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SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human use (CHMP)

Concept paper on the need for revision of the addendum on acute cardiac failure of the note for guidance on clinical investigation of medicinal products for the treatment of cardiac failure (CPMP/EWP/2986/03)

Agreed by Efficacy Working Party	April 2010
Adoption by CHMP for release for consultation	20 May 2010
End of consultation (deadline for comments)	31 August 2010

The proposed addendum will replace addendum (CPMP/EWP/2986/03).

Comments should be provided using this template. The completed comments form should be sent to EWPSecretariat@ema.europa.eu

Keywords	*Acute heart failure, acute decompensated heart failure, acute heart failure syndromes, CHMP, Chronic heart failure, guidelines, dyspnoea, BNP.*

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1. Introduction

The CHMP guideline on the clinical investigations of medicinal products for the treatment of Acute Heart Failure addresses the development issues in this specific patient population. Acute Heart Failure Syndromes (AHFS) represent a very heterogeneous group of patients. The traditional approach for patient selection which is described in the current guideline, is mainly based on the aetiology of the disease and the clinical determinants of acute decompensation. Emerging data from recent clinical trials have shown the determinant role of the patient clinical profile at presentation on the outcome of the studies, in particular the key role of systolic blood pressure (SBP) and renal function. A more selected enrolment of patients should therefore be discussed in the guideline. To better detect an improvement of clinical symptoms or demonstrate a clinical benefit in AHFS, new composite end-points have emerged in clinical trials that are particularly challenging for regulatory decisions. More clarity is needed on the applicability of these composite end-points for regulatory purposes. The expanding role of B-natriuretic peptide (BNP) in the clinical management of AHFS patients should also be discussed.

2. Problem statement

AHFS continue to be a growing public health problem, affecting a large heterogeneous patient population with a high post-discharge event rate. Post-discharge mortality and re-hospitalisation rates reach 10 to 20% and 20 to 30% respectively within 3 to 6 months. Although this may reflect the severity of heart failure, myocardial injury and/or renal impairment occurring in AHFS may contribute to this grim prognosis. Improving post-discharge mortality and prevention of readmissions are the most important goals in AHFS.

Over the last decade, most pivotal trials conducted to date in AHFS have been negative in terms of efficacy and/or safety although encouraging sings were often seen in early phase trials. This may have been related to a specific intervention or drug, patient selection, dose selection and/or end-points chosen in the pivotal studies. It is also possible that the limited understanding of the pathophysiology of AHFS has translated into a lack of consensus in the design of clinical trials, especially in the choice of inclusion/exclusion criteria, dose selection for pivotal trials and end-points.

The overall efficacy of a drug or intervention in AHFS is very much dependant on the patient's clinical profile at presentation. Recent clinical trials and observational studies have identified emerging prognostic factors in patients admitted with AHFS. Among these, the following have come to the fore: Blood pressure, renal impairment and myocardial ischemia. Systolic BP on admission and at early discharge is an important predictor of in-hospital and post-discharge mortality. Renal impairment is often present at time of admission. Approximately 30% of AHFS patients have worsening renal impairment during hospitalisation. An increase of blood urea nitrogen during the early post-discharge period is one of the most important predictors of early mortality. Many of the negative results in AHFS may have been related to the deleterious effects of the drug that was used in an unselected patient population e.g. ulatiride and nesiritide which have vasodilatory effects, in patients who were hypotensive, which resulted in a further decrease in BP and worsening renal function. Enrolment of patients should be adequate with regards to the drug's expected effects. For such agents, selection of patients with very high BNP level and a cut-off BP at entry (i.e. more than 130 mmHg) may have assured a better response. On the other hand, an inotrope that is not causing myocardial injury may be suited for patients presenting with a low BP due to a low cardiac out-put. Thus patient selection may need to be drug or class specific. The emerging key role of patient clinical profile at presentation in the drug overall response is currently not adequately discussed in the addendum in acute heart failure.

Significant and clinically meaningful improvement in symptoms compared to standard care is a valuable therapeutic goal in AHFS. However, due to the subjective nature of clinical symptoms (e.g., dyspnea, functional status), the high placebo effect have most often prevented to provide a clear demonstration of drug efficacy. Furthermore, in a number of studies the delay in randomisation could have resulted in the lack of demonstration of benefit as standard care has considerable impact on the symptomatology. Additionally, lack of standardisation of measurement of symptoms have contributed to the disparity in results. In an attempt to overcome this difficulty, investigators have suggested a number of new composite end-points in recent clinical trials. One of the most frequent proposals is the "*categorical composite"* which divides patients into three categories: "improved"; "unchanged" and "worsening". Components of this composite are various but often a mix of subjective signs eg dyspnea, functional status, to more objective data: physical signs, renal function, use of IV diuretic, mechanical ventilation, hospitalisation and even hard components may be added eg cv or total mortality. Furthermore, the "*categorical composite*" for statistical efficiency may be converted into a scoring system by weighting each component with an arbitrary number. This scoring system has been used in the regulatory approval of medical devices especially the ventricular assist device.

The combination in the composite end-point of components which have markedly different weight in term of clinical benefit is problematic and particularly challenging for regulatory decisions. Although the current Addendum on acute heart failure does address the issue of composite end-points, the text is too general and should be more specific.

The role of BNP measurements in the management of AHFS is expanding. The use of BNP to define a high risk group may be valuable. However, the tailored approach with drug therapy or clinical intervention in response to BNP levels is not well established in AHFS. This issue has to be discussed in the guideline.

3. Discussion

It is proposed that there should be discussion regarding the need to update the Note for guidance on clinical investigation of medicinal products for the treatment of cardiac failure-Addendum on acute Heart failure (CPMP/EWP/2986/03) in order to further enhance the following aspects:

1. The critical aspect of patient's clinical profile at presentation for the proper assessment of drug efficacy/safety in AHFS especially the key role of systolic blood pressure, renal function and myocardial inschaemia.
2. The scope of applicability for regulatory purposes of composite end-points in particular the use of the "*categorical composite*".
3. Standardisation of time to enrolment (randomisation) and measurement of time points for symptoms (e.g., < 12 hours of ER admission).
4. To better define the role of BNP level in the drug evaluation process.

4- Discuss the value of invasive haemodynamic measurements in the light of new scientific knowledge.

5. Provide a more detailed definition of the short-medium term safety profile in terms of worsening renal failure and myocardial injury.

4. Recommendation

It is not totally clear whether at present unequivocally feasible and scientifically sound proposals can be made to address the major problems identified. Consequently, prior to start drafting revised regulatory recommendations it seems prudent to initiate discussion with experts from academia to exchange views on the current degree of validation of putative proposals.

5. Proposed timetable

A period of 3 to 6 months to arrange appropriate expert consultation will be needed. Once the viability of the revision of current guidelines can be concluded, it is anticipated that a draft document may be released 6-9 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

It is not anticipated that expert consultation will require to convene any specific formal meeting at the EMEA premises.

The preparation will involve the EWP Cardiovascular drafting group. 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.

Involvement of the SWP may be required.

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 AHFS drugs and providing advice in this field.

8. Interested parties

The interested parties in the guideline include, the industry (PhARMA, EFPIA, JPMA and others), Academia, European Society of Cardiology, clinical trialists in heart failure and other regulatory agencies.

9. References to literature, guidelines etc

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