EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Mini-COMP exercise
(COMP: Committee for Orphan Medicinal Products)

A new company, Gaudipharm, is developing a drug for the treatment of cystic fibrosis. This compound, which will be known as Antonicaftor has shown activity in cell systems and animal models. The company is now seeking orphan designation and hopes to submit an application for marketing authorisation after clinical studies are completed.

What is a cystic fibrosis?

Cystic fibrosis is a hereditary (genetic) disease that affects the production of secretions (such as mucus) from the glands in the body. It affects the lungs and the digestive system (gut) in particular. Cystic fibrosis is caused by abnormalities in a gene called 'cystic-fibrosis transmembrane conductance regulator' (*CFTR*). The *CFTR* gene is responsible for the production of CFTR, a protein that regulates the production of mucus and digestive juices by acting as a chloride-ion channel to allow proper movement of salt and water in and out of certain cells in the lungs and other tissues. In patients with cystic fibrosis, there is an overproduction of mucus in the lungs and a reduced production of digestive juices from the pancreas (an organ near the stomach). This leads to long-term infection and inflammation of the lungs and problems with the digestion and absorption of food resulting in poor growth.
Cystic fibrosis is a long-lasting and life-threatening disease.

What is the estimated number of patients affected by the condition?

At the time of designation the prevalence of cystic fibrosis was estimated based on a review of publications. The conclusion adopted is that cystic fibrosis affects approximately 1 in 10,000 people in the European Union (EU). This was equivalent to a total of around 60,000 people, and is below the threshold for orphan designation, which is 5 people in 10,000.

What treatments are available?

At the time of submission of the application for orphan drug designation, lung infection and inflammation in cystic fibrosis patients were mainly treated with physiotherapy and antibiotics. Other medicines used to treat the lung disease included bronchodilators (medicines that help to open up the airways in the lungs) and mucolytics (medicines that help dissolve the mucus in the lungs). In addition, patients are often given other types of medicine such as pancreatic enzymes (substances that help to digest and absorb food) and food supplements. They are also advised to exercise and to undergo physiotherapy.

Antonicaftor might be of potential significant benefit for the treatment of cystic fibrosis because it is expected to bring relief of the symptoms of the disease by acting in a different way to existing treatments. This assumption will have to be confirmed at the time of marketing authorisation. This will be necessary to maintain the orphan status.

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How is this medicine expected to work?

Antonicaftor is thought to restore the ability of CFTR channels to transport chloride ions into and out of cells. This is intended to help maintain the proper level of salt and water on airway surfaces, reducing the formation and accumulation of mucus in the lung, and thus improving the symptoms of the disease.

What is the stage of development of this medicine?

Extensive results from non-clinical studies investigating both pharmacology as well as toxicology have been provided.

Three clinical studies (two phase I studies and one phase II study) have been conducted. Altogether, Antonicaftor has been administrated to 32 healthy adults and 50 patients with CF carrying the specific mutation delta F508. Overall the product has been well tolerated in these studies demonstrating an acceptable safety profile. This has been indirectly compared to historical data.

In pharmacokinetic studies, Antonicaftor has demonstrated more advantageous profile. However, it does not result in significantly improved efficacy in clinical studies.

Orphan Drug Criteria include:

1. That the product is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition not affecting more than five in ten thousand persons in the European Community
2. That the product is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition and is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment
3. There exists no satisfactory method of diagnosis, prevention or treatment of the condition that has been authorised in the European Community

Please note:

Medical plausibility

Since in many cases, at the time of designation, little or no clinical experience is available, it is important that the relevance of in vitro and in vivo preclinical models presented in the application is discussed in the context of the condition and when appropriate, reference should be made to other products developed for the same condition.

Significant benefit is a clinically relevant advantage or a major contribution to patient care

For a claim of 'significant benefit', i.e. a clinically relevant advantage or major contribution to patient care to be sustained, the COMP will evaluate whether there is a high probability for the patients to experience a clinically relevant benefit.

Reference:

Recommendation on elements required to support the medical plausibility and the assumption of significant benefit for an orphan designation
(http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guideline/2010/07/WC500095341.pdf)

Process for designation and maintenance for Orphan Medicinal Products

Your tasks

Part A. Decide whether data fulfil the criteria and whether you would grant an orphan designation to Antonicaftor:

1. Is the Condition a 'distinct medical entity'? How should the COMP react to the data being obtained in patients with a specific mutation of the disease?
2. Is the prevalence of the Condition acceptable according to the criteria?
3. Is the Condition serious, life-threatening or seriously debilitating?
4. Has the Company shown Medical Plausibility for the claimed activity of their product?
5. Has the company justified that the product will be of significant benefit?

Part B. Review Orphan designation at the time of marketing authorisation

After four years of development the sponsor has submitted a marketing authorisation and is close to receiving a positive opinion on marketing authorisation from the CHMP (Committee for Human Medicinal Products).

In the document where the sponsor justifies the maintenance of the orphan designation, the sponsor refers to a phase II clinical trial where the product was administered to patients with cystic fibrosis (mild) carrying mutation delF508. A total of 135 patients were recruited and no control group was included in the open-label study. The results of the study indicate that:

- In adults a clinically relevant change in FEV1 is seen. (FEV1 represents the maximum amount of air a person can expel from the lungs after a maximum inhalation in the first second of expiration.)
- The study duration is 6 months as recommended for the demonstration of efficacy.

Another product for cystic fibrosis with a similar mechanism of action and data is already authorised.
The sponsor also provided data from a non-validated survey that shows that patients prefer Antonicaftor compared to their previous experience in terms of its lower frequency of administration (twice a week instead of daily).

Nevertheless in the study, 23% of the patients did not show preference for Antonicaftor.

Questions:

1. What data is relevant for the demonstration of significant benefit? How does this relate to the basis for benefit: i.e. clinically relevant advantage or major contribution to patient care?

2. Can you point out the strongest and weakest points of the data provided?

3. What would be your conclusion on the fulfilment of the criteria and maintenance of orphan status?

Type of study	Population	Number	Variable	Outcome
Survey (non-validated questionnaire)	Patients	135	Preference of current drug in terms of tolerability compared to previous experience	77% rate current treatment as better; 23% no change
Phase II open label	Mild CF with mutation delta F508 deletion	135	FEV1	FEV1 clinically relevant improvement compared to baseline in 73% patients