



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

13 December 2012
EMA/CHMP/778582/2012
Committee for Medicinal Products for Human Use (CHMP)

Concept paper on the need for a paediatric addendum to the Guideline on clinical investigation of medicinal products for the treatment of acute heart failure (CHMP/EWP/2986/03 Rev. 1)

Agreed by Cardiovascular Working Party	28 November 2012
Adopted by CHMP for release for consultation	13 December 2012
Start of public consultation	15 January 2013
End of consultation (deadline for comments)	15 April 2013

Comments should be provided using this [template](#). The completed comments form should be sent to CVSWPsecretariat@ema.europa.eu

Keywords *Acute heart failure, Addendum, CHMP, guidelines, paediatric*



1. Introduction

The CHMP guideline on the clinical investigations of medicinal products for the treatment of Acute Heart Failure (AHF) addresses the development issues in this specific patient population but is restricted to adults. Acute Heart Failure Syndromes (AHFS) represent a very heterogeneous group of patients. In children the diagnosis of AHF has different aetiologies, different pathophysiology and clinical presentations. The development of medicinal products for treatment of this serious condition in children is therefore influenced by a set of complex factors that differ from the adult population. Unsurprisingly, the main symptoms and clinical manifestations also differ.

2. Problem statement

Acute heart failure (AHF) occurs in children as a consequence of congenital or acquired disorders, either systemic or involving only the cardiovascular system. Heart failure due to congenital structural heart disease typically presents early in life, while cardiomyopathy (CM), more frequently presents later in childhood. This failure of cardiac function is often divided into two categories in children:

- ▲ Increased systolic output with pulmonary over-circulation: in this setting, left ventricular (LV) systolic function is typically preserved and the most common causes are a large ventricular septal defect, or a large patent arterial duct. Common symptoms seen are tachypnoea, sweating, and failure to thrive.
- ▲ Low cardiac output: in this setting the symptoms often reflect the underlying anatomic cause such as hypoplastic left heart, critical aortic stenosis, or severe coarctation of the aorta and cardiomyopathies. The infants often present with decreased pulses, pallor, and circulatory collapse, while unexplained tachycardia, pallor, fatigue, syncope or abdominal pain are commonly noted in older children.

While definitive treatment of AHF in children often involves corrective surgery for congenital lesions or heart transplantation for cardiomyopathy, stabilisation with aggressive medical therapy for AHF before surgical treatment is of utmost importance, often in the intensive care setting.

The treatment of paediatric AHF is characterised by the use of drugs where the indication for use, dose, efficacy, and safety has not been adequately studied. This is partly explained by the number of limitations to conduct clinical trials in paediatric AHF, which include relatively small patient numbers, varying aetiologies, the absence of well defined clinical endpoints and a lack of consensus regarding optimal study design. Given the low incidence of paediatric heart failure, enrolment of paediatric patients into clinical trials is often inadequate which can lead to an insufficient sample size for an appropriately powered statistical analysis.

3. Discussion

The problems related to clinical trials in paediatric heart failure have been the focus of two recent meetings (Expert Group Meeting of Paediatric Heart Failure, EMA London November 2010, and First European Meeting on Paediatric Heart Failure and Heart Transplantation, September 2011). A number of points were raised in relation to the differences between adult AHF and paediatric AHF and their management. In order to enhance the availability of medicinal products for paediatric use in this context and to encourage data collection in the paediatric population including conduct of clinical trials, a regulatory guideline that outlines the requirements is considered not only helpful but also essential. The discussion points to be addressed by the guideline include:

- ▲ Clinical trial designs
- ▲ Selection of patients (in relation to the heterogeneity of the population)
- ▲ Baseline evaluations including echocardiography and biochemical parameters
- ▲ Primary and secondary end points, including also a discussion on surrogate and composite end points
- ▲ Safety endpoints that are expected to differ in children as compared to the adults population (hypotension, arrhythmias, need for prolonged ICU stay, changes in renal function, failure to thrive, growth retardation or delay in achieving expected milestones)

The absence of a guideline covering these areas was acutely felt and expressed in both meetings.

4. Recommendation

The Cardiovascular (CVS) Working Party at the EMA and the Paediatric Committee (PDCO) recommend the CHMP to consider an Addendum to the above mentioned Guideline in line with the criteria stated above.

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 3 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 co-operation between the CVS Working Party and the PDCO. One rapporteur from both: CVS Working Party and PDCO will be involved and the document is predicted to be discussed on 2-3 CVSWP and at least 2-3 PDCO meetings.

7. Impact assessment (anticipated)

The document is intended to provide guidance to industry when performing trials to develop drugs in AHFS. It should also provide a clear basis for the CHMP when assessing data from studies for paediatric AHF and providing advice in this field.

8. Interested parties

These include: the pharmaceutical Industry, the Academia (paediatric cardiologists and heart failure specialists), and the national competent authorities in Europe. It is likely that the guideline will have an impact worldwide.

9. References

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