### COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

#### DRAFT

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

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**Note:**

Any comments on this Note for Guidance should be sent to the EMEA EWP-CVS secretariat:
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GUIDELINE ON THE CLINICAL INVESTIGATION OF ANTI-ANGINAL MEDICINAL PRODUCTS IN STABLE ANGINA PECTORIS (CPMP/EWP/234/95/rev. 1)

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1. INTRODUCTION

These notes are intended to provide guidance on clinical investigations to determine the value 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. 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.

Stable angina is a common and disabling disorder. There is, however, no consensus as to the optimal strategy of investigation and treatment. Furthermore, its therapy 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.

These Notes for Guidance should be read in conjunction with part 3 of the Annex of Directive 75/318/EEC, as amended, and CHMP/EWP and ICH guidelines for conducting clinical trials.

The clinical profile of such a drug 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'.

2. 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 objective character, it is assumed that improved exercise capacity may be a surrogate for the patient benefit in terms of better quality of life. 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 QOL should also be provided in the major therapeutic trials.

2.1 Exercise based variables

2.1.1 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, by itself, as a primary endpoint in therapeutic clinical trials. Total exercise capacity can be defined as
the maximal duration 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 related to symptoms (e.g. Borg score ≥ 3) and signs of myocardial ischaemia. With adequate study conditions (low intraindividual variability of the initial results, adequate patient selection), the variability of consecutive measurements is 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 total exercise capacity into METs provides a standard measure of performance regardless of the type of exercise test or protocol used.

2.1.2 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.

2.1.3 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.

2.1.4 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.

2.2 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 CCS Classification. However 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. For this reason 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. However, this parameter is highly variable and today is considered of limited clinical value and should only be considered a secondary end point

2.3 Measurement of Quality of Life
The evaluation of treatment effect on patient’s quality of life provides relevant supportive information on the overall treatment benefit. Therefore, a quality of life assessment is recommended, provided the questionnaire is validated in the context of the proposed target group.
2.4 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. 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).

3. METHODS TO ASSESS EFFICACY

3.1 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.

Maximum exercise capacity is measured by maximum exercise duration, 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. Expressing efficacy of an antianginal drug in METS gain allows an standardised view of the results of different studies using different exercise tests, and does not pose major problems when interpreting the clinical relevant of the observed effect. Therefore, it is expected that, as the main outcome measure, maximum 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.

3.2 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 of anginal pain should whenever possible be registered by patients using available log books. The Canadian Cardiovascular Society Angina Grading System is widely recognised method to categorise angina severity on the basis of the physical efforts that produce angina. Although this system has not been formally validated, it has been accepted for use in clinical trials.

3.3 Quality of Life (QOL)
Validated questionnaires should be shown to be clinically responsive and capable of differentiating clinically important improvement or deterioration from random or non-specific changes.

3.4 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.
4. 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 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.

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 exercise capacity with symptom limited exercise test, the patients to be included in the study must be capable of exercise testing according to standardised protocols. Only patients in whom stable angina is the limited factor and 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 shall have been unchanged during this period of time.

At least in some studies 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.

5. STRATEGY - DESIGN

5.1 Initial studies

5.1.1 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 antischæmic 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

5.1.2 Pharmacokinetics
Data should be in accordance with EC requirements. Special attention should be paid to pharmacokinetic and pharmacodynamic interactions

5.1.3 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.

5.2 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 interruption of 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.

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

These studies should provide sufficient information allowing to elucidate the role that the new drug is expected to play in the treatment of stable angina. Therefore, studies where the new drug is administered as both monotherapy and add-on therapy should be carried out. These studies should be performed in a randomised, double-blind, controlled parallel group design. Active controlled 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.

Add-on placebo and active controlled trials are, in principle required. In any case, the background therapy should be optimised and properly defined in the study protocol.
6. 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).