MEDICINAL PRODUCTS IN THE TREATMENT OF CARDIAC FAILURE

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ANNEX
MEDICINAL PRODUCTS IN 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 4 of the Annex to Directive 75/318/EEC, as amended, and all other relevant guidelines as applicable and is intended to assist in the application of the Directive.

1. INTRODUCTION

Cardiac failure (C.F.) is a clinical syndrome caused by an abnormality of the heart and manifest as symptoms and signs on exercise and ultimately at rest. 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, most (e.g. renin-angiotensin system) are detrimental and lead to peripheral or pulmonary vasoconstriction and create a vicious cycle of deteriorating circulatory function.

The prognosis in C.F. is poor. Acute C.F. 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 C.F. Sudden death is common, ranging from 30% to 60% of the total number of deaths according to the series.

“High output” heart failure is not considered in this guideline because the primary abnormality is not the heart and its the function is not reduced at rest. Neither does this guideline apply to asymptomatic left ventricular dysfunction.

2. CLINICAL TRIALS

All parameters of scores or endpoints to assess efficacy in clinical trials should be defined prior to the start of the trial and included in the protocol. Parameters which are developed during the analysis are unlikely to be acceptable. Major efficacy endpoints in heart failure do not correlate with each other. This has important implications in the overall design of clinical trials. One parameter cannot necessarily serve as a reliable surrogate for others. To demonstrate that a particular medicinal product produces improvement in the major treatment endpoints in congestive heart failure, each endpoint must be studied as an independent variable. Composite endpoints, specified a priori and when justified, may also be appropriate.

As the therapeutic goals in established cardiac failure may be diverse, i.e. improvement in symptoms and 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 medicinal product in order to make a reasoned decision regarding its approval.

3. CRITERIA OF EFFICACY

3.1 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. in myocardial infarction or following cardiac surgery.

The main aim of treatment is to improve the patients' haemodynamic state within minutes to hours and equally importantly, relieve their symptoms and other manifestations of acute cardiac failure. Depending on the indications claimed, mortality is also an endpoint of importance in patients treated for acute cardiac failure.

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 medicinal product for acute C.F. Data gained during studies in acute C.F. are very useful in planning trials in chronic C.F., but it has to be emphasised that these studies cannot be regarded as therapeutic pilot studies in chronic C.F.

3.2 Chronic cardiac failure

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 may improve the patient's condition in several ways. The most important objectives in the treatment of heart failure are improvement in symptoms and signs, morbidity, and survival.

Endpoints of efficacy may be divided into those that are primary (survival, morbidity, clinical status, and functional capacity) and those that are supportive (quality of life, ejection fraction and neuroendocrine status).

Depending on the positive endpoints of efficacy, a marketing authorisation may be granted for an indication in chronic cardiac failure in terms of its severity, the nature of therapeutic benefit anticipated and if appropriate, any restrictions (for example, specifying subsets of clinically identifiable patients or as add-on or second-line therapy).

3.2.1 Primary endpoints of efficacy

3.2.1.1 Clinical status

Improvement of clinical status (symptoms and signs) such as dyspnoea or fatigue with limitation of effort and evidence of fluid retention (venous pressure and/or oedema) are important in evaluating efficacy. Symptomatic relief is more important than improvement in clinical signs.
3.2.1.2 Exercise Capacity

Although exercise testing is less subjective than improvement of clinical status, it is not a surrogate variable of the clinical status. The methodology should be accurately and fully documented.

The most commonly used method is measurement of total exercise duration using a bicycle or treadmill protocol. This parameter is objective, quantifiable and a useful tool for the evaluation of medicinal product efficacy in patients with cardiac failure. Alternatively, the 6-minute walk test appears to be reproducible and more closely correlated to daily activities.

3.2.1.3 Morbidity

Cardiac failure has a high morbidity due to progression of the underlying disease, often requiring therapeutic intervention, a visit in the emergency department, or hospitalisation and changes in background therapy. A favourable influence on the natural course of the disease has become another objective of the treatment.

3.2.1.4 Survival

This information is of the greatest interest since studies have demonstrated that certain medicinal products given to patients with symptomatic cardiac failure (NYHA Classes II - IV) are associated with a significant reduction in mortality. However, other medicinal product classes have been shown to increase mortality (despite an improvement in clinical status and/or exercise capacity) e.g. agents acting through an increase in the intracellular c-AMP concentration such as phosphodiesterase inhibitors and the sympathomimetic agents. Survival studies are therefore required when specific claims are made and for safety reasons.

3.2.2 Supportive endpoints of efficacy

3.2.2.1 Quality of life

Prominent components of quality of life measures which require addressing are physical function, social and emotional function, intellectual function, symptoms and their consequences, occupational activities, job satisfaction, leisure activities, sexual adjustment, perceived health status, life satisfaction and interpersonal relationships.

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

3.2.2.2 Haemodynamic state

Although some haemodynamic parameters such as ejection fraction, cardiac index and wedge pressure are good predictors of prognosis, the correlation of other haemodynamic variables with prognosis is either poor or has not been established. Neither 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 medicinal product, defining 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.
3.2.2.3 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 as supportive data only.

4. 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:

4.1 Clinical status

Several systems have been proposed to assess the clinical status of the patient. The one most commonly used is the classification system of the New York Heart Association. However, its use is limited by subjectivity, relative insensitivity and poor reproducibility. Another classification developed more recently is the Specific Activity Scale.

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 particularly helpful in evaluating changes following acute diuresis. The evaluation of fluid retention by physical and radiologic examination remains highly subjective and is not easily quantified. Tests of renal function and measurement of electrolytes also provide valuable information on fluid retention and tissue perfusion.

4.2 Exercise testing

Exercise testing should be carried out using appropriate (maximal and/or 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 two tests should be less than 15% and kept to a minimum.

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.
4.3 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 hospitalisations may also be an endpoint of interest if there is no increase in mortality due to the investigational medicinal product. In multicentre studies, any effects due to large inter-centre differences in the need for changes in therapy or hospitalisations should be carefully and critically considered, if this is to serve as a valid efficacy endpoint.

4.4 Survival

As surrogate end points for survival are not available, the effect of any therapeutic intervention on mortality can be assessed in the context of a randomised placebo-controlled trial in a large number of patients. Survival studies using positive control medicinal product(s) may be acceptable.

4.4.1 Mortality Data

Even if survival is not the end point 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 status (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 from cardiac deaths.

4.4.2 Mortality Endpoint

When a reduction in mortality is claimed as an indication, 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).

4.5 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.

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 effects of therapy on daily activity and self-care, sleep, recreational and pleasure activities, in performing social roles, intellectual and cognitive functions, life satisfaction and expectations from the
therapy require particular assessment. 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 well validated beforehand. Nevertheless, at present these data must be viewed as supportive only.

4.6 Haemodynamic effects

Ventricular dysfunction is the hallmark of 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 status or functional capacity. Although haemodynamic data are valuable in defining dose response relationships, the value of these measures in evaluating the efficacy of the medicinal product in patients with cardiac failure during long-term treatment is very limited, if at all.

Therefore, haemodynamic data which may include ventricular dimensions, ejection fraction and indice of systolic and diastolic functions (e.g. LVedp) should be regarded as supportive only.

4.6.1 Acute C.F.

Invasive studies (e.g. cardiac output, cardiac index, contractility index, dp/dt, filling pressures) are desirable for trials dealing with acute C.F. Whilst these studies may be useful for some pilot studies in chronic C.F., to define a dose response relation, their value in establishing the dose for pivotal studies now appears questionable.

4.6.2 Chronic C.F.

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

Non-invasive techniques including echocardiography, Doppler studies and systolic time intervals 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.

4.7 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 and sympathetic nervous system. The data, however, must be regarded as supportive only.

5. 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.

5.1 Acute cardiac failure

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

5.2 Chronic cardiac failure

Patients should suffer from dyspnoea and/or fatigue and should exhibit some criteria of systolic and/or diastolic left ventricular dysfunction. Patients with all grades of cardiac failure should be studied. Separate studies should be designed for ambulatory patients and for hospitalised patients.

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 aetiology must be carefully examined and the proportion of patients with ischaemic and non-ischaemic cardiomyopathy must be specified. Since the response to treatment may vary depending on the severity of the C.F., it is essential that the patients chosen for study should exhibit a wide range of severity of C.F. 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. It is not unusual for a medicinal product effective in mild heart failure to be detrimental in severe heart failure. Stability of the patients recruited into the trials deserves special attention.

5.2.1 Patients

The natural history of chronic C.F. is of relapses and remissions, the long-term course being downhill. The rate of progression varies from patient to patient.

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) should be excluded because their cardiac status may be unstable. In patients with severe cardiac failure, a shorter period, 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).

5.2.2 Background treatment

When the medicinal product under evaluation is added to previous treatment it is mandatory to avoid any change and/or adjustment in medication during the 2 weeks preceding the study.
6. STRATEGY - DESIGN

6.1 Initial Tolerance Studies

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

6.1.1 Pharmacodynamics

These studies will include data on haemodynamic parameters, effects on the (intra-cardiac) impulse formation and conduction, neurohumoral parameters, renal and pulmonary effects, and tolerance. 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, myocardial oxygen consumption, and diastolic/systolic function and the absence of a proarrhythmic effect of the investigational medicinal product.

6.1.2 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 medicinal product 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.

6.2 Initial 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.

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 medicinal products. At least 3 dosages should be studied (low, medium, high) with a total therapy phase of at least 12 weeks. Such studies should assess clinical status as well as haemodynamic responses (invasively and/or non-invasively if well validated). The dose schedule selected for pivotal studies must be justified on the basis of pharmacokinetic and pharmacodynamic data in the target population.

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.
6.3 Main therapeutic studies

6.3.1 Acute C.F.
Randomisation is mandatory but double-blinding may not be possible. 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 medicinal product for the whole of this period, an adequate in-hospital follow up is essential for evaluation of post-therapeutic risk/benefit of the investigational medicinal product.

6.3.2 Chronic C.F.
A run-in period of not less than two weeks is recommended during which the investigator must carry out full clinical and laboratory assessment and verify the stability of patient's clinical status and performance in exercise testing.

Controlled double-blind randomised studies are required. A control group on active comparator is preferable. It is always useful to include a placebo group and when it is proposed to indicate the investigational medicinal product as an add-on to an existing treatment, a placebo group is mandatory. The decision to include a placebo group in other situations should only be made after careful scientific and ethical considerations.

Groups should be as similar as possible in respect of age, sex, pathology, state of disease, severity of disease and duration of symptoms. Stratified allocation may be desirable.

Controlled studies of at least three months' duration are mandatory to demonstrate efficacy in relation to symptomatic benefit or morbidity. Long-term controlled studies (at least one year in duration) will certainly be required in order to confirm a specific claim of reduction in mortality. Although in principle, one large well controlled trial of adequate statistical power may be sufficient to confirm the efficacy of a new medicinal product - 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 medicinal products tested for the treatment of chronic cardiac failure, it is prudent to plan at least two such trials (see guideline on Biostatistical Methodology in Clinical Trials, section 2.2). Sample sizes should be chosen so that a predefined clinically relevant difference between the treatment groups can be recognised as being statistically significant. The applicant must indicate clearly the degree(s) of severity for which the medicinal product is appropriate and also the criteria by which suitable patients could be identified for medicinal product administration clinically.

7. SAFETY ASPECTS

As treatment in C.F. is usually prolonged, long-term data on adverse effects and interactions should be provided. If the investigational medicinal product 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 characteristic of the class of medicinal product being investigated. Particular attention should be paid to the following specific adverse effects:

7.1 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.

7.2 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.

7.3 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.

7.4 Pro-ischaemic effects
Medicinal products in heart failure may increase myocardial oxygen consumption. Together with potential hypotensive effects, this may lead to angina pectoris and myocardial infarction.

7.5 Morbidity and mortality
This has already been discussed under 4.3 and 4.4.

7.6 Interactions
Considerable progress has been made recently on the rational investigation of medicinal product 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 medicinal product interactions may be predicted on the basis of isozymes involved in the metabolism of the new medicinal product. 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 medicinal products of different modes of action or chemical classes are also essential.
ANNEX

Although the note for guidance Cardiac Glycosides (Council Recommendation 87/176/EEC, Annex 111) contained valuable information with regard to bioavailability and problems arising from the low therapeutic/toxic dose ratio, it did not specify how cardiac glycosides should be evaluated clinically with regard to efficacy and safety. Ambiguity remained about the number of patients needed to be studied, the way studies should be carried out and the parameters which needed to be assessed to demonstrate efficacy especially in heart failure. Recent years have shown some major developments in this field, necessitating more detailed guidance.

This note for guidance on Medicinal Products in the Treatment of Cardiac Failure addresses most of these items and is indispensable for the clinical evaluation of cardiac glycosides. The same applies for the other indications for cardiac glycosides, the treatment of supraventricular arrhythmias. The note for guidance on Medicinal Products for the Treatment of Arrhythmias provides detailed information about the evaluation of the antiarrhythmic effects, the selection of patients and safety, all of which are also essential in the clinical investigation of cardiac glycosides. Therefore the combination of these two notes for guidance largely replaces the earlier note on cardiac glycosides.