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NOTE FOR GUIDANCE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS FOR THE TREATMENT OF CARDIAC FAILURE

ADDENDUM ON ACUTE CARDIAC FAILURE

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Note:

This Addendum will be part of the Note for Guidance on Clinical Investigation of Medicinal Products for the Treatment of Cardiac Failure (CPMP/EWP/235/95, Rev 1), which was adopted in December 1999.

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NOTE FOR GUIDANCE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS FOR THE TREATMENT OF CARDIAC FAILURE

ADDENDUM ON ACUTE CARDIAC FAILURE

- This NfG document should be read in conjunction with Directive 2001/83/EC, as amended, as well as in conjunction with other pertinent regulatory European and ICH documents, with special emphasis on:
- Note for Guidance on General Considerations for Clinical Trials (CPMP/ICH/291/95)
- Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95)
- Note for Guidance on Dose Response Information to support Drug Registration (CPMP/ICH/378/95)
- Note for Guidance on Statistical Principles for Clinical Trials (CPMP/ICH/363/96)
- Note for Guidance on Choice of Control Group for Clinical Trials (CPMP/ICH/364/96)
- Points to Consider on Switching between Superiority and Non-inferiority (CPMP/EWP/482/99)
- Note for Guidance on the Investigation of Drug Interactions (CPMP/EWP/560/95)

The CPMP Note for Guidance on the Clinical Investigation of Medicinal Products for the Treatment of Cardiac Failure (CPMP/EWP/235/95, rev. 1) provides only partial and incomplete regulatory guidance for development of medicinal product for the treatment of acute heart failure. Therefore, this document is aimed to cover these deficiencies and substitute those chapters of the mentioned document related to Acute Cardiac Failure.

1. INTRODUCTION

Acute heart failure is characterised by a wide spectrum of symptoms and signs of acute onset such as shortness of breath or cardiogenic shock accompanied by haemodynamic abnormalities and neuroendocrine activation. The currently available treatment modalities include bed rest, morphine, oxygen, diuretics, vasodilators and inotropic agents with or without vasodilating effects. These therapeutic measures aim to relieve symptoms, and/or reduce morbidity and mortality and sometimes are intended to gain time for bridging to definitive treatment modalities which address the underlying cause. This NfG is intended as a broad guideline to be taken into consideration when setting up a clinical development plan for a new drug in the treatment of acute heart failure.

Mechanical circulatory support with intra-aortic balloon counterpulsation and left ventricular assist devices are sometimes used as interim measures prior to corrective surgery or as adjunctive therapy in presence of poor cardiac function. Trials to establish the efficacy of these modalities are beyond the scope of this document.

2. BACKGROUND

Acute heart failure is defined as rapid onset of symptoms and signs secondary to abnormal cardiac function. It is often life threatening and requires urgent treatment. It may occur with or without previous cardiac disease. The cardiac dysfunction can be related to systolic or

diastolic dysfunction, to abnormalities of cardiac rhythm or to preload and afterload mismatch.

Perioperative or postoperative acute heart failure should be studied as a separate entity as the symptoms cannot be assessed and other clinical parameters should be used. Secondly the mechanism of acute heart failure in these patients is due to various causes, ischaemia, pain, anaemia, and even anaesthetic agents.

Management of severe acute heart failure not only requires rapid relief of congestion and improvement in haemodynamic status but also assessment and when possible correction of the underlying cause.

The term acute heart failure in this document refers to acute left or both sided concomitant ventricular failure. Isolated acute right heart failure differs from other forms of AHF often as regards aetiology and management and is not covered in this guideline.

There are two clinical presentations – acute decompensated heart failure and cardiogenic shock. The characteristic haemodynamic features of acute decompensated heart failure are elevated left ventricular filling pressure, decreased cardiac output and increased systemic and pulmonary vascular resistance. Pulmonary oedema represent more severe syndromes. Patients with AHF may also present with signs of cardiogenic shock, characterised by low arterial pressure, marked peripheral hypoperfusion and oliguria.

The pathophysiology in acute left ventricular failure due to acute myocardial infarction (AMI)/acute coronary syndrome may differ from those with acute-on chronic failure. Acute heart failure due to AMI is characterised by acute haemodynamic changes unlike acute-on-chronic failure where fluid retention may be an additional main feature.

3. EFFICACY CRITERIA

Clinical improvement either in terms of reduction in mortality or improvement in symptoms/quality of life must be shown.

A new therapeutic agent is expected to improve haemodynamics , induce diuresis and inhibit unwanted neuroendocrine activation. This will depend on the type of drug and mode of action.

These changes alone are not sufficient for marketing authorisation. Improvement in haemodynamic parameters has not necessarily been associated with improvement in survival with the exception of elevated PCWP that has been shown, in some studies, to be predictive of sudden death and progressive decompensation.

Haemodynamic parameters should be used in phase II studies for dose determination or to study pharmacodynamic response. These could be carried out as applicable, in healthy volunteers, and patients to ensure proper information on the minimum efficaceous and maximum tolerated doses. Pharmacokinetic and dynamic modelling will need to be provided in patients depending on the pharmacologic profile and action of the agent. Invasive assessment of these parameters could also provide supportive evidence of efficacy of the product in acute stage, and for new inotropic agents is considered necessary. (Refer to 5.1 and 5.2).

3.1 Primary Endpoint

3.1.1 All-cause mortality

The preferred primary endpoint is all cause mortality. This should include in-hospital mortality during admission for the acute episode and mortality data at 30 days from the presentation.

In case that the reference drug has not demonstrated an improvement in survival in patients with AHF, a non-inferiority approach is not considered appropriate.

3.1.2 Symptoms

Symptoms should be carefully assessed under standard conditions with regards to background oxygen therapy.

While all cause mortality is the preferred primary endpoint, symptomatic improvement may be acceptable provided no deleterious effects are shown as regards mortality both immediate and delayed. In this context dyspnoea (breathlessness) remains the most important symptom. General well being, fatigue and mental confusion are also important symptoms but difficult to measure particularly at baseline.

The difficulty of assessment of dyspnoea at baseline in patients who are acutely ill should not deter from inclusion of this endpoint for demonstration of symptomatic improvement. In practice the improvement in clinical state is judged largely by assessment of dyspnoea, both by patients and investigators. This should be seen in conjunction with haemodynamic improvement. Any impact of standard care on potential benefit should be addressed. Change in background therapy cannot be accepted as surrogate for symptomatic improvement.

Various grading for dyspnoea have been used in clinical studies with drugs for the treatment of acute heart failure. These have either been three-point scale based on improved, worse or same or five point scale with 1 designated for `none' and 5 for `severe'. Other dyspnoea scales like BDI (Baseline Dyspnoea Index) and TDI (Transition Dyspnoea Index) have been used in settings of obstructive airways disease. Instruments like VAS scales and 7-level Likert scale have also been used, the later frequently in clinical trials.

Whatever method is chosen it should be well validated, justified and defined a priory. The timing of the assessment of dyspnoea should be clearly specified in the study protocol (usually at baseline, at 6 hours and sequentially thereafter, and 24 hours post-treatment after initiation).

Other symptoms like fatigue are important in patients with acute heart failure but are difficult to assess. A global assessment of the patient's clinical status may be useful complementary information to the assessment of dyspnoea. Its use as co-primary endpoint is highly recommended.

Any impact of standard care on potential benefit should be addressed. However, any reduction in need for uptitration of background therapy for AHF is not considered an appropriate component of a combined endpoint related to symptomatic improvement.

The effect of a particular drug on symptoms should be seen in conjunction with its haemodynamic effects (See section 3.1.3). Necessary precautions should be taken in order to avoid that the investigator's awareness of the haemodynamic drug effect on each individual patient may influence the evaluation of symptoms.

3.1.3 Haemodynamic measurements

Haemodynamic parameters particularly PCWP before and after therapy with test drug are unlikely to be sufficient for a drug approval if no survival or symptomatic benefit is shown. Therefore, PCWP and other measurements like blood pressure, CO, CI, SVR and PVR should be used as relevant secondary endpoints.

If there is no positive effect on all cause mortality, improvement in dyspnoea with reduction in PCWP, either from same or different studies, would be acceptable evidence of efficacy provided deleterious effects on mortality and morbidity, both immediate and delayed, are excluded.

In summary

Preferred Endpoint: Mortality

Acceptable Endpoint: Provided that a deleterious effect on mortality is ruled out, improvement in symptoms and correlation of haemodynamic improvement with clinical findings can be accepted as evidence of efficacy. Haemodynamic findings are useful and needed but not enough as sole basis for approval of a medicinal product.

3.2 Secondary endpoints

3.2. 1 Cardiac and non-cardiac deaths

Cardiovascular deaths should be included as secondary endpoint. These might include sudden cardiac death, death due to myocardial infarction, arrhythmic death and worsening heart failure. Non-cardiac (vascular) deaths could be due to embolism and/or cerebrovascular accidents (strokes).

3.2. 2 Hospitalisation

Duration of hospital stay may be another secondary endpoint. This should include number of days in intensive/coronary care units and total in-patient stay. The time to stepdown in care and time to fitness for discharge may be other useful secondary endpoints.

During long term follow-up of acute treatment, the number of rehospitalisations (all cause, cardiovascular or due to heart failure) may be considered an additional secondary endpoint as rehospitalisation rate over 6 months in acute decompensated heart failure patients is as high as 50%. This along with cardiac and non-cardiac deaths are considered most important secondary endpoints.

Composite endpoints at present are not acceptable unless well validated.

3.2. 3 Recurrent ischaemic events

In patients with acute heart failure due to myocardial ischaemia/infarction reduction in recurrent ischaemic events (recurrent MI, need for intervention strategies) may be a secondary endpoint.

3.2. 4 Other objective measurements

Enhanced diuresis (MEB) may indicate haemodynamic improvement and/or diuretic effect and can be used as a secondary endpoint.

Any change in concomitant medication, oxygen therapy and intubation/assisted ventilation could also be used as secondary endpoints.

In case of low output or cardiogenic shock the use of measures of tissue perfusion (serum creatinine, lactate, SGOT, SGPT and venous or arterial O_2 saturation could be considered as supportive evidence for improvement.

3.2.5 Quality of life/Global clinical status

Improvement in quality of life and/or patients self assessed global clinical status, based on 7-point ordinal response relative to baseline, could be measured as secondary endpoint.

3.2.6 BNP

Measurement of B-type natriuretic peptide (BNP) before and within hours after study medication can be used for monitoring of therapy. However these peptides, at present, are most useful for their negative predictive value at baseline (see 4.4). BNP cannot be used as clinical endpoints to measure efficacy.

4. SELECTION OF PATIENTS

Reference is made to section 2 (Background).

At present, there is no universally accepted definition for acute heart failure. However, it is accepted that symptoms in acute heart failure develop within hours or days. Different relative weight may be put on clinical, haemodynamic abnormalities and cardiac dysfunction by the clinicians involved in the management (General practitioners, Emergency room physicians, Cardiologists, Anaesthesiologists, ICU physicians) and their diagnostic judgement. Depending on the indications claimed, stratification of patients for acute and acute-on chronic basis would be necessary. Preferably, these two categories should be studied separately. If patients from both categories are included in one trial, an adequately sized sub-group analysis will be needed to explore consistency of effects.

Patients should be selected according to the proposed indication. An attempt should be made to differentiate between patients presenting with acute left ventricular failure (e.g due to myocardial infarction or acute coronary syndrome)and those with acute on chronic heart failure.

Other classifications based on anatomical (congenital or acquired abnormalities), functional (NYHA class), or etiological (myocarditis, acute myocardial infarction post-cardiac surgery) features have been used.

Patients will be selected on the basis of the following criteria:

4.1 <u>Signs and symptoms</u>

Shortness of breath is the predominant symptom but confusion or disorientation may also be present. The initial symptoms may be worse in patients whose cardiac function was normal prior to the injury leading to the heart failure (acute heart failure). Chest X-ray may provide confirmation of pulmonary oedema/pulmonary congestion. Symptoms may be less severe when an acute episode supersedes on chronic process, as compensatory mechanisms are

already operative and medical treatment has already been initiated (acute on chronic). Where possible, the aetiology of acute heart failure should be identified.

Physical examination may reveal tachycardia, hypo or hypertension, pulmonary rales, 3rd and 4th heart sounds, pulsus alternans and occasionally Cheyne-Stokes respiration. Combination of these symptoms and signs in the context of acute or acute-on-chronic heart failure almost invariably warrant hospitalisation. Chest X-ray is confirmatory for the diagnosis and classification of acute heart failure and the presence of pulmonary oedema/pulmonary congestion. ECG gives additional information regarding aetiology and diagnosis.

4.2 Haemodynamic abnormalities

Invasive haemodynamic assessment will confirm the diagnosis by findings of increased pulmonary capillary wedge pressure (PCWP), reduced cardiac output, reduced cardiac index and increased systemic and pulmonary vascular resistance. Baseline assessment of haemodynamic parameters is useful to monitor the progress of patients, and to assess the effects of therapeutic intervention, but invasive haemodynamic measurements are not routinely made in many centres and practice may differ from continent to continent. Thus, in therapeutic confirmatory trials patients can be included without these invasive measurements, but strict adherence should be paid to the criteria mentioned under 4.1, 4.3 & 4.4. In the context of new inotropic drugs the haemodynamic assessment is considered unavoidable at some stage in the clinical development.

4.3 Cardiac dysfunction

It is useful to differentiate patients with systolic dysfunction and those with preserved systolic function (baseline EF). Echocardiography may provide useful information regarding left ventricular dysfunction, ventricular dilatation, cardiac output, and state of the valves and papillary muscles. Alternatively, left ventricular dysfunction could be measured by ventriculography or scintigraphy. In order to have reliable data on the effects of study drugs in patients with systolic dysfunction and those with preserved systolic function (baseline EF), a stratified randomisation (or atleast a prespecified subgroup analysis) is suggested.

4.4 BNP

Assessment of B-type natriuretic peptide (BNP) at present is most useful for negative predictive value.

5. STUDY DESIGN

It is acknowledged that the conduct of clinical trials in this group of patients presents a challenging task.

5.1 Human Pharmacology

Human pharmacology studies for a product to be used in patients with acute cardiac failure are unlikely to be different to those described for patients with chronic cardiac failure. For this, the reference is made to the CPMP note for guidance on clinical investigation of medicinal products for the treatment of cardiac failure (EWP 235/95).

5.2 Initial therapeutic studies

Some information regarding doses would have been derived from pharmacodynamic studies. Further data should be generated from phase II invasive haemodynamic studies. Attempt should be made to determine the minimum effective dose, dose escalation and the maximum duration on the basis of response on PCWP and safety. The dose ranging studies should be performed in patients close to the aimed clinical indication and include haemodynamic data.

A dose escalation or a parallel dose response study may be acceptable but the most appropriate design would depend on the characteristics of the study substance. This should be based on haemodynamic pressure changes.

The proof of principle studies in subgroups should be specified and planned aforehead.

5.3 Main therapeutic studies

Phase III studies are expected to be double blind and randomised. The absence of double blinding may compromise the interpretation of symptoms-based studies. This may then require harder clinical endpoints (e.g. all cause mortality).

Placebo controlled studies are required only if the new product is intended as add-on therapy to current conventional treatment and belongs to a new therapeutic class or to a therapeutic class which has not previously been considered for the treatment of AHF. In this scenario the efficacy of the new drug is expected to be shown in placebo-controlled trials where the new drug/placebo is added to an optimised background therapy well defined in the study protocol. The absence of placebo-controlled studies in these situations will need to be justified.

If the new medicinal product belongs to an existing therapeutic class, a double blind, randomised, active comparator controlled study against another licensed product of the same therapeutic class is necessary. In this case, when a hypothesis of non-inferiority is the selected approach, the quality of the study design, in order to ensure an adequate assay sensitivity, becomes essential.

The choice of the comparator depends on the haemodynamic effects of the compound. For vasodilators, nitroglycerine or nitroprusside are the preferred comparators. For diuretics, furosemide is the most widely used and hence the expected control drug for assessment of a new diuretic. Dobutamine, alone or in combination is the most widely used inotropes in patients with acute heart failure. These are the preferred comparators and choice of other comparators should be justified.

The 6-month mortality data is required for safety evaluation even if no claim is made regarding survival benefit. In this context, evidence that there are no more deaths in active group compared to placebo/reference product group would be acceptable.

5.3.1 Duration of therapy

The duration of therapy will depend upon the class, type and route of administration of the drug under development, ranging from a few hours to a few days. When administered as i.v infusion, duration usually varies from 6 - 48 hours but may occasionally be required for longer than 48 hours. Any deviation from this should be justified in the trial design and study protocol. Longer-term infusion may require careful risk: benefit evaluation.

5.3.2 Dosage

In comparative trials appropriate licensed doses should be used and dose adjusted according to the response.

5.3.3 Concomitant medication:

Patients already on medications such as ACE -inhibitors, beta-blockers, digoxin, diuretics etc should continue to receive this medication unless contraindicated in view of an acute situation or unless decided otherwise by the attending clinician. The use of concomitant therapy should ideally be optimised and, in all cases, predefined in the study protocol. The information on the use of concomitant drugs should be carefully documented and its potential impact on the effect of the drugs under study assessed.

6. SAFETY CRITERIA

6.1 Morbidity/mortality

The safety issues that could arise from the use of inotropic agents in acute heart failure include life threatening arrhythmias, sudden death, ischaemia and hypotension. Even if the claim is made for symptomatic benefit only, mortality data over six months are required to exclude possibility of any deleterious effect. Increased mortality has been noted with inotropic agents.

The safety database for each group of patients characterised by the indication should be large enough to rule out a detrimental effect on mortality and morbidity (e.g, if a claim is made for patients with acute on chronic cardiac failure, the database in this group must be sufficient)

6.2 Haemodynamic effects and related symptoms

The occurrence of tachycardia, hypotension, flushing and headache should specifically be reported.

6.3 Cardiac events

Major ischaemic events and occurrence of arrhythmias should carefully be documented.

It is important to carefully monitor for any possibility of QTc prolongation. It is expected that QTc prolongation would also have been evaluated during early drug development.

Patients at special risk e.g. elderly, children, females, patients with diabetes/hepatic disease should be observed for any exaggerated pharmacological response.

6.4 Renal function

Assessment of renal function is important as invariably this determines the outcome. Development of renal insufficiency, and need for initiation of dialysis are important safety issues. These data collected prospectively should be provided in addition to 30 day and 6 month mortality data.