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Guideline on clinical investigation of medicinal products for the treatment of chronic heart failure

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This guideline replaces the Note for Guidance on clinical investigation of medicinal products for the treatment of cardiac failure (CPMP/EWP/235/95, Rev 1).

Keywords	***chronic heart failure, heart failure with preserved ejection fraction, heart failure with reduced ejection fraction, hospitalisation, clinical trial, mortality, functional capacity, exercise testing, patient reported outcomes***

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Guideline on clinical investigation of medicinal products for the treatment of chronic heart failure

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Executive summary

This guideline addresses the EU regulatory position on the clinical development of new medicinal products in the treatment of patients with chronic heart failure (CHF). The aim of this document is to update the *Note for guidance on clinical investigation of medicinal products for the treatment of cardiac failure (CPMP/EWP/235/95, Rev. 1)*. The principal changes from the previous document relate to:

i. differentiation of types of heart failure between reduced and preserved ejection fraction;

ii. inclusion of patients that are clinically stable early after hospitalisation for heart failure;

iii. description of ways to measure worsening of heart failure;

iv. reassessment of efficacy criteria and the need for morbidity and mortality trials.

1. Introduction (background)

It is recognised that chronic heart failure encompasses heterogeneous groups of patients with a wide spectrum of symptoms and different causes, resulting from an abnormality of cardiac structure or function. Within this spectrum, patients may either have heart failure with reduced ejection fraction (HFrEF) or with mid-range ejection fraction or preserved ejection fraction (HFpEF) (1). The distinction between patients with HFrEF from those with HFpEF is important because they represent groups with different underlying pathophysiologic, haemodynamic and neurohormonal abnormalities, distinctly different clinical characteristics, and dissimilar efficacy of existing therapies (2).

Patients with CHF may experience reoccurring episodes of decompensation requiring hospitalisation. Reoccurring hospitalisations for heart failure (HFH) are relatively common in patients with CHF and despite their significance they are rarely used as an endpoint in clinical trials compared to "time to first HF hospitalisation”(3, 4). Accounting for reoccurring events may further characterise and quantify the occurrence of morbid events throughout the follow-up period, but experience is limited and this approach gives rise to additional methodological issues.

One of the main therapeutic goals in the treatment of CHF is to reduce mortality. Some drug classes (ACE-inhibitors, beta-blockers, mineralocorticoid receptor antagonists, If channel blockers, vasopeptidase inhibitors) have shown to improve prognosis in patients with CHF while other classes (e.g. certain inotropes) have had a detrimental effect on mortality despite a short term positive effect on intermediate endpoints. In general, mortality/morbidity data should be provided prior to approval of new therapeutic agents for the treatment of CHF.

2. Scope

The scope of this guideline is restricted to the development of medicinal products for the treatment of patients with CHF including those in the post-acute phase of heart failure.

This guideline is intended to assist applicants during the development phase and for guidance only. Any deviation from the guideline should be explained and discussed in the application.

3. Legal basis and relevant guidelines

This guideline has to be read in conjunction with the introduction and general principles (4) and part I and II of the Annex I to Directive 2001/83 as amended and other pertinent elements outlined in current and future EU and ICH guidelines, especially those on:

- *Studies in Support of Special Populations: Geriatrics (ICH topic E7; CHMP/ICH/379/95) and related Q&A document (EMA/CHMP/ICH/604661/2009);*
- *Dose Response Information to Support Drug Registration (CPMP/ICH/378/95; ICHE4);*
- *Statistical Principles for Clinical Trials (CPMP/ICH/363/96; ICH topic E9);*
- *Choice of the control group in clinical trials (CPMP/ICH/364/96; ICH topic E10);*
- *EMA Guideline on clinical development of fixed combination medicinal products (CHMP/EWP/240/95 Rev. 1);*
- *Pharmacokinetic Studies in Man (3CC3A);*
- *Note for Guidance on the Investigation of Drug Interactions (*CPMP/EWP/560/95/Rev. 1 Corr. 2** *);*
- *Guideline on clinical investigation of medicinal products for the treatment of acute heart failure (CHMP/EWP/2986/03 Rev. 1);*
- *Guideline on the choice of the Non-inferiority margin (EMEA/CPMP/EWP/2158/99);*
- *Points to Consider on Switching between Superiority and Non-inferiority (CPMP/EWP/482/99);*
- *Points to consider on an Application with 1) Meta-analyses 2) One pivotal study (CPMP/EWP/2330/99);*
- *Reflection paper on assessment of cardiovascular safety profile of medicinal products (EMA/50549/2015);*
- *Ethnic factors in the acceptability of foreign clinical data (ICH E5(R1)) and Reflection paper on the extrapolation of results from clinical studies conducted outside the EU to the EU-population (EMEA/CHMP/EWP/692702/2008) and Q&A to ICH E5 (R1);*
- *Draft Guideline on multiplicity issues in clinical trials (EMA/CHMP/44762/2017);*

4. Assessment of efficacy

The main therapeutic goals in the treatment of CHF are to reduce cardiovascular mortality and to prevent deterioration of the clinical status and hospitalisations; these goals should represent the primary aim of new agents developed for the treatment of CHF. Improvement in functional capacity may also be a relevant treatment goal in selected patients.

The therapeutic effects on symptoms and quality of life are also of great importance to patients with CHF but they are more difficult to measure and have lower reproducibility and can be interpreted without ambiguity only in the absence of a detrimental effect on the main therapeutic goals. Haemodynamic changes (e.g. left ventricular ejection fraction [LVEF], left ventricular remodelling and biomarkers) are considered to provide only supportive data.

The aims of treatment and assessment of endpoints are not different between patients with HFrEF and those with HFpEF, but the effects on these endpoints may be different.

4.1. Choice of efficacy criteria

4.1.1. Mortality

One of the main therapeutic goals in the treatment of CHF is to reduce mortality. Thus, mortality is to be considered as the primary endpoint either alone or as a component of a composite endpoint in combination with endpoint(s) related to worsening of heart failure (for special circumstances and alternatives see 4.1.3 and 4.1.4). Assessment of mortality in confirmatory trials should include both all-cause mortality and cardiovascular mortality (see section 5.1).

4.1.2. Worsening of heart failure

An episode of worsening of heart failure (WHF) may qualify as an episode managed either in a hospital setting or on an outpatient basis by an emergency visit (see also 5.2).

Time to first Heart Failure Hospitalisation (HFH) can be included as part of a primary endpoint or as a secondary endpoint in clinical trials.

Endpoints accounting for recurrent HFH events may under certain conditions better characterise the prognosis of patients with CHF. Recurrent events are also important as they represent a large burden to patients. The inclusion of recurrent events as co-primary endpoint may be considered, but this setting needs further justification, adjudication of the events and a clear methodological strategy.

It should be recognized that patients with WHF are also increasingly being managed in non-hospitalized settings (e.g. visits in emergency departments, specialized clinics, observation units, hospital-at-home services) (7). The capture of emergency visits for WHF without hospitalisation may be warranted as an additional endpoint. Given their frequency and prognostic importance, evolution in heart failure care, and the global nature of modern trials, the inclusion of these visits in composite primary endpoints may even be considered, but its setting needs further justification and adjudication.

4.1.3. Functional status

Exercise testing allows objective evaluation of functional status in patients with CHF. In selected patient populations with high unmet medical need (e.g. patients with end stage CHF, CHF with cachexia or hypertrophic cardiomyopathies and other specific etiologies), the effect of the treatment on exercise capacity may be considered as a primary endpoint. The effect size should be clinically meaningful and consistent with an improvement in patient reported outcomes and the cardiovascular safety profile of the product should be adequately characterised (see also 7.5 and 8.1). Further confirmation with morbidity and mortality data after registration may be required. Consideration of exercise capacity as secondary outcome could also be meaningful to quantify an objective correlation with the patient reported outcomes (see 4.1.4).

4.1.4. Patient reported outcomes

Patient reported outcomes (PROs) may include improvement of symptoms (NYHA classification) and quality of life (QoL). Improvement in symptoms must be clinically relevant in magnitude, consistently achievable and sustained over an extended duration of treatment.

PROs are usually measured as secondary endpoints in CHF studies and should be considered as supportive. In selected patient populations with high unmet medical need (see above under 4.1.3) effects on PROs may be relevant in support of the effect on exercise capacity. In case these patients

are unable to undergo exercise testing due to HF-related or unrelated physical limitations, measures of symptom burden may even be acceptable as a primary endpoint, provided that their outcome is consistent with other endpoints and the CV safety profile of the drug is adequately characterized.

4.1.5. Haemodynamic parameters

Although worsening in some haemodynamic parameters (left ventricular function, cardiac index, pulmonary wedge pressure) are associated with poor prognosis, the correlation between improvement of haemodynamic parameters and prognosis and/or symptoms has not been adequately established. Measurements of changes in haemodynamic parameters may be useful to elucidate the mode of action and the required dose of a therapeutic agent in early phase studies but cannot be used as primary endpoint in a pivotal trial.

4.1.6. Biomarkers

In epidemiological studies several biomarkers (neuroendocrine, renal, and cardiac) have been shown to be independent predictors of the clinical outcome in patients with CHF, however none has been shown to be a reliable surrogate for clinical outcomes in the context of therapeutic interventions. To this end, biomarkers cannot be included as primary endpoints in phase III clinical trials in CHF. Biomarkers, in particular BNP, NT-proBNP, MR-proANP or pro-enkephalin, and procalcitonin may be used to better identify patients with CHF and some of these may help identify subsets of patients likely to benefit from specific interventions. Appropriate biomarkers can be considered for dose selection in the early drug development phases.

4.1.7. Events from implantable devices

Implantable cardioverter devices (ICDs) improve survival in patients with CHF and provide opportunity to record episodes of life-threatening arrhythmia/ventricular fibrillation (see also 8.4). If the ventricular fibrillation or ventricular tachycardia leads to a discharge/therapy from the device, the event may be used as an endpoint (equivalent to sudden death) and reduction of such events would serve as a measure of efficacy of the medicinal product. Such device interventions could include shocks or anti-tachycardia pacing to overcome sustained VT. It will be necessary to carefully distinguish improper or inappropriate shocks from successful appropriate therapies. The inclusion of such events as endpoints needs central adjudication.

4.1.8. Composite endpoints

Composite endpoints can be applied to CHF studies with the composite including mortality (overall or cardiovascular) and WHF. If a ranked endpoint is preferred, mortality and WHF should be the first two hierarchical endpoints in the ranking procedure. Please refer to the *Draft Guideline on multiplicity issues in clinical trials (EMA/CHMP/44762/2017).*

5. Methods to assess efficacy

Precise descriptions of the effects of treatment that the trial seeks to quantify should be documented. These should, in turn, inform choices related to trial design and statistical analysis. The manner in which the treatment effect will be measured and quantified should be clearly specified, in particular concerning events occurring post-randomisation such as non-CV death if this is not part of the endpoint definition (see section 5.1). The statistical analysis plan should be closely tailored to the specified treatment effects of interest.

Efficacy variables may be influenced by changes in concomitant background medications and adherence to randomised treatment. If possible, every effort should be made during the conduct of a study in patients with CHF to maintain stable background therapy throughout the study. The influences of background treatment modifications on efficacy endpoints should be critically evaluated. Regardless of adherence to randomised treatment, efforts should be made to follow all patients for assessment of outcome events.

5.1. Mortality

Even though cardiovascular death is an adequate clinical oucome to reflect the disease process targeted by treatments for heart failure, all-cause mortality may in many cases be the preferred choice. The use of all-cause mortality as an endpoint (or as a component of a composite endpoint) simplifies statistical analysis since all deaths are treated as events rather than non-cardiovascular deaths needing to be handled through a statistical model with associated assumptions and risks of bias. This is of specific importance in trials when the expected incidence of non-cardiovascular mortality is difficult to predict.

In situations when the incidence of non-cardiovascular death is expected to be negligible (eg based on previous knowledge of similar products and or patient populations) and hence the possibility of important bias in the estimated treatment effect can be assessed as being small, cardiovascular death can be used as a primary endpoint (or as a component of a composite endpoint) provided that the study population is representative of the target population with respect to baseline risk of non-cardiovascular death. In this case, all-cause mortality should be planned and presented as a secondary endpoint (or as a component of a composite endpoint).

It is mandatory to report and centrally adjudicate all mortality data in all studies in patients with CHF. Efforts should be made to define the specific cause of death occurring in the studies (e.g. sudden cardiac death, pump failure, acute coronary events).

5.2. Worsening of heart failure

Patients with CHF often visit the emergency room or are hospitalized for non-cardiac causes or for reasons unrelated to worsening of CHF. In order to qualify as an episode of WHF treated either with hospitalisation (HFH) or on an outpatient basis, objective evidence of cardiac de-compensation as cause of worsening should be provided. Criteria for cardiac decompensation must be rigorously defined in the protocol by signs and symptoms of deteriorating clinical conditions along with signs of cardiac overload and changes in biomarkers (see 4.1.6) as appropriate. The need for acute treatments for CHF (e.g., increase in diuretic dose, intravenous diuretics, or intravenous vasodilators/inotropes) should be included. These events will need to be well documented and adjudicated independently and centrally, whether it is a component of a primary composite endpoint or not. Also, other cardiovascular causes for WHF (not primarily due to CHF) must be noted and adjudicated as such events (e.g. new myocardial infarction or stroke) and may be responsible for other therapeutic interventions in patients with CHF. Therefore, the reasons for a change in the background therapy should always be carefully recorded and the criteria for these events must be pre-specified in the protocol.

As described in 4.1.2, quantifying recurrent HFH events may better characterise the effect of treatment in some circumstances, but experience with this type of endpoint is limited (10). Analysis and interpretation of recurrent events may be complicated by so-called terminal events (i.e. death, heart transplant, Left Ventricular Assisted Device (LVAD) implant) which limit the total number of HFH per subject. These 'terminal events' will usually need to be addressed explicitly in the statistical analysis. Due to methodological issues involved, it is recommended to seek scientific advice when recurrent

event end-points are considered as a part of a primary endpoint. Any request for a scientific advice should contain discussion on the ways in which recurrent hospitalisations may be characterised and aspects of trial planning in respect of sample size, duration of follow-up and effect size(s) (considering the effect of treatment on HFH rate and the rate of terminal events) that can be regarded as being of clinical importance, in addition to the approach to statistical analysis.

Patients should be followed for events of interest regardless of adherence to randomized treatment, with all events included in the primary analysis unless otherwise justified.

Further, the threshold for hospitalisation is highly variable across (and within) regions of the world which may affect the interpretability and applicability of study results to the European population. This should be taken into account when planning the studies, e.g. by implementing similar criteria for hospitalisation and stratification by regions.

5.3. Functional capacity

Measurements of maximal oxygen consumption during bicycle or treadmill exercise (MVO2) and a supervised 6MWT are both reliable methods for the assessment of functional capacity. These can be applied to most patients with CHF. However, other functional tests, such as stair climb test, Short Physical Performance Battery (SPPB) or hand-grip strength assessment, may be more appropriate in selected patient populations (elderly, frail patients, those with cachexia, etc.).

Exercise testing should be performed using appropriate protocols specifically designed for the functional assessment of patients with CHF (5). The reason(s) for termination of sub-maximal exercise tests should be specified a priori. Patients naïve to exercise protocols (bicycle, treadmill, and measurement of oxygen consumption) should first be made familiar with the technique before they are included in the trial. Repeated baseline and repeated follow-up testing may reduce variability of the results and increase statistical power.

5.4. Clinical Symptoms

Several symptoms scores or global or disease-specific assessments are available to assess the effect of a new pharmacological agent on clinical symptoms. The most commonly used classification system for the assessment of symptoms in patients with CHF is the New York Heart Association (NYHA) classification. Other scales or scores can be used for the assessment of symptoms provided that they are validated in the populations (and in the languages) in which they are being tested. Whatever scale is used, it must be capable of providing robust evidence of symptomatic improvement. However, NYHA class as an established standard should always be documented to allow comparisons across trials.

5.4.1. Quality of Life (QoL)

Several QoL questionnaires can be used for the assessment of the treatment effect in patients with CHF. Questionnaires to be used must be fully validated for the disease (e.g. Minnesota Living with Heart Failure Questionnaire or Kansas City Cardiomyopathy Questionnaire). In order to be considered, questionnaires must be translated and validated in all the languages spoken in the countries of patients included in the clinical studies.

5.5. Haemodynamic parameters

A variety of techniques are available for both non-invasive and invasive measurements of cardiovascular haemodynamics and left ventricular function and may include ventricular dimensions,

ejection fraction and indices of systolic and diastolic functions (e.g. left ventricular end diastolic pressure [LVEDP]).

New techniques used to study the haemodynamic effect of an agent in CHF must be validated beforehand and justified. Non-invasive techniques including echocardiography, Doppler studies, radio-isotope ventriculography and cardiac magnetic resonance imaging have been proven to be objective and quantifiable. Some of these techniques show inter-operator variability. Measurement of LVEF by an isotopic method and/or by cardiac magnetic resonance imaging and/or echocardiography is desirable to quantify the degree of systolic ventricular dysfunction and its response to treatment. They are also useful in defining patient subgroups (e.g. HFrEF versus HFpEF). Given the inter-operator variability, the investigators from each centre should specify the norms for their laboratory and the inter- as well as intra-operator variability. Variability can be reduced by core laboratory analyses.

6. Selection of patients

Patients with CHF can be defined as those with an abnormality of cardiac structure or function leading to failure of the heart to deliver blood at a rate commensurate with the metabolic requirements. Patients to be included in clinical trials will have to be diagnosed with CHF according to current guidelines (1). Attention should be given to the representativeness of the study population with regard to the real life population. Appropriate efforts should be made to include elderly patients, such as a relevant number of patients over 75 years of age.

Patients with CHF must be differentiated according to the degree of preservation of left ventricular function (left ventricular ejection fraction [LVEF]) between those with reduced ejection fraction ([HFrEF]; LVEF <40%), those with mid-range ejection fraction ([HFmrEF]; LVEF 40-49%) and those with normal/preserved LVEF ([HFpEF], typically considered as LVEF ≥50%). The cut-off of 50% for a diagnosis of HFpEF is arbitrary; patients with an LVEF between 40 and 49% are often classified as HFpEF in clinical trials (1). The cut-offs for the ejection fraction (EF) should be defined before inclusion in the study and discussed. Studies can be conducted in a large population encompassing all degrees of EF or they can be limited to one or two subgroups.

Patients hospitalised because of an acute episode of de-compensation who are stabilized on standard therapy and are not receiving parenteral treatments but remain hospitalised can be included in studies to assess the effect of chronic therapies that are started during hospitalisation, at discharge or during the 90 days after hospital discharge.

Patients entering phase IIb and III clinical trials with agents for the treatment of CHF (NYHA class II-IV) should be treated at study entry as per clinical practice guidelines. Given the worldwide variability in therapeutic practices a sizeable number of patients included in clinical trials should be representative for the European population with regards to their background treatment and standard of care (1).

The pathophysiology of CHF studied should be defined in terms of aetiology as much as possible. Clinical trials in distinct subsets of chronic HF patients other than those simply identifiable from the left ventricular function may be conducted, like genetically determined subpopulations and populations with specific cardiac metabolic phenotypes (e.g. amyloid, drug-induced, diabetic, hypertrophic cardiomyopathies). This will largely depend on the indication claimed.

In some trials it may be necessary to "enrich" the number of events by further restriction of LVEF or other patient characteristics. This should be discussed further within the context of the external validity for the claimed indication. This also applies to selection of patients on the basis of pre-treatment and tolerance of the drug.

7. Study design

For studies to be conducted in patients with CHF, a period of stability of CHF medications is required before inclusion, unless not feasible due to new diagnosed disease or a recent acute decompensation. However, in patients with recent decompensation (e.g. patients included in the study during a hospital stay) efforts should be put in place in order to uptitrate first line therapies according to current clinical practice guidelines (1).

7.1. Pharmacodynamics

Apart from the evaluation of tolerability, pharmacodynamic (PD) studies may include, depending on the mechanism of action, the effect of the agent on haemodynamic parameters (e.g. stroke volume, Pulmonary Capillary Wedge Pressure [PCWP]), heart rate, as well as the effect on impulse formation, conduction and repolarisation (i.e., QT/QTc intervals) and cardiac arrhythmia, neuro-hormonal parameters (e.g. sympathetic nervous system) and renal function.

Patients with degrees of CHF ranging from mild to severe may need to be studied, depending on the indication claimed. The PD activity of the substance needs to be defined with regard to cardiac contractility, arterial and venous tone, and diastolic/systolic function of the heart. If an effect on cardiac electrophysiology of the investigational agent is proposed for or if it is involved in the beneficial effects of the agent, a potential for pro-arrhythmic effect should be fully explored. Further studies - depending on the mechanism of action of the product - may include assessment of myocardial oxygen consumption, and coronary and regional blood flow.

7.2. Pharmacokinetics

It must be taken into account that in patients with CHF, drug absorption, distribution, metabolism and excretion as well as its delivery to various tissues may be altered. Therefore, depending on results of early PK studies, additional data may be requested for the population studied.

7.3. Interactions

Special attention should be devoted to potentially useful or unwanted PK and PD interactions with other drugs that might be used alongside the investigational drug for combined treatment of CHF and its most common co-morbidities.

7.4. Exploratory therapeutic studies

The objectives of these studies will be to determine the appropriate therapeutic dose-range including dose-exposure-response relationship of the new investigational agent and to identify patients who may benefit from the medicinal product. Dose ranging studies in CHF should thoroughly assess the lower end of the effective dose range. A parallel, fixed dose, double blind placebo controlled design may be useful in evaluating new drugs. The dose(s) selected for pivotal studies must be justified on the basis of the results of the dose-finding studies in the target population. The endpoints in dose-ranging studies should be tailored according to the medicinal product in question and such studies could assess clinical symptoms and evaluation of other parameters including neurohumoral response, functional capacity, echocardiographic parameters and renal function depending on the mechanism of action. If an appropriate dose schedule cannot be established in these initial studies, it may become necessary to investigate more than one dose in the main therapeutic studies.

Based on the information from dose-exposure-response relationships, dose schedules should be clearly defined for patients with varying degrees of congestive heart failure, renal dysfunction and/or hepatic dysfunction, as appropriate.

7.5. Confirmatory therapeutic studies

Controlled, double blind, randomised studies are required. One large well controlled trial of adequate statistical power may be sufficient to confirm the efficacy of a new drug - provided it is soundly based and well designed, executed, reported and the results are robust, clinically relevant, should be internally consistent and be externay valid. A control group on placebo is preferable if ethical considerations permit, in particular when it is proposed to indicate the investigational drug as an add-on to an existing therapy.

Confirmatory studies using an active control may also be acceptable depending on its place in therapy and the benefit established with the reference therapy. These should be designed to demonstrate the non–inferiority or superiority of the new agent to the active comparator.

Every effort should be made to record deaths and other relevant endpoints that occur after the withdrawal of double-blind treatment.

Groups should be sufficiently balanced in respect of age, sex, pathology, co-morbidities, state of disease, severity of disease and duration of symptoms. Stratified allocation is mandatory for gender and may sometimes be desirable for the other factor listed above. Concomitant background treatment should be kept as similar as possible during the study. Background therapy should be given according to current guidelines.

At least one controlled study of a minimum duration of 6 months is mandatory to demonstrate efficacy in relation to functional benefit when this is the primary endpoint. In this case sufficient data to characterise the cardiovascular safety profile will be needed before approval (see also sections 4.1.3 and 8.1).

7.6. Studies in special populations

The efficacy studies should include patients reflecting the real life population of patients with CHF. Generally these will mainly include patients with mild to severe CHF. Subgroup analyses for gender, race, age, etc. are desirable in order to demonstrate consistency across groups. Studies in specific subgroups may be conducted. Adequate representation of elderly and very-old patients should be ensured (also in PK/PD and safety studies). Guidance on paediatric medicine clinical development is outside the scope of this guideline.

Given the frequent drug-drug interactions and the need of dose re-adjustments in patients with heart failure and important co-morbidities (diabetes mellitus, COPD, renal failure, cachexia and/or sarcopenia, anaemia) additional data may be obtained in these patients. Specific studies may be needed if specific claims are proposed. Dose schedules should be clearly defined for elderly patients, for those with impaired renal function and those with various risk factors, as appropriate.

8. Safety aspects

As treatment of CHF is usually prolonged, long-term data on adverse effects should be provided.

All adverse effects occurring during the course of clinical trials should be fully characterised and documented. Any groups especially at-risk should be identified. Special efforts should be made to

assess potential adverse effects that are characteristics of the class of drug being investigated. Particular attention should be paid to the following specific side effects:

8.1. Cardiovascular safety

If the basis for an approval is functional and/or symptomatic data, without a cardiovascular outcome study, cardiovascular and all cause mortality data are expected to be available in the database in order to ensure that the cardiovascular safety profile is adequately characterized. Such data could arise either from several trials or alternatively within the pivotal study by the use of (cardiovascular/all-cause) mortality as a secondary endpoint with a well defined and an acceptable non-inferiority margin. For further evaluation and quantification of cardiovascular safety reference can be made to the *CHMP Reflection paper on assessment of cardiovascular safety profile of medicinal products (EMA/50549/2015).*

8.2. Hypotension/bradycardia

These may be either symptomatic or asymptomatic. Special attention should be paid to first-dose phenomenon, hypotension and bradycardia following an increase in dose.

8.3. End-organ consequences (kidney, heart, CNS)

Effect of alterations in regional blood flow in other organ systems, especially the kidney, heart and brain, may be studied. Special emphasis should be put on renal function and electrolyte homeostasis.

8.4. Effect on cardiac rhythm

It is essential to investigate the potential for pro-arrhythmic effects. These investigations should include electrocardiography and continuous ambulatory monitoring which may require to be supplemented by some electrophysiological studies. In patients with implanted devices events recorded by the device are acceptable.

8.5. Pro-ischaemic effects

Drugs used in the treatment of CHF may increase myocardial oxygen consumption. Together with potential hypotensive effects, this may lead to angina pectoris and myocardial infarction. Therefore, the safety data should include details which characterise the potential pro-ischaemic effects of the drug.

Definitions

6MWT= 6 Minute Walking Test

CHF= Chronic Heart Failure

COPD= Chronic Obstructive Pulmonary Disease

CNS= Central Nervous System

ESC= European Society of Cardiology

EU= European Union

FDC= Fixed Dose Combination

HFA= Heart Failure Association

HFH= Heart Failure Hospitalisation

HFrEF= Heart Failure with reduced Ejection Fraction

HFpEF= Heart Failure with preserved Ejection Fraction

LA= Left Atrium

LV= Left Ventricle

LVAD= Left Ventricular Assisted Device

LVEDP = Left ventricular end diastolic pressure

LVEF= Left Ventricular Ejection Fraction

MVO2= Maximum Oxygen Uptake acronym for Cardiopulmonary Exercise Test

NYHA= New York Heart Association

PCWP= Pulmonary Capillary Wedge Pressure

PROBE= Prospective Randomized Open Blinded Endpoint

PROs= Patient Related Outcomes

QoL= quality of life

VF= Ventricular Fibrillation

VT= Ventricular Tachycardia

WHF= Worsening heart failure

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