08 October 2012
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Committee for Medicinal Products for Human use (CHMP)

Overview of comments received on "Paediatric addendum to CHMP guidance on clinical investigation of medicinal products in the treatment of lipid disorders (EMEA/CHMP/EWP/213057/2010)"

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

Stakeholder no.	Name of organisation or individual
1	EFPIA
2	Merck Sharp and Dohme
3	Medicines Evaluation Board, The Netherlands
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SCIENCE MEDICINES HEALTH

1. General comments - overview

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
1 1,4	EFPIA welcomes this very valuable addendum that points out paediatric specific issues. It is important that the guidance is pragmatic and aligned to current clinical practice rather than require measures not yet suitable to form the basis for the design of the studies. EFPIA have the following major concerns: **Scope:** This addendum is quite LDL-C focussed and may not reflect current research which focuses on other lipids and targets.	Partially agreed. Other lipids and targets are not yet available for children with HoFH and HeFH. Beside LDL-C surrogate markers as endpoints like c-IMT and FMD are also discussed. Other primary cq hereditary lipid disorders are extremely rare. Secondary lipid disorders are more common, HDL-C and TG are important.
1	**General comments:** - It is important to underline that efficacy and safety should be established in adults before children are included in trials investigating lipid disorders. - Since the population which will be subject to the disease is a post-pubertal population we suggest that this addendum is focused on the adolescent group, e.g. from 12 years old onwards. - Enrolment is a big issue for paediatric studies, which is why many of those studies took many years to complete. Therefore, it is possible that some	Agreed. Not agreed. The target group is from 6 years onwards and not 12 or post-pubertal. Not agreed. Nowadays children are enrolled before the age of 17 years to

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	adolescent patients at enrolment may become adults at end of the studies. It would be helpful if this guidance covers the way to deal with this kind of situation.	avoid that they get inferior treatment beyond the age of 18 years, some becoming adults during the trial. This should be addressed in the protocol. Specific guidance not possible within this guideline.
1	**Efficacy:** - This addendum states that approval for paediatric use could be based on surrogate endpoint indicators for lipid level. However, no details about design for lipid-lowering studies have been provided. For example, it did not mention whether those studies should be double-blind studies or could be open-label studies. - Due to the lack of relevant data, sample size calculation for paediatric studies in most cases is challenging. It would be useful if this guidance describes how to decide sample size for paediatric studies - Furthermore, measures of vascular damage are of course of highest scientific interest and value, but should not at this point of time be required other than as descriptive variables.	Not agreed. The studies should start as controlled and thereafter open label. See also 6.3. Not agreed Sample size calculation is a matter of statistics. Also dependent on type of disorder. Not agreed. Complete vascular normalisation related to dose is an acceptable measurement, where LDL-C level does not correlate to this. The goal is reduction of vascular damage and not only LDL-C reduction. Yet statins seem to be strongly related to LDL-C decrease and vascular wall normalisation, this observations are still unclear for other

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		drugs. See also 4.3 and 6.3
1	**Safety aspects:** - Although several sentences refer to long term follow up in children, the length may be defined in a more detailed way, depending on active drug mechanism of action, in order to assess potential adverse events. - As these treatments may potentially impact on children's growth, sexual maturity, a minimum of safety parameters (no modification of vitamin concentrations or hormone activity) during studies should be included in study protocols. These reference values may be established by a paediatric experts' panel.	Agreed, but exact definition is not possible. A two year follow-up is now recommended. See also section 7. Agreed, but not established yet. A European Paediatric trial consortium for lipid disorders is established and works on these issues.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Introduction	1,2	**Comment:** Though the focus of this document is on LDL-C, it does touch on other lipids. The risk of pancreatitis with severe hypertriglyceridemia and potential intervention should be noted.	Agreed, but this addendum focuses primarily on hypercholesterolemia with an increase risk for atherosclerotic disease.
Scope			
Line 65	1,4	**Comment:** The scope of this addendum should be made wider to focus also on other familial lipid disorders, particularly with lipid abnormalities such as decreased HDL. **Proposed change (if any):** To add reference to other familial lipid disorders.	Partially agreed. In childhood other forms are extremely rare below the age of 18 years and often a problem to be a target for therapeutic trials. Insufficient data are available to give specific recommendations. Instead, a reference is added (*Haney EM, Huffman LH, Bougatsos C, et al. Screening and treatment for lipid disorders in children and adolescents: Systematic evidence review for the US Preventive Services Task Force. Pediatrics 2007; 120; e189-e214*.).
Section 4.1			
Lines 81-86	1,2	**Comment:** Given the low rate of CV disease in children and young adults, and unsure longer-term compliance with lipid lowering medication, it seems very unlikely that observational follow-up studies from paediatric lipid lowering trials will provide useful information	Not agreed. These studies are ongoing with results after 10 years of follow up and provide useful information related to efficacy, in which children surpass the age where their

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		relating to efficacy.	parents had CV disease. Compliance is related to age at which statin drug treatment was introduced and to the life style aspects. Before puberty they will incorporate it in their lifestyle and are proven to be extremely compliant.
Section 4.2			
Lines 87-94	1,2	**Comment:** The potential risks of cholesterol lowering on growth and development have always been raised, but to date no evidence of deleterious effects have been documented. It is appropriate to note this as a potential risk, but the lack of effect to date should also be noted.	Not agreed. Although to date no evidence of deleterious effects have been documented, which is promising, it is still too early to draw any conclusions in children with LDL cholesterol < 3 mmol/L.
Section 4.2			
Lines 92-93	1,4	**Comment:** This section is not giving enough consideration to lipids beyond LDL-C given these patients are often already optimally treated for LDL-C. HDL-C is a potential target in these patients as they often have a low HDL-C as part of their lipid profile. Triglycerides should also be considered. **Proposed change (if any):** Add more discussion regarding the overall atherogenic lipid profile.	The text has been adapted. It now states the possibility of HDL-C to be included as primary and secondary parameters in the trials.
Section 4.3			
Lines 95 - 106	1,2	**Comment:**	

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		There is no recommendation of minimum duration of clinical trials with either LDL-levels or vascular damage surrogate endpoints. Furthermore, there is no mentioning of reference therapy/placebo control in the surrogate marker endpoint trials. Will placebo controlled trial with short duration (maybe up to 3 months as stated in section5.3) be allowed? **Proposed change (if any):** Quantification of chosen primary efficacy parameter (e.g. LDL-C below a pre-specified level) to support an indication in children would be welcomed. **Comment:** Again this is very LDL-C focussed and does not consider the difficulties in performing IMT or FDM in a population still at risk of atherosclerotic disease but on statins which makes clinical detection of changes difficult. **Proposed change (if any):** Address beyond LDL-C and consider the difficulties with available accepted techniques to detect changes in statin treated patients with combination therapy.	Regarding controlled studies a period of 3 - 6 months with open label extension for 1 year is now in the guideline (see section 6.3). Short term placebo controlled studies are now mentioned without specification (see section 6.3). Not agreed. The goal is normalisation of the vascular wall. C-IMT and FMD provide more information about the state of the vascular wall than LDL-C and HDL-C. The difficulty is that a longer follow up about one year compared to LDL-C in a number of weeks is needed. Therefore, a longer follow-up is now mentioned (see section 6.3).
Lines 96-102	4	Comment: Again this is very LDL-C focussed and does not consider the difficulties in performing IMT or FDM in a population still at risk of atherosclerotic disease but on statins which makes clinical detection of changes difficult.	Not agreed. The trial needs sufficient power and a period of follow up. Regression of abnormalities of the vascular wall serves as a valid secondary surrogate endpoint.

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		Proposed change (if any): Address beyond LDL-C and consider the difficulties with available accepted techniques to detect changes in statin treated patients with combination therapy.	
Lines 102-104	1,2	**Comment:** It seems unduly definitive to state that irreversible vascular damage starts at 18-20 years of age. We believe it is impossible to define such a specific age for this pathologic milestone.	Partially agreed. In childhood and adolescence, all data known to date indicate that vascular damage is still reversible. No data support vascular damage irreversibility. Thereafter, the irreversible vascular damage may occur, although indeed the exact age when this occurs is not known. The text has been altered.
Section 4.4 (currently section 5)			
Line 112	1,4	**Comment:** to include statement on Apo A1. **Proposed change (if any):** "... of the disorder in children. ***Additionally, in children with genetic hypoalphaproteinemia diagnostic should be based on HDL-levels***.	Agreed. The text has been changed.
Lines 117-119	1,2	**Comment:** In selection of patients- the draft guideline states that children less than 10 should be statin naive in trials. While this probably is not a problem now, but as potentially more children become treated with earlier screening and recommendations, this could become more problematic in the future and impact trial feasibility.	Agreed. The text has been deleted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): Children below the age of 10 should be statin-naïve ***if possible*** in trials. Or omit the sentence.	
Section 5.1 (currently section 6.1)			
Lines 131-3	1,4	**Comment:** Should this be in patients with disease e.g. FH in this case? Please clarify. **Comment:** If the adult formulation is appropriate also for paediatric use, then there is no reason to develop a new formulation. **Proposed change (if any):** The development of special paediatric formulations is encouraged ***as appropriate***.	Agreed. The text has been changed.
Section 5.2 (currently section 6.2)			
Lines 135-137	1,4	**Comment:** More clarification is required on what is an exploratory study. Would a PD study in patients fall into this, despite some PD markers e.g. HDL-C being non-accepted?	Not agreed. Definition of exploratory study has been described elsewhere. Reference is made to adult guideline, further specification will depend on type of drug.

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Section 5.3 (currently section 6.3)			
Line 143	1,4	**Comment and Rationale:** In view of the lack of outcome data supporting the value of CETP inhibition in adults, perhaps outcomes benefit should be demonstrated in adults before accepting surrogate endpoints such as change in HDL-C for approval in children. **Proposed change (if any):** A limited number of lipid lowering agents, including some statins, fibrates and cholesterol adsorption inhibitors have been tested and are available as reference therapy~~, but newer treatments such as improved niacin products or CETPi are currently being studied~~.	Agreed. Sentence deleted.
Line 145-146	1,4	**Comment:** A 3 month study is acceptable with an accepted surrogate such as LDL-C but might not long enough for other surrogates such as IMT and other imaging. This is not adequate for safety with a new class/drug. This section needs to state that 3 months may be acceptable for some placebo controlled studies depending on the agreed endpoint. **Proposed change (if any):** A 3 month duration ~~is~~ ***may be*** acceptable for ***some*** placebo controlled studies ***depending on the chosen endpoint***.	Agreed, but the text has been amended, time periods are more flexible (see section 6.3).
Line 147	1	**Comment:** Lipid modulating drugs are approved on the basis of lipid profile	Not agreed. For adults myocardial infarction,

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		changes alone. Since imaging studies are not acceptable surrogates for adults, it's not clear why they should be conducted in children. As stated in line 80, beneficial effects on CV outcomes have to be extrapolated from adults. **Proposed change (if any):** Apart from effects on lipid levels, the use of other parameters, such as vascular imaging and/or function ***could*** be included.	morbidity and mortality have to be incorporated as endpoint, but in children even in HoFH this happens extremely rare. Therefore, surrogate markers for vascular damage measurement are the only acceptable and validated markers in childhood. It is now stated that lipid levels are the primary endpoints, whereas investigations of vascular damage are supportive secondary endpoints.
Section 6 (currently section 7)			
Lines 153 - 161	1	**Comment:** The section about safety aspects is very general and does not include any specific growth, cognitive development or sexual maturity parameters to be investigated and the duration of trials to document no long-term adverse effects of the investigational drug. A specification of the requirements by the Authorities would be helpful to reduce time from adult indication to approval of indication in children.	Partially agreed. No specific recommendations can be given, but the text has been extended with parameters that can be used.
The first sentence in section 6 [safety] of the addendum	3	**Comment:** It would be recommended to remove the word 'absent' in the section on adverse effects as this seems unfeasible and also not in line with recent art. 45 procedures. In these procedures e.g. the case of atorvastatin, the phrase was included that adverse effects were to-be-expected that were known of statins in adults.	Partially agreed. The drug is started at the age that parents can monitor adverse events. It is the aim to reach absent adverse events, which is in the observation of parents and children achieved in almost all of them with

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		Proposed change (if any): "To obtain optimal effect of the drug, minimal ~~or absent~~ adverse effects should be present to prevent the negative impact of reduced compliance."	an effective dose. Sometimes adverse events are discovered in due time and adjusted. Minimal is not the aim and is so far not the result of clinical trials and practice. The aim is absent, we accept minimal. The text has been amended.
Lines 154-161	1,4	**Comment:** These patients require life long therapy so to adequately assess safety with a new drug, especially a new class long term therapy is needed. This contradicts the statement that a 3 months placebo controlled study is acceptable. **Proposed change (if any):** This section and the section 5.3 need to reflect this	The text has been amended, time periods are more flexible. The 3 months controlled study focuses on short term effects and safety, but long term follow-up is needed as already mentioned in the text.
Line 161	1,4	**Comment:** Clarification is needed about which parameters (biochemical, others) should be looked at and for how long? Is there a need for a dedicated study?	Agreed. No single parameter can be demanded, but accepted are: clinical, stature-ponderal growth, sexual development, muscular cramps. Biochemical, liver toxicity (transaminases), hormonal status (steroids, FSH, LH, estradiol, testosterone, ACTH, DHEAS, cortisol), muscle enzymes (creatinine phosphokinase). The text has been changed.