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Committee for Medicinal Products for Human use (CHMP)

Paediatric addendum to CHMP guideline on clinical investigation of medicinal products in the treatment of lipid disorders

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7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8613
E-mail info@ema.euro□a.eu **Website** www.ema.europa.eu

Executive summary

This is an addendum to the Guideline on Clinical Investigation of Medicinal Products in the Treatment of Lipid Disorders (EMA/CPMP/3020/2003). It is not meant as a guidance document on its own but rather highlights differences from adult patients with lipid disorders and points out specific paediatric issues.

1. Introduction

The atherosclerotic process in children with inherited lipid disorders, so called **primary lipid disorders**, begins in childhood with progression mediated by well identified risk factors[1,2]. These disorders include monogenic dyslipidemia due to homozygous (HoFH) and heterozygous familial hypercholesterolaemia (HeFH), and familial defective apolipoprotein B. Vascular damage starts from birth and morphological and functional vascular changes have been demonstrated from as early as 8 years[3]. Ideally, treatment goal for children is the complete reversal of vascular damage at an early age with full compliance and in absence of adverse effects. Early intervention is needed to prevent/delay morbidity and mortality. Whenever possible, primary prevention should be achieved through lifestyle intervention, diet and physical activity. This approach is usually insufficient in these genetic disorders and should be combined with medication, initiated from an early age[4]. Revised recommendations now propose to start pharmacological intervention, in particular with statins, at the age of 8 years or even earlier, depending on the actual LDL levels, gender, presence of other risk factors and a family history of premature vascular disease[5,6]. So far, these disorders have been the primary focus of studies with lipid lowering agents in children. Other familial lipid disorders, such as familial combined hyperlipidemia, dysbetalipoproteinemia and familial hypoalphalipoproteinemia, (such as lecithin:cholesterol acyl transferase (LCAT) ABCA1 and apolipoprotein A1 (ApoA1) deficiency), may also be candidates for early pharmacological treatment, but sufficient data are not available to make specific recommendations regarding the treatment of lipid abnormalities other than elevated LDL-cholesterol, particularly elevated triglycerides and/or decreased HDL levels[5,7].

Other lipid disorders in children, so called **secondary lipid disorders**, may be the expression of an underlying cause, such as diabetes mellitus type 1 and type 2, transplantation, HIV infection, Kawasaki disease, systemic lupus erythematosus, congenital liver disorders, and obesity. These disorders include patients with hypercholesterolemia, but also patients with concurrent or isolated hypertriglyceridemia and/or low HDL-cholesterol. The majority of children with dyslipidemia will have idiopathic dyslipidemias (polygenetic, risk factor-associated or multifactorial)[7,8]. Obesity may be a major contributing factor to the disease in these patients. Complications occur in most cases later in life and it still has to be established if and when treatment has to start before the age of 18 years. Emphasis will be on healthy life style and behaviour modification. However, in certain high risk patient groups, cardiovascular events may occur early in life, with recommendations to start medication aimed at correction of lipid abnormalities at an early stage[1,5,6].

In general, efficacy and safety should be established in adults, before children are included in trials investigating lipid disorders. However, extrapolation from adults to children is not a straightforward process for several reasons: 1) the type of lipid disorder may be different resulting in a different treatment response; 2) target lipid levels and use of other surrogate endpoints, such as vascular imaging and function are not the same; and 3) specific safety issues need to be taken into consideration.

2. Scope

Similar to the Guideline on Clinical Investigation of Medicinal Products in the Treatment of Lipid Disorders (EMA/CPMP/3020/2003), this addendum will focus on hypercholesterolemia, in particular in children with primary lipid disorders[8].

3. Legal Basis

This addendum to the Guideline on Clinical Investigation of Medicinal Products in the Treatment of Lipid Disorders is to be read in conjunction with the introduction and general principles of the Annex I to Directive 2001/83/EC as amended. All pertinent elements outlined in the current and future EU and ICH guidelines and regulations should also be taken into account especially the following:

- Guideline on Clinical Investigation of Medicinal Products in the Treatment of Lipid Disorders - EMA/CPMP/3020/2003
- Clinical Investigation of Medicinal Products in the paediatric population - CPMP/ICH/2711/99 (ICH 11)
- Guideline on clinical trials in small populations - CHMP/EWP/83561/2005.

4. Criteria of Efficacy

4.1. Morbidity and mortality

The primary goal is to prevent cardiovascular morbidity and mortality associated with lipid disorders. There has not been, nor is it likely that there will be a controlled trial comparing the effect of risk reductions beginning in childhood on the subsequent development of cardiovascular disease[2]. Therefore, the beneficial effects on cardiovascular outcome have to be extrapolated from studies in adults, if available. However, observational studies after marketing may provide additional information and should be part of the follow-up plan once paediatric use is approved on the basis of surrogate endpoint indicators for lipid levels as well as for vascular damage.

4.2. Lipid levels

In young children lowering LDL-cholesterol to ≤ 3.5 mmol/L might be sufficient to reverse vascular damage[9,10]. Whether further lowering of LDL-cholesterol will result in further morbidity and mortality reduction without compromising the cholesterol synthesis and its products in growing and maturing children is currently unknown. Other lipid parameters, in particular HDL-cholesterol, may be included as primary of secondary end points. They may be predictive of vascular changes as well but their correlation with cardiovascular outcome needs further validation[11]. The age/gender specific reference values should be applied where indicated (6-18 years).

4.3. Vascular damage / effects

Evaluation of vascular damage may be of value and has been used in clinical trials in children[5,10]. Atherosclerosis progression can be evaluated in young children by carotid intima-media thickness (cIMT)[11]. Other possible functional evaluation of endothelial tissue (flow mediated dilation (FMD)) or ultrastructure of the vasculature may be useful for short term observations[12]. Newer techniques, such as magnetic resonance imaging (MRI) and positron emission tomography (PET) may provide valuable additional information on effects of vascular damage but they need to be further validated[13,14]. Below the age of 18 years, vascular abnormalities may be completely reversible due to

unloading of lipid from macrophages in the arterial wall. The relationship between vascular damage and LDL cholesterol levels may be variable to some extent and an inclusion of a full lipoprotein profile may provide further information.

5. Selection of patients

Criteria for diagnosis and classification of **primary lipid disorders** in children, in particular in homo- and heterozygous familial hypercholesterolaemia (HeFH) and familial defective apolipoprotein B (FDB) in children, should be based on LDL-cholesterol levels, family history, and, if indicated (e.g. homozygous hypercholesterolemia), supported by genetic analysis[6,7,8,9]. Additionally, in children with genetic hypoalphaproteinemia, diagnosis should be based on HDL-levels. Elevated levels of LDL-cholesterol are related to the genetic variant, ranging from 3.5 to 12.0 mmol/L in conjunction with decreased HDL-cholesterol levels[6]. Treatment benefit in genetic, low HDL-cholesterol disorders should be studied first in adults before including children. Some genetic variants have elevated triglycerides as well. When conducting studies during adolescence, the age, ethnic background and gender differences should be taken into account. Cholesterol levels are lower during growth spurt[15]. Dietary and lifestyle intervention should be initiated prior to a pharmacological intervention study.

The criteria for diagnosis and classification of **secondary lipid disorders** will depend on the type of dyslipidemia and its associated cardiovascular risk, as discussed in section 1. Therapeutic recommendations are less well defined than in primary lipid disorders and should be based on current knowledge. These criteria should also take into account underlying cause, concomitant treatment, ethnic background and gender differences. Dietary and lifestyle intervention should be initiated prior to a pharmacological intervention study.

6. Strategy – Design

6.1. Human Pharmacology Studies

The development of special paediatric formulations is encouraged, as appropriate. Tablet or capsule size may be important in this regard. Pharmacokinetic data should be provided for the claimed age group.

6.2. Exploratory Therapeutic Studies

These studies should determine the appropriate dose for the confirmatory trials. Placebo-controlled studies as suggested in the adult guideline are not always acceptable or feasible in children, for instance in patients with homozygous hypercholesterolemia. This should be discussed by the sponsor.

6.3. Confirmatory Therapeutic Studies

These will mostly be controlled studies lasting three to six months that will usually be followed by an open label extension for 1 year. The applicant should provide a rationale for the sample size calculation. Lipid levels are the primary endpoints, whereas the investigations of vascular damage should be supportive secondary endpoints. Further study extension may be performed to assess vascular changes or for safety reasons (chapter 7). Below the age of 6 years, patients with HoFH will be studied for PK/PD only.

Limited numbers of lipid lowering agents, including some statins and cholesterol adsorption inhibitors have been approved for use in children and are available as reference therapy[5,6,7,8,13]. For drugs of the

same class, an actively controlled study in a monotherapy/add-on setting could be sufficient, depending on the indication. If no reference therapy is available, in particular in case of multiple drug therapy, short term placebo controlled trials may be necessary to assess effects on lipid levels. Also, healthy siblings could serve as controls to study long term effects, including vascular effects.

Children are eligible for investigation of drugs of a new class of agents as add-on treatment in case of insufficient response to current treatment, in particular statins. When efficacy as add-on therapy has been shown sufficiently, a withdrawal design for statins and/or comparative trial(s) with monotherapy may be initiated. Inclusion in monotherapy trials can also be considered when other therapy has failed or is not tolerated.

7. Safety Aspects

To obtain optimal effect of the drug, adverse effects should be limited as much as possible in order to prevent the negative impact of reduced compliance. Studies should include instructions for down titration of the drug when any adverse event occurs. Long-term issues in relation to growth, cognitive development and sexual maturity are of particular importance, as well as changes in muscular and liver enzyme levels (similar to adults). Acceptable parameters are clinical effects, including muscular cramps, auxological parameters, sexual development, biochemical, liver toxicity (transaminases), hormonal status (steroids, follicle-stimulating hormone, luteinizing hormone, estradiol, testosterone, adrenocorticotropic hormone, dehydroepiandrosterone sulfate, cortisol), muscle enzymes (creatinine phosphokinase). A follow-up of at least two years is recommended for drugs of a new class of agents. Follow-up cohorts after marketing will provide additional information, including data on cardiovascular outcome. Treatment with the HDL-cholesterol raising drugs should be followed for changes in steroid hormone profiles and their biological actions.

Definitions

Refer to section 1.

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