The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

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CONCEPT PAPER ON THE DEVELOPMENT OF A COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP) NOTE FOR GUIDANCE ON THE EVALUATION OF MEDICINAL PRODUCTS FOR THE TREATMENT OF DYSLIPOPROTEINAEMIA

1. INTRODUCTION

Hyperlipidaemia, particularly in the form of raised LDL cholesterol, is a well-established risk factor for the development of cardiovascular disease (CVD). The World Health Organisation's Clofibrate Trial raised concerns regarding the benefit/risk of lowering cholesterol levels and emphasised the importance of long term trials in assessing efficacy regarding hard endpoints and safety. Primary prevention trials in hypercholesterolaemic males with cholestyramine and gemfibrozil (the lipid research clinics coronary prevention trial and the Helsinki Heart Study) showed a reduction in CVD, but no effect on total mortality. The clinical benefit of lowering cholesterol, particularly in secondary prevention, did not become evident until the results of the large statin trials were published. Although the LDL cholesterol hypothesis must be considered proven beyond doubt, statins have pleiotrophic effects and other mechanisms than altering lipid levels may partly explain their effects on morbidity and mortality.

Low HDL cholesterol is strongly associated with an increased risk of CVD. There is substantial evidence that raising HDL by treatment reduces the incidence of coronary artery disease, but this hypothesis has not been tested primarily. Trials such as AFCAPS/TexCAPS and Va-Hit, including patients with low HDL cholesterol, are supportive.

The importance of raised triglycerides in CVD is debated in the scientific community and the clinical benefit of lowering triglyrides by treatment still needs to be established.

The statin trials indicate that other manifestations of CVD, such as stroke and CHF, are reduced by treatment. Still these findings need to be substantiated.

2. PROBLEM STATEMENT

Regulatory guidance on the development of medicinal products in the treatment of dyslipoproteinaemia is currently not available. Within the EU there is a clear need to provide guidance in this area, as exemplified by recent regulatory experiences and scientific advice procedures. There is a considerable disharmony in the SmPCs for lipid altering drugs within the EU.

As described in the introduction and shown by the list below, there are a number of important issues to be addressed.

3. MAIN TOPICS TO BE ADDRESSED

- Criteria for diagnosis and classification of hyper- and dyslipoproteinaemias, including how to determine lipids and lipoproteins
- Established therapy and treatment goals
  - non-pharmacological and pharmacological treatment
- Licensing requirements regarding first-line, second-line and add-on therapy
- Primary and secondary efficacy endpoints
  - relevance of lipid/lipoprotein parameters (including ratios, such as LDL/HDL, effects on apo B, apo A etc)
  - whether to focus on absolute/relative changes in lipid parameters or reaching target levels

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- validity of intermediate endpoints such as the degree of atherosclerosis determined by different imaging methods (angiography, MR ultrasound etc)
- definition of hard endpoints such as total and coronary artery disease (CAD) mortality, CAD morbidity
- other cardiovascular endpoints such as stroke, congestive heart failure etc.

- Concomitant diseases and risk factors (hypertension, diabetes, smoking, obesity, metabolic syndrome, chronic renal disease)
- Indication claims (type of hyper-or dyslipoproteinaemia and whether primary or secondary (diabetes mellitus, renal disease etc.), Primary or secondary prevention, efficacy (effects on lipid parameters, CVD mortality/morbidity, overall mortality)
- Special populations
  - elderly, women, children, diabetes, renal disease etc.
- Comparators and placebo
  - established therapy
  - when and for how long is placebo treatment acceptable?
  - add on studies
- Duration of studies
- Safety

4. RECOMMENDATION

It is proposed to draft a CPMP Note for Guidance document to provide a consensus regulatory view within the EU on the above-mentioned issues.

5. PROPOSED TIMETABLE

It is anticipated that a first draft document will be available for discussion at the EWP by November 2001.

6. RELEVANT REFERENCES

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