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Paediatric addendum to CHMP guideline on the clinical investigations of medicinal products for the treatment of pulmonary arterial hypertension

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Executive summary

This is an addendum to the Guideline on the Clinical Investigations of Medicinal Products for the Treatment of Pulmonary Arterial Hypertension for Adults. It is not meant as a guidance document on its own but rather highlights differences from adult pulmonary arterial hypertension PAH patients and points out paediatric specific issues.

1. Introduction (background)

The most common forms of paediatric PAH are idiopathic Pulmonary Arterial Hypertension (iPAH) and associated Pulmonary Arterial Hypertension (aPAH) (refer to table 1 adult guideline). Left untreated, children with IPAH fare less well than adults. The predicted survival after diagnosis is less than a year compared to 2.8 years in adults.

Although the definition of PAH is basically the same in both populations, extrapolation from adults to children is not straightforward for several reasons: 1) The prevalence of the subtypes of PAH is different among both populations e.g the idiopathic form is more prevalent in adults, whilst PAH associated with congenital heart disease is more frequent in children; 2) the anticipated lifespan of children is longer; 3) children may have a more reactive pulmonary circulation which may result in greater vasodilator responsiveness; and 4) despite clinical and pathological studies suggesting increased vasoreactivity in children, before the advent of long-term vasodilator/antiproliferative therapy, the natural history remained significantly worse for children compared to adult patients.
The choice of a relevant endpoint to demonstrate efficacy in the paediatric population is also considered problematic.

2. Scope

This guidance document focuses on IPAH and APAH as well as persistent pulmonary hypertension of the new born (PPHN). It explicitly includes APAH due to congenital heart disease [Eisenmenger syndrome, PAH associated with systemic to pulmonary shunts (small, moderate or large defects) and PAH after corrective cardiac surgery].

3. Legal basis

This addendum to the CHMP guideline on Clinical Investigations of Medicinal Products for the Treatment of Pulmonary Arterial Hypertension has to be read in conjunction with the introduction and general principles of the Annex I to Directive 2001/83 as amended.

All pertinent elements outlined in current and future EU and ICH guidelines and regulations should also be taken into account especially those on:

- ICH 11 Clinical Investigation of Medicinal Products in the paediatric population (CHMP/ ICH/ 2711/ 99)
- Guideline on clinical trials in small populations (CHMP/ EWP/ 83561/ 2005).
- Reflection paper on the regulatory guidance for the use of health related quality of life (HrQL) measures in the evaluation of medicinal products.

4. Criteria of efficacy

4.1. Idiopathic pulmonary arterial hypertension and associated pulmonary arterial hypertension

Depending on the proposed indication the investigated primary and secondary endpoints may vary. Choice of the endpoints is also dependent on the age of the recruited children.

For children ≥ 12 years, the proposed claims and the investigated endpoints generally follow those in the adult guideline i.e the primary endpoints may include time to clinical worsening or exercise testing, in particular the 6-MWT. If this age group is included in the adult clinical program, adequate representation should be ensured to allow for any specific claims and results should be presented separately. A PIP waiver for this age group could accordingly be considered.

In younger age groups both the choice of the primary endpoint and recruitment are recognized problems. For children < 12 years, measures of exercise capacity are problematic to assess. In the age group 7-11 years, the use of relevant exercise tests, in particular 6-MWT needs further validation. In children ≤ 6 years, adequate performance of exercise testing may not even be possible.Time to clinical worsening can be measured, in line with the adult guideline, but especially in this age population recruitment problems will hamper its assessment as a primary efficacy endpoint.
Therefore, a flexible approach in children < 12 years should be considered on a case by case basis. When efficacy of a drug has been demonstrated in adults based on exercise testing or clinical endpoints, extrapolation to younger age groups can be acceptable provided that the results of other feasible endpoints show comparable results in both age groups. This applies particularly to invasive haemodynamic measurements and also to those obtained by non-invasive techniques such as echocardiography. Effect on quality of life (QoL) can be measured acknowledging that indirect assessment by involving the child's parents/carers is inevitable for the younger patient groups. Weight and length gain are also considered relevant indicators of response and well being.

4.2. Persistent pulmonary hypertension of the new born (PPHN)

Persistent pulmonary hypertension of the newborn is a clinical syndrome characterised by failure of the elevated foetal pulmonary vascular resistance to regress after birth. PPHN is multifactorial in origin, although commonly associated with congenital and acquired hypoxic lung disease and congenital heart defects. Idiopathic forms are rare. Severe forms are associated with significant morbidity and mortality. Limited data are available regarding relevant endpoints in this field.

The following endpoints are suggested; the first two endpoints are considered of higher clinical relevance and less disputable value:

- all-cause mortality;
- need for extracorporeal membrane oxygenation (based on standardized criteria e.g. oxygenation index).
- need for additional drug treatment targeting PAH;
- time on NO;
- time to weaning from mechanical ventilation;
- ventilation index;
- time on supplemental oxygen;
- duration of ultrasound-detectable right-left shunting (hours or days).

5. Patients

5.1. Selection

Paediatric age groups should be adequately represented depending on the proposed claim.

5.2. Background treatment

Stabilisation on background medications before recruitment in a study may not always be practicable in paediatric trials as children often present to the hospital with acute deterioration. The rate of deterioration can be fast. Therefore, the use of rescue medication should be set out in the protocol (e. g. intravenous epoprostenol in IPAH). The use of rescue medications should be centrally adjudicated.

6. Strategy – Design

6.1. Human pharmacology studies

The development of special paediatric formulations is encouraged.

6.1.1. IPAH and APAH

Adult data should be extrapolated where possible, but adequate definition of the associated condition, in particular the type of congenital heart disease is important. Additional drug-drug interaction studies might be necessary in the paediatric population, particulary interactions with warfarin.

6.1.2. PPHN

Separate studies are needed to study the mechanism of action of the drug for this specific indication.

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 in children. Correlation of doses with haemodynamic response might be possible. Plasma level measurements should be performed in order to establish a PK/ PD relation.

6.3. Confirmatory therapeutic studies

6.3.1. IPAH and APAH

Protocols should clearly state whether paediatric patients will be included in the adult program. Difficulties in performing exclusive paediatric studies are recognised since children show considerable variability in clinical outcome partly due to the heterogeneity of the disease aetiology and partly due to the rapid changes in the course of the untreated disease. Recruitment problems may hamper the implementation of randomised, controlled trials. Due to the difficulty in performing such studies, it is recommended to seek advice regarding the study design.

Patients should be stratified into IPAH and APAH. Further stratification into subgroups depends on the proposed indication. Duration largely depends on the chosen endpoint. Longer-term studies of at least 6 month duration are encouraged especially if the chosen endpoints measure clinical endpoints. If the primary endpoint does not include mortality, this has to be additionally investigated in an open-label extension to exclude any negative safety signal. The extension studies should include all the patients regardless of their reason for discontinuation. Close monitoring and the possibility of modification of the treatment should be clearly set out in the protocol.

6.3.2. PPHN

As previously mentioned, PPHN has to be studied separately. The ethics of performing of placebo-controlled trials when nitric oxide (NO) is the standard therapy is questioned. Accordingly, mainly add-on trials in patients failing treatment with NO should be considered.

7. Safety aspects

Long-term issues in relation to growth and sexual maturity are of particular importance.

Definitions

Refer to section 1.

References

Barst RJ et al.: Vasodilator therapy for primary pulmonary hypertension in children. Circulation 1999 Mar 9; 99(9): 1197-208).

Lammers AE et al.: Epoprostenol treatment in children with severe pulmonary hypertension. Heart 2007; 93: 739-743.

Maiya S et al.: Response to bosentan in children with pulmonary hypertension. Heart 2006; 92: 664-670.

Li AM et al.: The six-minute walk test in healthy children: reliability and validity. Eur Respir J 2005; 25: 1057-60.

Ivy DD et al.: Weaning and discontinuation of epoprostenol in children with idiopathic pulmonary arterial hypertension receiving concomitant bosentan. Am J Cardiol 2004; 93: 943-6.

Haworth SG: The management of pulmonary arterial hypertension in children. Arch Dis Child 2008; 93: 620-625.

Haworth SG: Pulmonary hypertension of the young. Heart 2002; 88; 658-664.

163 Peterson AL et al.: Correlation of echocardiographic markers and therapy in persistent pulmonary
164 hypertension of the newborn. Pediatr Surg Int 2008; 24: 1101-1104.
165 Rosenzweig and Barst: Pulmonary arterial hypertension in children: a medical update. Current opinions
166 in pediatrics 2008; 20: 288-293.
167 Haworth SG et al.: Survival and quality of life in children with severe pulmonary hypertension. Heart
168 2006; 92 (Supple II): A14.
169 Simonneau, G., Clinical classification of pulmonary hypertension. JACC, 2009; 54(1): S43-S54.