European Medicines Agency

London, 22 January 2009
Doc. Ref. EMEA/CHMP/EWP/644261/2008

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

CONCEPT PAPER ON THE NEED FOR THE DEVELOPMENT OF A PAEDIATRIC ADDENDUM TO THE CHMP GUIDELINE ON THE CLINICAL INVESTIGATIONS OF MEDICINAL PRODUCTS FOR THE TREATMENT OF PULMONARY ARTERIAL HYPERTENSION

AGREED BY EFFICACY WORKING PARTY	January 2009
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	22 January 2009
END OF CONSULTATION (DEADLINE FOR COMMENTS)	31 March 2009

Comments should be provided using this template to EWPSecretariat@emea.europa.eu

KEYWORDS	*pulmonary arterial hypertension PAH, persistent pulmonary hypertension of the new born PPHN, congenital heart disease CHD*

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20)
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

1. INTRODUCTION

The CHMP guideline on the clinical investigations of medicinal products for the treatment of pulmonary arterial hypertension (PAH) addresses the regulatory aspects during the development of drugs for the treatment of PAH in adults. Five drugs are already registered through the centralized procedure for adult PAH, but no drug is specifically developed for this disease in the paediatric population. This concept paper discusses the need for regulatory guidance on the clinical development of drugs for PAH in the paediatric population.

2. PROBLEM STATEMENT

The precise frequency of PAH in children as well as in adults remains unknown. Despite its rarity, increasingly frequent reports of confirmed cases suggest that more patients (both children and adults) have PAH than had been previously recognized. 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. idiopathic is more prevalent in the adults, while congenital is more frequent in the paediatric population; 2) The anticipated lifespan of children is longer; 3) children may have a more reactive pulmonary circulation raising the prospect of greater vasodilator responsiveness and better therapeutic outcomes; 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.

3. DISCUSSION

The definition of PAH in children is the same as for adult patients. Basically, the pathologic processes that characterize PAH in adults are the same as in children except for the higher prevalence of the acute vasoreactivity in the latter group.

Of particular importance in the paediatric development are the PAH patients with congenital heart disease (CHD) who form a heterogeneous group, that can not be simply addressed as one entity e.g. patients with cardiac defects with systemic-to-pulmonary shunts and pulmonary hypertension distinguish themselves from those with cardiac defects lacking such shunts. The prognosis of these subtypes is also different.

Safety issues are especially important in the paediatric development program considering the chronicity of the drug administration and the developmental phase of the child. The impact of the method of administration on compliance and the quality of life is also relevant to the paediatric population.

The approval of the currently registered specific PAH drugs is based on exercise improvement in the 6-minute walk test. According to expert opinion, the validity and utility of this endpoint is limited in patients < 6 years value. Additionally, its predictive value on the long term improvement of the disease is not established in the adult population, questioning its usefulness in the paediatric population > 6 years. Potential efficacy endpoints relevant to the paediatric development include haemodynamic measurements or time to clinical worsening as recommended for the adult development.

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

1. Relevant subpopulations according to aetiology (essentially iPAH, and PAH associated with congenital heart disease CHD and the subpopulations of CHD).
2. The need to address Persistent pulmonary hypertension of the newborn PPHN as a separate entity.
3. Ethical issues regarding the use of placebo-controlled trials.
4. Development of specific paediatric formulations/ or the need for waivers based on the method of administration in certain age groups.
5. Efficacy endpoints relevant to the different age groups. The acceptability of waivers for certain age groups already addressed in the adult development programs.

6. The need for long term safety data to adequately assess special safety issues in children e.g. growth and sexual maturation.

4. RECOMMENDATION

The CHMP recommended drafting a paediatric addendum to the CHMP guideline on the clinical investigations of medicinal products for the treatment of pulmonary arterial hypertension.

5. PROPOSED TIMETABLE

It is anticipated that a draft document may be released 2 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-CV will be involved and the document is predicted to be discussed on 2-3 EWP-CV meetings and on two EWP meetings.

7. IMPACT ASSESSMENT (ANTICIPATED)

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

8. INTERESTED PARTIES

Association for European Paediatric Cardiology (AEPC), European Academy of Paediatrics (EAP-CESP), European Society of Cardiology (ESC), Task-force in Europe for Drug Development for the Young (TEDDY).
It will be sufficient to consult interested parties during an appropriate external consultation period.

9. REFERENCES TO LITERATURE, GUIDELINES ETC

Barst RJ et al.: Vasodilator therapy for primary pulmonary hypertension in children. Circulation 1999 Mar 9; 99(9): 1197-208).
Haworth SG: The management of pulmonary arterial hypertension in children. Arch Dis Child 2008; 93: 620-625.
van Albada and Berger, R.: Pulmonary arterial hypertension in congenital cardiac disease – the need for refinement of the Evian-Venice classification. Cardiol Young 2008; 18: 10–17
Rosenzweig and Barst: Pulmonary arterial hypertension in children: a medical update. Current opinions in pediatrics 2008; 20: 288-293.