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NOTE FOR GUIDANCE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE TREATMENT OF LIPID DISORDERS

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NOTE FOR GUIDANCE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE TREATMENT OF LIPID DISORDERS

This note is intended to provide guidance for the evaluation of drugs in the treatment of lipid disorders. They should be read in conjunction with Directive 2001/83/EC, as amended, as well as in conjunction with other pertinent regulatory European and ICH documents, with special emphasis on:

- Note for Guidance on General Considerations for 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 of Control Group for Clinical Trials (CPMP/ICH/364/96)
- 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 94)
- Note for Guidance on Multiplicity

1. INTRODUCTION

Lipid disorders are commonly classified according to the prevailing laboratory abnormality, but it should be noted that 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 a case the underlying conditions should be treated and lipid levels should be reassessed once the disease has been controlled.

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. 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 from high to low. 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, that 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. ASSESSMENT OF EFFICACY CRITERIA

2.1 Morbidity and mortality

The primary goal of treating lipid disorders is to prevent cardiovascular morbidity and mortality associated with lipid levels (however in rare cases of very high trigyceride levels, the initial aim is to prevent acute pancreatitis). Most HMG-CoA reductase inhibitors have recently accrued considerable evidence demonstrating reduced 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. 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 are unknown.

2.2 Lipid levels

Although ideally a new lipid-modifying agent is expected to demonstrate an effect on the prevention of cardiovascular morbidity and mortality, a relative reduction in LDL cholesterol is acceptable in patients with primary hypercholesterolemia as a valid surrogate endpoint, provided that no claims are made regarding morbidity and mortality. Reduction in triglyceride levels and/or increase in HDL-cholesterol might also be considered as a relevant component of the primary endpoint for particular target populations. However, an isolated effect on these parameters is in principle 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 as well (see Section 3.2). 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 6.4).

2.3 Vascular damage

Although target organ damage of heart, brain, kidneys and, in particular, blood vessels is presumably and plausibly associated with morbidity and mortality, the prognostic value of these drug effects with regard to morbidity and mortality remains to be established; this holds particularly true for changes in intimal media thickness (IMT) and plaque stability. For the time being, the effect of a particular drug (or combination of drugs) on the arteriosclerotic burden at a particular site cannot be considered as a valid surrogate for cardiovascular morbidity and mortality. Therefore, these endpoints can be particularly valuable for the scientific community as they may bring information on how the medications act and can have

clinical protective effects. As more becomes known, such studies may substitute clinical studies using hard clinical endpoints in selected subgroups.

3. METHODS TO ASSESS EFFICACY

3.1 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.

3.2 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, 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 measurements of lipid disorders, such as apoprotein Al and AII, apoprotein B, or the balance between apoB and apoA-1, 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 (like small and dense or oxidized LDL), that may become prime targets for new forms of lipid modifying agents.

3.3 Vascular damage

Atherosclerosis progression can be measured by validated and reliable techniques, e.g. quantitative B-mode ultrasound, MRI and intravascular ultrasound (IVUS). Whatever the technique used, its validity should be justified properly. The latter technique is also used to measure plaque stability. Whichever the method used, its validity and reliability for assessing the atherosclerotic burden at each specific site should be properly documented. As stated in section 2.3, today these parameters are not considered as surrogates for hard clinical endpoints, but they may constitute appropriate secondary endpoints to support information on progression or regression of atherosclerosis.

4. 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 moderately 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. For the evaluation of the clinical outcome, 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.

5. STRATEGY-DESIGN

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 randomisation 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 farmer foods should be recorded and remain unchanged throughout the trial duration.

5.1 Pharmacodynamics

These studies should include evaluation of tolerability, duration of action, and relevant 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.

5.2 Pharmacokinetics

Data should be in accordance with EC requirements. Special attention should be paid to pharmacokinetic interactions (see also **7.**).

5.3 Therapeutic studies

5.3.1 Therapeutic exploratory studies

Dose-response studies should be randomised, 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 randomisation 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.

5.3.2 Therapeutic confirmatory studies

5.3.2.1 Drugs intended to be used as monotherapy

These studies will mostly be controlled trials with reference therapy, as placebo controlled trials are no longer acceptable in large groups giving the efficacy and safety of particular drugs. Comparative studies with accepted therapy are mandatory. 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 one 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.

5.3.2.2 Drugs intended to be 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.

6. 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:

6.1 Liver

Signs and symptoms of hepatitis may occur. ALT and other hepatic biochemistry should be routinely measured and analysed separately according to mean changes and numbers of patients with values > 1x and > 3x ULN. Information should be submitted on patients with pre-existing hepatic damage, in particular cirrhosis, unless contra-indicated.

6.2 Muscles

Various lipid-modifying agents from various classes have been associated with CK elevations with associated symptoms. Specific attention should be paid to signs and symptoms of myopathy. CK levels should be routinely measured and analysed separately according to mean changes and numbers of patients with values > lx, > 3x, > 5x and > l0x ULN. As severe muscle disorders are usually rare, a postmarketing surveillance should be considered to monitor CK and muscle symptoms.

6.3 Kidney

Pre-clinical data have reported nephrotoxic effects on tubular cells of lipid-modifying agents. Renal function and proteinuria should be monitored.

6.4 Long-term effects on mortality and cardiovascular morbidity

Non-cardiovascular morbidity and mortality, may not be alike. Even negative effects have been suggested. 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 rule out any suspicion of a detrimental effect of the new drug on mortality. 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.

7. 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).