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Paediatric addendum to the note for guidance on the clinical investigation on medicinal products in the treatment of hypertension

Draft

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Executive summary

This is an addendum to the *Guideline on Clinical Investigation of Medicinal Products in the Treatment of Hypertension (EMA/238/1995/Rev. 3, 18 November 2010)*. It is not meant as a guidance document on its own but rather highlights differences from adult patients with arterial hypertension and points out paediatric-specific aspects.

1. Introduction (background)

Hypertension is a relatively uncommon problem in childhood, but it is seen as an important cardiovascular risk factor that can have significant health implications, especially the tendency for an elevated blood pressure in childhood to predict the development of adult hypertension.

The definition of hypertension in children and adolescents is based on the normative distribution of blood pressure (BP) in healthy children. Diagnostic criteria for elevated BP in children are based on the concept that BP in children increases with age and body size, making it impossible to utilize a single BP level to define hypertension, as done in adults.

Hypertension in children and adolescents is defined as systolic BP (SBP) and/or diastolic BP (DBP) that is, on repeated measurement, at or above the 95th percentile. BP between the 90th and 95th percentile in childhood had been designated “high normal.”

Extensive paediatric normative data on auscultatory clinic measurements have been provided for the United States, based on more than 70 000 children. BP percentiles have been calculated for each sex, age group and for seven height percentile categories. Height percentiles are based on the growth charts of the Center for Disease Control and Prevention. In Europe, reference values were obtained in 1991 by pooling data from 28 043 individuals using the auscultatory method, but tables do not include age, sex and height together.

Because of the large amount of data available, the Task Force for Blood Pressure in Children (NHBPEP 2004) is considered the study of reference also by the European Society of Hypertension (ESH). ESH however points to the fact that the data of the US Task Force do not refer to a European population and that at all ages they are several mmHg lower than those measured by the same auscultatory method in an Italian normative study and about 10mmHg lower than the oscillometric data of a Northern European study. Validated oscillometric data are even scarcer than those for auscultatory method.

There are no prospective studies with sufficiently long follow-up to directly link childhood BP levels to the occurrence of cardiovascular disease or mortality. Therefore, surrogate markers of hypertensive end-organ damage (heart, blood vessels and kidney) have been used instead, although the body of available data is substantially smaller than in adults.

Recent clinical studies using non-invasive techniques demonstrate that childhood levels of BP are associated with carotid intimal-medial thickness and large artery compliance in young adults. Adolescents with BP levels at the higher end of the normal distribution show decreased brachial artery flow-mediated vasodilatation. Evidence is increasing that even mild BP elevation can have an adverse effect on vascular structure and function in asymptomatic young persons.

Left ventricular hypertrophy (LVH) is the most prominent clinical evidence of target-organ damage caused by hypertension in children and adolescents. With the use of echocardiography to measure left ventricular mass, LVH has been reported in 34–38 per cent of children and adolescents with mild, untreated BP elevation.

In severe childhood hypertension, emergent complications also may include encephalopathy, seizures, stroke, acute heart failure, cerebrovascular accidents, pulmonary oedema, dissecting aortic aneurysm, acute renal failure.

The prevalence and rate of diagnosis of hypertension in children and adolescents appear to be increasing in the developed countries with the prevalence figures of hypertension reaching 2-4% (8% in some EU countries). This is seen to be due in part to the increasing prevalence of childhood obesity as well as growing awareness of this disease. The overall incidence of hypertension in infants has been reported to be less than 1%.

The majority of hypertensive children are adolescents with mild to moderate primary hypertension, and the majority of those have elevated SBP. Hypertensive children less than 6 years of age often have hypertension secondary to renal or renal vascular disease, co-arctation of the aorta or endocrinopathies mainly involving the thyroid, parathyroid and adrenal glands. Renal parenchymal and renovascular diseases are the most common (60% to 70%) causes. The degree of BP elevation associated with secondary hypertension is often more severe in these patients and may necessitate a very aggressive management approach.

In general, the principles of adult hypertension management apply to paediatric hypertension: correction of contributing causes when possible, non-pharmacologic measures and, when necessary, use of anti-hypertensive medication in a step-wise fashion until the BP is controlled.

In spite of recent efforts only a limited number of antihypertensive drugs in suitable formulations have been tested and are available for children and adolescents.

2. Scope

Guidance is provided on the design of clinical studies considered to be of relevance for the evaluation of antihypertensive drugs in children of all age groups (0-18 years). More attention is devoted to the younger patients with mostly secondary forms of hypertension. Methods to establish the dosing recommendations and safety of antihypertensive products in children are the focus of this addendum.

Aspects of fixed dose combinations are not dealt with in this addendum as these are as a rule not optimal for use in paediatric pharmacotherapy and their use in the treatment of essential hypertension in late adolescence has little difference from adults. Aspects of study of products for immediate blood pressure control have not been addressed by this addendum as the experience in their paediatric trials so far is very limited.

3. Legal basis and relevant guidelines

This addendum to the *Guideline on Clinical Investigation of Medicinal Products in the Treatment of Hypertension (EMA/238/1995/Rev. 3, 18 November 2010)* 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:

- ICH E11, Clinical investigation of medicinal products in the paediatric population (CPMP/ICH/2711/99);
- Role of pharmacokinetics in the development of medicinal products in the paediatric population (EMEA/CHMP/EWP/147013/2004/Corr);

- Discussion Paper on the Impact of Renal Immaturity when Investigating Medicinal Products Intended for Paediatric Use (CPMP/PEG/35132/03);
- Clinical trials in small populations (CHMP/EWP/83561/2005);
- Draft guideline on pharmaceutical development of medicines for paediatric use (EMA/CHMP/QWP/805880/2012 Rev. 1).

4. Criteria of efficacy

4.1. Morbidity and mortality

The primary goal of hypertension treatment is to prevent cardiovascular mortality and morbidity associated with high BP. The remoteness in time of incident cardiovascular events and the relative rarity of the severe paediatric hypertension make it impossible to perform large intervention studies measuring the direct clinical benefit.

Therefore, the beneficial effects of antihypertensive treatment in children have to be extrapolated from evidence obtained in adults. While this can be relatively reliable in essential hypertension, the effects in severe forms of secondary hypertension in children are difficult to relate to the adult population. Post-authorisation long-term follow up and observational research are encouraged to better understand the clinical correlation of antihypertensive treatment in childhood and the role of intermediate markers in the estimation of clinical benefit.

4.2. Arterial blood pressure

Reduction in BP is accepted as a valid surrogate endpoint in order to assess whether the goal to prevent morbidity and mortality associated with high BP can be achieved by an antihypertensive agent.

4.3. End-organ damage

Many hypertensive children, although often asymptomatic, have evidence of end-organ damage as microalbuminuria, left ventricular hypertrophy, increased carotid intima-media thickness and retinopathy. The effect on the kidney should be regularly monitored in the paediatric clinical trials of hypertension. LVH remains to date the most thoroughly documented form of end-organ damage caused by hypertension in children and adolescents. Assessment of presence and progression of other types of organ damage is advisable in longer-term studies in children to clarify the relationship between the BP reduction and organ protection.

5. Methods to assess efficacy

5.1. Arterial blood pressure

5.1.1. Office / clinic BP

The preferred method of BP measurement is auscultation by office/clinic measurements and correct measurement requires a cuff that is appropriate to the size of the child's upper arm. The timing of measurement in most paediatric studies with once daily dosing has been at 24-hours post-dose ('trough'). Similarly to the adult studies, the BP lowering effects of anti-hypertensive therapy should be documented as the pre-/post-treatment reduction of BP.

In the absence of prospective long-term studies linking BP levels to cardiovascular outcomes, paediatric BP control may be defined as a BP below the 95th age-, sex- and height-specific percentiles, but it has also been advocated to use a BP below the 90th percentile. The cut-off used should be justified.

Defining lower BP targets (and successful control values) in renal and diabetic disease in adults have been much discussed and may be appropriate in children when justified based on relevant paediatric data.

5.1.2. Home BP, ABPM

The use of home BP and (in older paediatric age-groups) ambulatory blood pressure monitoring (ABPM) is emerging and has shown superior reproducibility but is mainly hampered by a relatively small population from which normative data have been derived (which limits meaningful categorization of patients and interpretation of data) in addition to practical considerations related to the use of ABPM in younger patients. The 24-hour ambulatory blood pressure assessment provides more descriptive information regarding the BP time-course and can provide reassurance that the dosing interval is appropriate and that there are no extreme BP swings between doses. It also allows exclusion of white coat hypertension which is unlikely to respond well to antihypertensive treatment and identifies less obvious BP patterns (dipping and non-dipping patterns of nocturnal BP) that are associated with end-organ damage in children). The limited availability of normative data may still allow the use in measurement of within- subject treatment effects. Their wider use in clinical trials where appropriate and feasible (e.g. to monitor attainment and maintenance of BP targets in children with renal disease in nephrology setting) is thus encouraged.

5.2. Assessment of end-organ damage

5.2.1. Kidney

Diagnosis of hypertension-related renal damage is based on a reduced renal function and/or elevated albuminuria. Renal insufficiency is classified according to the glomerular filtration rate (GFR) calculated by the Schwartz formula. Permanently reduced estimated GFR indicates renal damage. Proteinuria (e.g. protein to creatinine ratio) should be included as an endpoint. The role of microalbuminuria assessment in paediatric essential hypertension has yet to be fully established.

5.2.2. Heart

Echocardiography is a tool sensitive enough to assess LVM in children. LVM should be standardized to height to minimize the effect of changes in body size during childhood.

5.2.3. Blood vessels

The first morphological changes of the arterial wall, thickening of the intima-media complex, can be identified by high-resolution ultrasound. Increased arterial stiffness has also been reported to be more common in hypertensive children than in normotensives.

5.2.4. Fundoscopy, digital retinal photographs

Vascular injuries to small arteries (narrowing of arterioles) may occur early in the development of hypertension. Few studies of retinal abnormalities have been conducted in children with hypertension so far.

6. Patients

6.1. Criteria for diagnosis

Please see sections Introduction and Definitions for the definitions of hypertension in children. The diagnosis should be established by office measurements. The currently available reference values for defining BP classes have been obtained by the auscultatory method, and values obtained with oscillometric equipments are considerably higher. Therefore, if hypertension is detected by the oscillometric methods, it must be confirmed by the auscultatory method. The role of the home BP and ABPM is currently limited by the shortage of Europe-wide normative data but may be used additionally to better describe the BP patterns. Organ damage evaluation should include kidney, heart, great vessels, central nervous system and retina where possible.

6.2. Sub-populations

All age groups should be adequately represented to allow right dosing and safe use. It may be necessary to use step-wise approach in involving the youngest age groups after the safety has been established in the older patients, especially in studies involving infants less than 6 months. This needs to be discussed in the context of the mechanism of action, non-clinical and clinical safety data and maturation of the function of the involved body systems.

It can be foreseen that data on efficacy and (less so) on safety in treating essential hypertension in adolescents may be under certain circumstances extrapolated from adult studies or from other agents of the same class (e.g. ACEi or ARB) already thoroughly studied in paediatric hypertension. Unnecessary studies in children should be avoided. This is not the case in products with new mechanism of action and in younger age groups were dedicated dose-ranging and safety studies are always necessary.

It may be more important to differentiate between the essential and secondary forms of hypertension and ensure sufficient data on the effects of the product in secondary hypertension patients rather than merely aim to involve all relevant age groups. The severity, pathophysiology, management strategy and efficacy of pharmacotherapy in secondary hypertension are largely different and are often more challenging to study. Nevertheless, the unmet medical need for well-studied age appropriate products in this condition is considerably larger than in the treatment of essential hypertension.

Relevance of the study results to the European target population needs to be kept in mind when a substantial proportion of patients with morbid obesity are envisaged to be enrolled in trials.

Ethical acceptability and safety aspects need to be addressed when evaluating the feasibility of studies in the more severe forms of hypertension (e.g. the use of placebo or fixed low dose of the product).

When the adult use has identified sub-groups where the product might be especially useful (e.g. CKD) or where the safety profile shows marked differences, this should be addressed while defining the paediatric study populations. Stratification of randomization according to the aetiology or patient characteristics needs to be discussed, e.g. CKD/ non-CKD patients.

7. Strategy – design

7.1. Human pharmacology studies

PK data for all relevant paediatric age groups should be provided. A need for a dedicated PK study or collection of PK data in a subset of patients in other studies needs to be justified based on the

knowledge of the pharmacology and adult PK of the product (possibly involving physiologically based PK and exposure-response modelling where relevant). A reasonably precise estimate of which range of doses provides sufficient exposure, equivalent to the doses determined to be efficacious in adults with hypertension, is needed. The number of patients proposed for PK assessment should allow robust description of potential differences of PK between adults and children taking into account the possibility of higher than expected variability in PK parameters (adjustment of sample size during the study may be planned). Measures to minimise pain and distress due to blood sampling in studies need to be foreseen and described (including study methods e.g. sparse sampling and population PK).

PD considerations to be addressed by the applicant include, but are not limited to, possible differences in pharmacology and PK/PD relationship/dose-response slope according to age, PD effect differences depending on the aetiology of hypertension. Based on PK and/or PD differences, higher doses than shown to be safe in adults may be necessary to achieve efficacy in children and/or certain subpopulations. The condition of hypertension may need pharmacotherapy in all paediatric age-groups, starting with infants up to the late adolescence. 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. All efforts must be made to develop a commercial paediatric formulation in time to use this formulation during paediatric studies (please see the *Draft guideline on pharmaceutical development of medicines for paediatric use, EMA/CHMP/QWP/805880/2012 Rev. 1*).

To ensure acceptance of the taste and compliance of small children to this long-term treatment the palatability of the oral solution needs to be established. The relative bioavailability of such formulation and the adult dosage form as well as food effect to PK when relevant can be established in healthy adult volunteers (please see the relevant guidance document for details, *Guideline on role of pharmacokinetics in the development of medicinal products in the paediatric population EMEA/CHMP/EWP/147013/2004/Corr*).

Children 6 years of age or older with hypertension may be given commercially available solid dosage forms if of suitable size and composition. In children over 4 years an age-appropriate solid dosage form (e.g. mini-tablet) may prove beneficial for more accurate dosing and acceptability to patient. See also the *Draft guideline on pharmaceutical development of medicines for paediatric use (EMA/CHMP/QWP/805880/2012 Rev. 1)*.

7.2. Therapeutic studies

It is assumed that in almost all cases the benefit-risk profile of a product developed for paediatric hypertension is known in adult hypertension. Thus, the main aim of the paediatric development is to establish the therapeutic dose as well as tolerability, palatability (where appropriate), short- and long-term safety. Collection of information on the effects on end-organ damage is advisable in longer-term studies.

Double-blind randomized studies are requested to establish effective therapeutic doses. Appropriate doses may vary by age, aetiologic subgroup and severity of HT. Two designs used most often have been a randomised, double-blind parallel study with 1) ≥2 arms receiving doses of the test drug followed by a randomised withdrawal to placebo and 2) placebo arm and ≥2 arms receiving different doses of the test drug.

A randomised withdrawal to placebo after the dose-ranging portion of studies has often been used to enable the interpretation of the study results should the dose response not be detected. Avoidance of a full placebo may enhance patient recruitment and minimize ethical concerns. As a better alternative, in short-term studies (up to 6 weeks) a true placebo arm could be considered in the age group 6-17 years. The use of a parallel placebo group in the very young and more seriously affected patient

population may not be feasible. Add-on designs to pre-existent/reference therapy in severe hypertension that does not allow placebo use may offer an option in some settings. Rescue treatments in case of insufficient response should be predefined.

The dose range needs to be sufficiently wide to allow the dose response to be established. Doses providing exposure from slightly lower than the lowest approved adult dose up to somewhat higher than the highest approved dose in adults (unless restricted by safety concerns) could be considered. Dose ranges will also depend on age-specific differences suggested by PBPK-modelling and/or paediatric PK data. The dosing regimen needs to ensure little or no overlap between the dose categories tested, preferably by using individual subject weight adjusted (per kg) dosing.

The primary endpoint for the dose-finding studies should be the change from baseline Mean Sitting Diastolic Blood Pressure (MSDBP) or Mean Sitting Systolic Blood Pressure (MSSBP), measured after a sufficient treatment period at a stable dose to see the maximum antihypertensive effect being present (change in blood pressure from baseline to the end of treatment period plus the inter-dosing interval or, in randomised withdrawal design, change in BP from the last on-treatment visit to the end of withdrawal period). The study duration should be long enough to avoid equivocal results or recommendations of larger doses than needed due to the fact that the full antihypertensive effect of product may not have been reached.

Since data which compare the effect of systolic and diastolic blood pressure on prognostic endpoints are lacking in the paediatric population no clear recommendation can be given as regards the more favourable endpoint. There are arguments that favour the choice of either MSSBP or MSDBP. Arguments in favour of MSDBP relate to the fact that systolic blood pressure is more difficult to control than diastolic blood pressure in the general population. It has also been demonstrated that in pre-school children with hypertension, systolic blood pressure is more variable than diastolic pressure, and systolic blood pressure is more reflective of white coat hypertension than diastolic blood pressure. On the other hand, elevated systolic blood pressure is more common in children and correlates well with clinical outcomes in adults. In the dose ranging studies the use of MSDBP has resulted in somewhat better ability to demonstrate dose response as the reduction in DBP was more closely related to the dosage of agent administered (Benjamin DK 2008). A primary endpoint of mean arterial blood pressure may be considered. If MSDBP is chosen as a primary endpoint, the MSSBP will serve as a secondary and vice versa. BP response and control rates should also be included as endpoints.

As controlled extension studies are required for safety it is recommended that the achieved blood pressure and hypertension control rates and the relationship between subject characteristics and antihypertensive efficacy, as well as organ related outcomes, where possible, be analysed over the full extended treatment period. Extension studies should allow individual dose titration (up and down) to optimal blood pressure control levels. Adherence to treatment could also be considered as an endpoint.

8. Safety aspects

Short-term tolerability and safety data should be collected in the controlled studies and compared with the known safety profile in adults. The trial program is expected to have a total of no less than 300 paediatric patients for safety reasons to identify adverse reactions occurring with a 1% frequency.

Extension studies with individual dose titration after completion of the short-term studies or dedicated safety studies are needed for collection of longer-term safety data. Completed studies with a number of anti-hypertensive agents in children now permit studies with active control and individual dose titration to address the safety profile of new products. Studies assessing the safety of combination therapy may be warranted.

At least 12-month extension studies are necessary to allow investigation of long-term safety in terms of growth (head circumference, weight and height) and development, including neurocognitive development. A longer follow-up could be appropriate for the assessment of end-organ damage or for drugs of a new class of agents. The difficulties in performing and interpreting neurocognitive testing in toddlers/preschool children are acknowledged but extrapolation from 6-17 year old children is not possible.

Younger age groups (infants, children under 6 years of age) have to be adequately represented and may need to be followed up longer (e.g. 24 months). Hypertensive children may be delayed in normal development due to their chronic illness and ways to discriminate the drug effects need to be foreseen.

Secondary forms of hypertension and CKD patients need to be sufficiently represented to allow detection of major safety differences in these sub-groups.

Identified safety concerns from adult or non-clinical studies may necessitate further data collection, e.g. echocardiographic assessments to clarify potential cardio-toxicity (inhibiting the growth of the heart) or ABPM to clarify the risk of hypotension.

Specific safety concerns during the studies in infants may need to be addressed by step-wise recruitment to the trials (interim safety data analysis before the inclusion of the youngest patients) or justified cut-off age.

Definitions

Normal blood pressure in children is defined as SBP and DBP less than 90th percentile for age, sex and height.

Children with average SBP or DBP 90th percentile or more but less than 95th percentile are classified as having **high-normal BP**. Adolescents with BP 120/80mmHg or more even if less than 90th percentile are also considered as having high-normal BP.

Hypertension in children is defined as SBP and/or DBP persistently 95th percentile or more, measured on at least three separate occasions with the auscultatory method.

Stage 1 hypertension is defined as BPs from the 95th percentile to the 99th percentile plus 5mmHg.

Stage 2 hypertension denotes any BP above the 99th percentile plus 5mmHg.

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