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Committee for Medicinal Products for Human Use (CHMP)

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

Draft

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Rev. 1 Revision on imaging surrogate endpoints
Rev. 2 Need for Outcome Studies Based on Safety Data at the Time of MAA

Comments should be provided using this template. The completed comments form should be sent to **cvswpsecretariat@ema.europa.eu**.

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Executive summary

This document is the revised version of the existing guidance note (CHMP/EWP/3020/03) on lipid modifying agents. The guideline 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. Latterly, there is an attempt to use imaging modalities as surrogate markers of outcome benefit with lipid modifying agents. This section has also been revised.

1. Introduction (and 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 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. Four categories of risk that modify LDL-C goals are discerned on the basis of:

- Presence of clinical forms of atherosclerosis (CHD, ischemic stroke or peripheral vascular disease): a distinction should be made between primary and secondary prevention
- Diabetes mellitus
- Integrated global risk scoring models (e.g. Euroscore)
- 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 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 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 point in 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:

- Guideline on the evaluation of medicinal products for cardiovascular disease prevention EMEA/CHMP/EWP/311890/2007
- 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)
- 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)
- Points to consider on multiplicity issues in clinical trials (CPMP/EWP/908/99)

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. In all cases, a detrimental effect on both cardiovascular and non-cardiovascular mortality and morbidity (see also 7.4) should be excluded prior to registration, especially for non-HMG-CoA reductase inhibitor lipid modifying agents.

4.1. Efficacy end points

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 consistent for 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. Such studies are not foreseen for the registration of a new HMG-CoA reductase inhibitor. For

other medicinal products acting on LDL-C, at least a detrimental effect on mortality and morbidity should be excluded prior to registration (see section 7.2). Until clinical trial data are available, it should be specifically mentioned in the 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 is required.

4.1.2. Lipid levels

A relative reduction in LDL-C 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.

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), 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 interaction with clinical end points such as outcomes (either all cause mortality or CV end points). 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 end point. 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 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. The onus therefore, 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 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 confound the interpretation of the results, and are accordingly not encouraged. If included, clinically relevant justifications should be provided. Standard definitions as proposed in the guidance document (EMEA/CHMP/EWP/311890/2007) 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 standardized, 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.

Other lipid parameters, such as apolipoprotein AI (apo A1), apolipoprotein B (apo B), or the balance between apo B and apo A1, 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 also is 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 IVUS, measure changes in plaque volume/burden including the number of plaques or measure changes in plaque composition but importantly it should be reproducible and correlate with an accepted clinical outcome measure. These could be achieved by several methodologies as detailed above (cIMT, IVUS, MRI or other). For any marker or methodology (cIMT or IVUS), it is important that the investigative staff receives 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 interobserver 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 4 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 10mm segments (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. Attention should be paid to effects of gender, race and age. Children and adolescents below 18 years are addressed in the paediatric addendum to the guideline. Subjects above 65 and 75 years should be adequately represented in the studies.

For the evaluation of the 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 to allow statistical (sub) group evaluation. 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 clinical, genetic, and/or functional criteria.

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.

Following initial screening, a dietary lead-in period is obligatory before randomization in the study. Inclusion criteria and the reliability of the methods used should be justified, taking into account such factors as the target population and assay accuracy. Lipid-modifying therapy 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

These studies should include evaluation of tolerability, duration of action, and relevant clinical or haemodynamic parameters. 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 (see also section 7).

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 elderly patients and high-risk patients. Duration will 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.

Comparative studies with accepted therapy are mandatory 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 constituted by patients not adequately controlled with a standard dose of the marketed drug in monotherapy. Specifically, 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 the superiority or the non-inferiority approach can be adopted. When using the non-inferiority approach, establishing assay sensitivity is of paramount importance. A placebo-controlled study aiming to demonstrate superiority if ethically acceptable, and if there is no established therapy for the specific target population is also acceptable.

7. Safety aspects

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.

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 analyzed 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. Long-term effects on mortality & morbidity

The target population for lipid-modifying agents includes to a large degree patients with co-morbidities and concomitant medications. Different safety aspects should therefore be evaluated in a dataset representative of this population. In addition to an assessment of overall safety data in multiple organ systems, it is essential to, as far as possible, exclude that the new medicinal product increases the risk of damage in any of the target organs normally affected by dyslipidemias (liver, muscle and also cardiovascular effects)..

7.2.1. Type of studies

The complete development program will be taken into account in order to detect potential signals that may suggest an increased risk for other rare adverse events including CV risk, muscle and liver toxicity. The following general elements should be considered:

- Non-clinical data

Non-clinical data in relevant animal models evaluating the potential effect of the test drug on different safety aspects, including CV risk, should be conducted and provided as an instrumental element of the safety evaluation. Animal studies should focus, amongst others, on athero-thrombotic findings, fluid retention, blood pressure, renal function, electrolytes homeostasis, cardiac functionality, repolarisation and conduction abnormalities (pro-arrhythmic effects), liver, muscle etc., as outlined in ICH guidelines (e.g. S7A and S7B). For certain agents, reactions relating to muscle and liver toxicity are of particular significance as are local tolerance and immunogenicity depending on the nature of the medicinal product. If the drug is developed in the paediatric population the guideline on the need for non-clinical testing in juvenile animals of pharmaceuticals for paediatric indications should be considered.

- Clinical data

There are two important aspects to consider in terms of detecting signals of adverse events; the overall size of the database and the time needed to detect the signal.

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 formulated early during the clinical development, optimally by the time of phase II studies. While the relevant ICH document provides a general guidance on the requirements of safety databases, a wider exposure is likely to be necessary commensurate with the target population for the medicinal product to refute the suspected safety issues. This program should take into consideration, key elements of the primary and secondary pharmacology as well as key toxicological findings from non-clinical studies.

Two approaches are conceivable:

1. A pooled, patient level meta-analytic approach to safety events. In such cases the size of database, as well as the mean duration of the studies, are expected to be adequate to detect signals for serious and uncommon events.

2. As an alternate approach or when there is suspicion of an adverse signal (CV or other organ from the database), a specific long-term controlled outcome study with at least 18 – 24 months follow-up (depending on the characteristic of the drug and baseline risk of the studied population) would be expected as part of the clinical development program for a lipid-modifying agents at the time of submission of the MAA.

The safety evaluation should include a prospective definition of adverse events, particularly cardiovascular safety outcomes of interest that is common for all phase II-III studies, facilitating

pooled analysis strategies. Furthermore, applicants should foresee a consistent central adjudication system for all predefined CV and other adverse events of interest during the phase II-III program. Detailed statistical analysis plan for the pooled CV safety data should be prospectively designed.

7.2.2. Study Population

In the development program, every effort should be undertaken to include a study population that mimics as much as possible the target population, regardless whether a meta-analytic approach or a specific study approach is used. In either case, an adequate number of high risk patients including elderly patients (above 75 years), subjects with cardiovascular risk factors (e.g. diabetes, hypertension), high risk for cardiovascular complications and confirmed history of ischemic heart disease and/or congestive heart failure should be included in the clinical development. Detailed clinical information allowing a proper characterisation of the baseline characteristics, including ischemic heart disease and congestive heart failure, for patients enrolled in controlled studies must be collected and summarised.

7.2.3. Safety outcomes

Concerning CV events, the emphasis will be on major cardiovascular events (MACE) (CV death, non fatal myocardial infarction and stroke) but hospitalisation for unstable angina could also be included in a composite endpoint if the main objective is to exclude a safety signal. It is important to ensure that these are centrally adjudicated. Other events such as revascularisation and/or worsening of heart failure can also be evaluated.

Clinically relevant changes in cardiac function (e.g. by echocardiography) should be evaluated if there is an indication of a detrimental effect on cardiac function.

Other safety outcomes should be chosen based on the known safety profile of the product class, the mechanism of action of the investigational drug and/or the non-clinical findings.

Use of relevant terms for coding AEs should be properly defined and harmonised across clinical development, allowing an efficient analysis of safety.

7.2.4. Evaluation of the results

For medicinal products belonging to a well-known class (and mechanism of action) a careful evaluation of the available medical literature together with the absence of pre-clinical and clinical signals of increased cardiovascular risk may lend some support to a meta-analytic approach provided there is no product specific signal from the database. If a benefit or at least absence of harm in terms of CV risk has been shown with other agents in the same class and product specific differences in the off target effects between agents are unlikely, this may reduce the need for a specific outcome study.

An integrated safety analysis with specific focus on cardiovascular safety (i.e. with adjudicated pre-determined MACEs) should be submitted at the time of MAA for any drug. An appropriately powered cardiovascular safety assessment, e.g. based on a dedicated CV outcome study, should be submitted before marketing authorization whenever a safety concern is intrinsic in the molecule/ mechanism of action or has emerged from pre-clinical/ clinical registration studies.

Independently of whether a meta-analytic approach or a specific outcome study approach is used, due consideration should be given to the range of analyses presented, as in the field of signal detection no single approach to the analysis of data is sufficient to guarantee that all relevant signals are actually captured.

The overall results of this safety program should be discussed in terms of internal and external validity and clinical justification of the safety outcomes. Acceptability of the data presented will be decided

based on its overall quality, the point and interval estimates obtained for the calculation of specific risks, including cardiovascular risk, and the reliability of these estimations. A summary of what is known about CV risk should be proposed for the SmPC. Indications of increased risk of certain adverse events or unacceptable lack of precision are important concerns and may trigger the request for additional specific long-term outcome trials to exclude an unacceptable increase in CV or other identified risks associated with the new agent. The risk management plan should cover identified and potential safety issues. Detailed guidance on RMPs is relevant here.

Definitions

ABBREVIATION	DEFINITION
ALT	Alanine amino transferase
CABG	Coronary artery bypass grafts
CHD	Coronary heart disease
MRI	Magnetic Resonance Imaging (cardiac or other end organ)
CCA	Common carotid artery
ICA	Internal Carotid artery
CVD	Cardiovascular disease
EAS	European Atherosclerosis Society
HDL-C	High density lipoprotein Cholesterol
HRT	Hormone replacement therapy
IMT (& cIMT)	Intima Media thickness (& carotid IMT)
IVUS	Intravascular ultrasound
LDL-C	Low density lipoprotein Cholesterol
NCEP	National Cholesterol Education Program
PCI	Percutaneous Coronary intervention
PTCA	Percutaneous transluminal coronary angioplasty
SMQ	Standard MedDRA Query
TC	Total cholesterol
ULN	Upper limit of normal
CK	Creatinine Kinase

References

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