European Medicines Agency
Evaluation of Medicines for Human Use

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CONCEPT PAPER ON THE DEVELOPMENT OF A COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP) NOTE FOR GUICANCE ON THE NEED FOR REGULATORY GUIDANCE IN THE EVALUATION OF MEDICINAL PRODUCTS FOR THE SECONDARY CARDIOVASCULAR PREVENTION

1. INTRODUCTION

Secondary prevention means prophylaxis of a new major cardiovascular event after one or several major event(s). Secondary cardiovascular prevention is normally understood as the prophylactic strategy in patients with established arterial disease, i.e. coronary heart disease (CHD, acute myocardial infarction or acute coronary syndrome), stroke and peripheral arterial occlusive disease (PAOD). Treatment strategy is guided by other risk factors also. According to evidenced-based medicinal recommendation patients can be classified to high and low risk groups. E.g. type II diabetes mellitus is generally regarded to introduce significant but low risk alone. However, some published literature advocate to include diabetic patients as having a similar risk to those having had a major cardiovascular event.

Due to immense scientific knowledge and continuous major breakthroughs in understanding pathogenesis of severe cardiovascular morbidity, and fast medicinal development in this area, regulatory guidance related to minimal requirements in the clinical evaluation of medicinal products in this area has to be kept at a general level, or it has to be dynamic (that is, continuously updated). The latter may be impossible, taken into account that the effective prophylaxis always means long perspective, and respectively, clinical trials have to have relatively long duration. Guidance may have not fulfilled its aim if requirements have been significantly changed, and a trial becomes inappropriate during its run.

2. PROBLEM STATEMENT

Recent regulatory experiences and scientific advice procedures have highlighted controversial issues when dealing with this kind of clinical developments.

Target population

To what extent the target population may include patients with a different level of risk according to the entry criterion (MI, Stroke, ACS, PAOD) and its implications when interpreting the results. To what extent the inclusion of high risk patients without previous cardiovascular events could be regarded as acceptable (i.e. diabetic patients).

Study design

Long-term clinical trials are expected to assess the effect of a new intervention intended for the secondary cardiovascular prevention. However, there exist controversy on the components of the composite endpoint to be used: a) cardiovascular vs. overall mortality; b) MI and Stroke vs. a wider definition of cardiovascular morbidity.

Moreover, and depending on the nature of the assayed drug, the need for placebo vs. active controlled trials should be discussed.

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Safety aspects

The need for specific safety monitoring and analyses depending on the nature of the experimental drug should be discussed.

3. MAIN TOPICS TO BE ADDRESSED

Guidance on the following issues could be of value:

- Definition of the target population.
- Definition and adequacy of the primary endpoint.
- Choice of the study design and statistical approach; recommendations regarding survival analyses.
- Definition of the non-inferiority margin and/or clinically relevant differences for mortality.
- Necessity and relevance of predefined subgroup analysis.
- The assessment of concomitant treatments.
- Specific safety analysis depending on the type of drug.

4. RECOMMENDATION

It is proposed to draft a CPMP Points to Consider Document which provides an EU consensuated regulatory view on the issues related to the claims concerning efficacy in secondary prevention.

5. PROPOSED TIMETABLE

It is anticipated that a first draft document is available for discussion at the EWP by January 2005.

6. RELEVANT REFERENCES

Note for Guidance on Clinical Investigation of Medicinal Products for the Treatment of Peripheral Arterial Occlusive Disease CPMP /EWP /714/98 rev 1, London, 25 April 2002