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DRAFT

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, with the discovery that patients with asymptomatic atherosclerotic disease or diabetes had a prognosis as grave as patients with established CVD, the terms primary/secondary prevention have yielded their place for a more comprehensive strategy aimed at treating patients at high risk of CVD. These include patients with multiple risk factors and a 10-year risk of coronary events > 20%. This population thus represents the top stratum of CVD risk and has a prognosis equivalent or worse than post-myocardial infarction patients.

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
- (EC) NfG on clinical investigation of medicinal products in the treatment of hypertension
- (EC) NfG on clinical investigation of medicinal products of anti-anginal medicinal products in stable angina pectoris
- (EC) NfG on clinical investigation of medicinal products in the treatment of lipid disorders
- (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
- (EC) NfG on anti-arrhythmics
- (EC) Fixed-combination products
- (ICH) Studies in support of special populations: Geriatrics
- (EC) Biostatistical methodology in clinical trials

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. 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 clinical symptoms.

-*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 synergistic 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 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 coronary heart disease 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. 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 e.g. 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 fatal events, the threshold for being at high risk is defined as equal or superior to 5%. For type 2 diabetes patients, risk equations have also been developed (UKPDS risk engine, ADA diabetes personal health decisions).

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 will be requested to justify the relevance of the submitted data for the EU populations.

-*Risk estimation based on clinical symptoms*

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 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 for the design of large prevention trials. The strategies to disease prevention are similar in both categories of patients: the one with clinically manifest ischemia and the one 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: diabetes, diabetes nephropathy, low ankle brachial index, asymptomatic carotid stenosis > 70%.

The main objective in defining the target population is to accurately estimate the level of risk and to select high-risk patients or patients with a risk level at which a preventive therapy is indicated. The two approaches described above may be used to select patient populations for prevention trials. However, the selection method should be adequate to define a patient population with a homogeneous and well-characterised risk level, thus allowing a straightforward interpretability and applicability of the study results to the whole target population. Mixing in the same trial, patients with significant different absolute risk levels is discouraged. If clinical subgroups of patients with similar level of

absolute CVD risk are to be included, the population in each subgroup should be large enough to support subgroup analysis with sufficient statistical power to draw reliable conclusions on the consistency of the treatment effect. 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. In addition, consistency of the study results in all clinical subgroups should be established. A well-defined clinical characterisation of the study population is also mandatory for the description of the target population in the SPC.

4.2 Study design and duration of treatment

According to the nature of the indication in general long-term controlled, parallel and preferably double-blind clinical trials are 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, but longer periods are often necessary. In patients with ACS, 6 months data are usually sufficient for evaluation of acute treatment effects, however to asses the CVD prevention, one year data are needed.

Studies have to be carried out on top of optimal treatment. 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 a sufficiently long run-in period prior to randomization. The clinical relevance of a treatment effect will be difficult to be assessed if patients are not on optimal baseline therapy or if risk factors, e.g. like 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 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 for the analysis of relevant subgroups is recommended.

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. With an active comparator every reasonable effort has to be made to make the study population as similar as possible to the study population in the original pivotal efficacy study of the comparator. A superiority-, or a non-inferiority-design are acceptable. If a non-inferiority approach is chosen, assay sensitivity should be ensured, paying special attention to the criteria defining the target population and the primary endpoint used. The choice of a non-inferiority margin depends on the best assumption of the effect of the comparator in comparison to placebo and on the clinical assessment. The delta finally proposed as non-inferiority should be conservatively selected and properly justified in terms of its clinical relevance. For overall mortality and cardiovascular mortality both confidence intervals and point estimate are relevant. Any point estimate considerably in favour of the comparator is a matter of concern. If there is more than one possible active comparator only one of these comparators is acceptable. The choice has to be justified based on efficacy and safety.

A placebo-controlled study aiming at superiority is adequate 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. The primary endpoint should be the one used when estimating the sample size.

In general, total mortality and fatal CVD events are acceptable as single 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.

Total mortality is preferred over cardiovascular mortality as primary endpoint or as one of its components. 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, in which multiple endpoints are combined, are frequently used as primary outcome measures in randomised trials to increase statistical efficiency. However, such measures may sometimes prove challenging for the interpretation of results. Confidence in a composite endpoint rests partly on a belief that similar reductions in relative risk apply to all the components. Furthermore, including in the composite, components, which have different weight in term of clinical benefit, may even more confound the issue. An example is the combination in the primary 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.

4.5 Secondary Efficacy Endpoints

If a composite primary endpoint is used, generally its separate components are secondary 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 organised into a hierarchical testing strategy that controls type I error. The secondary end-points 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 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 IVUS 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. 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, drug mechanism disease stage and subpopulation.

5. CLINICAL SAFETY EVALUATION

All of the above-mentioned primary and secondary efficacy endpoints are also regarded 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 like blood pressure lowering effects, bleeding or other relevant pharmacodynamic or pharmacokinetic drug-drug interactions. 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.