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

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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)* for adults and should be read in conjunction with this guideline. This addendum includes guidance on paediatric medicine clinical development, highlighting paediatric specific issues and differences from adult acute heart failure.

1. Introduction (background)

Acute Heart Failure (AHF) covers a very heterogeneous group of patients. In the paediatric population, the aetiology, pathophysiology and clinical manifestations of AHF are often varied and the main symptoms depend on the pathology. 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 cardiomyopathies (CM) frequently present later in childhood.

The failure of cardiac function in children is often divided into two categories. One category consists of conditions with increased systolic output with pulmonary over-circulation as seen with large atrial or ventricular septal defects or patent arterial duct. In the second category with low cardiac output, symptoms often reflect the underlying anatomic cause, for example 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, one of the main aims of medical therapy for AHF is to stabilise patients both in the short term as well as for longer term, for example before and after palliative surgery or as a bridge to transplantation. The use of pharmacological therapy for treating volume overload and enhance cardiac output needs to be optimised. However, the pharmacological treatment of paediatric AHF is characterised by the use of drugs that may not have been adequately studied in children but follow the similar principles as adult AHF. Volume and fluid overload are 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 a debatable role but are often used in clinical practice.

The reasons for lack of evidence based treatment modalities for paediatric AHF are many fold. The limitations for conducting clinical trials in paediatric AHF 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 limited resulting in an insufficient sample size for an appropriately powered analysis. Multicentre co-operation and the foundation of networks of paediatric cardiology centres ready to participate in clinical trials can support the conduct of studies in paediatric AHF patients.

In view of these limitations, a guideline that addresses the development of pharmacological treatment options in children is considered crucial.

2. Scope

In order to enhance the availability of medicinal products for paediatric use and to encourage data generation in the paediatric population including conduct of clinical trials, a guideline that outlines the requirements is 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 view of the heterogeneity of the population), primary and secondary endpoints, a note on surrogate and composite endpoints, and safety endpoints.

This addendum discusses the pharmacological treatment strategies for children with heart failure irrespective of the structural abnormality or cause. 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 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 should 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 endpoints)

The efficacy of pharmacological treatment modalities in paediatric AHF could be evaluated in clinical trials using any of the following parameters. They include mortality, time to specific events, use of

ventricular assist devices, changes in cardiac function, clinical scores, symptom scores, duration of hospitalisation or ICU stay, hemodynamic measurements and biochemical parameters (see sections 4.1 – 4.6 below).

It is recognised that mortality events are not frequent events in the paediatric population and other important parameters (e.g., reduction in the need of ventricular assist devices or referral for heart transplantation) may assume greater significance and provide important indication of benefit.

Combination of several parameters as a composite offers advantages when sample size is limited. The components should be chosen carefully to capture the spectrum of relevant clinical parameters. It is advantageous to ensure directional concordance of the components. When centre specific differences of care are common, composite endpoints could be challenging particularly those composites that include parameters sensitive to such differences and should be carefully addressed. Ranked composite endpoints may offer certain advantages and a need to develop more sensitive composite endpoints is recognised. Applicants and sponsors are advised to seek scientific advice if use of such endpoints is foreseen.

4.1. Mortality

Reduction in all cause death or cardiovascular death, could be considered as part of the composite goals of treatment of paediatric heart failure. However it is recognised that mortality is a rare event in this particular context. 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. There should be clarity in the definitions of each of these parameters and they should be objectively evaluated.

4.2. "Time to" Events

"Time to" events are helpful parameters as endpoints in certain situations. These include time to transplantation, referral for transplantation, duration of stay in intensive care and duration of hospital stay (or time to discharge). 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 referral for transplantation using objective and pre-specified criteria is considered the more useful indicator as time to actual transplantation is dependent of many factors including geographical location and organ availability. *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) could be used as measures of efficacy of the medicinal product. Duration of stay may be influenced by a variety of factors, such as variability in regional or institutional practice, non-cardiac related factors and organisational aspects. The use of Ventricular assist devices both as a short term bridge (to cardiac transplantation) or as long term treatment modality should be recorded. *Time to worsening heart failure* on therapy and *time to step down care* are other parameters that might be useful in the medium to longer term studies.

4.3. Cardiac function (echocardiographic parameters)

Echocardiographic measures of ventricular function (especially the systemic 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 following a pre-specified protocol and analysed by a blinded, 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 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

Changes in clinical scores could be useful as measures of efficacy provided their use is validated and consistent. 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 patients' 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 (hs CRP or interleukins). The natriuretic peptides (BNP and NT-pro BNP) levels are currently useful as clinical trials inclusion criteria. Thus far, there are few data linking changes in these biochemical parameters with treatment and clinical outcome measures, but their use is encouraged to establish such a link.

Improvement in renal function or improvement in renal blood flow are less useful as measures of efficacy as these are influenced by complex set of factors and may not be directly related to the pharmacology of the medicinal product.

5. Patient selection

The criteria and diagnosis of AHF should be based on baseline evaluation of functional or clinical scoring systems, combined with imaging such as echocardiographic parameters or cardiac MRI to establish structural abnormalities. 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, selection of patients will be guided by this parameter. Patients with differing structural abnormalities leading to muscle dysfunction could be included.

It is recognised that heart failure may present after palliative or corrective surgery with varied manifestations. When these patients are included in clinical studies, care should be taken to ensure that the parameters for defining heart failure are clearly laid out in the protocol.

The aetiology of HF may vary depending on age, gender and ethnic background. This should be accounted for and accommodated. In adolescents, the aetiology of heart failure may differ from those in younger children (Congenital heart defects are predominant in young children). 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.

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.

If paediatric development (as usual) follows studies in adults, studies in children will mainly be designed to reflect specific questions 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 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 and/or PD between the adults and children arising from organ immaturity that impacts the dosing strategies is anticipated, specific PK and/or PD studies may be necessary. Where possible, use of PK/PD modelling based on data derived from adult populations should be performed 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 and/or PD information. PD mechanisms defined in adults will be applicable in children but specific dose titration studies may be required.

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 using exposure response analyses and modelling, but specific dose titration studies may sometimes be required. It is however recognised that feasibility of such studies may be a consideration.

6.3. Confirmatory Therapeutic studies

It is recognised that large randomised clinical trials to evaluate the benefit risk may not be feasible for medicinal products intended for use in paediatric AHF taking into account the limitations for conducting clinical trials in this population. Therefore, paediatric development needs to build on information on safety and efficacy of the medicinal product from the adult population. Information gathered from all other types of studies in children should be maximised including exploratory and PK studies conducted across groups. It is recommended to streamline the designs of these studies appropriately to facilitate collection of adequate information.

The need for confirmatory trials should therefore be considered on a case by case basis. Scientific advice could be asked for. If needed, the baseline assessments of confirmatory therapeutic trials 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 cardiomyopathies 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.

When confirmatory trials are placebo controlled, an add-on design to the best standard of care is recommended. In such studies, demonstration of clear superiority in terms of efficacy and safety should be the aim. Use of an appropriate comparator is encouraged when placebo controlled studies are not feasible in this particular population due to variability of patient groups and treatment practices. 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 but establishing a standard of care within the clinical study is encouraged. 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, to overcome limitations in using placebo or standard of care.

7. Evaluation of safety

Safety evaluation in paediatric AHF is expected to be generally similar to adults with additional parameters (or endpoints) that are important in children. These include parameters such as hypotension or low BP (using age-appropriate definitions), hypoperfusion, arrhythmias, in addition to failure to thrive, growth retardation or delays in neuro-motor and neurocognitive development 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.

Abbreviations

AHF Acute heart failure

CM cardiomyopathy

ICH International Conference on Harmonisation

NYHA New York Heart Association

PHFI Pediatric Heart Failure Index

BNP B-type natriuretic peptide

MRI Magnetic resonance imaging

ICU Intensive care unit

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