European Medicines Agency

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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

CONCEPT PAPER ON THE NEED FOR THE DEVELOPMENT OF A PAEDIATRIC ADDENDUM TO THE CHMP NOTE FOR GUIDANCE ON THE CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE TREATMENT OF LIPID DISORDERS

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1. INTRODUCTION

The CHMP note for guidance on the clinical investigation of medicinal products in the treatment of lipid disorders addresses the regulatory aspects during the development of drugs for the treatment of lipid disorders in adults. A limited number of lipid lowering agents, including some statins, fibrates and cholesterol adsorption inhibitors have been tested and are available for children 8 years and older and adolescents. This concept paper discusses the need for regulatory guidance on the clinical development of lipid lowering drugs in this target population.

2. PROBLEM STATEMENT

Lipid screening and cardiovascular health in childhood are drawing increasing attention. Research over the last 40 years has increasingly indicated that the process of atherosclerotic cardiovascular disease may begin early in life and, and as a consequence, may warrant early treatment. This includes the pharmacological treatment of lipid disorders, where in some cases it is now recommended to start at a young age. As the age for lipid screening in certain high risk groups is becoming lower, it is expected that the number of children who are eligible for pharmacological treatment will increase. Thus, more studies in paediatric patients will be needed, both for old and new products, not only to study effects on the lipid disorder itself, but perhaps even on long term outcome.

Because the studies are almost always conducted at the end of the drug patent life, the need of the pharmaceutical companies to complete studies within the shortest period of time increases the importance of the exclusivity extension. Initiating childhood trials coincident with, or very shortly after, adult trials should be compatible with extending the period of recruitment, resulting in a larger number of subjects from any given centre and overcoming the problem of the small number of children recruitment.

3. DISCUSSION

Based on the normative distribution, cut points for lipids, in particular LDL cholesterol, have been identified in children and adolescents with abnormal lipid and lipoprotein concentrations. These can be used to select patients for whom pharmacological intervention should be considered. This concerns in the first place patients with a primary or genetic lipid disorder, in particular patients with homozygous or heterozygous familial hypercholesterolemia (FH), who are primary candidates for pharmacological treatment already at a young age. Certain other paediatric disease states are also associated with accelerated atherosclerosis that may warrant early pharmacological treatment to obtain optimal LDL-cholesterol levels as part of a general risk-reduction plan. These include diabetes mellitus, type 1 and 2, chronic kidney disease, Kawasaki disease, congenital heart disease, and chronic inflammatory disease. Also improved treatment in children and adolescents with childhood cancer, HIV infection and heart transplantation may result in a high prevalence of risk factors for atherosclerosis and, as a consequence, lipid-lowering therapy.

Among others, the following key aspects of the clinical development of lipid lowering drugs in these paediatric patients are considered of particular relevance:

1. Diagnostic criteria including usefulness and limitations of using LDL-C and other lipid parameters at a young age and other methods to identify genetic lipid disorders and young patients at risk.
2. Relevant subpopulations according to age in relation to aetiology and comorbidity
3. Potential waivers in particular groups according to age and/or relevant co-morbidities
4. Usefulness and limitations of LDL-C and other lipid parameters to assess efficacy in children and adults.
5. Usefulness and limitations of surrogate parameters, in particular non-invasive measures of early atherosclerosis.
6. The need for separate long term outcome studies in children and adolescents.
7. The need to perform specific dose-range studies to account for potential pharmacological differences between adult and paediatric population and the need to produce child-specific formulations.
8. The (un-)feasibility of controlled studies in children and adolescents, type of control (if appropriate) and length of minimum follow-up.

9. Need for specific safety requirements related to age.

4. RECOMMENDATION

The CHMP recommends drafting a paediatric addendum to the CHMP guideline on the clinical investigations of medicinal products for the treatment of lipid disorders.

5. PROPOSED TIMETABLE

It is anticipated that a draft document may be released 6 months after adoption of the Concept Paper by the relevant committees. The draft document will then be released for 6 months of external consultation and following the receipt of comments it will be finalised within approximately 3 months.

6. RESOURCE REQUIREMENTS FOR PREPARATION

The preparation will involve the EWP Cardiovascular drafting group, with the active participation of experts nominated by the PDCO. External experts will be contacted when needed. One rapporteur from the EWP-CV will be involved and the document is predicted to be discussed on 2-3 EWP-CV meetings and on two EWP meetings.

7. IMPACT ASSESSMENT (ANTICIPATED)

The document is intended to provide guidance to industry when performing trials to develop lipid lowering drugs. It should also provide a clear basis for the CHMP when assessing data from paediatric studies for lipid-lowering drugs.

8. INTERESTED PARTIES

Association for European Paediatric Cardiology (AEPC), European Academy of Paediatrics (EAP-CESP), European Society of Cardiology (ESC), Hyperlipidemia, Education, Action, Research and Treatment (HEART EU), Task-force in Europe for Drug Development for the Young (TEDDY), European Atherosclerosis Society, International Atherosclerosis society.

9. REFERENCES TO LITERATURE, GUIDELINES ETC

1. Kavey RW, Allada V, Daniels SR et al. Cardiovascular risk reduction in high-risk pediatric patients. Circulation 2006; 114: 2710-2738.
2. Lipid screening and cardiovascular health in childhood. Pediatrics 2008; 122: 198-208.