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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**
7 **Draft**

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8 Comments should be provided using this [template](#). The completed comments form should be sent to
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29 **1. Introduction**

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

35 **2. Background and Scope**

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

41 It is now expected that the development programmes of new medicinal products in these therapeutic
42 areas adequately characterize the cardiovascular safety profile enabling an evaluation of the
43 cardiovascular risk in the marketing authorisation application (MAA). This refers in particular to
44 products with a new mechanism of action or products belonging to a drug class for which the
45 cardiovascular safety profile is not yet established or fully understood.

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

49 **3. Legal Basis and Relevant Guidelines**

50 This reflection paper should be read in conjunction with the introduction and general principles and
51 Annex I to Directive 2001/83 as amended and with the following guidelines:

- 52 • Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes
53 mellitus (CPMP/EWP/1080/00 Rev. 1);
- 54 • Guideline on clinical evaluation of medicinal products used in weight control (CPMP/EWP/281/96
55 Rev.1);
- 56 • Guideline on clinical investigation of medicinal products in the treatment of hypertension
57 (EMA/238/1995/Rev. 3);
- 58 • Guideline on clinical investigation of medicinal products in the treatment of lipid disorders
59 (EMA/CHMP/748108/2013);
- 60 • Points to Consider on Application with 1. Meta-analyses; 2. One Pivotal study
61 (CPMP/EWP/2330/99);
- 62 • Draft guideline on the investigation of subgroups in confirmatory clinical trials
63 (EMA/CHMP/539146/2013).

64 **4. Recommendations**

65 **4.1. Evaluation of cardiovascular risk**

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

72 **4.2. Clinical outcome data**

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

75 **4.2.1. A meta-analytic approach**

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

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

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

97 **4.2.2. A dedicated cardiovascular outcome study**

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

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

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

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

113 **4.3. Study population**

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

121 **4.4. Duration of studies**

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

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

138 **4.5. Safety outcomes**

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

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

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

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

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

156 **4.6. Quantification of cardiovascular risk in patients**

157 As a general rule, assuming a comparison against a placebo or standard of care (SOC), the evidence
158 based on cardiovascular risk should be planned to obtain an upper limit of the confidence interval
159 (95%, two sided) for the Hazard Ratio (HR) below 1.8 in the event that $HR \approx 1$. This would constitute a
160 reasonable basis for regulatory assessment of the cardiovascular risk at the time of initial licensing and
161 requires an adequate number of cardiovascular events. Other targets for the upper confidence limit
162 (UCL), including narrower targets, may be more appropriate based on the particular target population,
163 known cardiovascular risk profiles of the comparators, previous experience in the class, presence or
164 absence of a signal for increased risk elsewhere in the dossier. This target for the UCL is regarded as a
165 planning assumption. The overall assessment of the cardiovascular risk and determination of need for
166 any post-authorisation studies will always take into account the internal and external validity of the
167 data (e.g. experience from other products within the class) and the overall benefit-risk balance of the
168 drug.

169 **4.7. Evaluation of results**

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

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

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