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GUIDELINE ON THE EVALUATION OF MEDICINAL PRODUCTS FOR CARDIOVASCULAR DISEASE PREVENTION

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1. INTRODUCTION

The prevention of cardiovascular disease represents one of the most important aspects of preventive medicine today. “Secondary prevention” was initially designated for patients who had a myocardial infarction. More recently, the term has been used to encompass patients with established clinical evidence of cardiovascular disease (CVD) e.g. coronary artery, cerebrovascular or peripheral artery diseases. “Primary prevention” usually means prevention of first clinical events in mostly asymptomatic subjects. However, as the terms primary/secondary prevention do not truly represent inherent cardiovascular risk, they have yielded their place for a more comprehensive strategy aimed at treating patients at high risk of CVD adopting the intensity of preventive interventions in accordance with the total CV risk. Using the SCORE model, a score of ≥ 5% of dying from CVD within a 10 year period is considered as high risk. This population thus represents the top stratum of CVD risk within the asymptomatic population and has a prognosis equivalent to some patients with documented CVD.

New evidence derived from large-scale intervention studies have confirmed the concept of a CVD continuum and reinforced the notion that intervention at selective points along this chain can modify CVD progression. In addition, the accumulated clinical evidence indicates that the events leading to disease progression overlap and intertwine. Clinical practice guidelines have been adapted to take into account this novel information. Current therapeutic strategies are aimed at identifying global CVD risk in an individual and treating all risk factors. Global risk intervention, rather than single risk modification is the standard of care.

2. SCOPE

This Guideline is intended to provide guidance for the evaluation of drugs in the prevention of cardiovascular events. This guidance document will not cover the specific treatment of known cardiovascular risk factors like arterial hypertension, hypercholesterolemia or diabetes mellitus, which is in the scope of specific guidelines.

3. LEGAL BASIS

It should be read in conjunction with Directive 2001/83/EC, as amended, and current and future EU and ICH guidelines, especially those on:

- (EC) NfG on clinical investigation of medicinal products for the treatment of peripheral arterial occlusive disease (CPMP/EWP/714/98)
- (EC) NfG on clinical investigation of medicinal products in the treatment of hypertension (CPMP/EWP/238/95)
- (EC) NfG on the clinical investigation of medicinal products of anti-anginal medicinal products in stable angina pectoris (CPMP/EWP/234/95)
- (EC) NfG on clinical investigation of medicinal products in the treatment of lipid disorders (CPMP/EWP/3020/03)
- (EC) Questions and answers document on the clinical development of fixed combinations of drugs belonging to different therapeutic classes in the field of cardiovascular treatment and prevention (CPMP/EWP/191583/2005)
- (EC) NfG on anti-arrhythmics (CPMP/EWP/237/95)
- (EC) NfG on fixed combination medicinal products (CPMP/EWP/240/95)
- (ICH Topic E7) Studies in support of special populations: Geriatrics (CPMP/EWP/379/95)
- (ICH Topic E9) NfG on statistical principles for clinical trials (CPMP/ICH/363/96)
- (EC) Guideline on the choice of the non-inferiority margin (EMEA/CPMP/EWP/2158/99)
- (EC) Points to consider on multiplicity issues in clinical trials (CPMP/EWP/908/99)
- (EC) Points to consider on an Application with 1) Meta-analyses 2) One pivotal study (CPMP/EWP/2330/99).

They are intended to assist applicants in the interpretation of the latter with respect to specific problems presented by products intended for the cardiovascular prevention

4. CLINICAL TRIALS

4.1 Patients characteristics and selection of patients

The rationale for an active approach to the prevention of CVD is firmly based on the observation that risk factor modifications have been unequivocally shown to reduce mortality and morbidity, in people with either unrecognised or recognised CVD. On an individual level preventive efforts are most efficient when they are directed at those at highest risk. Furthermore, the balance between benefit and harm of the preventive therapy is related to CVD risk and in particular to the threshold of risk beyond which benefit will probably exceed harm. Therefore, when designing clinical trials for CVD event prevention, an accurate definition of the CVD risk of the target population is fundamental. There are two approaches for the definition of the target population at CVD risk: integrated global risk scoring models or CVD risk estimation based on *the presence of cardiovascular disease*.

-Integrated global risk scoring models

Absolute CVD risk (e.g. the probability that a patient will have a CVD event in a defined period) is determined by the cumulative effect of all CVD risk factors present, and absolute differences in risk can vary more than 20-fold in patients with the same blood pressure or cholesterol levels. Moderate elevation of single risk factors such as blood pressure or cholesterol has a minor effect on a patient's absolute risk in the absence of other risk factors. This evidence has been the rationale for the development of CVD multifactorial risk models. Several risk prediction scores are available and usable in clinical practice. Two such risk models are the Framingham risk scoring equations and the European SCORE system. Many scores have been derived from the Framingham Heart Study. These Framingham equations display risk of any cardiovascular event, fatal or non-fatal based on categories of age, sex, smoking status, total cholesterol and systolic blood pressure. Using these scores a 10-year absolute risk of 20% has been recommended as a threshold for intervention. However, this threshold is a matter of debate. The question on the perfect applicability of a risk function derived from US data to the European populations has led to the development of a more European specific risk function: the SCORE system. This model predicts any kind of fatal atherosclerotic end-point i.e. fatal CVD events over a 10-year period. In SCORE the following risk factors are integrated: gender, age, smoking, systolic blood pressure, either total cholesterol or the cholesterol/HDL ratio. Since the chart predicts only fatal events, the threshold for high risk is defined as 5% or greater 10 year absolute risk. For type 2 diabetes patients, risk equations have also been developed (UKPDS risk engine, ADA diabetes personal health decisions).

Risk scores can be used in the asymptomatic population. They help screen for low risk patients e.g. in placebo controlled trials and in high risk primary prevention patients. The main issue is the predictive accuracy of these scoring models and their applicability for patient screening for large interventional trials. To be adequate, the scoring system should predict all events in a small, definable and treatable high risk group. Regional differences in risk profile are expected, therefore, the Applicant could be requested to justify the relevance of the submitted data for the EU populations taking into account that some integrated global risk scoring models (e.g. SCORE) have been adapted to countries with high and low cardiovascular risk.

-Risk estimation based on the presence of cardiovascular disease

The obvious clinical characterisation of patients at CVD risk is to select patients with symptomatic arterial diseases. Patients with a history of prior ischemic events are undoubtedly at particular risk for recurrence and this represented the "classical" secondary prevention trial populations. Although the recurrent events may be in the same arterial territory as the initial event, there is also substantial risk for an event in another artery. For example, patients with a history of ischemic stroke are at risk for not only recurrent stroke but also myocardial infarction. Similarly, asymptomatic patients with diabetes like patients with a multiplicity of risk factors for atherosclerosis are at high risk for ischemic events. Therefore, selection of the target population at CVD risk based on clinical characteristics goes far beyond the simple distinction between secondary and primary prevention. Clinical characterisation of patients is easy to implement and may be suitable and more efficient for the design of large global

prevention trials. The strategies for disease prevention are similar in both categories of patients: those with clinically manifest ischemia and those with sufficiently elevated risk of developing ischemia.

In addition to overt arterial disease criteria, several major atherothrombotic risk factors may be utilised for patient selection: e.g. diabetes, diabetes nephropathy, low ankle-brachial index, asymptomatic carotid stenosis > 70%.

In addition to a well-defined clinical characterisation of the study population being required for the description of the target indication in the SPC, an important objective in defining the target population is to accurately estimate the absolute level of risk and to select high-risk patients or patients with a risk level at which a preventive therapy is indicated. Pre-specified thresholds may not be needed. The two approaches described above may be used to select patient populations for prevention trials, both combined or separately. However, the selection method should be adequate to define a population including patients with homogeneous and well-characterised risk levels, thus facilitating straightforward interpretation and applicability of the study results to the whole target population. If clinically distinct subgroups of patients with similar levels of absolute CVD risk are to be included, investigations of internal consistency should proceed as outlined in ICH E9 and in the Points to Consider (PtC) document on an Application with 1) Meta-analyses 2) One pivotal study CPMP/EWP/2330/99. It is recommended that the number of patients recruited to each subgroup relevant for prognosis is large enough to draw reliable conclusions on the consistency of the treatment effect. Mixing in the same trial, patients with significant different absolute risk levels is discouraged, in particular where the magnitudes of the treatment effects are likely to differ according to absolute level of risk. In this instance, an analysis pooling data from all types of patient to establish efficacy would be difficult to justify. Demographic factors like gender and age should be considered in a way that the enrolled populations are a true reflection of the current prevalence of the disease among the different strata.

4.2 Study design and duration of treatment

According to the nature of the indication, long-term controlled, parallel and preferably double-blind clinical trials are generally necessary for both safety and efficacy. The duration depends both on the incidence of the primary endpoints, the expected duration of the therapy and specific safety requirements associated with the study drug. Treatment should usually last at least 12 months and preferably longer, notably when the intended use is lifelong. When the latter is the case, duration up to five years is reasonable. For example, in patients with ACS, 6 months data are usually sufficient for evaluation of acute treatment effects, however to assess the CVD prevention, data on at least one year of treatment are needed.

Studies have to be carried out on top of optimal drug treatment and lifestyle changes. It is crucial to implement mechanisms to ensure optimal baseline therapy and to control cardiovascular risk factors over the whole study period. Depending on the group of patients this requires an appropriate run-in period prior to randomization. The clinical relevance of a treatment effect will be difficult to assess if patients are not on optimal baseline therapy or if risk factors, e.g. smoking habits, unrelated to the presumed mechanism of action of a drug are influenced differentially.

One large-scale pivotal trial may be acceptable if all of the requirements of the PtC document on an Application with 1) Meta-analyses 2) One pivotal study CPMP/EWP/2330/99 are met.

Predefined subgroup analyses are necessary for the evaluation of safety and efficacy. Stratification of relevant subgroups should be considered.

4.3 Control groups

The choice of the comparator (placebo or active control) depends only on establishing an effective treatment in the specific target group (see ICH E10). Either the superiority, or the non-inferiority approach can be accepted. When using the non-inferiority approach, establishing assay sensitivity is of paramount importance. The trial must be high quality and the study population should be as similar as possible to the study population in the original pivotal efficacy study of the active comparator. The choice of a non-inferiority margin depends both on the best assumption of the effect of the active control in comparison to placebo and on a clinical assessment of the potential differences between treatments. The non-inferiority margin should be conservatively selected and properly justified in terms of its clinical relevance (CPMP/EWP/2158/99) in light of overall risks and benefits of each

treatment. There are circumstances where it is difficult to justify any choice of non-inferiority margin and alternative strategies should be discussed. If there is more than one possible active comparator, only one of these comparators is acceptable.

A placebo-controlled study aiming to demonstrate superiority provides an absolute estimate of the treatment effect. This is the preferred approach, if ethically acceptable, and if there is no established therapy for the specific target population or for a group of patients that is very similar. In this case, optimising background therapy and life-style modifications becomes an issue of paramount importance.

4.4 Primary Efficacy Endpoints

Clinical outcome endpoints should be objective and clinically relevant. In general, all-cause mortality and fatal CVD events are acceptable as primary endpoints. Usually, objective CVD events need to be hospital-verified. A clinical event is most likely to be suitable if there are accepted specific criteria for its definition and can be objectively established (e.g. myocardial infarction, ACS, stroke). Other events, like transient ischemic attack, silent MI or stable angina pectoris are less likely to be objectively defined. Therefore, clinically relevant justifications should be provided when using them as components of a composite primary endpoint.

All-cause mortality is preferred over cardiovascular mortality as primary endpoint or as one component of the primary endpoint. Cardiovascular mortality, if objectively and conservatively defined, may also be acceptable and may be more sensitive to detect differences in non-inferiority approaches. Sufficient confidence regarding overall mortality and non-CV mortality is necessary in this case.

Composite outcomes, including fatal and non-fatal CVD events, in which multiple endpoints are combined, are frequently used as primary outcome measures in randomised trials to reflect a number of outcomes that are of clinical importance and to increase statistical efficiency when event rates are low. Handling of composite endpoints is described in the PtC on multiplicity issues in clinical trials (CPMP/EWP/908/99). Composite endpoints may be appropriate in trials of CV disease prevention when including hard clinical events (e.g. nonfatal myocardial infarction, stroke). However, including in the composite, components which have a markedly different weight in term of clinical benefit is discouraged. An example is the combination in the primary composite endpoint of fatal events and clinician decision outcomes: hospitalisation, coronary revascularisation, amputation, use of rescue therapy, hospitalisation for heart failure. In such case, the statistical significance of the primary composite endpoint is often driven by the clinician-decision outcome component, presenting further challenges for the interpretation of the study overall results. The more clearly components of a composite endpoint directly refer to the disease process, the less there is any problem of interpretation. The more likely it is too that the components of the composite will move in the same direction given an effective treatment, which is important for sound interpretation. The primary analysis of a composite endpoint should be based on a ‘time-to’ first event (survival) analysis.

To provide supportive information, and to ensure reliable interpretation, analyses of each separate component of the composite should be presented. For overall mortality and cardiovascular mortality both confidence intervals and point estimate are relevant for assessment. Any point estimate considerably in favour of the comparator is a matter of concern.

4.5 Secondary Efficacy Endpoints

If a composite primary endpoint is used, generally its separate components are secondary or tertiary endpoints, which are analysed separately if clinically meaningful and validated. Other secondary endpoints may include relevant cardiovascular morbidity measures. Any secondary outcome measures on which a claim is to be made should be embedded into the confirmatory testing strategy appropriately controlling type I error (see CHMP Points to Consider on Multiplicity in Clinical Trials). The secondary endpoints should also be related to the questions to be answered in the clinical trial.

Beyond the traditional risk factors and clinical event endpoints, non-invasive imaging techniques and serum markers have been suggested for both identifying asymptomatic individuals at risk and/or as surrogate endpoints for clinical trials. A number of such markers of target-organ damage have been investigated to determine their reliability in the clinical setting and usefulness in risk stratification. Examples include left ventricular hypertrophy, carotid intima-media thickness, coronary artery

calcification, coronary intravascular ultrasound plaque volume, proteinuria; and as serum markers C-reactive protein, homocysteine. Cardiovascular imaging and biomarkers may merit regulatory consideration in several situations including dose-selection, early phase I/II feasibility trials for decision or line extension. Validation of surrogate markers relies on 3 basic principles with demonstration of (1) biological plausibility, (2) correlation with epidemiological studies and (3) treatment effects on the surrogate that predict treatment effects on outcome. Ultimately, surrogate marker changes should be correlated with the changes in clinical risk. Results must always be considered in a context that recognises that the effect may be limited to the particular drug, the drug mechanism, the disease stage and to the subpopulations studied.

5. CLINICAL SAFETY EVALUATION

All of the above-mentioned primary and secondary efficacy endpoints are also regarded as important safety endpoints. Neither overall mortality nor cardiovascular mortality should indicate a detrimental effect. If a long-term treatment is envisaged, long-term data on mortality and cardiovascular morbidity are necessary of as a rule at least 1 year. Special attention has to be drawn to possible inadvertent effects adherent to the study drug on parameters which may impact the cardio-vascular risk profile like blood pressure lowering effects, effects on lipid profile or glucose regulation. In addition bleeding or other relevant pharmacodynamic or pharmacokinetic drug-drug interactions should be monitored. Consideration should be given to all of the above-mentioned relevant subgroups and special patient populations at risk like the elderly, patients with renal, hepatic and cardiac failure.