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Guideline on Lipid Lowering agents

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This addendum replaces some chapters of the NfG on lipid lowering agents (CPMP/EWP/3020/03).

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. It also refers to any special considerations that may be applicable in each of these situations. Latterly, there is an attempt to use imaging modalities as surrogate markers of outcome benefit with lipid modifying agents and the main highlights of this revision are updates to the sections on imaging markers and their possible role in drug development for regulatory submissions.

1. Introduction (and background)

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 correlation and causal relationship between serum cholesterol level, particularly serum LDL cholesterol, and the risk of coronary heart disease (CHD). Other clinical manifestations of atherosclerosis also appear linked to plasma LDL cholesterol levels such as cerebrovascular disease (i., stroke) or peripheral vascular disease. In addition, clinical trials have shown that LDL-lowering therapy reduces risk for CHD. The relationship between LDL cholesterol 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, but possibly non-linear, increasing risk from very low to “normal” and high levels of cholesterol. Treatment decisions are based not only on the level of cholesterol, but on the overall, multifactorial level of cardiovascular risk.

Three categories of risk that modify LDL-cholesterol goals are discerned on the basis of

- presence of CHD and other clinical forms of atherosclerosis: a distinction should be made between primary and secondary prevention
- diabetes mellitus
- number of risk factors

Therefore a workable definition of hypercholesterolemia could be that level of cholesterol that is associated with increased CVD risk and above which treatment has been shown advantageous and safe. Concomitantly other lipid disorders may be present, in particular hypertriglyceridemia (“mixed hyperlipidemia”), but lipid disorders may also implicate isolated or prevalent endogenous hypertriglyceridemia and/or low HDL-cholesterol. Elevated triglycerides are an independent CHD risk factor, but the treatment strategy for elevated triglycerides depends on the causes of the elevation and its severity. Low HDL cholesterol level, whether or not in conjunction with elevated triglyceride levels, is also a strong independent risk factor for CHD, which warrants clinical attention although the goal of therapy needs further specification. Although this NfG focuses on hypercholesterolemia, attention will also be paid to other lipid disorders.

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 (i.e., lipid modifying agents) with particular emphasis on clinical trials that form the basis for establishing efficacy and safety of such products.

3. Legal basis

This guideline should be read in conjunction with the introduction and general principles (4) and Annex I to Directive 2001/82 or 2001/83 as amended.

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

For lipid modifying drugs efficacy may be evaluated using a number of parameters from simple lipid levels to effect on outcomes and this has become possible as majority of statins (HMG Co-A reductase inhibitors) have accrued sufficient evidence of effect on outcome. In this section each of these efficacy indicators are discussed.

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 lipid levels in rare cases of very high triglyceride levels, the initial aim is to prevent acute pancreatitis). Most HMG-CoA reductase inhibitors have accrued considerable evidence demonstrating reduction of cardiovascular events (including stroke) and overall mortality in patients at high cardiovascular risk, irrespective of their cholesterol levels. Some data also suggest that fibrates have been shown to reduce the rate of coronary events both in patients with mixed hyperlipidemia and in men with coronary heart disease with only low levels of HDL cholesterol without hypercholesterolemia. Therefore, this (reduction of morbidity/mortality) should ideally be the primary end point for most lipid modifying agents. Positive effects on mortality and morbidity can only be evaluated properly in large scale and long-term clinical trials, in patients with lipid disorders and/or high cardiovascular risk. Until clinical trial data are available, it should be specifically mentioned in the SPC that beneficial effects on mortality and morbidity have not been evaluated.

4.1.2. Lipid levels

Notwithstanding the above expectations, based on the current epidemiological knowledge, a relative reduction in LDL cholesterol is acceptable in patients with primary hypercholesterolemia as a valid surrogate endpoint, provided that claims in the label are restricted to a lipid lowering effect. Reduction in triglyceride levels and/or increase in HDL-cholesterol might also be considered as relevant components of the primary endpoint for particular target populations. In any of these situations, effect on morbidity and mortality should be demonstrated if such a claim is made (see 4.1 above) as

currently the epidemiological data do not show a strong relation for these parameters. In principle, an isolated effect on triglycerides 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 mechanism (see section 4.2.2). A new lipid-modifying agent is only acceptable for registration when there is no suggestion of a detrimental effect on both cardiovascular and non-cardiovascular mortality and morbidity (see also 7.4).

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 measurement (intima media thickness), IVUS (intravascular ultrasound), MRI (magnetic resonance imaging), have evolved over 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. 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 needs to be specifically documented particularly at each specific site including its interaction with clinical 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. Importantly, demonstration of regression of atherosclerotic burden is the preferred parameter or effect rather than lack of progression. Evidence may be generated from a single study of adequate sample size that evaluates imaging outcomes in the short term and CV outcomes in the long term as part of validation. If two independent studies are used, directional concordance for effect of intervention, for example, with lipid modifying agents is expected. And 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 use placebo should be taken into account.

At the present time, in adults, it is difficult to envisage an indication based on use of these markers alone as, their independent contribution to the risk stratification or as a risk marker when adjusted for conventional risk factors remains to be fully 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 of vascular damage in the chosen patient population.

4.2. Methods to assess efficacy

4.2.1. Evaluation of morbidity and mortality

When planning a mortality study, emphasis should be put both on all-cause mortality and/or cardiovascular mortality, as adjudicated by a blinded, independent committee. If cardiovascular mortality is chosen as (co-)primary endpoint, effects on non-cardiovascular mortality should also be taken into account. The evaluation of

cardiovascular morbidity should especially take into account signs and symptoms of organ damage (e.g. myocardial infarction, stroke) and their therapeutic management (e.g. number of CABG and PTCA and/or interventions on other vascular districts). Giving the efficacy and safety of particular drugs (mainly statins) placebo controlled trials are no longer acceptable in large groups of patients and high risk subjects.

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, as justified by the sponsor. In patients with primary hypercholesterolemia reduction in LDL-cholesterol is the primary endpoint to support the indication of hypercholesterolemia or mixed hyperlipidemia. 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 triglycerides, total cholesterol and HDL-cholesterol should also be studied as secondary parameters as they are becoming increasingly used to assist treatment recommendations. Measurements of lipid disorders other than LDL-cholesterol such as changes in triglycerides and HDL-cholesterol may become primary efficacy measures, if considered relevant to the target population (e.g. diabetic hyperlipidemia), provided that no detrimental effects on other lipid parameters are observed or outcome data are provided. Other lipid parameters, such as apolipoprotein A-I and A-II, apolipoprotein B, or the balance between apolipoprotein B and apolipoprotein A-I, 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 should be recognized that not only quantitative lipid abnormalities exist, but qualitative abnormalities as well such as small and dense or oxidized LDL, 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 needs to: measure changes in plaque volume/burden, measure changes in plaque composition, be reproducible and correlate with an accepted clinical outcome measure. For either methodology, 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 interobserver variability should be discussed in the study report. Observer variability should be minimised and the impact such variability should be discussed in any regulatory submission.

cIMT

For cIMT, images of right as well as left common and internal carotid arteries need to be obtained. The pre/post intervention difference in IMT needs to be defined a priori and adequately justified (e.g., 0.05 mm) 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). 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 coronary arteries 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 of instance, justification that the chosen value is of clinical significance will be required. 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 cholesterol levels. Attention should be paid to effects of gender, race and age. Children and adolescents below 18 years need to be studied separately when its use is claimed; otherwise its use in these age groups is not recommended. Number of subjects above 65 years should be representative of the population**.** For the evaluation of the clinical outcomes, populations should be selected according to their global cardiovascular risk, irrespective of the presence of coronary artery disease and irrespective of their baseline cholesterol level. 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. This also applies to other forms of lipid disorders, including familial forms of dysbetalipoproteinemia and hyperchylomicronaemia.

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 and former foods 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. Drugs intended to be used as monotherapy

These studies will mostly be controlled trials with reference therapy, as placebo controlled trials alone are no longer acceptable. Comparative studies with accepted therapy are mandatory for evaluating the efficacy and safety of newer lipid-modifying drugs. The choice of the comparator will depend on the drug studied and the indication claimed. The appropriate comparator(s) should be selected based on the pharmacological class and 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, up to 12 months, depending on dose titration and the time to achieve maximal response. The dose should be increased according 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.

Clinical benefit in terms of improved outcome can be studied in comparison with other lipid modifying agents that have already shown such benefit. These studies usually have a longer duration.

6.3.2.2. Drugs used 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. 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.

7. Evaluation of 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, patients who died while on therapy and clinical laboratory results.

Specific target organs monitored for safety should be reflective of the nonclinical 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:

7.1. Liver

Signs and symptoms of hepatitis may occur. ALT and other hepatic biochemistry should be routinely measured and analyzed separately according to mean changes and numbers of patients with values > 1x and > 3x ULN. Information on patients with pre-existing hepatic damage, in particular cirrhosis (Child-Pugh Classification), unless contra-indicated should be included in the regulatory submission dossier.

7.2. Muscles

Various lipid-modifying agents from different classes have been associated with 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. These should be analyzed separately according to mean changes and number of patients with values >1x, >3x, >5X and >10x ULN. It is also recommended that myopathy / muscle toxicity be defined with clear and consistent definitions using standard MedDRA SMQ. As severe muscle disorders are usually rare, a postmarketing surveillance and risk management plans should be considered to monitor CK and muscle symptoms. In both, consistent definitions of myopathy and serious muscle events should be used as in the clinical development programme.

7.3. Kidney

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

7.4. Long-term effects on mortality & cardiovascular morbidity

Non-cardiovascular morbidity and mortality may not be akin to cardiovascular mortality/morbidity. Even negative effects have been suggested in certain cases. Therefore, a sufficient cohort of patients of both sexes and all ages should be continuously exposed to the drug for at least a year, but preferably longer. This cohort should be representative for the clinical conditions in which lipid-modifying drugs are generally prescribed, such as diabetes mellitus, ischemic heart disease and hypertension. The safety database should be large enough to reasonably exclude any suspicion of a detrimental effect of the new drug on mortality, cardiovascular or non-cardiovascular. This requirement acquires special relevance in case of drugs belonging to a new therapeutic class. The available data on mortality and cardiovascular morbidity from the clinical program should be thoroughly analysed, taking also into account pre-clinical data and the results obtained from other drugs of the same lipid-modifying class and other classes as well. A new lipid-modifying agent is only acceptable for registration if there is no suggestion of a detrimental effect on morbidity and mortality. Otherwise, additional studies to clarify the drug effect on these parameters are mandatory.

8. Drug–drug interactions

Drug interactions should be studied, both in general by analysing the effects of concomitant medication in the clinical studies and by specific studies; parent compound and active metabolites should be taken into account. Combination of various lipid-modifying agents may enhance efficacy, but also certain side effects, in particular the occurrence of myopathy and/or liver dysfunction due to pharmacokinetic and/or pharmacodynamic interactions. This should be studied very carefully in sufficient numbers of patients. The same applies when combination is made with other agents known to cause specific organ damage, in particular the liver, muscles and kidney, in particular drugs generally prescribed in patients at high risk of cardiovascular events, such as antiplatelets and oral anticoagulants. Specific interaction studies will depend on the pharmacokinetic and pharmacodynamic properties of the new drug. Interaction studies with drugs affecting its absorption (e.g. antacids) and metabolism (e.g. cyclosporin, inhibitors of cytochrome P450 enzymes) should be considered, as well studies with vitamin K antagonists and oral contraceptives/hormonal replacement therapy (HRT).

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

References

- *http://publications.europa.eu/code/en/en-250304.htm* for guidance on referencing published information.
- *http://publications.europa.eu/code/en/en-130102.htm* for guidance on referencing EU texts. References to related guidelines should also be included.
- *Procedure for EU Guidelines'* for further guidance.
- Note for Guidance on General Consideration in Clinical Trials (CPMP/ICH/291/95)
- Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95)
- Note for Guidance on Dose Response Information to support Drug Registration (CPMP/ICH/ 378/95)
- Note for Guidance on Statistical Principles for Clinical Trials (CPMP/ICH/363/96)
- Note for Guidance on Choice for Control Group for Clinical Trails (CPMP/ICH/364/96)

- Note for Guidance on the Investigation of Drug Interaction (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)
- Note for Guidance on Multiplicity issues