London, 16 December 1999
CPMP/EWP/235/95, Rev 1

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

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

DISCUSSION IN THE EFFICACY WORKING PARTY (EWP)	April 1998 - January 1999
TRANSMISSION TO THE CPMP	February 1999
RELEASE FOR CONSULTATION	February 1999
DEADLINE FOR COMMENTS	August 1999
RE-DISCUSSION AT THE EWP	September 1999 - November 1999
ADOPTION BY THE CPMP	December 1999
DATE FOR COMING INTO OPERATION	June 2000

Note: This revised Note for Guidance will replace the previous guideline, adopted in November 1995.

CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS FOR THE TREATMENT OF CARDIAC FAILURE

This note is intended to provide guidance for the clinical investigation of medicinal products in the treatment of cardiac failure. It should be read in conjunction with Part 3 of the Annex of Directive 75/318/EEC, as amended, and all other relevant guidelines as applicable and is intended to assist in its application.

1. INTRODUCTION

Cardiac failure (CF) is a clinical syndrome caused by an abnormality of the heart and manifest as symptoms and signs on exercise and ultimately at rest. Objective evidence of cardiac dysfunction is also necessary for the diagnosis of cardiac failure.

"High output" heart failure is not considered in this guideline because the primary abnormality is not the heart and its function is not reduced at rest; nor does this guideline apply to asymptomatic left ventricular dysfunction.

Cardiac failure is a heterogeneous syndrome with a variety of causes. The abnormality of the heart may be related to primary impairment of myocardial function or to (chronic) pressure and/or volume overload. Cardiac failure can be acute or chronic and usually becomes progressively worse, the rate of this progression being dependent both on the primary pathology and the activity of the so called "compensatory" processes, the most important of these being neural, endocrine, renal and morphological. Although some of these processes (e.g. atrial natriuretic peptide) are beneficial in the short-term, most chronic compensatory processes (e.g. renin-angiotensin system) are detrimental. There is peripheral or pulmonary vasoconstriction which creates a vicious circle of deteriorating circulatory function.

The prognosis in CF is poor. Acute CF may lead to death in minutes. For patients with chronic CF in NYHA functional class IV (= symptomatic at rest), the 1-year mortality rate is at least 50%. Less than half of the patients survive five years after first diagnosis of chronic CF. Sudden death is common, ranging from 30% to 60% of the total number of deaths according to the series.

2. CRITERIA OF EFFICACY

As the therapeutic goals in cardiac failure may be diverse, i.e. improvement in symptoms and cardiovascular morbidity and reduction in mortality, attention should be paid to each of these aspects, even when no specific claims are made. Both benefits and risks should be clearly defined during the course of the development of a drug in order to make a reasoned decision regarding its approval.

2.1 Acute Cardiac Failure

This condition presents as a medical emergency. It is usually linked to acute failure of the left ventricle and may occur in the course of chronic failure or as a primary event, e.g. following myocardial infarction, cardiac surgery or acute myocarditis.

The main aims of the treatment are:

- to relieve the patients' symptoms

- to improve their haemodynamic state as soon as possible

- to relieve their other manifestations of acute failure (including their need for positive inotropic support and vasodilatory therapy)

- in-hospital survival

Depending on the indications claimed, long-term mortality is also an endpoint of importance in patients treated for acute cardiac failure. Duration of hospitalisation may also be an endpoint of clinical interest.

In addition to a positive effect on clinical status and haemodynamics, in-hospital mortality is a valid endpoint reflecting well the risk/benefit ratio of a new drug for acute CF. Data on mortality during the 4 weeks following discharge from the hospital should be provided to support a favourable effect on mortality.

2.2 Chronic Cardiac Failure

The pathophysiological category of chronic cardiac failure studied should be clearly defined in terms of etiology (ischaemic versus non-ischaemic and systolic versus diastolic dysfunction). Whatever the clinical features, the underlying cause (e.g. coronary artery disease, arterial hypertension, cardiomyopathy) or the precipitating cause (e.g. infection, arrhythmias, pulmonary embolism), treatment of these underlying factors may improve the patient's condition. The most important objectives in the treatment of heart failure are improvement in symptoms, cardiovascular morbidity and mortality.

For the purpose of regulatory approval of the therapeutic use of drugs in chronic CF, endpoints of efficacy must be clinically relevant and may be divided into two categories:

- Primary endpoints
  clinical symptoms, cardiovascular morbidity and all-cause mortality.

- Secondary endpoints
  quality of life, exercise capacity, physical signs, haemodynamic changes (eg ejection fraction), renal function and neurohumoral variables

Depending on the population studied, design of the clinical trials and which endpoints of efficacy show beneficial effects, a marketing authorisation may be granted for an indication in chronic cardiac failure in terms of its etiology, severity and the nature of therapeutic benefit anticipated. If appropriate, restrictions may also be placed on its clinical use (for example, specifying subsets of clinically identifiable patients or as add-on or second-line therapy).

Whatever the endpoints selected, it must be shown that the drug does not have adverse effects on morbidity or survival.

2.2.1 Primary endpoints

2.2.1.1 Cinical symptoms

Long-term improvement of CHF-specific clinical symptoms is important in evaluating efficacy. However, even the studies aimed at showing improvement in symptoms must show at least positive trends in symptom-related morbidity and that there is no adverse effect on mortality.

2.2.1.2 Cardiovascular morbidity

Cardiac failure is associated with a high morbidity due to progression of the underlying disease, often requiring therapeutic intervention, changes to background therapy, a visit to the emergency department, and disease-related hospitalisation. A favourable influence on the natural course of the disease has become another objective of treatment. Therefore, data on overall morbidity should pay particular emphasis on disease-specific morbidity (directly related to cardiac failure) as well as cardiovascular morbidity.

2.2.1.3 Mortality

This information is of the greatest interest since studies have demonstrated that certain drugs (eg ACE inhibitors and β-blockers) given to patients with symptomatic cardiac failure (NYHA Classes II -IV) are associated with a significant reduction in symptoms and mortality. However, other drug classes have been shown to increase mortality in the long-term despite a short-term improvement in clinical symptoms and/or exercise capacity eg agents acting through an increase in the intracellular c-AMP concentration such as phophodiesterase inhibitors and the sympathomimetic agents. Therefore, many drugs are likely to require a trial which includes survival among its primary objectives before requesting an approval, regardless of the claims being sought. If the investigational drug belongs to a new pharmacological class or when agents in the same class have been associated with detrimental effects, a prospective, randomised, controlled survival study will be required.

Every effort should be made to establish the cause of death when this is not immediately obvious. Although the primary focus of a survival study in heart failure should be all cause mortality, careful attention should also be paid to underlying cause and a distinction should be made between instantaneous death which was unexpected, death due to acute deterioration of clinical symptoms (e.g. due to a myocardial infarction) and death due to chronic progression of heart failure. Deaths due to any other intercurrent events (e.g. stroke or pulmonary embolism) should also be distinguished.

2.2.1.4 Composite endpoints

Composite endpoints, specified a priori and when justified, may also be appropriate. Such an endpoint may include selected aspects of cardiovascular morbidity together with all cause mortality. Alternatively, it may be appropriate to combine objective and subjective symptoms scores with morbidity and mortality events. Whatever the choice of the components of composite endpoint, they must all be clinically relevant.

2.2.2 Secondary endpoints

2.2.2.1 Quality of life

Measurements should include evaluation of several components of the quality of life (see section 3.4).

2.2.2.2 Exercise Capacity

Although exercise testing is less subjective than improvement of clinical symptoms it is not a reliable surrogate variable for clinical symptoms.

The most commonly used method is measurement of maximal exercise duration using a bicycle or treadmill protocol. This test has been claimed to have some prognostic value but cannot always be performed by patients who are dyspnoeic at rest and is highly subject to bias from motivation and training effect. However, the 6-minute walk test has also been used in many studies with success. This submaximal test of functional capacity seems to correlate better than the maximal exercise test with the effect of the drug on daily clinical symptoms.

In view of this, no specific recommendation on methodology can be made in this guideline. However, it may be advisable to use a combination of both the tests in some of the patients or different methods in different studies.

2.2.2.3 Haemodynamic state

Although some haemodynamic parameters such as ejection fraction, cardiac index and systolic blood pressure (low pressure has worse prognosis) are good predictors of prognosis, the correlation of other haemodynamic variables with prognosis is either poor or has not been established, nor do they correlate with the quality of life. Thus haemodynamic data alone are insufficient to demonstrate benefit and their value as surrogate endpoints of benefit is highly

questionable. Haemodynamic studies may be useful for determining the mode of action of a drug, providing guidance on dose-response relationships and in demonstrating changes in a patient's state over the study period relative to baseline rather than absolute measures reproducible from patient to patient.

2.2.2.4 Neuroendocrine status

Current understanding of the pathophysiology of heart failure emphasises the role of other organs particularly the autonomic nervous system and various peptide hormones. Therefore information on changes in neuroendocrine parameters may be included, but should be considered as supportive only.

2.2.2.5 Physical signs and renal function

Changes in physical signs and renal function do not correlate well with changes in symptoms and these are discussed further in section 3.7. This information too should be considered as supportive only.

3. METHODS TO ASSESS EFFICACY

There are many diverse methods available for studying patients with heart failure when investigating the efficacy and the safety of new therapeutic interventions. A number of endpoints of efficacy are subject to placebo effects. Changes in the efficacy variables may also be brought about by changes in concomitant medications. Their influences on efficacy endpoints should be carefully considered and critically scrutinised. Methods which can be used to evaluate efficacy are the following:

3.1 Clinical Symptoms

Any study aimed at showing improvement in clinical symptoms should focus on CHF-specific symptoms. Effects on symptoms must not only be reliably shown to exist but must also be clinically important in size, and regularly achievable in practice over an extended duration of treatment (at least 6 months). It is recommended to use a set of scales in some of the patients or different scales in different studies.

Several systems have been proposed to assess the clinical symptoms of the patient. Various symptoms scores or global or disease-specific assessments may be used to evaluate an effect on clinical symptoms. The one most commonly used is the classification system of the New York Heart Association. Another classification developed more recently is the Specific Activity Scale. It is not currently possible to endorse any specific symptom score so that, whatever scale is used, sponsors will need to ensure that they are capable of providing the robust evidence of symptomatic improvement required.

However, even the studies aimed at showing improvement in symptoms must show in addition that there is no adverse effect on morbidity and mortality. Point estimates and 95% confidence intervals for the effect on morbidity and mortality should be provided to allow assessment of the risk/benefit of the new drug.

3.2 Morbidity

As heart failure has a progressive nature, subjective and objective evidence of worsening heart failure severe enough to require a therapeutic intervention may be used as endpoint for efficacy. This may be indicated by a change in the background therapy, a visit to the emergency department, or hospitalisation. A decrease in frequency of disease-related hospitalisations may also be an endpoint of interest if there is no increase in mortality due to the investigational drug.

A number of cardiovascular events (eg new myocardial infarction or stroke) may be responsible for therapeutic intervention in patients with chronic cardiac failure and the more common of these (e.g. progression of LV dysfunction) are important endpoints in their own right and indeed, constitute the most important of the morbidity measurements. Therefore, the reasons for a change in the background therapy, a visit to the emergency department, or hospitalisation (for at least 24 hours) should always be carefully recorded. For proper validation of the critical events, the criteria for these events must be pre-specified in the protocol and a blinded review by an independent committee is recommended. Any measure of morbidity should be accompanied by measures of mortality.

Combined endpoint of effects on morbidity and mortality may be acceptable particularly when related to time from randomisation. Individual components should also be examined separately to ensure that the effect on one component is not negated by the effect on another component of the combination. In multicentre studies, the possibility that the treatment benefit are influenced by large inter-centre differences in the need for changes in therapy or hospitalisations should be carefully and critically considered.

3.3   Survival

As surrogate endpoints for survival are not available, the effect of any therapeutic intervention on mortality can only be assessed definitively in the context of a randomised placebo-controlled trial in a large number of patients such that the patients are randomised to control or the investigational drug on top of their conventional treatment. Survival studies using positive control drug(s) may be acceptable but are difficult to interpret and are resource-intensive. All such trials must permit an analysis according to the 'Intent-to-treat' principle and hence, all patients must be followed up for the intended duration of the trial. Analysis should also consider data gathered during the run-in as well as during the dose-titration periods. Every effort should be made to record deaths that occur after the withdrawal of double-blind treatment.

3.3.1   Mortality data

Even if survival is not the endpoint of the study, it is mandatory to report all mortality data. These data should be specified with regard to underlying cause and a distinction should be made between instantaneous death which was unexpected (almost certainly due to arrhythmias), death due to acute deterioration of clinical symptoms (e.g. due to a myocardial infarction) and death due to chronic progression of heart failure. Every effort should be made to distinguish deaths due to any other intercurrent events (e.g. stroke or pulmonary embolism) from cardiac deaths.

3.3.2   Mortality endpoint

When a reduction in mortality is claimed, long-term controlled studies will be necessary to confirm the therapeutic benefit. Data should be gathered so as to enable evaluation of the clinical causes of reduction in mortality (such as arrhythmias, stroke, pulmonary emboli).

3.4   Quality of Life

A broadly based assessment of the quality of life scales is recommended in heart failure studies because almost all the components of the life quality may be influenced by an intervention for heart failure.

Various quality of life questionnaires have been used in the past and new ones devised. Unless these have been fully validated, evidence of efficacy derived from quality of life questionnaires must be viewed as supportive only.

It is particularly important to consider whether (a) the scale is linear over the range of measurements, (b) is sensitive to the changes anticipated, (c) it is valid and useful to adjust results using the baseline scores, (d) there is any correlation between the score and the objective responses, (e) the observer and the patient should be blinded and (f) training of both the observer and the patient is necessary.

Rating scales to assess quality of life should also be considered and should have been validated beforehand in the context of the proposed trial and its aims. The Minnesota Living With Heart Failure Questionnaire is one of the many systems used in cardiac failure. Translations of questionnaires used should also have been thoroughly validated beforehand.

3.5 Exercise Testing

Exercise testing should be carried out using appropriate (maximal or preferably, submaximal) protocols. These protocols should be designed to reflect the capabilities of patients with cardiac failure by starting at a low workload and with small (rather than large) increments in energy requirements.

Protocols should specify a priori the symptoms that will terminate the tests. Other symptoms during the exercise test are also important when evaluating the results of these tests. However, it is highly dependent on the motivation of both the patient and the physician and therefore, the patient should first be made familiar with the technique before the patient is included in the trial and variability between repeated tests should be kept to a minimum.

The methodology should be accurately and fully documented. The value of exercise capacity is limited by its poor correlation with the more important endpoints of clinical symptoms, morbidity and mortality. The decision to terminate exercise is necessarily subjective and based on a variety of reasons. This parameter is reasonably objective and quantifiable - although it is useful in grading the severity of chronic CF at baseline, it is of doubtful value in the evaluation of treatment of cardiac failure.

Maximal exercise testing may also provide complementary information. The value of laboratory-based treadmill or bicycle exercise tests may be enhanced by the measurement of respiratory variables of gaseous exchange in a small but adequate number of patients during Phase II studies.

3.6 Haemodynamic Effects

Ventricular dysfunction is the hallmark of low output cardiac failure. A variety of techniques are available for both non-invasive and invasive measurements of ventricular function.

Confounding factors e.g. increased pulmonary and/or systemic vascular resistance especially during the first invasive study should be carefully taken into account.

Changes in various invasive and non-invasive measures of left ventricular performance have not been shown to correlate closely with each other and many of them do not correlate with clinical symptoms or functional capacity. Although haemodynamic data are valuable in defining dose-response relationships, the value of these measures in evaluating the efficacy of the drug in patients with cardiac failure during long-term treatment is very limited. Therefore, haemodynamic data which may include ventricular dimensions, ejection fraction and indices of systolic and diastolic functions (e.g. LVedp) should be regarded as supportive only.

3.6.1 Acute cardiac failure

Invasive studies (e.g. cardiac output, cardiac index, contractility index, dp/dt, filling pressures) are desirable for trials dealing with acute CF. Whilst these studies may be useful

for establishing doses to be used in early pilot studies in chronic CF, their value in establishing the dose for pivotal studies now appears questionable.

3.6.2 Chronic cardiac failure

The use of these newer techniques used to study drug action and efficacy and safety in heart failure must be validated beforehand and justified.

Non-invasive techniques including echocardiography, Doppler studies and isotope ventriculography have been proven to be objective and quantifiable. They have particular appeal in evaluating systolic ventricular dysfunction but some of these techniques show inter-operator variability. Measurement of ejection fraction by an isotopic method and/or by 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. systolic versus diastolic dysfunctions). In view of the inter-centre variability of norms, the investigators from each centre should specify the norms for their laboratory and the criteria adopted for recruitment of patients and evaluation of efficacy.

3.7 Physical signs and renal function

Changes in signs do not correlate well with changes in symptoms. Changes in signs of fluid retention can be assessed by physical examination, body weight, measurement of fluid balance and the detection of pulmonary congestion by chest radiography. These changes are not helpful in evaluating changes in clinical symptoms particularly following acute diuresis because of the delay between diuresis and effect on these signs. The evaluation of fluid retention by physical and radiologic examination remains highly subjective and therefore, not easily quantified. Tests of renal function and measurement of electrolytes may provide better information on fluid retention and tissue perfusion.

3.8 Neuroendocrine Status

Because of the importance of the neuroendocrine systems in patients with cardiac failure and their modulation by therapeutic interventions, measurement of effects on neurohumoral compensatory mechanisms is highly desirable in the evaluation of a new therapeutic agent. This applies specially to effects on the renin-angiotensin system, atrial natriuretic factor, endothelin levels and sympathetic nervous system. The data, however, must be regarded as supportive only.

4. SELECTION OF PATIENTS

The criteria used for the diagnosis of cardiac failure in patients recruited into the clinical trials must be clearly defined. Criteria for patient selection and stratification should be stated clearly with reference to the normal values for each criterion at each centre.

A log should be provided on the patients screened and not randomised. The patients enrolled into clinical trials must be representative of the target population in terms of demography and co-morbidity.

4.1 Acute Cardiac Failure

Patients hospitalised with acute left ventricular failure should be defined according to underlying disease, severity and concomitant treatment.

4.2 Chronic Cardiac Failure

This guideline is not concerned with the investigation of drugs for use in patients with asymptomatic LV dysfunction. Patients should suffer from dyspnoea and/or fatigue either at rest or during exertion (either ambulatory or hospitalised) and should exhibit some criteria of systolic and/or diastolic left ventricular dysfunction. Patients with all grades of cardiac failure should be studied.

Treatment groups should be balanced in respect of patient demography, underlying cause, systolic or diastolic dysfunction, severity of disease and duration of symptoms. The question of etiology must be carefully examined and the proportion of patients with ischaemic and non-ischaemic cardiomyopathy must be described. Since the response to treatment may vary depending on the severity of chronic CF, it is essential that the patients chosen for study should exhibit a wide range of severity of chronic CF. Alternatively, the same information may be obtained by restricting clinical trials to specific severity of disease for example, one study to patients with mild heart failure and the other to patients with severe heart failure. Only with this approach is it possible to formulate the most appropriate indications and contraindications. Stability of the patients recruited into the trials deserves special attention:

4.2.1 Patients

The natural history of chronic CF is of relapses and remissions, the long-term course being downhill. The rate of progression varies from patient to patient. The need for a period of pre-randomisation stabilisation should be considered on a case-by-case basis on the basis of the severity of disease and the pharmacology of the investigational drug.

Depending on the nature of the claim sought and of the investigational drug, patients who have had an acute episode or a period in hospital within the preceding 6 weeks (3 months in the case of acute myocardial infarction) may need to be excluded because their cardiac status may be unstable. In patients with severe cardiac failure, a shorter period from screening to randomisation, for example 2 weeks, might be sufficient. It is advisable to exclude patients with a short history of disease (e.g. less than 3 months or those suspected of subacute myocarditis).

4.2.2 Background treatment

When the medicinal product under evaluation is added to previous treatment it is desirable to avoid any change and/or adjustment in medication during the 2 weeks preceding the study. It is recognised that this may not always be possible when studying patients with severe chronic heart failure.

5. STRATEGY – DESIGN

All endpoints in a clinical trial and all statistical analyses of these endpoints must be prespecified in the original protocol. Measures of effects and analytical approaches which are developed during the analysis are unlikely to be acceptable. The major endpoints in a clinical trial supporting an approval must be clinically relevant and reflect direct measures of the clinical benefit of a drug. The trials must not focus on secondary or supportive endpoints.

The treatment effects on major efficacy endpoints in heart failure do not correlate with each other reliably. This has important implications in the overall design of clinical trials. One endpoint cannot necessarily serve as a reliable surrogate for others. To demonstrate that a particular drug produces improvement in the major treatment endpoints in congestive heart failure, each endpoint must be studied as an independent variable. Therefore, when defining the primary endpoint(s) for evaluating the effects of the drug, it may be necessary for a trial to have more than one primary endpoint. The levels of statistical significance need not be

adjusted for multiplicity if all of them are required to reach statistical significance. Composite endpoints, specified a priori and when justified, may also be appropriate.

Secondary endpoints may also be defined but their evaluation may be difficult if the trial does not achieve the desired effect on primary endpoint(s). Secondary or supportive endpoints by themselves are not sufficiently reliable as a basis for decisions on approval of drugs.

5.1 Human Pharmacology Studies

Studies involving the first administration of medicinal products for CF to man do not essentially differ from those dealing with other cardioactive medicinal products.

5.1.1 Pharmacodynamics

Depending on the nature of perceived mechanism of the effect of the drug, these studies will include data on haemodynamic parameters, effects on the (intra-cardiac) impulse formation and conduction, neurohumoral parameters, renal and pulmonary effects, and tolerability. Varying severities of heart failure, ranging from the mild to the severe, need to be studied.

The pharmacodynamic activity of the substance needs to be defined as much as possible with regard to cardiac contractility, arterial and venous tone, and diastolic/systolic function of the heart. If an antiarrhythmic mechanism is proposed for or involved in the beneficial effects of the drug, a potential for proarrhythmic effect should be fully explored.

5.1.2 Pharmacokinetics

The pharmacokinetic information required is stated in detail in the appropriate guidelines on "Pharmacokinetic Studies in Man". In this context it is important to bear in mind that drug absorption, distribution, metabolism and excretion as well as its delivery to various tissues may be altered substantially during the treatment of congestive heart failure. Apart from the pharmacokinetic studies in healthy volunteers, studies should be performed in the elderly, in patients with varying degrees of congestive heart failure and in patients with varying degrees of renal dysfunction and/or hepatic dysfunction.

The pharmacological activity of the main metabolites should be quantified and studied in detail if they are likely to contribute substantially to the therapeutic or toxic effects.

5.1.3 Interactions

Considerable progress has been made recently on the rational investigation of drug interactions. Apart from investigating the pharmacokinetic and the pharmacodynamic interactions with widely used agents in the target population, interactions with other substrates of the same isozyme should be investigated. It is recognised that drug interactions may be predicted on the basis of isozymes involved in the metabolism of the new drug. Interactions are most likely with other substrates and/or inhibitors of that isozyme. It has become evident that interactions predicted from enzyme kinetic considerations have later been shown to occur *in vivo*. Studies to exclude any interactions between anti-failure drugs of different modes of action or chemical classes are also essential.

5.2 Exploratory Therapeutic Studies

The objectives will be to identify patients who may benefit from the medicinal product and to determine the appropriate therapeutic range including dose-concentration-response relationship. It is recommended that before starting a morbidity/mortality trial, the optimal/appropriate clinical dose be identified by adequately powered carefully designed dose-response study(ies) using clinically relevant endpoints.

Data gained during studies in acute CF may be useful in planning trials in chronic CF, but it has to be emphasised that these studies cannot be regarded as therapeutic pilot studies in chronic CF.

Although small controlled pilot studies are by no means impossible, trials which are not blinded and without a control group are acceptable early in this phase of investigation. When sufficient data are gained controlled studies are necessary. Dose ranging studies in congestive heart failure of patients should thoroughly assess the lower end of the effective dose range. A parallel, fixed dose, double blind placebo controlled design has proved useful in evaluating new drugs. At least 3 dosages should be studied (low, medium, high) with a total therapy phase of at least 12 weeks. The endpoints in dose-ranging studies are difficult to define but such studies should assess clinical symptoms as well as well validated non-invasive haemodynamic responses. The dose schedule selected for pivotal studies must be justified on the basis of pharmacokinetic and pharmacodynamic data in the target population. 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-concentration and concentration-response relationships, dose schedules should be clearly defined for patients with varying degrees of congestive heart failure, renal dysfunction and/or hepatic dysfunction.

5.3 Confirmatory Therapeutic Studies

5.3.1 Acute cardiac failure

These studies should be randomised and unless ethically undesirable, double blind. The trial should continue not only until the haemodynamic and clinical status of the patient is normal, or what is regarded as normal for that patient (such an endpoint should be described in the report) but until the patient is discharged from the hospital. It is appreciated that although the patient may not be in receipt of the investigational drug for the whole of this period, an adequate in-hospital follow up is essential for evaluation of post-therapeutic risk/benefit of the investigational drug.

5.3.2 Chronic cardiac failure

A run-in period of appropriate duration (usually 2 weeks if possible) is recommended during which the investigator must carry out baseline evaluation of the patient, including full clinical and laboratory assessment and verify the stability of patient's clinical symptoms. Baseline functional capacity of the patient using a sub-maximal exercise protocol should also be documented.

Controlled double blind randomised studies are required. A control group on placebo is preferable if ethical considerations permit. It is always useful to include a group on active comparator. When it is proposed to indicate the investigational drug as an add-on to an existing therapy, a placebo group is mandatory.

Provided the study is properly randomised, groups should be sufficiently balanced in respect of age, sex, pathology, state of disease, severity of disease and duration of symptoms. Stratified allocation may sometimes be desirable. Concomitant background treatment should be kept as similar as possible during the study.

At least one controlled study of a minimum duration of 6 months is mandatory to demonstrate efficacy in relation to symptomatic benefit or cardiovascular morbidity.

At least one long-term controlled study of a minimum duration of 12 months will usually be required to evaluate the effect on mortality even if a claim of reduction in mortality is not being pursued. Although in principle, 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 and reported - in practice these ideals are difficult to achieve in the field of heart failure. Hence, for drugs tested for the treatment of chronic cardiac failure, it is prudent to plan at least two such trials. These should be designed to demonstrate either (i) the superiority of the new agent over a placebo or an active comparator, or (ii) the unquestionable equivalence of the new agent to an active comparator, the efficacy of which has previously been clearly established in a well designed placebo-controlled trial.

If discordant effects of a new drug on different endpoints are observed, further confirmatory trial(s) may become necessary.

6. SAFETY ASPECTS

As treatment in chronic CF is usually prolonged, long-term data on adverse effects and interactions should be provided. If the investigational drug belongs to a new pharmacological class or when agents in the same class have been associated with detrimental effects, a prospective, randomised, controlled survival study will be required in order to establish safety over a minimum period of 12 months in patients with chronic heart failure.

All adverse effects occurring during the course of clinical trials should be fully documented. Any groups specially at-risk should be identified. Any information available concerning clinical features and therapeutic measures in accidental overdosage or deliberate self-poisoning should be provided. 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:

6.1 Hypotension

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

6.2 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.

6.3 Effect on Cardiac Rhythm

It is essential to investigate the potential for proarrhythmic effects. These investigations should include electrocardiography and continuous ambulatory monitoring which may require to be supplemented by some electrophysiologic studies.

6.4 Pro-ischaemic Effects

Drugs in heart failure 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.

6.5 Morbidity and Mortality

This has already been discussed under 3.2 and 3.3