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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

CONCEPT PAPER ON THE NEED FOR A GUIDELINE ON THE DEVELOPMENT OF NEW MEDICINAL PRODUCTS INTENDED FOR THE MANAGEMENT AND TREATMENT OF CYSTIC FIBROSIS

AGREED BY THE EFFICACY WORKING PARTY	February 2007
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Comments should be provided to EWPSecretariat@emea.europa.eu

Fax +44 20 74 18 86 13

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 13
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

1. INTRODUCTION

Definition of cystic fibrosis

Cystic fibrosis (CF) is an autosomal recessive disorder caused by mutations in the gene encoding for the cystic fibrosis transmembrane conductance regulator (CFTR), a protein that acts as a chloride channel. The most common mutation is deletion of phenylalanine at position 508 of CFTR. The mutation has been named F508del.

Pathogenesis

The disruption of chloride and sodium transport, associated with water transport abnormalities, results in viscous secretions in the respiratory tract, pancreas, gastrointestinal tract, sweat glands, and other exocrine tissues. Increased viscosity of these secretions makes them difficult to clear and patients develop progressively exocrine gland dysfunction of multiple organ systems in childhood, resulting in chronic respiratory disease, pancreatic enzyme insufficiency, hepatic and biliary abnormalities, intestinal obstruction, and reduced fertility due to agenesis of the vas deferens in males and delayed menarche in females.

In the lower respiratory tract, the hyperviscous mucus impairs mucociliary clearance, first line of host defence, while the thick, sticky mucus retains particulate material and bacteria. The antibacterial properties of mucus are also decreased. Infection and associated inflammation maintain a vicious circle, with progressive damage of the lungs. Chronic (mainly *P. aeruginosa)* infection is associated with chronic lung injury and reduced survival, with *P. aeruginosa* rarely being eradicated. *Burkholderia cepacia* has more recently been isolated in older cystic fibrosis patients and its isolation from sputum has been causally associated with a rapid decline in pulmonary function progressing to death.

In the pancreas, abnormal mucus secretion causes obstruction and dilatation of pancreatic ducts, with progressive destruction of pancreas.

Symptoms

Frequent clinical manifestations include lung disease, exocrine pancreatic insufficiency (80-90% of patients), diabetes mellitus, nasal polyps, obstructive biliary tract disease (15-20% of patients), and azoospermia (> 90% of affected men).

Lung disease

Main symptoms are related to infection and process: cough, expectoration of sputum, dyspnoea, decreased tolerance to effort, loss of appetite. They are increased in case of exacerbation and associated with dyspnoea and loss of weight.

Pancreatic disease

Exocrine pancreatic insufficiency is clinically manifested by malabsorption (steatorrhoea) and malnutrition which both contributes to poor growth, poor weight gain and bone formation in paediatric patients. Malnutrition favours infections and decreases life expectancy independently from respiratory impairment. In older patients diabetes mellitus may follow exocrine pancreatic insufficiency (50% of patients at age 30).

Patient who are pancreatic insufficient are more likely to have more severe lung disease and liver involvement while patients who are pancreatic sufficient are at higher risk of developing pancreatitis.

Diagnosis

Clinical suspicion of CF is confirmed by evaluation of chloride secretion in sweat, assessment of nasal transepithelial potential difference (TEPD) and sequencing of the CFTR gene to confirm the presence of some mutations.

Management of CF

Management of cystic fibrosis is mainly symptomatic and focuses on respiratory tract disorders. However, a multi-disciplinary team in specialised centres is recommended to manage malnutrition, digestive problems including hepatobiliary disorders and diabetes.

Standard therapeutic management of pulmonary disease

1) Inhaled and systemic antibiotic (ATB) therapy to treat and prevent infections and bronchiectasis
2) Mucolytic therapy to improve mucociliary clearance of lower-airway secretions and treat the chronic obstructive pulmonary disease. Hypersaline solutions are used to decrease mucus viscosity (osmotic mechanism). rhDNAse (Pulmozyme) (viscosity and clearance)
3) Inhaled bronchodilator: little scientific evidence (β2-mimetics only).
4) anti-inflammatory therapy (inhaled and systemic corticoids, ibuprofen, macrolides – anti-inflammatory properties) to delay disease progression
5) physiotherapy treatment

Standard therapeutic management of pancreatic disease

1) Pancreatic enzyme preparations (PEP) (enzyme replacement to prevent malnutrition). Pancreatic enzyme supplements contain lipases, proteases and amylase were first marketed in the form of powder, tablets and capsules and were made up of porcine pancreatic extracts. More modern pancreatic enzyme products are capsules that contain enteric-coated microencapsulated enzymes, either as microspheres or microtablets with acid-resistant film to prevent inactivation of the enzymes by gastric acid. The ratio of proteases to lipases differs in various brands of enzymes
2) nutritional supplements

2. PROBLEM STATEMENT

CF is a life threatening and chronically debilitating disease, impairing the Quality of life, characterised by progressive bronchiectasis and obstructive pulmonary disease (> 90% patients) [1; 2]. The lower respiratory tract involvement is the primary cause of morbidity and mortality in patients with CF (> 90% of fatalities). Ninety percent of CF patients are colonised with *Pseudomonas aeruginosa* (PA) [3], and PA infections are the cause of mortality in 80% of those patients[4].

CF is mainly a paediatric disease. Life expectancy is considerably shortened due to respiratory damage-induced morbidity and mortality. However, due to the advances of past 20 years in the prophylaxis of chronic respiratory infection, along with the systematic supplement of pancreatic enzyme and decrease in malnutrition CF patients reach a mean 30 to 40 years of age, and the proportion of adult CF patients increases.

The guidance will focus on:

- clinical trials design in lung involvement and clinically relevant endpoints (mucociliary clearance and broncho-pulmonary infections (mortality), in particular: treatment of PA early colonisation, chronic infection and exacerbations; prophylaxis of chronic PA infection; slowing/stopping lung damages (fibrosis, bronchiectases)
- clinical trials design in pancreatic involvement, in particular management of exocrine pancreatic insufficiency and malnutrition

3. DISCUSSION (ON THE PROBLEM STATEMENT)

Cystic Fibrosis is a rare disease starting at paediatric age and persisting in adulthood. Medicinal products for the treatment often have an Orphan designation.

In the guideline the following issue needs to be addressed.

- ***Choice of patient population***

Definition of inclusion criteria is critical especially in the paediatric population. Range of age categories

- Need for stratification with regard to severity of the disease
- Need for separate studies in adults, children neonates for efficacy and safety

- ***Study design***

- Appropriate study design for **pulmonary disease** and for **pancreatic disease, e.g. parallel group studies, crossover trials, add-on design**
- Appropriate primary and secondary endpoints for pulmonary disease and pancreatic dysfunction e.g. lung function, hard clinical endpoint, place of microbiological endpoint, QoL, Mortality
- Choice of comparator and standardisation on concomitant therapies: placebo, active control, and best supportive care
- Duration of studies

- ***Safety data***

- Long-term safety data needed
- Small population → need to collect and gather data from other populations?
- Influence on growth and development
- Emergence of resistance to the test drug and to other ATB
- Treatment specific safety data e.g. data on hepatic, renal toxicity, ototoxicity, fibrosing colonopathy (related to high doses of lipases)

4. RECOMMENDATION

The Working Party recommends writing a guideline on the development of medicinal products in the management of cystic fibrosis patients, focusing on lung and pancreatic disease.

5. PROPOSED TIMETABLE

It is anticipated that the first draft guideline may be available in 3 months after adoption of the concept paper.

6. RESOURCE REQUIREMENTS FOR PREPARATION

The preparation of this Guideline will involve the EWP.

7. IMPACT ASSESSMENT (ANTICIPATED)

The new guideline will provide guidance for both industry and Regulatory Authorities regarding the clinical development and assessment of medicinal products for Cystic Fibrosis. It is expected to achieve a consistent approach in development and assessment of these products.

8. INTERESTED PARTIES

- EUROPEAN CYSTIC FIBROSIS SOCIETY (ECFS)
  (formerly known as the European Working Group for Cystic Fibrosis)
- Patient organisations

9. REFERENCES TO LITERATURE, GUIDELINES ETC

1. **Consensus Reports** on Issues Associated with Clinical Aspects in Cystic Fibrosis

- Döring G, Conway SP, Heijerman HGM, Hodson ME, Høiby N, Smyth A, Tow DJ for the Consensus Committee. **Antibiotic therapy against *Pseudomonas aeruginosa* in cystic fibrosis**: a European consensus. *European Respiratory Journal* 2000; 16: 749-767 -

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- Döring G, Høiby N for the Consensus Study Group **Early intervention and prevention of lung disease in cystic fibrosis**: a European consensus. *Journal of Cystic Fibrosis* 2004; 3: 67-91
- Kerem E, Conway S, Elborn S, Heijerman H for the Consensus Committee **Standards of care for patients with cystic fibrosis**: A European consensus; *Journal of Cystic Fibrosis* 2005; 4: 7-26

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- Davis PB et al. Am J Respir Crit Care Med; 1996,154: 1229-56
- Hoiby et Frederiksen 2000
- Koch et al. Lancet 1993

3. Related guidelines

- Guideline on Clinical Trials in Small Populations CHMP/EWP/83561/05
- Guideline on the Role of Pharmacokinetics in the Development of Medicinal Products in the Paediatric Population CHMP/EWP/147013/2004
- Note for Guidance on Evaluation of Medicinal Products Indicated for Treatment of Bacterial Infections CPMP/EWP/558/95
- Points to Consider on the Requirements for Clinical Documentation for Orally Inhaled Products (OIP) CPMP/EWP/4151/00