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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

CONCEPT PAPER ON THE DEVELOPMENT OF A CHMP GUIDELINE ON THE CLINICAL INVESTIGATIONS OF MEDICINAL PRODUCTS FOR THE TREATMENT OF PULMONARY HYPERTENSION

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1. INTRODUCTION

Pulmonary hypertension is classified into five groups based on the aetiology (Revised WHO Classification of PH).

Clinical Classification of Pulmonary Hypertension - Venice 2003

1. Pulmonary arterial hypertension (PAH)
1.1. Idiopathic (IPAH)
1.2. Familial (FPAH)
1.3. Associated with (APAH):
1.3.1. Collagen vascular disease
1.3.2. Congenital systemic-to-pulmonary shunts
1.3.3. Portal hypertension
1.3.4. HIV infection
1.3.5. Drugs and toxins
1.3.6. Other (thyroid disorders, glycogen storage disease, Gaucher disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, splenectomy)
1.4. Associated with significant venous or capillary involvement
1.4.1. Pulmonary veno-occlusive disease (PVOD)
1.4.2. Pulmonary capillary hemangiomatosis (PCH)
1.5. Persistent pulmonary hypertension of the newborn
2. Pulmonary hypertension with left heart disease
2.1. Left-sided atrial or ventricular heart disease
2.2. Left-sided valvular heart disease
3. Pulmonary hypertension associated with lung diseases and/or hypoxemia
3.1. Chronic obstructive pulmonary disease
3.2. Interstitial lung disease
3.3. Sleep-disordered breathing
3.4. Alveolar hypoventilation disorders
3.5. Chronic exposure to high altitude
3.6. Developmental abnormalities
4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease
4.1. Thromboembolic obstruction of proximal pulmonary arteries
4.2. Thromboembolic obstruction of distal pulmonary arteries
4.3. Non-thrombotic pulmonary embolism (tumor, parasites, foreign material)
5. Miscellaneous
Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

The main focus of this guideline is group 1, though it may address subgroups 4.1 and 4.2 as well.

Pulmonary arterial hypertension (PAH) is disease of the small pulmonary arteries that is characterised by vascular proliferation and remodelling. It results in a progressive sustained increase in pulmonary arterial pressure to more than 25 mm Hg at rest. The disease ultimately leads to right ventricular failure and death. A diagnosis for primary (or idiopathic) pulmonary hypertension is made when no etiological risk factor is identified.

Several therapies are prescribed for patients with PAH. Conventional treatment for PAH included calcium-channel blockers, anti-coagulants, diuretics and oxygen. For more advanced cases, new classes of drugs have entered the market, including prostanoids: epoprostenol, treprostinil and iloprost; endothelin antagonists: bosentan and sitaxentan and phosphodiesterase-5 inhibitors: sildenafil. These drugs are approved for NYHA patients III-IV.

Thus, an increasing number of applications for marketing authorization and national scientific advice was filed for the treatment PAH raising a number of registration issues including among others, patient inclusion criteria and choice of endpoints. Moreover, the design of these clinical trials came under strong scrutiny in peer reviewed articles (*Peacock et al. 2004; Kawut and Palevsky, 2004; Rich, 2007, and Macchia et al., 2007*) showing major flaws in many aspects in the study design. These issues call

for drafting a guideline for sponsors in order to specify the regulatory requirements to conduct such studies.

2. PROBLEM STATEMENT

To date, the above mentioned agents were mostly registered in the EU on basis of placebo-controlled trials, mostly in patients with class III NYHA, with the 6 minute-walk test as the primary endpoint for efficacy tested in week 12. Although these criteria appeared valid or justified at one point, there is a current need to set more ambitious goals for the clinical development program of any new agent. The design of future clinical trials will have to meet a combination of ethical, scientific and feasibility requirements which is quite challenging considering the rarity of the disease. The proposed guideline should direct the sponsors into conducting more innovative research addressing important and relevant issues avoiding the clinical trials aiming at minimal accepted benefit with the least amount of testing.

3. DISCUSSION (ON THE PROBLEM STATEMENT)

Main problems to be addressed include:

Endpoints

Primary endpoints

The suitability of 6-MWT as a primary endpoint should be discussed considering it is influenced by age, gender, height, weight and degree of motivation. Improvement in performance was recently shown not to correlate with survival. However, it is an acceptable measure of functional capacity provided it is modified and validated to give more meaningful data and allow more objective comparisons across studies. More robust and clinically relevant endpoints such as time to clinical worsening (identified by need for IV epoprostenol, or lung transplantation) or death may be required.

Secondary endpoints

Haemodynamic studies: One important issue that need to be discussed is whether these studies have to be part of the development program. Other endpoints could include functional tests (e.g. cardiopulmonary exercise testing, shuttle walk test), biomarkers, or the development of a PAH-specific quality of life questionnaire.

Target Population

The target population should be defined depending on the claimed indication. Although the guideline will focus on group 1 in the above classification the definition of this specific population and populations with other forms should be defined further. Also, severity of disease warrants further discussion. The RCTs have thus far concentrated on functional class III but this did not always correlate with distance walked in the 6MWT.

Study Design

With five registered drugs for PAH, the possibility of placebo-controlled studies is questioned. Non-inferiority studies should be addressed. Other study designs, including add-on, or factorial designs need to be discussed as well.

Duration of the studies

Demonstration of long-term efficacy may require a longer study duration than the standard 12 weeks currently accepted for RCTs in this indication. New recommendations should be made.

Safety issues

These should be defined and guidance should be given, in particular within the context of the “orphan drug” status of many of these products.

4. RECOMMENDATION

In the light of the many unresolved regulatory issues, a CHMP Guideline on the clinical investigation of medicinal products for the treatment of pulmonary hypertension is highly advisable.

5. PROPOSED TIMETABLE

Release for consultation on 24/01/08, deadline for comments 31/04/08, discussion in EWP July 08; proposed date for release of draft guideline third quarter 2008.

6. RESOURCE REQUIREMENTS FOR PREPARATION

Drafting this guideline will involve two Rapporteurs (NL and ES). Draft documents will be discussed in three regular meeting of the CVS group. No special resources will be required.

7. IMPACT ASSESSMENT (ANTICIPATED)

It is anticipated that this guideline will help industry and regulatory authorities in developing better drugs for this rare, but often fatal disease.

8. INTERESTED PARTIES

Specialists in the field will be actively consulted during the draft of this guideline, apart from the regular consultations.

9. REFERENCES TO LITERATURE, GUIDELINES ETC

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