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Paediatric Addendum on the CHMP Guideline on clinical investigation of medicinal products for the treatment of acute heart failure

Draft

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Draft Paediatric Addendum on the CHMP Guideline on clinical investigation of medicinal products for the treatment of acute heart failure

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Executive summary

This is an addendum to the *Guideline on Clinical Investigation of Medicinal Products in the Treatment of Acute Heart Failure (CHMP/EWP/2986/03 Rev. 1)*. It is not meant as a guidance document on its own but rather highlights differences from adult patients with Acute Heart Failure (AHF) and points out paediatric-specific aspects.

1. Introduction (background)

Acute Heart Failure Syndrome (AHFS) covers a very heterogeneous group of patients. In the paediatric population, the aetiology and pathophysiology of AHF is varied although some clinical manifestation may be similar. The main symptoms and clinical manifestations also differ. 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.

AHF in children can occur as a consequence of congenital or acquired disorders, either systemic or involving only the cardiovascular system. The prevalence and rate of diagnosis of heart failure in children and adolescents appear to be stable in the developed countries notwithstanding the reported increase of certain predisposing factors such as hypertension. 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. One category is those with 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. In the second category with low cardiac output setting, symptoms often reflect the underlying anatomic cause such as hypoplastic left heart, critical aortic stenosis, or severe coarctation of the aorta and cardiomyopathies.

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. One of the main aims of medical therapy for AHF is to stabilise patients both short and medium to long term. Treatment of volume overload is of priority and an increase in cardiac output is desirable and use of pharmacological therapy for these purposes needs to be optimised.

The pharmacological treatment of paediatric AHF is characterised by the use of drugs that may not have been adequately studied specifically in children. For example, volume and fluid overload is managed by use of intravenous diuretics in the intensive care setting and high output states are managed with vasodilators and supportive therapy. In adults, vasodilators are established for treatments of AHF even though high output states are only a small part of the spectrum. In children, inotropic agents are frequently used in the treatment of low output states albeit their use in adults has waned as sustained benefit remains controversial. Newer drugs such as phosphodiesterase inhibitors and calcium sensitizers have an even more debatable role but are used in the clinical setting. The lack of specific trials in the paediatric population is multifactorial and related to the essential differences in aetiology of AHF between children and adults. This addendum discusses the pharmacological treatment strategies for children with heart failure due to cardiomyopathies (i.e., muscle weakness) with parallels to the adult population. Some of the principles would be applicable to other forms of AHF.

1.1. Reasons for Limitation of Rx modalities

Issues related to clinical trials in paediatric heart failure have been the focus of two meetings: Expert Group Meeting of Paediatric Heart Failure, EMA London in 2010, and 1st European Meeting on Paediatric Heart Failure and Heart Transplantation, in 2011, UCL Institute of Child Health. The limitations to conducting clinical trials in paediatric AHF are noted and include relatively small patient numbers, varied aetiologies, the absence of well-defined clinical endpoints and a lack of consensus regarding optimal study design. Enrolment of paediatric patients into clinical trials is often inadequate resulting in an insufficient sample size for an appropriately powered statistical analysis. These issues can only be addressed by multicentre co-operation and the foundation of network of paediatric cardiology centres willing to participate in clinical trials.

In view of these limitations, a guideline that addresses the development of pharmacological treatment options in children is considered crucial. New drugs for paediatric AHF should ideally have demonstrable safety and efficacy in the paediatric population. The mechanisms may involve, blockade of renin-angiotensin-aldosterone system (RAAS), improving endothelial function, vasodilatation, anti-inflammatory, anti-arrhythmic and diuretic effects.

2. Scope

In order to enhance the availability of medicinal products for paediatric use and to encourage data collection in the paediatric population including conduct of clinical trials, a guideline that outlines the requirements could be considered helpful. Guidance is therefore included on the design and conduct of studies intended for use in children of all ages (0-18 years) when developing products for AHF. The discussion points that are addressed in the guideline include clinical trial designs, selection of patients (in relation to the heterogeneity of the population), primary and secondary end points, a note on surrogate and composite endpoints, and safety endpoints. Safety endpoints differ in children as compared to the adult population. They not only include hypotension, arrhythmias, need for prolonged ICU stay, but also changes in renal function, failure to thrive, growth retardation or delay in achieving expected mile stones.

Aspects relating to surgical treatment such as correction of congenital defects and mechanical support that are an integral part of treatment of heart failure in the paediatric population are beyond the scope of this guideline.

3. Legal basis and relevant guidelines

This Paediatric Addendum to the Guideline on Clinical Investigation of Medicinal Products in the Treatment of Acute Heart Failure (CHMP/EWP/2986/03 Rev. 1) 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);

- Concept Paper on the impact of liver immaturity when investigating medicinal products intended for neonatal use (EMEA/CHMP/PEG/194605/2005);
- Guideline on the investigation of medicinal products in the term and preterm neonate (EMEA/267484/2007);
- Concept Paper on the Impact of Brain Immaturity (CHMP/PEG/181377/06);
- Clinical trials in small populations (CHMP/EWP/83561/2005);
- Guideline on pharmaceutical development of medicines for paediatric use (EMA/CHMP/QWP/805880/2012 Rev. 2);
- Ethical considerations for clinical trials on medical products conducted with the paediatric population: Recommendations of the ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use 2008.

4. Efficacy evaluation (including end points)

The efficacy of pharmacological treatment modalities in paediatric AHF should be evaluated using any of the following parameters singly or in combination as primary endpoints. They include mortality, cardiac transplantation, changes in cardiac function, time to step down care and clinical scores. It is recognised that all cause death and CV mortality events may not be frequent events in this paediatric population and other important parameters (e.g., reduction in the need of ventricular assist devices or referral for heart transplantation) assume greater significance and could be evaluated as measures of clinical benefit of a medicinal product. Symptom scores, duration of hospitalisation or ICU stay, hemodynamic measurements and echocardiographic measures of LV function could serve as secondary or supportive endpoints. For younger children, achieving expected milestones at appropriate times could also be relevant.

4.1. Mortality

Reduction in all cause death or cardiovascular death, should be the primary goals of treatment of paediatric heart failure. There should be clarity in the definitions of each of these parameters and they should be objectively evaluated. While all-cause mortality would be the preferred endpoint, it is **not** anticipated that in this paediatric population all cause death will differ significantly from CV death as the population is unlikely to have complex co-morbidities in contrast to the adult population with AHF. It is important to include sudden death (or death due to arrhythmia when documented) in evaluating mortality. On occasion, in cases of sudden death, there will be need for confirmation of absence of other causes and this may include a post mortem examination.

4.2. "Time to" Events

"Time to" events are helpful parameters as endpoints in certain situations. *Duration of stay in intensive care unit (ICU)* or *duration of hospitalisation* both indicate time to stabilisation (for step down care or discharge as appropriate) and they could be used as measures of efficacy of the medicinal product. A delay in *time to referral for transplantation* (as an indicator of stabilisation of the clinical status) and, *time to transplantation* without other adverse consequences (e.g., reduced overall survival or end organ damage) could be measures of beneficial effect of the medicinal product. Time to actual transplantation is dependent of many factors including geographical location and organ availability but referral for transplantation using objective and pre-specified criteria could be a useful indicator of

success or failure of therapy with the medicinal product. *Time to worsening heart failure* on therapy is another parameter that might be useful in the medium to longer term studies.

Additionally, *time to referral for surgical correction of the structural abnormality* including valve surgery could be assessed as measure of effectiveness of the medical therapy as need for early surgery often indicates failure of medical therapy in the relevant population.

4.3. Cardiac function (echocardiographic parameters)

Echocardiographic measures of ventricular function (especially left ventricle) including end diastolic or systolic dimensions, end diastolic or systolic volumes could be used as measures of efficacy. Similarly, ejection fraction or fractional shortening have been used as measures of left ventricular function and can be easily measured using echocardiography. Echocardiography should be performed blinded in a centralised laboratory with trained observers/readers. With multicentre trials, it is also important that standardised training is provided to the recording technicians and, interobserver as well as intraobserver variability are evaluated to permit a robust assessment of left ventricular function. Central adjudication may be necessary in certain cases when blinded reading in a centralised laboratory facility has not been deployed.

When these parameters are used as endpoints, it is anticipated that they will be linked to other hard clinical measures of outcome. At this present point in time, left ventricular remodelling has not been proven as a surrogate endpoint for medium to long term outcome.

4.4. Clinical or symptom scores

Several clinical scoring systems are in use, which help classify or stratify patients according to severity of disease. These include New York Heart Association (NYHA) Functional Classification, the Ross Heart Failure Classification or Paediatric Heart Failure Index (PHFI New York University). Each of these classifications has their merits and the most appropriate scoring system should be chosen taking into account the patient's age, type of heart failure. It is recommended that the choice should be defined *a priori* and adequately justified.

4.5. Haemodynamic measurements

Often haemodynamic measurements are used especially in adult AHF as measures of efficacy in the proof of concept and dose finding studies. There is no mandatory requirement to evaluate invasive haemodynamic parameters in paediatric AHF and use of these should be guided by the clinical situation and aetiology of heart failure. In adults and in many cases in children, changes in haemodynamic measures such as pulmonary capillary wedge pressure (PCWP) or changes in ejection fraction are not linked to improved outcomes. Inotropic agents are good examples that produced statistically important changes in such parameters in the short term but resulted in poor outcomes. Therefore, it is important to link the medicinal product's effect on haemodynamic measures to clinical outcome measures such as mortality or removal of the need for transplantation.

4.6. Biochemical parameters

Biochemical markers of heart failure could indicate severity and response to treatment. Thus far, markers evaluated include natriuretic peptides (B-type natriuretic peptide [BNP] and N-terminal pro-BNP [NT-pro BNP]) and inflammatory markers. The natriuretic peptides (BNP and NT-pro BNP) levels are currently useful as clinical trials inclusion criteria. Their surrogate value remains to be established

as there are few data linking natriuretic peptide level changes with treatment and clinical outcome measures.

Measurement of biochemical parameters such as natriuretic peptides and inflammatory markers (hs-CRP or interleukins) is encouraged in paediatric AHF trials as exploratory parameters to establish a link with clinical outcome measures.

4.7. Composite and co-primary endpoints

Combination of certain parameters either as a composite or co-primary endpoints has increased as it offers some advantages when sample size is limited. They have to be chosen carefully to serve a specific purpose of increasing the power of small studies and capture a number of relevant clinical parameters. Notwithstanding the above, composite endpoints are challenging and may be difficult to use in paediatric AHF trials due to centre specific differences of care.

5. Patient selection

The criteria and diagnosis of AHF should be based on baseline evaluation of functional or clinical scoring systems combined with echocardiographic parameters. Echocardiography should be used to establish the aetiology and structural abnormalities including congenital defects, the type of defect and the physiological states- high output or low output states. As the pharmacological treatment of paediatric AHF is mostly aimed at improving cardiac muscle dysfunction (cardiomyopathies), selection of patients will be guided by this parameter. Patients with structural abnormalities leading to muscle dysfunction could be included.

As the aetiology is varied, ideally some form of stratification may be necessary to separate patients based on the different pathophysiological states. It is recognised that due to the small numbers involved distinct studies in different aetiologies may not be possible.

When conducting studies during adolescence, the age, ethnic background and gender differences should be taken into account as the aetiology of heart failure in adolescents is different from those occurring in young children (where congenital heart defects are predominant). In adolescents, the aetiology of myopathies may vary depending on age, gender and ethnic background.

6. Clinical trials strategy & design

Taking into consideration the difficulties in performing clinical investigations for paediatric AHF, it becomes necessary to maximise the information gathered from other types of studies. Therefore, the study designs need to be streamlined by application of specific principles.

As paediatric development usually follows studies in adults, studies in children will be mainly to establish specific questions as applicable to this group of patients. It is not expected that there will be phase I studies (healthy volunteer studies) employed routinely and information should be derived and extrapolated from healthy volunteer studies in adults.

6.1. Human Pharmacology studies (Pharmacokinetic/Pharmacodynamic [PK/PD])

The pharmacokinetic and pharmacodynamic (PK/PD) data from the adult heart failure population will guide the level of PK information and studies required in the paediatric population. If a difference in the PK between the adults and children arising from organ immaturity that impacts the dosing strategies is anticipated, specific PK studies may be necessary. Where possible use of PK/ PD modelling based on

data derived from adult populations is encouraged to explore the pharmacokinetic behaviour in children to determine the need for specific studies, and to optimize the design of these studies. Depending on the drug substance and the metabolism, sparse sampling in the clinical studies could be used to provide PK information.

There is likely to be a necessity to develop special paediatric formulations as appropriate for different age groups (infants, young children and adolescents).

6.2. Exploratory Therapeutic studies

Exploratory studies are expected to function as dose finding studies for confirmatory trials and could be placebo controlled where feasible. In the majority of instances, it may be possible to derive dose information from adult studies but specific dose titration studies may sometimes be required.

These studies should also aid in defining the population of subjects the product is expected to show the benefit and guide the design of confirmatory therapeutic trials. Such studies may be used to evaluate haemodynamic effect of the medicinal products (for specific circumstances and indications) but should include clinical parameters as endpoints in order such that they could function as supportive evidence of efficacy.

6.3. Confirmatory Therapeutic studies

It is recognised that large randomised clinical trials may not be feasible in paediatric AHF to evaluate the benefit risk of all medicinal products intended for use in this clinical condition when the difficulties in performing clinical investigations are taken into account. Therefore some of the safety and efficacy of medicinal products in the paediatric population may need to be derived from the adult population. Therefore, it becomes necessary to maximise the information gathered from all other types of studies and the study designs need to be streamlined by use of specific principles.

The baseline assessments should include consistent use of clinical scores (NYHA, PHFI or the Ross Heart failure classification) as appropriate and the choice of the scoring system should be adequately justified accounting for differences in type of heart failure. Diagnostic criteria for AHF should be consistently applied with the use of standard diagnostic imaging techniques such as echocardiography with or without biochemical markers of heart failure (e.g. BNP).

The varied aetiology of paediatric heart failure offers opportunities for inclusion of patients with diverse set of characteristics thereby increasing the heterogeneity of the study population. It is recommended that inclusion and exclusion criteria should be well defined to identify common functional characteristics (e.g., evidence of myopathies or muscle dysfunction). If inclusion of heterogeneous population is unavoidable, stratification by aetiology or stratified randomisation may be used as an attempt to maximise the information gleaned from the trial.

Use of an appropriate comparator is encouraged as placebo controlled studies may not always be feasible in this particular population. As very few therapies for AHF with good supporting evidence for efficacy and safety are approved for use in children, studies using approved active comparators are difficult. It may be necessary to consider the use of an appropriate class of agent approved in adults with established use in children if such were available, in order to overcome limitations in using placebo. Placebo-controlled studies using add-on design to best standard of care are another possibility. When confirmatory trials are placebo controlled, demonstration of clear superiority in terms of efficacy and safety (i.e., exclusion of harm) should be the aim.

7. Evaluation of safety

Safety evaluation in paediatric AHF is expected to be generally similar to adults with additional parameters that are important in children. These include parameters such as hypotension or low BP, arrhythmias, need for prolonged ICU stay, changes in renal function in addition to failure to thrive, growth retardation or delay in achieving expected mile stones and may all be relevant safety end-points.

Measures of renal function such as creatinine or glomerular filtration rate may serve as safety end-points in paediatric AHF trials. Improvement in renal blood flow and thereby improved renal function are less useful as efficacy end point as these are influenced by complex set of factors and may not be directly related to the pharmacology of the medicinal product.

Definitions

AHFS Acute Heart Failure Syndromes

AHF Acute heart failure

CM cardiomyopathy

LV Left ventricular

ICH International Conference on Harmonisation

UCL University College London

RAAS Renin-angiotensin-aldosterone system

NYHA New York Heart Association

PHFI Pediatric Heart Failure Index

BNP B-type natriuretic peptide

ICU Intensive care unit

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