



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

25 February 2016
EMA/CHMP/50549/2015
Committee for Medicinal Products for Human Use (CHMP)

Reflection paper on assessment of cardiovascular safety profile of medicinal products

Draft agreed by Cardiovascular Working Party	January 2015
Adopted by the Committee for Medicinal Products for Human Use for release for consultation	21 May 2015
Start of public consultation	12 June 2015
End of consultation (deadline for comments)	30 September 2015
Agreed by Cardiovascular Working Party	November 2015
Adopted by the Committee for Medicinal Products for Human Use	25 February 2016

Keywords	<i>cardiovascular safety, cardiovascular outcome study (CVOT), major cardiovascular event (MACE), cardiovascular and metabolic disease, diabetes, obesity, hypertension, hypercholesterolaemia</i>
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Table of contents

1. Introduction.....	3
2. Background and Scope.....	3
3. Legal Basis and Relevant Guidelines	3
4. Recommendations.....	4
4.1. Evaluation of cardiovascular safety profile	4
4.2. Clinical outcome data.....	4
4.2.1. A meta-analytic approach	4
4.2.2. A dedicated cardiovascular outcome trial	5
4.3. Study population	5
4.4. Duration of studies	5
4.5. Safety outcoms	6
4.6. Quantification of cardiovascular safety profile in patients.....	6
4.7. Evaluation of results	7

1. Introduction

The purpose of this reflection paper is to provide recommendations for the evaluation of the cardiovascular safety profile of new (non-generic, non-biosimilar) medicinal products that are intended for long-term treatment of certain cardiovascular and metabolic diseases (see section 3). This paper aims to clarify the requirements for these medicinal products at the time of assessment of the marketing authorisation application with respect to data needed for the evaluation of the cardiovascular safety profile. For the evaluation of medicinal products in therapeutic areas not listed in section 3, the same principles of data generation and assessment may apply if a detailed evaluation of their cardiovascular safety profile becomes necessary.

2. Background and Scope

Cardiovascular safety concerns have been raised during the last decade for some medicinal products approved or being developed for the long-term treatment of cardiovascular diseases and metabolic diseases. In some cases such concerns have led to the non-approval or withdrawal/suspension of the medicinal product in the EU/EEA. Therefore, the development programmes of new medicinal products for which it has been considered necessary to perform a more in depth assessment of cardiovascular safety (see section 3), should include data that enables an adequate characterization of the cardiovascular safety profile at the time of licensing.

Cardiovascular safety issues can in some cases also be relevant for certain other cardiovascular drugs, e.g. in heart failure or angina pectoris, or for new drugs developed for non-cardiovascular diseases (i.e. therapeutic areas not listed in section 3) if there are signs of an increased cardiovascular risk based on e.g. the mechanism of action and/or pre-clinical data.

The evaluation of potential cardiovascular benefits associated with medicinal products intended for the treatment of cardiovascular or metabolic diseases is outside the scope of this reflection paper. This is addressed in the available CHMP guidelines for these therapeutic areas (see section 3).

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, but can in some cases also be applicable to therapeutic areas not listed below:

- 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.2)
- Draft guideline on clinical investigation of medicinal products in the treatment of hypertension (EMA/238/1995/Rev. 4)
- 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, rev. 1. (CPMP/EWP/2330/99)
- Draft guideline on the investigation of subgroups in confirmatory clinical trials (EMA/CHMP/539146/2013)

- Statistical Principles for Clinical Trials (ICH E9, CPMP/ICH/363/96)
- Choice of Control Group in Clinical Trials (ICH E10, CPMP/ICH/364/96)

4. Recommendations

4.1. Evaluation of cardiovascular safety profile

Data from the entire non-clinical and clinical development programme (e.g. atherothrombotic findings, fluid retention, heart rate, renal function, electrolyte homeostasis, LDL cholesterol, blood pressure) will be taken into account during the evaluation of the cardiovascular safety profile of new medicinal products for which it has been considered necessary to perform a more in depth assessment of the cardiovascular safety profile. The main emphasis during the evaluation of the cardiovascular safety profile will, however, be on clinical outcome data generated in a population that is representative for the intended target population (see section 4.2).

Deviations from these general rules might be foreseen when the new drug is intended for the treatment of a rare disease (e.g. certain rare lipid disorders) or when there is already very strong evidence to exclude cardiovascular harm. The same principles of data generation and assessment outlined in this paper may also apply to new medicinal products developed for non-cardiovascular diseases if a detailed evaluation of their cardiovascular safety profile becomes necessary. In cases like these, companies are advised to seek Scientific Advice from EMA to discuss whether such circumstances might apply, and what type and amount of clinical data is considered necessary for the evaluation of the cardiovascular safety profile at the time of assessment of a marketing authorisation application.

4.2. Clinical outcome data

Two approaches are generally conceivable with respect to the presentation of clinical outcome data enabling an evaluation of the cardiovascular safety profile: a meta-analytic approach (section 4.2.1) and a dedicated cardiovascular outcome study (section 4.2.2).

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 (“failed studies”) should generally be included in the meta-analysis. 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. Rules and rationale for excluding or including a study should be presented and discussed.

All studies envisaged to contribute to the meta-analysis should be designed and conducted to high standards in respect of assessment of cardiovascular outcomes. Consideration of which trials to include should follow the EMA Guideline on an application based on a meta-analysis (CPMP/EWP/2330/99), and the marketing authorisation 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 trial

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

A dedicated cardiovascular outcome trial 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. The hypothesis to address cardiovascular safety or to confirm absence of detrimental effect to a higher degree of precision may be embedded within a trial design ultimately attempting to demonstrate superiority (i.e. a cardiovascular benefit associated with the drug). 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, as well as issues of maintaining trial integrity, in particular considering the risks of individuals connected with patient management and trial conduct becoming aware, even in broad terms, of interim trial data (see section 4.7).

4.3. Study population

In general, the study population included in the studies supporting the marketing authorisation application should resemble the target population for the medicinal product. However, a higher representation of subjects with a high baseline risk for cardiovascular diseases and complications (exact definition depending on the indication in question) compared to the target population may be acceptable for the purpose of assessing cardiovascular safety profile regardless of whether a meta-analytic or a dedicated cardiovascular outcome trial approach is used. An important consideration when enrolling enriched populations should be that these patients are still amenable to treatment in the planned study duration and not cause high dropout rates that might hamper interpretation of the results.

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 section 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 safety profile of the new medicinal product. Similarly, it must be avoided that a high

proportion of events are missed because of failure to follow patients after cessation of randomized treatment. The duration of eligible follow-up for events to contribute to the primary analysis should therefore be adequately justified.

All events 'on-treatment' should be included. Events after discontinuation of treatment should continue to be collected but, after time, events will be less likely due to randomised treatment and more likely due to the background event rate, hence only adding noise to the treatment comparison and reducing sensitivity to detect a real treatment difference. Analyses based on a restricted duration of follow-up in those patients discontinuing randomised treatment should be planned and presented alongside analyses that include all events collected. Sensitivity analyses addressing issues related to patients who withdraw from randomised treatment or from follow-up, including different exposure times in the two groups, should be planned.

An applicant must be able to justify that the results from either a dedicated cardiovascular outcome trial or a meta-analysis, in particular the duration of drug exposure and follow-up, are adequate for an assessment of the cardiovascular safety profile (see section 4.6). Any claims of a 'similar' (or even lower) cardiovascular risk of a medicinal product compared to a control should be based on truly similar (or improved) 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 non-fatal stroke. A homogeneous definition of MACE across studies is desirable (e.g. definition of MI, including or not including MI post percutaneous coronary intervention).

In some instances, depending on the characteristics of the medicinal product in question, additional cardiovascular outcomes like hospitalisation for cardiovascular causes (e.g. unstable angina, need for revascularization, acute heart failure/worsening of existent heart failure), TIA and sudden death could also be included in a composite "MACE-plus" endpoint. 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 medicinal 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 pre-defined cardiovascular events included in the composite endpoint.

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 could also be systematically collected whenever this is considered relevant (e.g. based on mechanism of action or pre-clinical findings). 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 safety profile in patients

As a general rule, assuming a comparison against a placebo or standard of care (SOC), the evidence based on the cardiovascular safety profile should be planned to obtain an upper limit of the confidence interval (UCL - 95%, two sided) for the Hazard Ratio (HR) below 1.8 in the event that $HR \approx 1$. This target for the UCL is regarded as a planning assumption and would constitute a reasonable basis for regulatory assessment of the cardiovascular safety at the time of initial licensing and requires an adequate number of cardiovascular events. Other targets for the 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 cardiovascular risk elsewhere in the dossier.

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 medicinal product.

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 safety profile 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 (e.g. LDL cholesterol, blood pressure) will also be taken into account. Indications of an increased risk of cardiovascular events, or an unacceptable lack of precision, may trigger the request for (additional) cardiovascular outcome trials. A summary of the results from the cardiovascular safety analysis should generally be presented in the SmPC of the new medicinal product.

If the use of interim data is considered in a marketing authorisation application, issues related to multiple testing and trial conduct should be taken into account. In addition part of sponsors' organisation and trial monitoring committees conducting and reviewing interim analyses may become aware of interim results. Standard methodology for maintaining the confidentiality of interim data may not suffice for this particular scenario. These issues of trial integrity as well as issues of data transparency merit detailed consideration and discussion with the EMA in case such an approach is considered.