GUIDELINE TITLE

Medicinal Products in the Treatment of Chronic Peripheral Arterial Occlusive Disease

Legislative basis
Directive 75/318/EEC as amended

Date of first adoption
February 1987

Date of entry into force
June 1996

Previous titles/other references
Clinical Investigation of Drugs for the Treatment of Chronic Peripheral Arterial Diseases, III/5936/94, CPMP/233/95

Additional Notes
This note for guidance is intended to provide guidance for the evaluation of medicinal products in the treatment of chronic peripheral arterial occlusive disease. It should be read in conjunction with Part 4 of the Annex of Directive 75/318/EEC as amended, and other guidelines for conducting clinical trials. This version replaces the previous 1987 guideline.

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MEDICINAL PRODUCTS IN THE TREATMENT OF CHRONIC PERIPHERAL ARTERIAL OCCLUSIVE DISEASE

These notes are intended to provide guidance for the evaluation of medicinal products in the treatment of chronic peripheral arterial occlusive disease. They should be read in conjunction with Part 4 of the Annex of Directive 75/318/EEC, as amended, and guidelines for conducting clinical trials, especially those on:

- Pharmacokinetic Studies in Man
- Clinical Investigation of Medicinal Products for Long-Term Use
- Dose Response Information to Support Product Authorisation
- Biostatistical Methodology in Clinical Trials
- The Extent of Population Exposure to Assess Clinical Safety for Medicines Intended for Long-Term Treatment of Non-Life-Threatening Conditions

1. INTRODUCTION

Peripheral Arterial Occlusive Disease (PAOD) is the term used to describe conditions caused by ischaemia in the legs due to atherosclerotic disease affecting the larger arteries of the legs.

This guideline concerns chronic ischaemia in the lower limbs. Acute ischaemia and peripheral vascular disorders of inflammatory or immunologic origin such as Buerger’s disease and necrotic vasculitis are not considered because these diseases differ from arteriosclerosis obliterans in their clinical picture, in their evolution and in their prognosis.

The chronic PAOD must be regarded as a marker of widespread atherosclerosis, and patients with intermittent claudication (IC) must be considered a high risk population for the development of clinical manifestations of cardiovascular disease.

Initial treatment decisions for IC without rest pain are based on concurrent illness, health behaviours, and life expectancy. Recommendations are generally conservative and are focused on symptomatic relief through risk factor modification (e.g. smoking cessation), exercise and, in some cases, active substance therapy. Although results with many other therapeutic modalities for IC have been published, their clinical usefulness remains uncertain among clinicians.

In patients with rest pain, ulcers or gangrene, it is recognised that invasive vascular interventions are the treatment of choice if such procedures are possible.

2. GENERAL CONSIDERATIONS

The diagnosis of PAOD is based on clinical symptoms (intermittent claudication, rest pain and trophic lesions) together with a physical examination suggestive of peripheral blood flow
obstruction (e.g. lack of peripheral pulses, ankle systolic blood pressure, ..). Investigations should be performed (e.g. angiography, Doppler) to confirm the diagnosis, type of occlusive lesion (stenosis, complete block) and its location.

Fontaine’s classification rates the PAOD in four stages. Such a classification is based on clinical parameters: asymptomatic patients (stage I), intermittent claudication (stages IIa and IIb), rest pain (stage III), and trophic lesions (stage IV). If another classification system is used, it should be properly justified.

The therapeutic clinical trials aimed at supporting the efficacy of different treatments in PAOD Fontaine’s stage II are conditioned by various factors:

a) The natural course of PAOD shows a high variability, and after 5 to 10 years 70% to 80% of patients remain clinically stable or even improve, in 20% to 30% the course of the disease is progressive requiring, if possible, surgical intervention and less than 10% of patients require amputation.

b) A major feature of IC is the marked placebo effect of any medication. This is often misinterpreted as an improvement due to the development of collaterals.

c) Regular physical exercise improves symptoms of claudication. Thus, the realisation of repeated exercise testing in clinical trials can lead to an improvement in exercise capacity not related with medicinal product treatment.

d) Because of the variable outcome it has been difficult to evaluate the effects of active substances in treating intermittent claudication. The cessation of smoking and a regular exercise programme are of greater importance in the treatment of this stage of PAOD.

Factors which could influence the results of therapeutic clinical trials aimed at supporting the efficacy of different treatments in PAOD, Fontaine’s stages III and IV:

a) The patients studied have a range of severity of the disease, and it is uncertain whether data from patients with less severe ischaemia can be extrapolated to those with a poorer prognosis and vice versa.

b) The high response rate in hospitalised patients of both rest pain and ulcer healing during placebo treatment. Therefore, the number of patients is often inadequate for showing confident differences between active treatment and placebo.

3. ASSESSMENT CRITERIA OF EFFICACY

The ultimate goal of treatment is to prevent or postpone major amputation and to prolong life. Thus, the goal to achieve is survival with a viable limb.

3.1 End-Points in Fontaine’s Stage II

3.1.1 Walking distance

The main efficacy criteria in stage II are the pain-free and the maximum walking distance. The assessment of both distances is recommended (the pain-free walking distance or both as primary endpoint).

Appropriate standardised exercise tests should be carried out at intervals of between 2 days and 2 weeks until sufficiently reproducible results are obtained before randomisation. The
maximum change between two tests performed at fixed time intervals should be less than 25% during the run-in phase. Absolute walking distances between 100 and 300 m in the run-in phase are recommended. Walking distances of more than 300 m may alter the results of the study via the development of a walking-through phenomenon. Walking distances of less than 100 m may influence the results due to the associated greater tendency towards progression. In patients with an absolute walking distance shorter than 100 m the upper limit should be reduced, and should be studied in a separate group from those with walking distances over 100 m. Exercise tolerance tests should be conducted on the treadmill and performed under standardised conditions: speed, slope, timing, environmental conditions, particular temperature, and preferably by the same investigator. The conditions should be kept constant during the trial.

3.1.2 Other clinical parameters

Other clinical parameters that should be taken into account are revascularisation procedures as well as frequency and height of amputations.

The measurement of arterial pressure at the ankle (Doppler sound) is a further control parameter. Here, the systolic pressures measured over the dorsalis pedis and posterior tibial arteries should be given in absolute units.

In long-term therapeutic studies with an appropriate sample size of patients, the assessment of quality of life should also be performed by using general or disease specific questionnaires. However, at present no fully validated scales are available for this purpose.

3.2 End-Points in Fontaine's Stages III/IV

3.2.1 Major amputation or death

The frequency of major amputation of either leg, (total) mortality and death resulting from deterioration of PAOD at 6 to 12 months following randomisation should be evaluated as major target valuables. The criteria for major amputations are to be specified à priori in the study protocol to avoid relevant centre-related effects, particularly conservative or radical attitude.

3.2.2 Trophic lesions

In stage IV, the main symptomatic efficacy end-point is complete healing of all necroses and ulcerations. Trophic lesions should be quantified, ulcer sizes should be evaluated by planimetry and necrosis documented photographically. As quantification of partial healing is difficult to assess objectively and the clinical relevance is unclear, only total healing of lesions should be reported as main efficacy criterion.

Increase or decrease in size or depth of existing ulcers, development of new ischaemic ulcers or gangrene can be investigated as secondary efficacy end-points.

3.2.3 Rest Pain

The main symptomatic efficacy end-point in stage III and a secondary symptomatic efficacy end-point in stage IV is pain relief at rest.
It is important in all trials that include patients with rest pain to ensure that the principal cause is truly ischaemia. The intensity of the pain should be assessed by means of standardised methods (e.g. visual analogue scale).

The consumption of analgesics should be assessed as secondary end-point, although objective measurements may be difficult.

### 3.2.4 Other clinical parameters

Other clinical parameters that should be taken into account are frequency of minor amputations as well as other revascularisation procedures.

The measurement of arterial pressure at the ankle (Doppler sound) is a further control parameter. Here, the systolic pressures measured over the dorsalis pedis and posterior tibial arteries must be given in absolute units.

In long-term therapeutic studies with an appropriate sample size of patients, the assessment of quality of life should also be performed by using general or disease specific questionnaires. However, at present no fully validated scales are available for this purpose.

### 4. SELECTION OF PATIENTS

The criteria used for the diagnosis of PAOD in patients recruited in the clinical trials must be clearly defined. The diagnosis, type of occlusive lesion (stenosis, complete block) and its location have to be confirmed by objective means. Diabetics and non-diabetics should be investigated in separate groups due to different clinical picture and prognosis. Treatment groups should be balanced in respect of patient demography, severity of disease, previous revascularisation procedures and duration of symptoms. Influences of risk factors such as body weight, smoking habits, intake of alcohol, relevant dietary habits, lipid abnormalities and concomitant hypertension should be carefully taken into consideration in the analysis and should be kept stable during the trial.

The entry criteria will depend on Fontaine's classification.

### 4.1 Selection of Patients in Fontaine's Stage II

The main inclusion criteria for stage II patients will be a history of typical leg pain of intermittent claudication with regard to site, relation to exercise and relief from rest combined with loss of peripheral pulses lasting for at least 6 months to ensure clinical stability. These findings should be complemented by some objective evidence of peripheral vascular disease (e.g. reduced ankle systolic blood pressure). Patients with high variability (greater than 20-25%) in the treadmill tests during the run-in phase should be excluded.

Under normal conditions, a patient should not be included in a study of a new active substance, if walking training (which should be the first treatment in stage II patients), has not previously been adequately tried. If walking training is applied during the study, this should be done according to a standardised procedure and the entry in the study as well as the study analysis should be stratified accordingly. Studies with stage II patients should not include patients suffering from illnesses limiting their exercise capacity (angina pectoris, heart failure, respiratory disease, ..).
4.2 Selection of Patients in Fontaine's Stages III/IV

The main inclusion criteria for stages III and IV patients are pain at rest of at least 2 weeks duration and trophic lesions for at least the previous 14 days with no signs of healing (no change in ulcer size or depth). These findings should be complemented by some objective evidence of peripheral vascular disease (e.g. reduced ankle systolic blood pressure). Only those patients should be allowed to enter the study in whom surgical intervention is not planned and revascularisation procedures are not possible.

Patients with instable disease should not be included.

4.3 Concomitant Therapy

Vasoactive substances other than the investigational product (e.g. pentoxifylline, buflomedil, prostacyclin analogues), haemodilution or rheological therapy are not allowed during the run-in and treatment phase. All other medicinal products can be given, as long as they have no established effect on the investigated parameters. However, their administration must be fully documented.

In stage IV basic local treatment (e.g. local wound treatment, removal of necrotic tissue, antibiotics) must be recorded and standardised as much as possible.

5. STRATEGY AND DESIGN OF CLINICAL TRIALS

5.1 Early Studies in Man

5.1.1 Pharmacokinetic Studies

The pharmacokinetic information required is stated in detail in the guidelines on Pharmacokinetic Studies in Man.

Parallel or cross-over designs could be used. Pharmacokinetic parameters after single dose and repeated doses should be presented.

Apart from the pharmacokinetic studies in healthy volunteers, studies should be performed in the elderly, in patients with chronic PAOD and in risk groups.

Preliminary pharmacodynamic and tolerability data can also be evaluated in these studies.

5.1.2 Pharmacodynamic Studies

The knowledge of the relationship between dose, serum medicinal product-concentration, and clinical response with immediate pharmacological effect is important for optimising the use of investigational active substances in further clinical research. These studies must assess pharmacologically relevant parameters and tolerability. A parallel group (placebo)-controlled design is recommended, although in some cases a cross-over design could be considered.

5.1.2.1 Effects on the arterial peripheral blood flow and microcirculation

Effects on arterial peripheral circulation can be assessed in different ways, e.g. changes in peripheral blood flow (ultrasound Doppler techniques, venous occlusion plethysmography); and changes in microcirculation (e.g. laser Doppler flow measurement, transcutaneous pO2). The methods of assessment should be fully described ensuring, when possible, their
accuracy and reliability. Due to their high variability, the value of these methods is limited and nowadays there is no evidence that the effects measured correlate to any useful extent with clinical efficacy.

Such methods may be of some value in screening new products, but if an applicant wishes to claim that such a technique actually demonstrates the clinical usefulness of a product its relevance must be proven.

5.1.2.2 Haemorheological Parameters

Medicinal products that are investigated in chronic PAOD may have effects on platelet aggregation, fibrinolytic activity, flexibility and aggregation of erythrocytes and plasma viscosity. These properties of the tested active substance should be investigated in order to elucidate underlying mechanisms and contributory factors. However, changes in these parameters are not necessarily correlated to changes in clinical parameters.

5.1.3 Medicinal product Interactions

Considering the chronic nature of this condition and the fact that these patients frequently receive concomitant treatments, it is mandatory to perform medicinal product interaction studies including both pharmacokinetic and pharmacodynamic measurements. Such studies should be performed taking into account the most frequent medicinal products used for the management of these patients (e.g. digoxin, diuretics, nitrates).

Parallel or cross-over designs could be used. The duration of treatment will depend on the effects to be investigated.

5.2 Dose Response Studies

The dose and therapeutic schedule should be selected according to the results of previous studies, and usually three dose levels (low, medium, and high) are assessed. These studies should be carried out in selected patients with strict inclusion and exclusion criteria and performed separately in Fontaine's stage II and stages III/IV.

A randomised, double-blind, parallel group, placebo-controlled design is recommended. Primary assessment criteria should be walking distance (stage II), relief of rest pain (stage III) and healing of ulcerations (stage IV). Treatment period should be 2 to 3 months. The overall duration, however, should be properly justified considering the mechanism of action and the main end-point of the study. A placebo run-in period of 4 to 6 weeks is recommended. In severe critical limb ischaemia a shorter run-in phase is possible (in Fontaine's stage IV a run-in period of 1-2 weeks is recommended).

For more general aspects of dose response studies see Dose Response Information to Support Product Authorisation.

5.3 Main Therapeutic Studies

As the aim of these studies is to assess the major clinically relevant long-term effects of the active substance, no surrogate haemodynamic or haemorheological measurements must be used as primary end-points. Therefore, the primary end-points should be the improvement in clinical status as mentioned above.

The difference between the verum and placebo group that would be considered clinically important should be indicated in the study protocol. The relevant difference may vary
according to the end-point of the study and to Fontaine's stage. For example, a sustained improvement (according to defined observation periods) with an observed difference of 30% in walking distance between placebo and the active substance should be considered relevant to patients in stage II. Provided that the sample size is estimated adequately, this will usually be the case, if an irrelevant difference (to be specified in the study protocol) between placebo and active treatment can be excluded.

The development of tolerance (tachyphylaxis) should be investigated.

5.3.1 Design

A placebo run-in phase of 4-6 weeks is recommended. In severe critical limb ischaemia a shorter run-in phase is possible (in Fontaine's stage IV a run-in period of 1-2 weeks is recommended).

A randomised parallel group, double-blind, placebo-controlled design is mandatory. A placebo should be used for the control group since suitable reference substances have not yet been established. The studies should be performed in a parallel group design. Cross-over studies were not recommended due to the progression of the disease. Treatment should last for a minimum of 6 months for oral administration, and up to 8 weeks if the parenteral active substance is not recommended for long-term use. In more severely ill patients (stages III and IV) an effect on rest pain and ulcer healing already may be established earlier. The duration of the trial depends on the main endpoint of the study.

Primary and secondary efficacy criteria should be assessed every 1 or 2 months during treatment period. Depending on the duration of active treatment, a follow-up period of up to 1 year should be performed. Confounding factors, especially changes in smoking habits, should be carefully documented during the trial and considered in the efficacy evaluation.

5.3.2 Biostatistical Methodology

The biostatistical design and analysis should be performed in accordance with the note for guidance on Biostatistical Methodology in Clinical Trials.

6. OVERALL SAFETY EVALUATION

The safety evaluation should usually address the following points:
- effects on blood pressure and heart rate;
- effects on neurohumoral activation and pro-arrhythmic and/or pro-anginal effects;
- rebound, withdrawal phenomena;
- effects on renal function;
- effects on cardiovascular morbidity and mortality;
- steal phenomenon.
6.1 Monitoring of Adverse Drug Events

Depending on the pharmacological and toxicological activity of the medicinal product, specific attention should be paid to any adverse events which may be expected on the basis of these activities.

Adverse drug events occurring during the course of the treatment should be carefully recorded throughout all study phases, including data about their nature, frequency, intensity, and relevance.

6.2 Safety Clinical Trials

Because many adverse reactions are rare, large sample sizes are necessary to detect them, and sometimes this is not feasible. Hence, the combination of results from all studies, mainly addressed to prove efficacy, is recommended. A separate analysis on cardiac morbidity and mortality should be made on basis of the major clinical trials. In order to establish the overall safety profile of a new compound, well-controlled studies are preferable. Usually, the randomised, double-blind comparative trials for efficacy can be followed by a longer exposure in open conditions. The duration of the follow-up periods should cover 6 months to 2 years. At least 100, if possible 300 patients, should be treated with the new active substance for one year.