26 February 2015
EMA/CHMP/68390/2015
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on ' Paediatric addendum to the note for guidance on the clinical investigation on medicinal products in the treatment of hypertension ' (EMA/CHMP/206815/2013)

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

Stakeholder no.	Name of organisation or individual
1	IFAPP (International Federation of Associations of Pharmaceutical Physicians)
2	Medicines Evaluation Board, The Netherlands
3	Sanofi-Aventis
4	Science pharma Ltd.
5	Swissmedic

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1. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes (If changes to the wording are suggested, they should be highlighted using 'track changes')	Outcome
279-286	1	Comment: Despite the recommendations of the Declaration of Helsinki, and despite the fact that this guideline is intended for paediatrics, in these lines there is a mention of a placebo group, in the clinical trial design. We believe that the administration of placebo, even for a limited time, in highly unethical, and this is even more evident when dealing with a paediatric population. We firmly believe that it is possible to design a parallel group study with different doses of active drug, and excluding a placebo group.	Not accepted. There is no guidance to use a placebo control if the study question can be answered in any other way. There is a possibility that a shallow dose or a wrong dose selection will not allow establishing a dose response but the drug is nevertheless effective in comparison with placebo. It would be a loss of chance for children not to take notice of this.
49-50	2	Comment: This should be supported by a reference. e.g. Lauer RM, Clarke WR. Childhood risk factors for high adult blood pressure: The Muscatine Study. Pediatrics 1989;84:633–41.	Not accepted. The CHMP aims to keep the Addendum as brief as possible for ease of reading and therefore the references are kept to a minimum.
70-76		Comment: More attention should be given to the difference in aetiology between US and EU children. BMI in US children is probably higher.	Not accepted The comment is probably true but it would be of limited relevance for the development program as we insist on different etiologies to be studied, lines 221-226.
75-79		Comment: This sections would benefit from some references	Not accepted. This is a general section on effects of elevated BP

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			on vascular structure. See comment on principle of referencing above.
97-103		Comment: Attention has to be given to a distinction between children less than 6 years of age where secondary hypertension is more common (due to renal (vascular) disease) and older children (adolescents) with more (chronic) primary hypertension or hypertension caused by overweight (large BMI). Secondary hypertension is also more common in severe hypertension.	Accepted. This comment is agreed with and is exactly what the addendum stresses both in the background section and in the section on patients to be studied.
135-136		Comment: …the effects in severe forms of secondary hypertension in children are difficult to relate to the adult population. Proposed change (if any): ... the effects on intermediate markers in severe forms of secondary hypertension in children are difficult to extrapolate from effects in the adult population.	Partially accepted: The section addresses the issue of problems with extrapolation of clinical benefits from the adult data to children, especially in secondary HTN. Therefore the study of intermediate endpoints (in general, with the view of validating these) is encouraged.
146		Comment: microalbuminuria is a definition of the amount of albumin excreted. Albuminuria is the correct term to identify albumin excretion without saying which amount of albumin is excreted. Proposed change (if any): Microalbuminuria should be changed to albuminuria (both micro- and macroalbuminuria)	Accepted.
162-164		Comment: Sentence should be rewritten Proposed change (if any): Defining blood pressure targets (and responders) in renal and diabetic disease as used in adults may also apply to children when justified based	Accepted with modification. “Defining lower blood pressure targets (and respectively using different responder definitions) in

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		on relevant paediatric data.	renal and diabetic disease as done in adults may also be used in children when justified based on relevant paediatric data."
179		Comment: Why this particular setting is mentioned as an example is not understood. Proposed change (if any): Delete example	Accepted.
185-187		Comment: This section can be improved as indicated below. Proposed change (if any): Where feasible, multiple estimations of GFR over time should be obtained to better estimate renal disease progression (single measurements are not sufficiently accurate). The role of albuminuria (or proteinuria) often assessed as albuminuria to creatinine ratio, to identify renal disease progression has not yet been fully established, but is highly encouraged. In particular in case of signs of kidney disease with (still) normal GFR values, albuminuria may be a better marker to assess success of antihypertensive therapy in the short-term, however, both (e)GFR and albuminuria should be obtained to better identify the effect on the long-term.	Accepted with modification. "Diagnosis of hypertension-related renal damage is based on a reduced renal function and/or level of albuminuria. Renal insufficiency is usually classified according to the glomerular filtration rate (GFR) calculated by the Schwartz formula. Where feasible, multiple estimations of GFR over time should be obtained to better estimate renal disease progression (single measurements are not sufficiently accurate). The role of albuminuria (or proteinuria) often assessed as albuminuria to creatinine ratio, to identify renal disease progression has not yet been fully established, but is highly encouraged. In

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			particular in case of signs of kidney disease with (still) normal GFR values, albuminuria may be a better marker to assess success of antihypertensive therapy in the short-term, however, both (e)GFR and albuminuria should be obtained to better identify the effect on the long-term."
189		Comment: LVM should be fully written Proposed change (if any): Left Ventricular Mass	Agreed. Proposed change: Echocardiography can be used to assess left ventricular mass (LVM) in children. LVM should be standardized to height to minimize the effect of changes in body size during childhood. Ref: ASE guideline 2010 (J Am Soc Echocardiogr 2010;23:465-95) de Simone G, Daniels SR, Devereux RB, Meyer RA, Roman MJ, de Divitiis O, Alderman MH: Left ventricular mass and body size in normotensive children and adults: Assessment of allometric relations and impact of overweight. J Am Coll Cardiol 20 :

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			1251 –1260, 1992 CrossRefMedline Daniels SR, Kimball TR, Morrison JA, Khoury P, Meyer RA: Indexing left ventricular mass to account for differences in body size in children and adolescents without cardiovascular disease. Am J Cardiol 76 : 699 –701, 1995
217		Comment: We would propose to add something on the information known about the pathophysiology and sensitivity of the cardiovascular system in pediatric patients. Proposed text: Little is known about the pathophysiology and pharmacology of the cardiovascular system in in different age groups except that some information is known about the developing RAAS system.	Not accepted: Line # possibly wrong, relates to 210-214, the lines say exactly that and there seems no need to amend.
218-220		Comment: We partly agree on the statement that especially in younger children studies are always necessary for products with a new mechanism of action. This statement could be somewhat softened as in a step-wise approach an important amount of efficacy and safety data can be obtained from older children. For the very young (<2 years or <6 months), data may be extrapolated in part using PK/PD modelling. In that case, only validation of the model is needed which reduces the number of patients to be studied. Another factor that is somewhat insufficiently addressed is that for the very young patients inter-patient-variability in BP can be high and sole studies without PK/PD modelling could be not informative enough. These	The comment is agreed with and does not seem to contradict the information provided in this draft GL.

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		comments should be further discussed.	
221-228		Comment: More attention should be paid to the difference in aetiology of hypertension between the younger age group (< 6 years) with secondary hypertension and older age groups (6-12, 12-18) with hypertension that can be caused by overweight. Subgroups should be studied according to cause ad severity of the underlying disease.	Partially accepted: This comment corresponds to what is said in the draft document for publication.
225-226		Comment: Not sufficient attention has been given to the role of non-pharmacologic lifestyle changes in essential hypertension.	Not accepted: The clinical importance of the non-pharmacologic treatment cannot be stressed enough, however, this is a guideline on establishing the efficacy and safety of pharmaceuticals in children.
246		Comment: Information of different ontology should be added. Proposed text: The ontology of the metabolic enzymes involved and the development of hepatic and renal function should be taken in to account.	Not accepted. This is considered to be covered by differences in (clinical) pharmacology.
244-246		Comment: The possibility of alternative sampling should be added to minimize pain and distress Proposed text: The use of alternative less invasive sampling techniques can be considered e.g. use of urinary samples to determine PK.	Accepted. “eg less invasive sampling techniques
250		Comment: Extra information on metabolism could be included. Proposed text: The predominant route of metabolism in adults in not necessary the predominant route of metabolism in children and therefore the metabolite pattern can be different in children. The clinical pharmacology of the predominant metabolites in children should be discussed.	Accepted: This is agreed with but this comment is not specific to this GL in HTN.

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252-262		Comment: Attention to children formulations is very limited. More information should be included on specific formulation for especially children < 6 years of age. This may include a separate heading. Or reference should be made to the Guideline on pharmaceutical development of medicines for paediatric use.	Agreed: This is covered by a specific PDCO guidance document, reference is included in the Addendum (Section 3)
59	3	**Comment**: We would recommend adding a reference to this document.	Partially accepted: Please refer to Line 64. The reference for the whole section is NHBPEP 2004.
61		**Comment**: We would recommend adding a reference to this document.	Please refer to Line 64.
191		**Comment**: Please clarify if it should read LVH? Or is it another meaning e.g. Left Ventricular Mass? In that case please provide meaning the first time the abbreviation is used.	Accepted: Left ventricular mass, accepted.
205		**Comment**: In this guideline the group of patients with "high-normal" blood pressure is defined in addition to that with hypertension (e.g. see definitions at the end of the document). It would be helpful to clarify if only the latter should be considered for treatment or if in some instances the first one too.	Not accepted: This is considered to be a treatment guideline related question. No new definitions are proposed in this Addendum and the indication accepted so far is arterial hypertension.
293		**Comment**: For a better understanding, it would be helpful to provide a short rationale of why only the "sitting" BP is recommended rather than the "supine or sitting" recommended for adults.	Not accepted: This is based on the normative data used in defining the blood pressure categories (p5 of the NHBPEP 2004).
		Comment: Please add an indication of the range of change (in mmHg)	Not accepted:

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303		for these endpoints that would be regarded as clinically meaningful similar to what is provided in the adult guideline would be helpful. If this cannot be provided for some reason (e.g. depends on age range etc.) it would be helpful to mention why this is not possible.	No support found for any specific effect size.
148-151	4	In the context of the sentence “Assessment of presence and progression of other types of organ damage is advisable in longer-term studies (…)”, it is not clear whether the assessment of LVH should be considered obligatory and/or whether that concerns long/short term-studies.	Not accepted There is no reference to the LVM assessment being obligatory.
210		It could be concluded from the first sentence in line 210 that all age groups i.e. 0-18 years, should be represented, what would be in opposition with the further information in this section. Proposed change: “All relevant age groups should be adequately represented to allow right dosing and safe use.“	This is meant to be a general rule to which some exceptions are potentially possible as described in the following sections.
210		It is not clear what is meant by groups “adequately represented”. This may be clarified by giving additional explanations e.g. that this should be adequately represented from the perspective of statistical analysis.	Not accepted: This is a scientific judgement for answering the clinical questions in the specific development – the extrapolability of data from other patient groups, nature of the drug (new molecule with limited adult data, first in class or a member of a well-studied drug class etc.).
337-338		It is not clear what is meant by sufficient representation that would allow detection of safety differences in patients with secondary HT and CKD. This may be clarified by giving additional explanations e.g. that this should be sufficiently represented from the perspective of statistical analysis.	Not accepted. It is difficult to state in strict terms the issue which is, similarly to the previous comment, entirely setting-specific and should be

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			decided on a case by case basis.
		However the document could be more concise and more focused on issues relevant for drug development. General issues such as diagnosis of hypertension, measurement of blood pressure and various complications may need to be mentioned, however, in this document this too broadly and even repetitively discussed. The text could be shortened by referring to practice guidelines of medical societies. It is felt important to separate between various conditions such as acute and chronic hypertension, hypertension associated with obesity, renal hypertension, hypertension accompanying endocrine disorders and in this context to focus on age related differences. While this is addressed in the text under headings paralleled to the adult guideline, it would be helpful to emphasize this by separate headers. The guideline should also mention treatment of acute hypertension, if not the title should say “for chronic hypertension”, the guideline should if at all addressing galenical forms in more details address fixed combinations (as this is heavily addressed in the adult guideline).	Not accepted: The scope has been stated in section 2, excluding the products for immediate BP control. The experience in paediatric trials of these products was felt to be too limited for giving guidance. The common definitions have been provided with references to the more comprehensive sources. The etiology of the disease has been discussed in relation to the population to be studied, based on the experience of the development programmes lacking the data to cover the whole disease spectrum in children.
58-70		Comment: This is addressed in every practice guideline. Proposed change (if any): delete	Not accepted. The source of definitions used is still considered important as it is a basis for further recommendations in the document (e.g. preference for office based sitting measurement).
71-86		Comment: This is a mixture on potential pharmacodynamic issues (with increasing evidence it is likely to be outdated in some future) and organ damage is addressed in a later section.	Not accepted. This is the basis of not requiring outcome studies but still

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		Proposed change (if any): delete	considering the treatment of hypertension necessary. This also explains the selection of outcomes to be measured.
99-101		Comment: This is not a practice guideline, the information is not useful for the design of clinical studies. Proposed change (if any): delete	Agreed. This is why the general HTN treatment strategy is summarised in 3 lines.
102-103		Comment: This is important and could be accompanied by the text in lines 254-267 in condensed form. Proposed change (if any): add information from lines 254-267, that is "For children 1 to < 6 years of age, a formulation that allows adequate dosing flexibility is a must to assure reliable administration and accurate weight-adjusted dosing". And perhaps the sentence on palatability.	This is a section on back-ground and reasons for the addendum to be written.
274		Comment: suggest a header "study design". Proposed change (if any):	Accepted.
269-273, 274-275		Comment: Treatment of hypertension in neonates, and secondary hypertension in young age groups, such as renal hypertension require distinct approaches and therefore the risk benefit profile may vary. Proposed change (if any):Start with lines 274-275 delete " It is assumed....." and start the following sentence with "The main.... to establish the effective dose	The sentence is meant to explain why (and when) we can only study dosing and safety in children.
286		Comment: Discuss also benefits and pitfalls of dose titration. Proposed change (if any): Add information	This may be more related to longer term studies and is briefly addressed in line 317.
293		Comment: a header like "endpoints" may be considered Proposed change (if any):	Accepted.