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GUIDELINE ON THE CLINICAL INVESTIGATIONS OF MEDICINAL PRODUCTS FOR THE TREATMENT OF PULMONARY ARTERIAL HYPERTENSION

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GUIDELINE ON THE CLINICAL INVESTIGATIONS OF MEDICINAL PRODUCTS FOR THE TREATMENT OF PULMONARY ARTERIAL HYPERTENSION

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EXECUTIVE SUMMARY

This guideline is intended to provide guidance for the evaluation of new medicinal products or drugs used in combination in the treatment of pulmonary arterial hypertension PAH.

1. INTRODUCTION

Pulmonary hypertension is a group of diseases characterized by a progressive increase of pulmonary vascular resistance (PVR) leading to right ventricular failure and premature death. It is defined by a mean pulmonary artery pressure (PAP) > 25 mmHg at rest.

Pulmonary hypertension is clinically classified into 5 groups as presented in table 1.

Table 1: Updated Clinical Classification of Pulmonary Hypertension (Dana Point, 2008)

1. Pulmonary arterial hypertension (PAH)
1.1. Idiopathic PAH
1.2. Heritable
1.2.1. BMPR2
1.2.2. ALK1, endoglin (with or without hereditary hemorrhagic telangiectasia)
1.2.3. Unknown
1.3. Drug- and toxin-induced
1.4. Associated with
1.4.1. Connective tissue diseases
1.4.2. HIV infection
1.4.3. Portal hypertension
1.4.4. Congenital heart diseases
1.4.5. Schistosomiasis
1.4.6. Chronic hemolytic anemia
1.5 Persistent pulmonary hypertension of the newborn
1'. Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)
2. Pulmonary hypertension owing to left heart disease
2.1. Systolic dysfunction
2.2. Diastolic dysfunction
2.3. Valvular disease
3. Pulmonary hypertension owing to lung diseases and/or hypoxia
3.1. Chronic obstructive pulmonary disease
3.2. Interstitial lung disease
3.3. Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4. Sleep-disordered breathing
3.5. Alveolar hypoventilation disorders
3.6. Chronic exposure to high altitude
3.7. Developmental abnormalities
4. Chronic thromboembolic pulmonary hypertension (CTEPH)
5. Pulmonary hypertension with unclear multifactorial mechanisms
5.1. Hematologic disorders: myeloproliferative disorders, splenectomy
5.2. Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis: lymphangioleiomyomatosis, neurofibromatosis, vasculitis
5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4. Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

The pathobiology of PAH is complex and the exact initiating processes are still unknown. However, the increase of pulmonary vascular resistance (PVR) is multi-factorial and involves vasoconstriction, obstructive remodelling of the pulmonary vessel wall, inflammation and thrombosis.

Several therapies are prescribed for patients with PAH. Conventional treatment for PAH include: calcium-channel blockers, anti-coagulants, diuretics and oxygen. For more advanced cases (NYHA II, III and IV), disease-specific classes of drugs currently registered on the EU market include: prostanoids, selective and non-selective endothelin antagonists and phosphodiesterase-5 inhibitors.

2. SCOPE

The main focus of this guideline is pulmonary arterial hypertension PAH, although the guideline can be applied to subgroups 4 as well. PAH in the paediatric population is addressed in a separate addendum.

3. LEGAL BASIS

This guideline has to be read in conjunction with the introduction and general principles (4) and Annex I to Directive 2001/83 as amended.
All pertinent elements outlined in current and future EU and ICH guidelines and regulations should also be taken into account, especially those on:

- Note for guidance on Clinical investigation of medicinal products for the treatment of cardiac failure CPMP/EWP/235/95, Rev 1.
- Clinical Trials in Small Populations CHMP/EWP/83561/05

4. CRITERIA OF EFFICACY

The efficacy of the currently registered medications in the management of PAH is mainly based on showing improvement in exercise capacity. However, it is now recognized that the therapeutic goals have broadened. The identification of multiple pathways involved in the pathogenesis of PAH, indicate the trend to investigate combination therapies, rather than monotherapy. Also trials are now expected to include patients with less severe symptoms as well and the endpoints will have to match the expected benefits in each patient group. Ideally, the objectives of a new treatment should be to prolong survival time, to reduce morbidity, to ameliorate symptoms and to improve quality of life.

Considering these challenges, the developers of such drugs are encouraged to seek protocol assistance from the Committee for Medicinal Products of Human Use CHMP before undertaking to conduct their clinical trials.

4.1 Relevant Efficacy Variables

4.1.1 All-cause Mortality

In a disease with a poor prognosis, all-cause mortality is of special relevance. PAH is a fatal disease and a new pharmacological intervention would be expected to prolong survival. Moreover, an improvement in symptoms is not always associated with prolonged survival, emphasizing the importance of investigating the latter. Although the focus should be all-cause mortality, careful investigation should be conducted to identify the exact cause of death, in particular CV death.

Possible difficulties are recognized when this endpoint is investigated in such a rare disease. Still, the inclusion of this endpoint in the investigational plan, in particular in patients with severe disease, is strongly encouraged (see section 2.2). Any new drug should at least be shown to have no detrimental effect on survival. It is mandatory to report all mortality data and their underlying cause. Specific claims on mortality can only be supported by long-term controlled studies including death as a primary endpoint.

4.1.2 PAH-related morbidity

The course of PAH is associated with considerable morbidity that can signify deterioration in the clinical condition, depending on the disease severity e.g. non-planned PAH-related hospitalization or deterioration in functional class (FC) or in exercise capacity. Accordingly, time to these events could be utilized to identify the relevance of medical treatments effects provided that clear, non-equivocal and prospective definitions are provided. Hospitalization for PAH should be clearly defined (e.g. for at least 24 hours caused by a clinical condition related to PAH such as right heart failure, arrhythmia, syncope, haemoptysis, chest pain, dyspnoea or hospitalization to implant a catheter to initiate epoprostenol treatment).

4.1.3 Clinical Symptoms

Clinical symptoms have been usually scored using the WHO/NYHA functional classification, which has been shown to have a prognostic predictive value in patients with iPAH on conventional treatment.

Long-term improvement in WHO/NYHA functional class is a clinically significant endpoint. However, the subjectivity of this functional classification that depends on both the patient and the caregiver, precludes its utility as a sole primary endpoint. Changes in FC can be used to indicate clinical worsening (see 4.2.2) or can be used as a separate secondary endpoint.

4.1.4 Exercise Capacity

The most frequently used primary endpoint in the pivotal studies for the registration of PAH drugs has been the short term improvement in the six-minute walk test (6-MWT), making it an important reference tool. As such, the test can still be used as a primary endpoint in investigating drugs for PAH when the proposed indication is restricted to improvement in exercise capacity (see 4.2.1). However, such an approach has its limitations considering the lack of clear correlation between improvement in exercise capacity and overall survival. For this reason, investigating deterioration in the 6-MWT (for example, defined as a decrease of 15 % from baseline confirmed by two consecutive 6-MWT, performed on different days) is encouraged to be used in conjunction with other efficacy endpoints when the claimed indication is an effect on clinical worsening in longer term studies (see 4.2.2).

The development and validation of other exercise capacity tests is encouraged.

4.2 Primary Endpoints

Depending on the proposed indication, the investigated primary endpoints can vary:

4.2.1 Improvement in Exercise Capacity

When the indication is restricted to an improvement in exercise capacity, the 6- MWT can be used as the primary endpoint, provided there is no negative impact on survival. The minimal meaningful clinical differences (clinical impact) in case of non-idiopathic PAH, less severe PAH patients, or in combination therapy should be adequately defined a-priori. The clinical relevance of the results should also be considered in conjunction with effects on other clinical endpoints.

4.2.2 Time to Clinical Worsening

The investigation of a composite primary endpoint that reflects, in addition to mortality, time to clinical worsening is encouraged. The composition of this composite endpoint may vary depending on the severity and the aetiology of the disease. The following components are suggested:

1. All-cause death.

2. Time to non-planned PAH-related hospitalization.

3. Time to PAH-related deterioration identified by at least one of the following parameters:

   i. increase in WHO FC;

   ii. deterioration in exercise testing

   iii. signs or symptoms of right-sided heart failure

Any chosen parameter should be clinically relevant, adequately defined, well validated and centrally adjudicated by a blinded adjudication committee. When defining the composite endpoint, the expected relative contribution of each component should be taken into account. Therefore, the need to tailor the definition to the clinical setting studied (e.g. severity of the target population) must be considered. Importantly, any specific claims should be adequately substantiated from the data. The influence of each individual component should also be examined separately as secondary endpoints to ensure that the effect of one component is not negating the effect of another.

4.3 Secondary Endpoints

4.3.1 Haemodynamic State

Although the diagnosis of PAH needs to be confirmed by right cardiac catheterization with appropriate haemodynamic measurements, the value of haemodynamic measurements in the evaluation of medicinal products is not as clear. Thus the place of these measurements is currently limited to the

diagnosis and as a secondary endpoint. Haemodynamic measures may play an important role during the early development of the drug to elucidate the mechanism of action or to define the dose-response relationship. The role of echocardiography and other imaging techniques (e.g. cardiac MRI, PET scanning) in estimating haemodynamic variables and cardiac dimensions is not well investigated but may offer potential non-invasive tools to evaluate the efficacy of the medicinal intervention.

4.3.2 Health-Related Quality of Life Measures

Drugs administered for PAH can impact the QoL of the patients considering their route of administration and/or associated adverse events. Measurements should accordingly include the patient's perception of the impact of his/her disease and its treatment on his/her daily life, physical, psychological and social functioning and well being.

4.3.3 Biological Markers

Based on current evidence, neuro-hormones e.g., natriuretic peptides, endothelin-1 and norepinephrine may play a direct role in the pathogenesis in PAH or may be associated with the severity of the disease. Although the investigation of such biomarkers is encouraged to elucidate the mechanism of disease, their value can currently only be considered as supportive for efficacy.

5. PATIENTS

5.1 Selection

The criteria for the diagnosis and the aetiology of PAH should be clearly stated. The baseline disease stage categorized mainly by clinical symptoms (NYHA/WHO) (and exercise testing and haemodynamic measurements if possible) should be adequately assessed. Incident versus prevalent patients, and time from diagnosis should also be stated. These criteria facilitate better characterization of the recruited patients and consequently the gained efficacy potential. This also allows comparison with other drugs. Proper representation of the subgroups is necessary if specific claims are made relating to aetiology, FC or concomitant PAH therapy. Targeting other FC is encouraged e.g. WHO II and IV.

5.2 Background Treatment

Because of the rarity of the disease, recruitment is usually world-wide and background therapy may be quite diverse, complicating interpretation of the results. The allowed background therapy should be clarified and standardized as much as possible. Empirical use of calcium channel blockers should not be allowed. Patients should be sufficiently stable on their background medications before recruitment in the clinical study. Considering that the future trend in PAH is combination therapy, the number of enrolled patients on a specific PAH-therapy (prostanoids, endothelin blockers or PDEs) should be sufficiently representative to allow corresponding claims of combined therapy. These claims have to be pre-specified in the protocol.

6. STRATEGY – DESIGN

6.1 Human Pharmacology Studies

These studies will not essentially differ from those dealing with other cardiovascular drugs.

6.1.1 Pharmacodynamics

The pharmacodynamic studies should elaborate on the mechanism of action and dose-response relationship. The effects on haemodynamic parameters, pulmonary effects and neurohormonal function are important at this stage and should be thoroughly studied, especially for a new class of drugs. Any specific PD parameter specific to the drug should be studied as well. Preferably, patients with PAH should be recruited for these studies.

6.1.2 Pharmacokinetics

The design of the pharmacokinetic studies should follow the appropriate guidelines. Depending on the metabolic pathway and the foreseen toxicities, special PK studies should be planned. As the number of patients is limited, important information on the drug pharmacokinetics can be gained from a well-designed population PK analysis.

6.1.3 Interactions

Special emphasis should be put on interaction studies between the medicinal product and the potential background therapies.

Considering the future trend of combination therapy, interaction studies between the investigational drug and that of specific PAH medications should be planned investigating possible both PK and PD interactions.

6.2 Exploratory Therapeutic Studies

The objectives of these studies will be to identify patients who may benefit from the investigational drug and to determine the appropriate therapeutic range including dose-concentration-response relationship. It is recommended to establish the optimal therapeutic dose before starting the confirmatory therapeutic studies. These studies could be placebo-controlled, investigating the efficacy of at least 2 doses on clinical symptoms and/or haemodynamic responses, although ethical problems in conducting such studies are acknowledged. In order to allow comparisons with other approved PAH treatments, the 6-MWT could be used. The duration of the study is dependent on the endpoint chosen; when using clinical symptoms the duration of the study should be long enough to show efficacy. In case of the 6-MWT the standard is a minimum duration of 12 weeks. In case the study is also sufficiently powered, it can be considered as part of the confirmatory studies. For a drug with a known mechanism of action, PD studies can be combined with dose finding studies.

6.3 Confirmatory Therapeutic Studies

Several issues determine the type and number of confirmatory therapeutic studies: the claimed indication, the rarity of this fatal disease, the poor prognosis and lastly the possible absence of an active comparator with their registered indications. Controlled double-blind randomized studies are required. If the proposed indication for the investigational drug is *add-on* to an existing therapy, a placebo-group is mandatory. If the proposed indication is *monotherapy to show improvement in exercise capacity*, actively-controlled studies should be considered and the non-inferiority margin should be adequately defined taking into account the relative small number of patients due to the orphan status of the disease. In case of a monotherapy administration claiming an effect on clinical worsening, the use of placebo-controlled studies will have to be justified by the applicant, taking into account ethical issues related to the presence of established therapeutic options. Other study designs are possible, but need to be thoroughly discussed and justified in the study protocol.

Duration will depend on the chosen primary endpoints. Studies using improvement in exercise testing may vary between 3 and 6 months. A minimum of 6 months is usually necessary to demonstrate an improvement in time to clinical worsening, but this will also depend on the composition of the endpoints and the severity of the disease. Even if a claim of prolonged survival is not made, effect on mortality should be reported. This can be done in an open extension phase.

For any proposed indication, provided the study is properly randomized, groups should be sufficiently balanced in respect to age, sex, aetiology, severity and background medication.

7. SAFETY ASPECTS

Due to the rarity of the disease, the safety database may be quite limited at the time of registration. Every attempt should be made to collect long-term data on adverse events and interactions even after drug registration. Recruitment of the patients enrolled in the controlled studies (exploratory or confirmatory) in open extension phases is recommended. Whatever the selected endpoints, every effort should be made to show that the drug does not have adverse effects on morbidity or mortality. Vigilant monitoring of anticipated adverse events based on signals from pre-clinical studies or due to the pharmacological class should be done e.g. liver toxicity by endothelin antagonists, or hypotension

with vasodilators. Safety issues inherent to the specialized delivery systems need to be addressed as well.

DEFINITIONS

Refer to section 1.

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