical studies. Indications of increased risk of certain adverse events are an important concern and may trigger the request for an additional dedicated long-term safety study before or after licensing.

7.1. Specific organs of interest

Specific target organs monitored for safety should be reflective of the non-clinical and clinical study results based on mechanism of action of the compound and potential safety signals seen with other compounds. Particular attention should be paid to the following:

Liver

Liver function tests should be routinely measured and analysed in line with accepted guidelines. Information on patients with different degrees of liver impairment (Child-Pugh Classification) should be included in the regulatory submission dossier.

Muscles

Various lipid-modifying agents from different classes have been associated with creatinine kinase (CK) elevations with associated symptoms. Specific attention should be paid to signs and symptoms of myopathy. It is recommended that muscle symptoms should be actively sought in the development programme/clinical trials and CK levels be monitored as part of safety evaluation regularly. As severe muscle disorders are usually rare, a post-marketing surveillance and risk management plans should be considered to monitor CK and muscle symptoms. Myopathy/muscle toxicity should be defined using standard MedDRA query (SMQs) throughout the clinical development programme.

Kidney

Pre-clinical data have reported nephrotoxic effects on tubular cells of some lipid-modifying agents. Furthermore, muscle-associated AEs of some lipid-modifying agents are known to be worse in those with impaired renal function. These aspects should be carefully studied in the development programme.

7.2. Cardiovascular Safety

It is expected that the drug development programme, containing all relevant clinical and non-clinical data, adequately characterizes the cardiovascular risk profile enabling an evaluation of the cardiovascular safety in the marketing authorisation application (MAA). This refers in particular to products with a new mechanism of action or products belonging to a drug class for which the cardiovascular safety profile is not yet established or questioned, e.g. in case of a detrimental effect on another cardiovascular risk factor.

Requirements for the evaluation and quantification of the cardiovascular risk at the time of licensing are further outlined in the CHMP's *"Reflection paper on assessment of cardiovascular risk of medicinal products"*.

8. Special populations

8.1. Older people

Subjects above 65 and 75 years should be adequately represented in the studies, taking appropriate care of issues relating to therapeutic choices, fitness to participate in the trial and overall general health. On occasion there may be need for specific studies in these older groups including PK and dose response. The number of older included in (pivotal) trials should be sufficient to assess both efficacy and safety in this group.

8.2. Subjects with organ impairment (renal or hepatic)

The database should include data on subjects with organ impairment that will guide the therapeutic options based on the metabolic profile of the medicinal product under investigation and may require specific studies. The approach adopted should be justified in the dossier.

8.3. Children/adolescents

Please see 'Paediatric addendum to CHMP Guideline on clinical investigation of medicinal products in the treatment of lipid disorders (EMA/CHMP/494506/2012)'.

Definitions

AE	Adverse events
ALT	Alanine amino transferase
Apo A1	Apolipoprotein A1
Apo B	Apolipoprotein B
CABG	Coronary artery bypass graft
CCA	Common carotid artery
CHD	Coronary heart disease
CK	Creatinine kinase
CV	Cardiovascular
CVD	Cardiovascular disease
EAS	European Atherosclerosis Society
HDL-C	High density lipoprotein cholesterol
HMG-CoA	3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA)
HRT	Hormone replacement therapy
ICA	Internal carotid artery
IMT (& cIMT)	Intima media thickness (& carotid IMT)
IVUS	Intravascular ultrasound
LDL	Low density lipoprotein
LDL-C	Low density lipoprotein Cholesterol
MAA	Marketing authorisation application
MACE	Major adverse cardiac event
MRI	Magnetic resonance imaging
NCEP	National cholesterol education program
PCI	Percutaneous coronary intervention
PD	Pharmacodynamics
PK	Pharmacokinetics
PTCA	Percutaneous transluminal coronary angioplasty

SmPC	Summary of product characteristics
SMQ	Standard MedDRA Query
TC	Total cholesterol
TG	Triglycerides
ULN	Upper limit of normal

References

- ESC/EAS Guidelines for the management of dyslipidaemias (<http://www.escardio.org/guidelines-surveys/esc-guidelines/GuidelinesDocuments/guidelines-dyslipidemias-FT.pdf>)