



European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

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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 NOTE FOR GUIDANCE ON THE CLINICAL INVESTIGATION ON
MEDICINAL PRODUCTS IN THE TREATMENT OF HYPERTENSION**

AGREED BY EFFICACY WORKING PARTY	October 2008
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1. INTRODUCTION

The note for guidance on the Clinical Investigation on Medicinal Products in the Treatment of Hypertension (CPMP/EWP/238/95 Revision 2) addresses general regulatory aspects in blood pressure lowering drug development in adults. A limited number of antihypertensive drugs in suitable formulations have been tested and are available for children and adolescents. This concept paper discusses the need for regulatory guidance on the clinical development of antihypertensive drugs in this target population.

2. PROBLEM STATEMENT

The prevalence and rate of diagnosis of hypertension in children and adolescents appear to be increasing. The underdiagnosis and undertreatment of hypertension in children is a matter of concern and new medicinal products suitable for being used in paediatric patients are needed.

3. DISCUSSION (ON THE PROBLEM STATEMENT)

Based on the normative distribution of blood pressure, hypertension in children and adolescents is defined as systolic BP (SBP) and/or diastolic BP (DBP), that is, on repeated measurement, \geq 95th percentile. BP between the 90th and 95th percentile is designated as prehypertensive level. The prevalence and rate of diagnosis of hypertension in children and adolescents appear to be increasing. This is due in part to the increasing prevalence of childhood obesity as well as growing awareness of this disease.

Most childhood hypertension, particularly in preadolescents, is secondary to an underlying disorder, renal parenchymal disease being the most common cause. In this age group, primary hypertension is normally an exclusion diagnosis. Conversely, in adolescents the majority of hypertension diagnoses correspond to essential hypertension. Significant risk factors for essential hypertension include family history and increasing BMI. Target organ damage in children and adolescents with hypertension does not differ significantly from adults.

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

- 1 Diagnostic criteria of hypertension in children
- 2 Relevant subpopulations according to age
- 3 Relevant populations according to aetiology (essential vs. secondary hypertension)
- 4 Potential waivers in particular groups according to age and/or relevant co-morbidities
- 5 The (un-)feasibility of controlled studies in children and adolescents will be discussed. Type of control (if appropriate) and length of minimum follow-up will be also discussed.
- 6 Efficacy criteria to be used. Usefulness and limitations of Ambulatory Blood Pressure Monitoring (ABPM)
- 7 Assessment of co-morbidities, particularly renal disease.
- 8 Usefulness and limitations of sSBP and sDBP
- 9 The need to perform dose-range studies (incorporate a wide range of dose and use information for adult trials to account for potential pharmacological differences between adult and paediatric population and the need to produce child-specific formulations.
- 10 Safety requirements (studies duration)
- 11 Neonates, children with the most acute differences in drug metabolism because of immature organ and biological systems and rapid developmental change, have been excluded from almost all studies. Consideration should be given to trials in the youngest children, recognizing the extra effort involved in recruiting and conducting trials in this age group.

4. RECOMMENDATION

The CHMP recommended drafting a paediatric addendum to the Note for Guidance on the Clinical Investigation on Medicinal Products in the Treatment of Hypertension (CPMP/EWP/238/95 Revision 2)

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 Cardiovascular drafting group will be involved and the document is expected to be discussed on 2-3 EWP Cardiovascular drafting group meetings and on two EWP meetings.

7. IMPACT ASSESSMENT (ANTICIPATED)

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

8. INTERESTED PARTIES

European Academy of Paediatrics, European Society of Cardiology, European Society of Hypertension

9. REFERENCES TO LITERATURE, GUIDELINES ETC

Revision of the Guidance on Fixed Combination Medicinal Products in the Treatment of Hypertension. CPMP/EWP/426093/06 Revision 2

Reflection paper: formulations of choice for the Paediatric population.
EMA/CHMP/PEG/194810/2005.

Guideline on the role of pharmacokinetics in the development of medicinal products in the paediatric population. EMA/CHMP/EWP/147013/2004 Corrigendum

Note for guidance on clinical investigation of medicinal products in the paediatric population.
CPMP/ICH/2711/99

NHBPEP. The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents. Paediatrics 2004;114:555-76