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(CHMP)**

**GUIDELINE ON
THE CLINICAL INVESTIGATION OF ANTI-ANGINAL MEDICINAL PRODUCTS IN
STABLE ANGINA PECTORIS**

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1. INTRODUCTION

This document is intended to provide guidance on the clinical investigation of medicinal products in the treatment of stable angina, with the aim to relieve symptoms and to improve physical activity, irrespective of the nature, mode of action, or route of administration of these products.

This Guideline should be read in conjunction with Directive 2001/83/EC, as amended, and all other pertinent elements outlined in current and future EU and ICH guidelines and regulations, especially those on:

- The Extent of Population Exposure to Assess Clinical Safety for Drugs CPMP/ICH/375/95 (ICH E1A).
- Dose-Response Information to Support Drug Registration CPMP/ICH/378/95 (ICH E4),
- Studies in Support of Special Populations: Geriatrics CPMP/ICH/379/99 (ICH E7),
- Statistical Principles for Clinical Trials CPMP/ICH/363/96 (ICH E9),
- Choice of Control Group in Clinical Trials CPMP/ICH/364/96 (ICH E10),
- Note for Guidance on the Investigation of Drug Interactions CPMP/EWP/560/95,
- Guideline on the Choice of the Non-Inferiority Margin CPMP/EWP/2158/99,

This Guideline is intended to assist applicants during the development of antianginal medicinal products. It is only guidance; any deviation from guidelines should be explained and discussed in the Clinical Overview.

2. BACKGROUND

Treatment of ischaemic heart disease includes also a number of therapeutic approaches aimed at preventing death and myocardial infarction, such as antithrombotic agents, lipid lowering drugs, and renin-angiotensin system inhibitors. These approaches are beyond the scope of this guidance.

Angina is regarded as stable if has been occurring over several weeks without detectable changes. Stable angina typically is of short duration (<20 minutes) occurs during effort and is promptly relieved by rest or by sublingual nitrates. In stable angina the angina threshold may vary considerably from day to day and even during the same day.

Treatment of stable angina has not been subjected to the same scrutiny by large randomized trials as has, for example, that of myocardial infarction and unstable angina. Thus, although much has been achieved in comparing the symptomatic benefit of different modalities of treatment, there is relative paucity of information about their prognostic effects.

Antianginal drugs have classically been aimed to reduce myocardial oxygen demand and/or increase blood flow to ischaemic area. However, other therapeutic approaches with novel mechanisms of action are currently under investigation, which may reinforce the emphasis that should be placed on the need of reassuring pharmacodynamic and safety databases.

The clinical profile drugs for stable angina needs to be studied in an acute stress testing setting, i.e. with provocation of anginal attacks due to cardiac ischaemia, which is assumed to represent the conditions of normal practice. Valid data are only likely to be obtained if sufficient account is taken of such factors as the pronounced placebo effect in angina pectoris, the substantial variation in the nature and severity of symptoms, and the subjective character of 'chest pain'.

3. CRITERIA OF EFFICACY

As the assessment of the effect of antianginal drugs based on clinical measurements alone is as yet considered too unreliable because of the possible influence of uncontrolled variables, it has become accepted that measurements of exercise capacity using standardised exercise testing should be, in spite of an intrinsic amount of variability, the major criteria of efficacy. In addition to its more objective character, it is assumed that improved exercise capacity may account for the patient benefit in terms of reduction of symptoms. Moreover, exercise testing provides evidence that the relief of angina and increased exercise capacity are mediated by an anti-ischaemic effect. In addition, clinical evidence of symptomatic improvement in terms of anginal pain and HRQoL (Health-Related Quality of Life) should also be provided in the major therapeutic trials.

3.1 Exercise based variables

3.1.1 Exercise capacity

Exercise testing provides a wide array of variables, all of which may contribute to the assessment of the antianginal effect. The assessment of total exercise capacity at trough which is defined as the residual effect at the end of the dose interval, is the primary efficacy criterion for antianginal drugs. Total exercise capacity (total exercise time or total workload performed) is probably the most meaningful measurement that can be obtained from exercise testing, and thus it should be considered as the primary endpoint in therapeutic clinical trials. Total exercise capacity can be defined as the - total exercise time or workload of exercise which can be performed by the patient in the setting of a standardised exercise test. The reasons for interrupting exercise should be recorded and could for instance include symptoms (e.g. Borg score ≥ 3) and/or signs of myocardial ischaemia. With adequate study conditions (low intraindividual variability of the initial results, adequate patient selection), the variability of consecutive measurements should be relatively low, thus ensuring acceptable reproducibility.

However, other exercise variables should be used for an adequate characterisation of the effect on antianginal effect in addition to total exercise capacity. A consistent result in these exercise variables should be demonstrated before accepting an effect on exercise capacity. The translation of exercise variables into METs (metabolic equivalent of the task) provides a standard measure of performance regardless of the type of exercise test or protocol used.

3.1.2 Time to the onset of angina

Time to the onset of angina has its limitation derived from the subjective nature of pain. Furthermore a significant amount of treated patients might have no limiting angina after treatment or might be limited in their exercise capacity by reasons other than angina.

3.1.3 Time to ST segment depression

Time to 1 mm ST segment depression in the precordial leads is a more objective variable and it is indicative of an anti-ischaemic effect which is an important fact in antianginal drug assessment. Nevertheless, although its prognostic value is recognised, at present, its extrapolation in terms of clinical benefit for the patient is unknown.

The above three variables can be considered to be relevant to therapeutic effect, and all of them should be measured in therapeutic trials. They must show consistency or at least no major contradiction between them in order to conclude efficacy of a new drug.

3.1.4 Other exercise variables

Additional exercise variables can also be measured. These include the rate-pressure product, the magnitude of ST deviation, the number of leads showing ST changes, the duration of ST deviation into recovery, the exercise induced ventricular arrhythmias, and the presence of exertional hypotension or chronotropic incompetence. These parameters could be considered in pharmacodynamics studies as supportive data.

3.2 Anginal pain / consumption of short acting nitrates

Frequency, intensity and duration of anginal pain should be documented. Whereas this variable is not considered to be a primary endpoint, it is relevant as a secondary endpoint in both short-term and long-term studies. The traditional method to rate the severity of angina is the Canadian Classification Society (CCS) Angina Grading System. This system is relatively general and may be insensitive to modest changes in symptoms or physical function and may not permit accurate comparisons among patients. However, although not formally validated, it has been accepted for use in clinical trials. Other questionnaires have been created to measure health status and physical function specifically in relation to the symptoms and limitations associated with stable angina. The concomitant use of short acting nitrates has been classically accepted as a supportive clinical measurement. This parameter is highly variable and today is considered of limited clinical value and should only be considered a secondary endpoint

3.3 Measurement of Health-Related Quality of Life (HRQoL)

The evaluation of treatment effect on patient's quality of life provides relevant supportive information on the overall treatment benefit. Therefore, an HRQoL assessment is recommended, provided the questionnaire is validated in the context of the proposed target group.

3.4 Morbidity and mortality

Since the target of antianginal therapy is essentially symptoms control, at present, there is no requirement to prove beneficial effect on these variables in terms of efficacy in order to obtain a marketing authorisation, unless specifically claimed (see section 6.3). However, effects on cardiovascular and total morbidity and mortality should be evaluated as a relevant safety parameter. This should be done in particular if there is a reasoned suspicion that a new drug might have detrimental effects on these parameters (See also section on safety).

4. METHODS TO ASSESS EFFICACY

4.1 Exercise testing

Bicycle or treadmill exercise tests should be employed to induce angina. The exercise protocols should be validated and follow the recommendations of international organisations of cardiology. The characterisation of ST segment abnormalities suggesting ischaemia should be based on internationally accepted criteria. At least two standardised exercise tests should be performed at the start of the study. The difference between the tests should not exceed 20 %. If patients are included with a larger difference a rationale for this should be given.

Total exercise capacity is measured by total exercise time, maximum MET level achieved, maximum workload achieved, maximum heart rate and the double product. The translation of total exercise capacity into METs provides a standard measure of performance regardless of the type of exercise test or protocol used and does not pose major problems when interpreting the clinical relevance of the observed effect. Therefore, it is expected that, as the main outcome measure, total exercise capacity is expressed in METS change from baseline.

Repeated measurements over time, e.g. every 2 to 4 weeks, should be performed.

The physiological testing of the patients must be performed under medical supervision in facilities equipped to treat any cardiac complication.

Exercise tests are expected to be performed and difference / benefit shown at trough levels (of the drug). Differences at peak level may also be included.

4.2 Anginal pain

The patient's experience of anginal pain should be recorded in a patient diary as well as the concomitant use of short-acting nitrates. The daily frequency, severity and duration, of anginal pain should whenever possible be registered by patients using available log books. The CCS Angina Grading System or other questionnaires may be used for assessing changes in symptoms or physical function. The selection of a particular tool need to be properly justified.

4.3 Health-Related Quality of Life (HRQoL)

Validated questionnaires should be shown to be clinically responsive and capable of differentiating clinically important improvement or deterioration from random or non-specific changes.

4.4 Morbidity and mortality

Cardiovascular morbidity and mortality can be measured in specially designed studies, if specifically claimed, but should always be evaluated and assessed using the pooled data of the (controlled) trials.

5. SELECTION OF PATIENTS

The patients included in the studies must suffer from stable angina pectoris on the basis of coronary heart disease, preferably documented by a history of proven myocardial infarction, previous coronary

revascularisation and/or coronary angiography. With regard to dose-finding studies the documentation of unequivocal coronary heart disease is mandatory. Angina is regarded as stable if it has been occurring over at least four weeks without detectable changes. Stable angina typically is of short duration (<20 minutes) occurs during effort and is promptly relieved by rest or by sublingual nitrates.

The studied population should capture those clinical situations reflecting the different clinical scenarios seen in clinical practice. Therefore, patients with stable angina after a revascularisation procedure should be included in clinical trials. In order to rule out that angina symptoms may be directly related to the procedure, these patients should only be included at least 6 months after the revascularisation procedure. Similarly, patients with stable angina more than 30 days after MI should be adequately represented. The necessity and relevance of these predefined subgroups and their analysis should be discussed in the development programme. Efficacy/safety of the new drug should be consistent across all these subgroups.

Women and elderly patients should be sufficiently represented in the study population. Efficacy and safety data in these patient populations should be consistent with the overall benefit/risk evaluation.

Since for confirmatory pivotal studies the primary efficacy end-point is total exercise capacity, patients to be included in the study must be capable of exercise testing according to standardised protocols. Only patients with an interpretable baseline ECG at rest should be studied.

The stability and reproducibility of the patient's symptoms and exercise performance are essential to the studies. The symptoms of angina pectoris and the nitrate consumption must have been stable at least during the 2 weeks preceding the study. Any concomitant medication should remain unchanged during the study.

At least in one study efforts should be made to enrol a study population without concomitant antianginal drug therapy where the test drug should be given as monotherapy.

Some of the trials should also include patients where the test drug is given as add on therapy and compared to an acceptable active control and /or placebo. In this case background antianginal therapy should be optimised and prospectively defined in the study protocol. Rescue medication with short acting nitrate therapy should always be allowed throughout the whole trial period.

6. STRATEGY - DESIGN

6.1 Initial studies

6.1.1 Pharmacodynamics

These studies should define the pharmacodynamic properties of the active ingredient and of any active metabolites. The studies should include, when appropriate, data on:

- Haemodynamic effects at rest and during exercise. In case of an antianginal drug with a novel mechanism of action, proper pharmacodynamic data showing the antischaemic action (e.g. myocardial perfusion imaging or MRI) should also be provided.
- Additional exercise variables can also be measured as indicated under 2.1.4
- Myocardial perfusion/left ventricular performance
- Coronary blood flow/
- Diameter of normal and stenosed coronary arteries
- Effects on heart rate, rhythm, conduction times and, if necessary, refractory period
- Effects on renal function and electrolytes
- Effects on the pulmonary function
- Effects on the metabolism, particularly of glucose and lipids
- Neurohormonal effects
- Platelet aggregation and other rheological effects

- Vital and laboratory parameters

6.1.2 Pharmacokinetics

Data should be in accordance with pertinent EMEA-CHMP requirements.

6.1.3 Interactions

Pharmacokinetic and pharmacodynamic interactions should be investigated primarily with other frequently coadministered drugs in the target population, e.g. other antianginal products, antihypertensive agents, drugs to treat heart failure, anticoagulant products, lipid lowering agents, antiarrhythmic drugs and antithrombotic agents. Interactions with other substrates of the metabolising isozymes should also be investigated.

6.2 Initial therapeutic studies

Withdrawal of concomitant antianginal medication prior to randomisation would allow a methodologically proper evaluation of the new antianginal drug as monotherapy.

A run-in period with placebo lasting at least 2 weeks should be considered in order to ensure the stability of the disease. Short acting nitrates are allowable for angina attacks. Efficacy throughout the whole dosing interval should be proven.

Dose-response studies should be randomised, placebo-controlled and double-blinded using at least three dosages to establish the clinically useful dose range as well as the optimal dose. These studies should preferably be designed as parallel group studies and should last at least six weeks.

The results of the dose-response studies of a new antianginal drug should provide robust evidence of its efficacy as compared to placebo, including precise quantitative estimates of its beneficial effects.

6.3 Main therapeutic studies

The objectives of the main therapeutic studies should be to confirm the efficacy and safety of the product.

These studies should be performed in a randomised, double blind, controlled parallel group design. Active control studies with an active comparator adequately dosed, of at least 12 weeks duration, should demonstrate comparable efficacy and safety to an appropriate standard therapy. These studies may last even longer in order to allow a comparison with respect to adverse drug reactions as well. Overall, the clinical development should provide sufficient information to give insight on the role that the new drug is expected to play in the treatment of stable angina. Studies where the new drug is administered as both monotherapy and add-on therapy should be carried out. In any case, the background therapy should be optimised and properly defined in the study protocol. When designing the clinical development program the established beneficial effect on mortality of betablockers in particular patients (i.e. those with previous history of myocardial infarction) will need to be considered.

7. SAFETY ASPECTS

Results of pharmacoepidemiological studies suggest that the influence of different antianginal drugs classes on (cardiovascular) morbidity and mortality may not be alike even though the antianginal effect is comparable. Effects on cardiovascular and total morbidity and mortality should be evaluated on the basis of phase II/III trials.

Long-term data on adverse events must be presented as the drug may be administered for long periods of time. A sufficient number of patients should be treated for a minimum of 6 months or for one year, preferably in controlled trials. All adverse events occurring during the clinical trials as well as morbidity and mortality data must be fully described, assessed and discussed in the context of current knowledge about antianginal drug therapy. Special attention should also be paid to serious adverse events and reasons for treatment withdrawals.

The safety aspects should usually address the following points:

Specific effects should be studied, in particular:

- pro-anginal and pro-arrhythmic effects as well as other cardiovascular effects
- withdrawal phenomena and any effects related to rebound phenomena
- general effects influencing the function of other organ systems, e.g. through alterations of regional blood flow

Both the time of occurrence and the frequency, severity, relevance and outcome of any adverse events must be documented and discussed.

Special attention should be paid to high-risk groups (e.g. elderly, heart failure, renal and hepatic failure, etc.) and to possible interactions with other medicinal products.

For antianginal drugs products with an entirely new mechanism of action (e.g.: angiogenesis) longer observation periods will be required (minimum 1-year) and specific safety assessments may be needed (e.g. effects on angiogenesis in other areas should be particularly studied).