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4 Reflection paper on assessment of cardiovascular risk of 5 medicinal products for the treatment of cardiovascular 6 and metabolic diseases

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Reflection paper on assessment of cardiovascular risk of medicinal products for the treatment of cardiovascular and metabolic diseases

Table of contents

1. Introduction

The purpose of this reflection paper is to provide recommendations for the evaluation of the cardiovascular safety profile of new, non-generic medicinal products that are intended for long-term treatment of cardiovascular and metabolic diseases. It aims to clarify the requirements for these products at the time of marketing authorisation with respect to data needed for the evaluation and quantification of the cardiovascular safety profile.

2. Background and Scope

Cardiovascular safety concerns have been raised during the last decade with respect to a number of medicinal products approved or being developed for the treatment of cardiovascular diseases (e.g. hypertension and hypercholesterolaemia) and metabolic diseases (e.g. type 2 diabetes and obesity). In some cases such concerns have led to the non-approval or withdrawal/suspension of the medicinal product in the EU/EEA.

It is now expected that the development programmes of new medicinal products in these therapeutic areas adequately characterize the cardiovascular safety profile enabling an evaluation of the cardiovascular risk 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 fully understood.

This reflection paper, which should be read in conjunction with existing guidelines addressing the development of these products (see section 3), aims to further clarify the requirements for the evaluation and quantification of the cardiovascular risk of medicinal products at the time of licensing.

3. Legal Basis and Relevant Guidelines

This reflection paper 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 clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus (CPMP/EWP/1080/00 Rev. 1);
- Guideline on clinical evaluation of medicinal products used in weight control (CPMP/EWP/281/96 Rev.1);
- Guideline on clinical investigation of medicinal products in the treatment of hypertension (EMA/238/1995/Rev. 3);
- Guideline on clinical investigation of medicinal products in the treatment of lipid disorders (EMA/CHMP/748108/2013);
- Points to Consider on Application with 1. Meta-analyses; 2. One Pivotal study (CPMP/EWP/2330/99);
- Draft guideline on the investigation of subgroups in confirmatory clinical trials (EMA/CHMP/539146/2013).

4. Recommendations

4.1. Evaluation of cardiovascular risk

Data from the entire non-clinical and clinical development program (e.g. atherothrombotic findings, fluid retention, effects on blood pressure, heart rate, renal function, electrolyte homeostasis, cardiac functionality, repolarisation and conduction abnormalities), will be taken into account during the evaluation of the cardiovascular safety profile when assessing a new MAA. However, the main emphasis of such an evaluation and quantification will be on cardiovascular outcome data generated in a population that is representative for the intended target population.

4.2. Clinical outcome data

In general, two approaches are conceivable with respect to the presentation of clinical outcome data enabling an evaluation and quantification of the cardiovascular risk in a new MAA:

4.2.1. A meta-analytic approach

A meta-analysis, or pooled analysis, should include data generated in the phase II and phase III studies. Studies to be combined should be pre-specified and the analysis should preferably be performed using individual patient data. Studies with negative outcomes for the primary efficacy outcome should generally be included. Information from doses below those proposed for marketing should generally be excluded from the meta-analysis. Trials with substantial differences in trial design (e.g. different treatment duration, or duration of placebo control) should not be included, unless it can be justified that they contribute equally to the question of interest. Sensitivity analyses might be required to address the impact of including or excluding certain trials from the meta-analysis. Consideration of which trials to include should follow the EMA guideline on an application based on meta-analysis, and the application should include a discussion of the adequacy of the pooling strategy from a cardiovascular safety perspective, including:

- Heterogeneity of the patient populations recruited to the contributing trials
- Heterogeneity of the control arms in different trials
- Heterogeneity in background regimens (add-on trials), in particular to quantify what is known about the cardiovascular risk associated with each regimen compared to other available regimens and, if possible, compared to no treatment/placebo to give an estimate of absolute risk for the control arm
- Consistency of the estimated effects across contributing studies
- Internal consistency of estimated effects from the pooled dataset across important subgroups, in particular factors defining underlying cardiovascular risk (e.g. “low” versus “high” risk)

The aspects listed above should also be considered when interpreting the results.

4.2.2. A dedicated cardiovascular outcome study

A dedicated cardiovascular outcome study could be necessary when indications of an increased cardiovascular risk have not been excluded in the meta-analysis of the phase II/III studies. A dedicated cardiovascular outcome study might also be favored whenever a cardiovascular risk is intrinsic in the molecule or mechanism of action, when cardiovascular signals have been observed in the pre-clinical studies, or when the drug is a “first in class”.

A dedicated cardiovascular outcome study should have an adequate control arm, and if an active control is used this should preferably be one for which the cardiovascular risk or absence thereof is already well characterized.

Multiplicity issues that may arise from interim analyses or multiple tests due to more than one active dose level need to be addressed with adequate methodology. If the use of interim data in a regulatory submission is considered, it is strongly recommended to seek Scientific Advice from EMA to discuss issues of impact on trial conduct, trial data integrity and validity of final study results.

The hypothesis to address cardiovascular safety may be embedded within a study design ultimately attempting to demonstrate superiority (i.e. a cardiovascular benefit associated with the drug), or to confirm absence of detrimental effect to a higher degree of precision.

4.3. Study population

In the development program, every effort should be undertaken to include a study population that closely resembles the intended target population, regardless whether a meta-analytic or a dedicated outcome study approach is used. In either case, depending on the baseline cardiovascular risk, an adequate representation of high-risk patients (definition depending on the indication in question), including a sufficient number of subjects with a high risk for cardiovascular diseases and complications, should be enrolled into the study. Ideally, an assessment of the cardiovascular risk should be possible in both “high” and “low” risk patients.

4.4. Duration of studies

It is expected that the size and the duration of clinical studies are driven by the number of events that need to be observed to ensure a satisfactory level of precision of the estimated effect (see 4.6). Duration and follow-up periods of the clinical studies (both those included in a meta-analysis or a dedicated cardiovascular outcome study) should be sufficient to capture an adequate number of cardiovascular outcome events that might be caused by the study drug. It should be avoided that exposure is too short for a detrimental effect of a study drug to be captured, since the events will then be (mainly) driven by a background event rate and thus not allow for an adequate evaluation of the cardiovascular risk of the study drug. Similarly, it must be avoided that a high proportion of events are missed after cessation of randomized treatment. The duration of eligible follow-up for events to contribute to the primary analysis should be discussed.

The applicant must be able to justify that the results from either a dedicated outcome study or meta-analysis, in particular the duration of drug exposure and follow-up, are adequate for an assessment of the cardiovascular safety profile (see also section 4.6). Any claims of a ‘similar’ (or even lower) cardiovascular risk of a study drug to a control should be based on truly similar (or lower) cardiovascular safety profiles and not be hampered by a lack of sensitivity to detect any true differences.

4.5. Safety outcomes

The preferred safety endpoint for the meta-analyses and dedicated cardiovascular outcome studies is a composite of all major cardiovascular events (MACE): i.e. cardiovascular death, non-fatal myocardial infarction and stroke.

In some instances, depending on the characteristics of the medicinal product in question, additional cardiovascular outcomes like hospitalization for cardiovascular causes (e.g. unstable angina, need for revascularization, acute heart failure or worsening of existent heart failure TIA, and sudden death

could also be included in a composite endpoint ("MACE-plus"). The use of a "MACE-plus" endpoint should be properly justified a priori, based on being more sensitive to detect any harmful cardiovascular effects of the investigational product. The components of the selected composite endpoint should always be presented separately as supportive analyses.

It is important to ensure that an independent committee adjudicates all major cardiovascular events included in the composite endpoint. A homogeneous definition of MACE across studies would be desirable (e.g. definition of MI, including or not including MI post percutaneous coronary intervention).

Additional parameters such as increase in body weight, oedema/fluid retention, occurrence of hypertension, significant changes in heart rate/arrhythmias, or increases in LDL-cholesterol should also be systematically collected. Clinically relevant changes in cardiac function should be evaluated by cardiac imaging, if there is an indication of a detrimental effect on cardiac function.

4.6. Quantification of cardiovascular risk in patients

As a general rule, assuming a comparison against a placebo or standard of care (SOC), the evidence based on cardiovascular risk should be planned to obtain an upper limit of the confidence interval (95%, two sided) for the Hazard Ratio (HR) below 1.8 in the event that HR≈1. This would constitute a reasonable basis for regulatory assessment of the cardiovascular risk at the time of initial licensing and requires an adequate number of cardiovascular events. Other targets for the upper confidence limit (UCL), including narrower targets, may be more appropriate based on the particular target population, known cardiovascular risk profiles of the comparators, previous experience in the class, presence or absence of a signal for increased risk elsewhere in the dossier. This target for the UCL is regarded as a planning assumption. The overall assessment of the cardiovascular risk and determination of need for any post-authorisation studies will always take into account the internal and external validity of the data (e.g. experience from other products within the class) and the overall benefit-risk balance of the drug.

4.7. Evaluation of results

Acceptability of the data presented will be based on its overall quality, the point estimates and confidence interval obtained for the calculation of the cardiovascular risk compared with the control group and the reliability of these estimations. The mechanism of action and effect, or lack thereof, on known cardiovascular risk factors will also be taken into account. Indications of increased risk of cardiovascular events or unacceptable lack of precision may trigger the request for (additional) cardiovascular outcome trials.

A summary of the results from the cardiovascular safety analysis should be presented in the SmPC.

Sponsors are encouraged to seek Scientific Advice from EMA on any specific issues relating to the cardiovascular safety of (new) medicinal products intended for use in cardiovascular or metabolic diseases and discuss the design of the meta-analytic approach addressing the cardiovascular risk, or a dedicated cardiovascular outcome study.