European Medicines Agency
Pre-authorisation Evaluation of Medicines for Human Use

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Committee for Orphan Medicinal Products

Public summary of positive opinion for orphan designation of aztreonam lysinate (inhalation use) for the treatment of gram negative bacterial lung infection in cystic fibrosis

On 21 June 2004, orphan designation EU/3/04/204 was granted by the European Commission to MoRa Pharm GmbH, Germany, for aztreonam lysinate (inhalation use) for the treatment of gram negative bacterial lung infection in cystic fibrosis.
The sponsorship was transferred to PAREXEL International Limited, United Kingdom, in July 2005 and subsequently to Gilead Sciences International Ltd, United Kingdom, in May 2007.

What is gram negative bacterial lung infection in cystic fibrosis?
Cystic fibrosis is an inherited disease. The genetic information that determines the characteristics of each individual is carried by genes located on structures called chromosomes. In humans, each cell has 23 pairs of chromosomes. For each pair one chromosome is inherited from the mother and the other from the father. Cystic fibrosis is caused by abnormalities of a specific gene, called CFTR, carried by the 7th pair of chromosomes. The CFTR gene is responsible for the production of a protein that regulates outflow of water and salts (like chloride) from cells that cover internal and external surfaces of the body, the so-called epithelial cells. Cystic fibrosis appears only when the CFTR is abnormal on both chromosomes of the 7th pair. The defective transport of water and salts due to the lack of the regulatory protein results in thickening of the secretions in several organs (e.g. lungs, pancreas). This leads to chronic infection of the lungs and chronic inflammation (a response to the injury caused to the tissue). Gram negative bacteria (primary characteristic of bacteria with a particular cell wall layer identified through staining) are micro-organisms that can cause certain types of infections. Chronic infection of the lung with gram-negative bacteria is a typical feature of cystic fibrosis. It can induce damage to the lung tissue and respiratory insufficiency, which is life threatening.

What is the estimated number of patients affected by the condition*?
At the time of designation, gram negative bacterial lung infection in cystic fibrosis affected approximately 1.3 in 10,000 people in the European Union (EU)[*]. This is equivalent to a total of around 50,000 people, and is below the threshold for orphan designation, which is 5 people in 10,000. This is based on the information provided by the sponsor and knowledge of the Committee for Orphan Medicinal Products (COMP).

[*]Disclaimer: The number of patients affected by the condition is estimated and assessed for the purpose of the designation, for a European Community population of 385,000,000 (Eurostat 2002) and may differ from the true number of patients affected by the condition. This estimate is based on available information and calculations presented by the sponsor at the time of the application.

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What treatments are available?
Gram negative bacterial lung infection in cystic fibrosis is treated mostly with antibiotics (drugs that kill micro-organisms) administered by a variety of routes, oral, intravenous and as an aerosol via nebulisation in the lungs (fine spray that the patient has to breath). Several antibiotics were authorised for the condition in some countries in the Community, at the time of submission of the application for orphan designation.
Satisfactory argumentation has been submitted by the sponsor to justify the assumption that aztreonam lysinate might be of potential significant benefit for the treatment of gram negative bacterial lung infection in cystic fibrosis. The assumption of benefit will have to be confirmed at the time of marketing authorisation. This will be necessary to maintain the orphan status.

How is this medicine expected to work?
Aztreonam lysinate is a synthetic antibiotic with activity against a wide range of gram-negative bacteria including *Pseudomonas aeruginosa*. The sponsor has developed a formulation for dry powder inhalation to be administered with a commercial device. It acts by disrupting protein synthesis (the building up) of the bacterial cell wall and this kills the microorganisms.

What is the stage of development of this medicine?
The effects of aztreonam lysinate were evaluated in experimental models.

At the time of submission of the application for orphan designation, clinical trials in patients with treatment of gram negative bacterial lung infection in cystic fibrosis were ongoing.

Aztreonam lysinate was not marketed anywhere worldwide for treatment of gram negative bacterial lung infection in cystic fibrosis or designated as orphan medicinal product elsewhere for this condition, at the time of submission.

According to Regulation (EC) No 141/2000 of 16 December 1999, the Committee for Orphan Medicinal Products (COMP) adopted on 14 May 2004 a positive opinion recommending the grant of the above-mentioned designation.

Update: Aztreonam lysinate (inhalation use) (Cayston) has been authorised in the EU since 21 September 2009 for the suppressive therapy of chronic pulmonary infections due to Pseudomonas aeruginosa in patients with cystic fibrosis (CF) aged 18 years and older.
The primary support for this indication is based on two single 28-day course placebo-controlled studies. The data to support the sustainability of the observed short term benefit over subsequent courses of treatment are limited. Consideration should be given to official guidance on the appropriate use of antibacterial agents.
For more information on Cayston, see:
www.emea.europa.eu/humandocs/Humans/EPAR/cayston/cayston.htm

Opinions on orphan medicinal product designations are based on the following three criteria:
- the seriousness of the condition;
- the existence of alternative methods of diagnosis, prevention or treatment;
- either the rarity of the condition (affecting not more than 5 in 10,000 people in the Community) or insufficient returns on investment.

Designated orphan medicinal products are products that are still under investigation and are considered for orphan designation on the basis of potential activity. An orphan designation is not a marketing authorisation. As a consequence, demonstration of quality, safety and efficacy is necessary before a product can be granted a marketing authorisation.

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Translations of the active ingredient and indication in all EU languages

Language	Active Ingredient	Indication
English	Aztreonam lysinate (inhalation use)	Treatment of gram negative bacteria lung infections in cystic fibrosis
Czech	Aztreonam lyzinát (k inhalaci)	Léčba gramnegativních bakteriálních plicních infekcí u cystické fibrózy
Danish	Aztreonamlysinat (til inhalation)	Behandling af gram-negativ bakteriel lungeinfektion i cystisk fibrose
Dutch	Aztreonam lysinaat (inhalatie)	Behandeling van longinfecties met gramnegatieve bacteriën in cysteuze fibrose
Estonian	Astreonaamlüsinaat (inhalatsiooniks)	Gram-negatiivsete bakterite poolt põhjustatud kopsuinfektsioonide ravi tsüstilise fibroosi korral
Finnish	Atstreonaamilysinaatti (inhalaatioon)	Gramnegatiivisten bakteerien aiheuttamien keuhkotulehdusten hoitoon kystisessä fibroosissa
French	Lysinate d'Aztreonam (voie inhalée)	Traitement des infections pulmonaires de la mucoviscidose causées par des bactéries gram négatif
German	Aztreonam-Lysinat (zur Inhalation)	Behandlung von gram-negativen bakteriellen Lungeninfektionen bei zystischer Fibrose
Greek	Aztreonam lysinate (Χρήση δια ειδπνοής)	Θεραπεία λοιμώξεων πνεύμονος από gram-αρνητικά βακτήρια σε κυστική ίνωση
Hungarian	Aztreonam lizinát (inhalációs alkalmazásra)	Gram negatív baktérium okozta tüdőfertőzések kezelése cysticus fibrosisban
Italian	Aztreonam lisinato (uso inalatorio)	Trattamento di infezioni polmonari da batteri gram-negativi nella fibrosi cistica
Latvian	Aztreonama lizināts (inhalācijām)	Gram-negatīvo baktēriju plaušu infekciju ārstēšana cistiskās fibrozes gadījumos.
Lithuanian	Aztreonamo lizinatas (inhaliacijoms)	Plaučių infekcijų, sukeltų gram-neigiamų bakterijų, gydymas sergant cistine fibroze
Polish	lizynian aztreonamu (inhalacja)	Leczenie zakażeń płuc wywołanych bakteriami gram ujemnymi w przebiegu zwłóknienia torbielowatego
Portuguese	Lisinato de aztreonam (via inalatoria)	Tratamento das infecções pulmonares por bactérias Gram-negativas na fibrose quística
Slovak	Aztreonam lyzinát (inhalácia)	Liečba gramnegatívnych bakteriálnych pľúcnych infekcií pri cystickej fibróze
Slovenian	Aztreonam lizinat (za inhalacijo)	Zdravljenje okužb pljuč povzročenih z gramnegativnimi bakterijami pri bolnikih s cistično fibrozo
Spanish	Lisinato de Aztreonam (vía inhalatoria)	Tratamiento de las infecciones pulmonares por bacterias Gram-negativas en la fibrosis quística
Swedish	Aztreonam-lysinat (användning för inhalation)	Behandling av lunginfektioner i cystisk fibros vilka uppvisar gramnegativa bakterier
Norwegian	Aztreonamlysinat (til inhalasjon)	Behandling av lungeinfeksjoner forårsaket av gramnegative bakterier hos pasienter med cystisk fibrose
Icelandic	Aztreonam lýsínat (til innöndunar)	Meðferð gram-neikvæðra bakteríusýkinga í lungum í slímseigjusjúkdómi

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