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COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

POINTS TO CONSIDER ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE CHRONIC TREATMENT OF PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

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Points to Consider have been developed to provide advice on selected areas relevant to the development of medicinal products in specific therapeutic fields.

This document will be revised in accordance with the scientific advances made in this area.

7 Westferry Circus, Canary Wharf, London E14 4HB, UK
Switchboard: (+44-171) 418 8400 Fax: (+44-171) 418 8613
E_Mail: mail@emea.eudra.org http://www.eudra.org/emea.html

CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS IN THE CHRONIC TREATMENT OF PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

I BACKGROUND

I.1 Definition

Chronic obstructive pulmonary disease (COPD) is characterised by long-term airway obstruction which is usually progressive but which may be partially reversible. It is usually associated with past or continued smoking and has three components of emphysema, chronic bronchitis and peripheral airway disease. The definition should follow the guidelines listed below under Section II-Diagnosis.

I.2 Current treatment of COPD

For the majority of patients with COPD the most important influence on their symptoms and prognosis is whether or not they continue to smoke. Exposure to other inhaled air pollutants may contribute to the disease in some patients.

The use of bronchodilators, theophylline and corticosteroids may provide symptomatic relief but has not been shown to alter the progress of the disease.

Non-pharmacological treatment is limited but includes oxygen therapy, assisted ventilation, exercise training, resection of bullae and physiotherapy.

It is anticipated that future applications may make claims for anti-inflammatory drugs or drugs proposed to alter with the pathogenesis of COPD.

I.3 Existing guidelines

The document is intended as a supplement to existing guidelines that already cover aspects of COPD. These include:

- General Considerations for Clinical Trials (ICH E8)
- Studies in Support of Special Populations: Geriatrics (ICH E7)
- The Extent of Population Exposure to Assess Clinical Safety of Medicines Intended for Long-term Treatment of Non- Life Threatening Conditions (ICH E1A)
- Statistical Principles for Clinical Trials (ICH E9)
- CPMP Pharmacokinetic Studies in Man Guideline

II DIAGNOSIS

When considering the eligibility of patients for clinical trials the definition and diagnostic criteria of COPD should be based on existing guidelines such as the European Respiratory Society guideline - ERS Consensus statement: optimal assessment and management of chronic obstructive pulmonary disease (COPD). Eur Respir J 1995;8:1398-1420); the American Thoracic Society guideline - Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1995;152:S77-120; and the British Thoracic Society guideline - BTS guidelines for the management of chronic obstructive pulmonary disease. Thorax 1997;52, supplement 5:S1-28.

It is suggested that two categories of assessment of airway reversibility are used for patients recruited into trials; one with beta adrenergic agonists and the second with oral or inhaled corticosteroids. The assessment should be carried out when the patients are clinically stable and free from infection. The differentiation between COPD and asthma may be difficult as these two conditions have considerable overlap but patients with predominant asthma should be excluded from these trials. Asthma should be carefully predefined using existing guidelines for its diagnosis with a protocol for assessing airway reversibility and a definition of the degree of reversibility that would classify a patient as asthmatic. When setting trial entry criteria a cut off for airway reversibility should be chosen, with reference to the European Respiratory Society and American Thoracic Society guidelines, so that the degree of reversibility of the trial population is defined clearly. The indication in the SPC will be restricted to the population treated in the Phase III trials.

III SMOKING AND CLINICAL TRIALS

A high proportion of the patients recruitable would be smokers or ex-smokers and smoking status may influence the outcome of any patient. In the efficacy trials formal stratification of patients according to smoking status (current smokers; ex-smokers) should be performed prior to randomisation. The main analyses should evaluate the effect of treatment relative to control in the whole trial population but should be stratified by smoking status at entry in order to improve precision and reduce the effect of any baseline imbalance. The interaction of smoking status at entry with the therapeutic benefits of treatment should also be examined by additional exploratory analyses. Tobacco exposure should be monitored carefully throughout the trial in all patients and changes in smoking status documented and reported. The influence of this exposure on the estimates of efficacy should be evaluated by quantifying and illustrating any differences in tobacco exposure between the treatment groups and discussing the possible quantitative effect of these differences on outcome.

The use of nicotine replacement therapy as an aid to smoking cessation should be recorded during clinical studies and any effect on outcome should be examined. The possibility of kinetic interactions between a proposed product and smoking or nicotine replacement therapy should be investigated.

IV DURATION OF PHASE III CLINICAL STUDIES

The duration of the trial should be appropriate to the claimed indication.

IV.1 Any indication for the symptomatic relief of COPD should be supported by the results from a trial of at least 6 months duration.

IV.2 When making a claim that a treatment prevents disease progression it will be necessary to demonstrate that the benefit of treatment is prolonged. One design to test this is to randomise patients to continue or stop treatment after a long period of treatment and then examine the rapidity and extent at which benefit is lost.

V CONCOMITANT TREATMENTS AND COMPARATORS

There are difficulties in selecting an appropriate comparator as several modes of action are possible for treating COPD. The most useful comparison would be with a placebo. Any active comparator could have anticholinergic, beta adrenergic, or anti-inflammatory activity. It is important that the use of all concomitant treatments including bronchodilators, oral corticosteroids, inhaled corticosteroids, antibiotics as well as mucolytic antioxidants should be documented carefully. An imbalance in the use of these medications between treatment groups

may affect the outcome and appropriate analysis plans should be made beforehand to account for this possibility.

VI RECOMMENDED PRIMARY AND SECONDARY ENDPOINTS

VI.1 In the major efficacy studies of symptomatic benefit the primary endpoint should reflect the clinical benefit the applicant wishes to claim in the future SPC. It should include the FEV_1 as a measure of lung function and include a measure of symptomatic benefit. A significant benefit for both endpoints, FEV_1 and the symptomatic benefit endpoint, should be demonstrated so that no multiplicity adjustment to significance levels is indicated. The timing of the measurement of FEV_1 should be standardised and recorded in relation to the last dose of trial and concomitant medication. The primary symptomatic benefit endpoint should be justified by referencing published data which support its validity; one example is the St George's Respiratory Questionnaire. In the analysis the primary endpoints should be summarised in a manner which provides maximum power to detect relevant effects, such as the average value over a treatment period, but should also illustrate the time profile.

There are a number of secondary endpoints which may provide useful information. These measure different aspects of the disease but they should be justified by referencing published data which support their validity; examples include pulmonary function tests, oxygen saturation, CO2 retention, exercise tolerance such as the 6 minute walk, symptom scales, exacerbation rates and quality of life assessment. Which are chosen will depend upon the claims being made in the SPC. Care should be taken with respect to statistical multiplicity if secondary endpoints become the basis for specific claims.

VI.2 If prevention of progression is claimed by analysing the deterioration in the forced expired volume in 1 second (FEV_1), the evidence should support a divergence in the rate of FEV_1 decline in favour of active treatment. Such a divergence should exclude the possibility of parallel declines in FEV_1, with the active treatment data offset by an initial and sustained bronchodilator effect.

VII SAFETY ASPECTS

Treatment in COPD is usually prolonged and long term data on adverse events and interactions should be provided where appropriate. This should be line with the ICH E1A guideline - The extent of population exposure to assess clinical safety of drugs intended for long term treatment in non-life threatening conditions.