(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
24 June 2004 (24.06.2004)

PCT

(10) International Publication Number
WO 2004/052333 A1

(51) International Patent Classification[7]: A61K 9/00, 31/00

(21) International Application Number:
PCT/EP2002/014061

(22) International Filing Date:
11 December 2002 (11.12.2002)

(25) Filing Language: English

(26) Publication Language: English

(71) Applicant *(for all designated States except US)*: **PARI GMBH** [DE/DE]; Moosstrasse 3, 82319 Starnberg (DE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **LINTZ, Frank-Christophe** [DE/DE]; Waldspielplatz 5, 82319 Starnberg (DE). **KELLER, Manfred** [DE/DE]; Hegegasse 5, 79189 Bad Krozingen (DE). **OPOLSKI VON, Simone** [DE/DE]; Hofbrunnstr. 33a, 81479 München (DE).

(74) Agent: **ALBRECHT, Thomas**; Kraus & Weisert, Thomas-Wimmer-Ring 15, 80539 München (DE).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/052333 A1

(54) Title: PHARMACEUTICAL COMPOSITIONS FOR THE PULMONARY DELIVERY OF AZTREONAM

(57) Abstract: The invention relates to pharmaceutical compositions for the delivery of therapeutic compounds to the respiratory system. More in particular, it deals with improved formulations of an antibiotic compound to prevent and treat bacterial infections of the respiratory system. The invention provides a solid pharmaceutical composition for the preparation of an aerosolizable liquid for inhalatin, comprising an effective amount of aztreonam and a basic excipient, wherein the ratio of aztreonam to the basic excipient is selected to yield a solution with a pH of about 3.5 to 5.5 when dissolved in water at an aztreonam concentration of about 30 to 200 mg/ml. Furthermore, the invention provides a pharmaceutical kit for the preparatin of an aerosolizable liquid for inhalation, comprising said solid pharmaceutical composition; and a method for the preparation of such a solid pharmaceutical composition.

Title: Pharmaceutical compositions for the pulmonary delivery of aztreonam

DESCRIPTION

Field of the Invention

The present invention relates to pharmaceutical compositions for the delivery of therapeutic compounds to the respiratory system. More in particular, it deals with improved formulations of an antibiotic compound to prevent and treat bacterial infections of the respiratory system. Such formulations are solid compositions which are dispersible or dissolvable in aqueous carriers to form inhalable liquid compositions. In other aspects, the invention relates to pharmaceutical kits for preparing inhalable liquid formulations which can be aerosolized and used for the pulmonary delivery of therapeutic compounds. The invention further relates to methods for preparing such kits and their components.

Background of the Invention

The delivery of therapeutic compounds to the bronchi and lungs has been used primarily for the local treatment of diseases and conditions of the respiratory system, such as asthma and bronchitis. More recently, the pulmonary administration of systemic drugs, such as insulin, has been proposed and actively pursued in product development programs, utilizing the large surface area of the lungs for absorption.

In principle, drug substances can be delivered to the respiratory system as aerosolized dry powders or liquids, the liquids representing either solutions or dispersions, such as drug suspensions. Various devices have been developed to

allow the inhalation of such powder suspension or liquid formulations. For all of them, one of the most important requirements is that they can deliver their contents as a finely divided aerosol. Depending on whether the drug should be delivered to the bronchi or to the deep lungs, the optimal droplet or particle size for typical formulations may vary from about 10 microns down to below one micron; larger particles may be useful if their density is very low.

Metered-dose inhalers deliver a measured dose of the drug in the form of a suspension of extremely small liquid or solid particles, which is dispensed from the inhaler by a propellant under pressure (Dictionary of Medicines, Oxford University Press). Such inhalers are placed into the mouth and activated to release drug as the individual takes a breath. This requires a certain amount of coordination and may therefore be unsuitable for children. Spacers, or spacing devices, which are available for use with some aerosol inhalers, extend the space between the inhaler and the mouth. This reduces the speed at which the aerosol travels to the back of the mouth, allowing more time for the propellant to evaporate and therefore reducing the impact of the propellant on the back of the mouth - which can cause irritation - and enabling a higher proportion of the particles of the drug to be inhaled. There is also less need to coordinate breathing in with activation of the inhaler. Breath-activated inhalers deliver the drug, in the form of an aerosol or a dry powder, only when the user places his mouth over the outlet and breathes in. This obviates the need to coordinate breathing in with depressing the dispenser. The dose of drug will still be measured or metered, and is not dependent on the size of breath taken.

Dry-powder inhalers, on the other hand, are loaded with capsules of the drug in powder form; as the inhaler is activated by taking a breath, the capsule is punctured and a type of fan mechanism disperses the powder so that it can be inhaled (these inhalers are known as "Spinhaler" or "Rotahaler"). "Turbohalers" are fitted with canisters that deliver measured doses of the drug in powder form.

Aqueous-based solutions and suspensions may also be inhaled with nebulizers. Various types of nebulizers are commercially available or presently being developed. A more traditional type is the jet nebulizer. More recently,

ultrasonic and vibrating membrane-type nebulizers were developed. An example of a modern electronic vibrating membrane nebulizer is the PARI eFlow™, which represents a major advance over conventional nebulizers in terms of output rates and patient convenience.

While traditional inhalation therapies were primarily directed to the prevention and treatment of allergic and inflammatory diseases and conditions of the respiratory system including asthma and obstructive bronchitis, novel therapeutical approaches have been developed more recently. For instance, the local treatment of pulmonary infections with antibiotics has been suggested and, with tobramycin being the first antibiotic approved for this use, successfully introduced to the therapy of certain severe or even life-threatening types of infection. Tobramycin, which is supplied as Tobi®, is a sterile, clear, slightly yellow, non-pyrogenic, aqueous solution with the pH and salinity adjusted specifically for administration by a compressed air driven reusable nebulizer. It is approved for the treatment of cystic fibrosis patients infected with Pseudomonas aeruginosa.

Other pulmonary antibiotic therapies have been proposed in the scientific and patent literature. For instance, WO 02/03998 discloses inhalable formulations of macrolide antibiotics, such as erythromycylamine, for delivery by aerosolization. The concentrated erythromycylamine formulations contain an amount of erythromycylamine effective to treat infections caused by susceptible bacteria. Unit dose devices having a container comprising a formulation of the macrolide antibiotic in a physiologically acceptable carrier are also described. The document further discloses methods for treatment of pulmonary infections by such formulations delivered as an aerosol having mass median aerodynamic diameter predominantly between 1 and 5 micrometers.

In WO 00/35461, a method for the treatment of severe chronic bronchitis (bronchiectasis) using a concentrated aminoglycoside antibiotic formulation is disclosed. The method includes delivering the antibiotic to the lungs endobronchial space including alveoli in an aerosol or dry powder having a mass medium diameter predominately between 1 and 5 microns. The method comprises the administration of the antibiotic at a concentration one to ten thousand times higher

than the minimal inhibitory concentration of the target organism. Preferably, the method comprises the endobronchial administration of aerosolized tobramycin to treat pseudomonal infections in severe chronic bronchitis patients.

On the other hand, a wide variety of gram-negative bacteria cause severe pulmonary infections, and many of these bacteria are or become resistant to commonly used or specialty antibiotics including tobramycin, and require treatment with new types of antibiotics. The pulmonary infections caused by gram-negative bacteria are particularly dangerous to patients who have decreased immunoprotective responses, such as cystic fibrosis (CF) and HIV patients, patients with bronchiectasis or those on mechanical ventilation. Thus, bacterial respiratory infections caused by resistant bacteria remains a major problem, particularly in CF and HIV patients. For example, chronic pulmonary infection with Pseudomonas aeruginosa in patients with cystic fibrosis is a major cause of their high mortality. The eradication of the chronic pulmonary infection is extremely difficult. It is estimated that more than 60% of all cystic fibrosis patients are infected with Pseudomonas aeruginosa bacterium strains which are largely resistant to most common antibiotics including piperacillin, ticarcillin, meropenem, netilmicin, and only to a small degree sensitive to azlocillin, ciprofloxacin, timentin and ceftazidime. Many strains have even been shown to develop resistance to tobramycin.

Cystic fibrosis, or mucoviscidosis, is an inherited disease of the exocrine glands, primarily affecting the GI and respiratory systems, and usually characterized by exocrine pancreatic insufficiency and abnormally high sweat electrolytes. Cystic fibrosis is the most common life-shortening genetic disease in the white population. Its incidence in the USA is about 1 in 3,300 white births, 1 in 15,300 black births, and 1 in 32,000 Asian-American births.

Fifty percent of CF patients present with pulmonary manifestations, usually chronic cough and wheezing associated with recurrent or chronic pulmonary infections. Cough is the most troublesome complaint, often accompanied by sputum, gagging, vomiting, and disturbed sleep. Intercostal retractions, use of accessory muscles of respiration, a barrel-chest deformity, digital clubbing, and

cyanosis occur with disease progression. Upper respiratory tract involvement includes nasal polyposis and chronic or recurrent sinusitis. Adolescents may have retarded growth, delayed onset of puberty, and a declining tolerance for exercise. Pulmonary complications in adolescents and adults include pneumothorax, hemoptysis, and right heart failure secondary to pulmonary hypertension. Early in the course, Staphylococcus aureus is the pathogen most often isolated from the respiratory tract, but as the disease progresses, Pseudomonas aeruginosa is most frequently isolated. A mucoid variant of Pseudomonas is uniquely associated with CF. Colonization with Burkholderia cepacia occurs in up to 7% of adult patients and may be associated with rapid pulmonary deterioration.

Other gram-negative bacteria, which are often resistant to tobramycin, may also complicate the care of a cystic fibrosis patient. These bacteria include Stenotrophomonas maltophilia and Alcaligenes xylosoxidans. Antibiotic therapy of these infections is usually ineffective or leads to rapid emergence of drug resistance.

In order to address the continuous need for an effective therapy for treatment of acute and chronic pulmonary bacterial infections caused by gram-negative bacteria and particularly those caused by Burkholderia cepacia, Stenotrophomonas maltophilia, Alcaligenes xylosoxidans, and multidrug resistant Pseudomonas aeruginosa, WO 02/051356 proposes the local therapy of the respiratory system by delivering a concentrated formulation of the monobactam antibiotic aztreonam as an inhalable aerosol, or as a dry powder formulation. According to the document, about 1 to 250 mg of aztreonam may be dissolved in 1 to 5 ml of saline or another aqueous solution. The formulation is delivered to the lung endobronchial space as an aerosol having mass medium average diameter particles predominantly between 1 and 5 micrometers, using a nebulizer capable of atomizing the aztreonam solution into droplets or particles of the required sizes. Alternatively, for the delivery of a dry inhalable powder, aztreonam is milled or spray-dried to particle sizes of 1 to 5 micrometers.

However, the document does not reveal how a sufficiently large dose of aztreonam, such as 100 mg, can be dissolved and accommodated in a small

volume, such as 1 or 2 ml of aqueous solution, to allow efficient nebulization and pulmonary delivery. Furthermore, the disclosure does not address the physicochemical, pharmaceutical problems arising from formulating aztreonam as a concentrated solution for inhalation, and does not teach how to reconcile the needs and requirements with regard to stability, osmolality- and pH-related tolerability, nebulization efficiency, and convenience in terms of a short inhalation time.

Objects of the Invention

It is an object of the invention to provide improved pharmaceutical compositions for the delivery of aztreonam to the respiratory system, and to overcome the limitations and disadvantages of currently known therapeutical compositions. The improved compositions should be stable, convenient and safe in their application, and physiologically tolerable. They should allow easy and efficient aerosolization using modern nebulizers, such as electronic nebulizers based on a vibrating membrane design.

It is a further object to provide pharmaceutical kits comprising such compositions in solid form, at the same time providing a metered dose of an appropriate liquid carrier to dissolve the solid compositions and to form an aerosolizable, inhalable liquid.

Yet another object is to provide methods for preparing such compositions and kits.

Further objects of the invention will become clear on the basis of the following description.

Summary of the Invention

In a first aspect, the invention provides a pharmaceutical composition for the preparation of an aerosolizable liquid for inhalation. The composition comprises an effective amount of the monobactam antibiotic aztreonam, and a basic excipient. The composition is a dry solid formulation which can be dissolved in an appropriate aqueous carrier to yield an aerosolizable liquid. The ratio of aztreonam to the basic excipient is selected to yield a solution having a pH of 3.5 to 5.5 when dissolved in water, or in an appropriate aqueous carrier without significant buffer capacity, at an aztreonam concentration of 30 to 200 mg/ml. A particularly preferred basic excipient is the amino acid lysine, or a salt or derivative thereof. The composition can be formulated as a powder, a granulate, a lyophilized unit form, a tablet, or as pellets. A particularly preferred formulation type is that of a lyophilate, i.e. a lyophilized powder or a coherent lyophilized form.

In a second aspect, the invention provides a pharmaceutical kit for the preparation of an aerosolizable liquid for inhalation. The kit comprises a dry, solid-state composition comprising an effective amount of aztreonam and a basic excipient, and an aqueous liquid composition to be used as carrier to dissolve the solid composition to yield an aerosolizable solution. In the kit of the invention, the relative amounts of aztreonam, the basic composition, and the aqueous liquid composition are selected to yield a solution having an aztreonam concentration of 30 to 200 mg/ml and a pH of about 3.5 to 5.5 upon dissolving the solid composition in the liquid composition. A preferred pH-range is from about 4.0 to 4.5.

In a third aspect, the invention provides a method for preparing a dry solid composition which is useful for the preparation of an aerosolizable liquid for inhalation. The method includes the steps of (a) preparing an aqueous solution comprising aztreonam and a basic excipient capable of at least partially neutralizing the aztreonam; (b) filtering said aqueous solution using a filter capable of removing substantially all microbial and viral contaminants to yield a sterile filtrate; and (c) lyophilizing said sterile filtrate under aseptic conditions. In one of

the preferred embodiments, the dry solid composition prepared by the method of the invention is a component of a pharmaceutical kit.

The aerosolizable liquid for inhalation may be nebulized and inhaled with commercially available nebulizers, including jet nebulizers such as PARI LC Plus®, ultrasonic nebulizers, or vibrating disc nebulizers such as PARI eFlow™.

Further aspects of the invention and more embodiments will become clear on the basis of the detailed description below.

Detailed Description of the Invention

The invention provides a solid pharmaceutical composition for the preparation of an aerosolizable liquid for inhalation. The composition can be dissolved in an appropriate aqueous carrier to yield an aerosolizable liquid which can be used for pulmonary administration. The composition comprises an effective amount of the monobactam antibiotic aztreonam, and a basic excipient. The ratio of aztreonam to the basic excipient is selected to yield a solution having a pH of 3.5 to 5.5 when dissolved in water, or in an appropriate aqueous carrier without significant buffer capacity, at an aztreonam concentration of 30 to 200 mg/ml.

As used herein, a solid pharmaceutical composition is a formulation comprising at least one active ingredient, processed to be in the basically dry and solid state. Solid-state formulations can be coherent single units, such as tablets or coherent lyophilized forms, or they can be designed and processes as multiple units, such as pellets, micropellets, granules, powders, or microcapsules. Presently preferred are formulation types selected from lyophilized coherent units, lyophilized powders, and granules. Particularly preferred are lyophilized units, i.e. coherent forms prepared by freeze drying a solution or suspension. As defined herein, the terms "lyophilate(s)" and "lyophilisate(s)" may be used interchangeably.

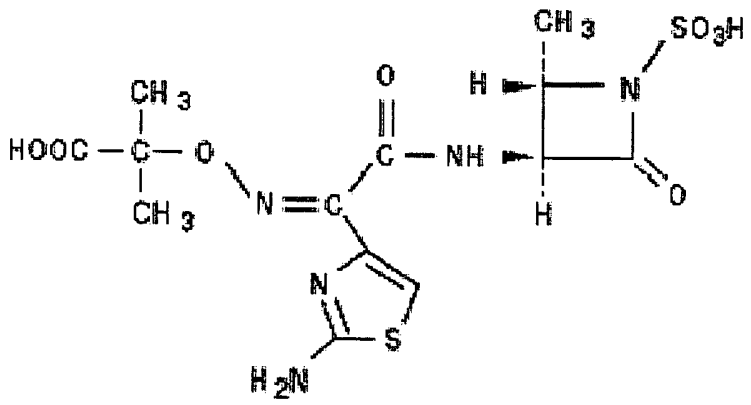
The solid composition can be dissolved in an appropriate carrier to form a solution which is aerosolizable and adapted for inhalation. In particular, the

solution should be useful for inhalation as an aerosol generated by a nebulizer. Thus, the ingredients of the composition should be soluble in aqueous carriers which are adapted for pulmonary administration. Therefore, the composition should be formulated with soluble excipients and, optionally, with excipients which may also enhance the solubility of the active ingredient. Even though it is generally not very common, and perhaps even difficult, to formulate solid pharmaceutical compositions without the use of insoluble excipients such as glidants and disintegrants, it is preferred that the composition of the invention is substantially free of such insoluble materials. Furthermore, the use of common polymeric binders, such as polyvinylpyrrolidone or gelatin, should be avoided, because these materials may not be cleared readily from the site of administration, and accumulate in the respiratory system. In one embodiment, the solid composition of the invention is substantially free of any polymeric constituents.

Typical dissolution times of the solid compositions are less than 3 seconds for lyophilates, preferably less than about 1 second; less than about 5 seconds for spray-dried powders with a mean particle size of about 5 to 20 µm; and less than about 10 seconds for granules with a mean particle size of about 150 to 500 µm.

Other formulation components of the solid composition should be selected as appropriate for pulmonary administration. Excipients which are known to be well tolerated by the respiratory system are preferred.

The composition of the invention serves the purpose of enabling the administration of the monobactam antibiotic aztreonam to the respiratory system by inhalation. As used herein, aztreonam refers to the compound chemically defined as (Z)-2-[[[(2-amino-4-thiazolyl)[[(2S,3S)-2-methyl-4-oxo-1-sulfo-3-azetidinyl]carbamoyl]methylene]amino]oxy]-2-methyl-propionic acid, or to any salt or derivative thereof. The chemical formula of aztreonam is:



$C_{13}H_{17}N_5O_8S_2$ MW 435.44

Aztreonam is marketed as Azactam® in the United States, an injectable product consisting of a sterile, nonpyrogenic, sodium-free, white powder containing aztreonam, and approximately 780 mg arginine per gram of aztreonam. Azactam® is formulated to be administered intravenously or by intramuscular injection, after reconstitution with an appropriate amount of a sterile liquid carrier, such as sterile water for injection.

Primarily due to its content of arginine, Azactam® cannot be used for inhalation. Arginine is considered toxic to the lungs and may cause lung tissue irritation, inflammation, bronchospasm and cough, and therefore is not suitable for a delivery by aerosolization. Therefore, Azactam® or aztreonam arginine salt is not approved for inhalation use.

Nevertheless, aztreonam itself may be considered a highly promising candidate for the local treatment of pulmonary infections caused by gram-negative bacteria, provided it is delivered in an appropriate manner. A more detailed discussion of the potential usefulness of inhalable aztreonam in pulmonary infections is found in WO 02/051356, which is incorporated herein by reference.

The solid composition of the present invention is particularly useful for the administration of aztreonam because this active compound is not sufficiently

stable in an aqueous liquid to allow for a shelf life of more than about 2 years without refrigeration. In contrast, in the form of a solid composition which is, prior to its use, dissolved to an aerosolizable, inhalable liquid, aztreonam can be stabilized over such a period of time. Even more preferred is a solid composition in which aztreonam is stable for at least three years. As used herein, the stability of a compound refers to the fact that under normal storage conditions, at least 90 wt-% of the compound remain chemically unchanged after the designated period of time.

Like Azactam®, the solid composition of the invention comprises, in addition to the active ingredient aztreonam, a basic excipient. The basic excipient is preferably not arginine, or a salt or derivative of arginine, or any other compound which is known to be harmful when inhaled. Furthermore, the ratio of aztreonam to the basic excipient is selected to result in a somewhat acidic pH of about 3.5 to 5.5 when the composition is dissolved in an appropriate carrier to yield an aerosolizable solution for inhalation having an aztreonam concentration of about 30 to 200 mg/ml, provided an aqueous carrier without any substantial buffer capacity is used. As defined herein, the requirement of achieving a pH of about 3.5 to 5.5 at an aztreonam concentration of about 30 to 200 mg/ml of the reconstituted, aerosolizable solution for inhalation is met when said pH is achieved at one of the concentration levels within the given concentration range; it is not required that said pH results at all concentrations within the given range. The actual concentration level at which the pH of 3.5 to 5.5 is attained resembles most likely the concentration at which the solution is to be administered.

In this respect, the present invention differs from known formulations of aztreonam, such as Azactam® or the compositions disclosed in WO 02/051356. While Azactam® comprises the basic excipient arginine which is undesirable for inhalation, WO 02/051356 recommends a pH range of 4.5 to 7.5, with a preference for the range of 5.5 to 7.0. However, even though it is correct that a basic excipient is needed in the formulation in order to at least partially neutralize the poorly soluble acid aztreonam and thereby increase its aqueous solubility and its tolerability to the lungs, a pH of 5.5 and higher has been found to be rather undesirable, primarily because of the large relative amount of basic excipient

needed to achieve this pH, which in turn may lead to an unphysiologically high osmolality. This problem is most pronounced for relatively concentrated aztreonam solutions which are desirable for achieving short inhalation times. It has been found that the rather acidic pH as defined herein is better tolerated by the lungs than very high osmolalities, such as more than about 600 mOsmol/kg. In fact, in a preferred embodiment, the aerosolizable aztreonam solution has a pH in the range of about 4.0 to 4.5. The fact that this pH may be well tolerated by the respiratory system is further supported by the low incidence of adverse reactions to the currently marketed product, Pulmicort®, which is a budesonide suspension for inhalation to be used with a nebulizer, which typically has a pH of about 4.1.

In principle, the basic excipient which is needed to at least partially neutralize aztreonam may be selected from a relatively large number of compounds which may safely be used in inhalable products. As used herein, the basic excipient may represent an organic or inorganic base, salt, or ion. It is understood by a person skilled in the technical field that, after being mixed with aztreonam, some or all of the basic excipient will react with the drug substance to form a salt. Therefore, the term "basic excipient" is used herein to include the ionic species resulting from the neutralization reaction of aztreonam and the basic excipient.

Alternatively, aztreonam and the basic excipient may not be incorporated into the composition as separate ingredients which form a salt during the preparation of the composition, but as a preformed salt. Therefore, instead of using aztreonam and a basic excipient to prepare the composition of the invention, an appropriate aztreonam salt may be used.

Examples of basic excipients, or cations derived therefrom, which may be used include ammonium, sodium hydroxide, calcium carbonate, magnesium carbonate, sodium bicarbonate, other alkali and alkaline earth metal ions, such as lithium, potassium, magnesium or aluminum, quaternary ammonium, and amine cations, including, but not limited to ammonium, ethanolamine, ethylenediamine, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, diethylamine; basic amino acids including lysine, histidine, and ornithine.

A particularly preferred basic excipient is lysine, or a salt or derivative of lysine. Alternatively speaking, a preferred salt of aztreonam which may be incorporated in the solid composition of the invention is aztreonam lysinate. Lysine has several advantages over other basic compounds. It is biocompatible and well tolerated when administered to the body via various routes including the pulmonary route. In compositions for the preparation of relatively concentrated aztreonam solutions for inhalation, it is advantageous over inorganic acids as it possesses a considerably lower osmotic activity.

One of the most useful properties of lysine in the context of the present invention, however, is that it appears to be very tolerable to the lungs, and even has a mild mucolytic and expectorant activity which may be supportive in the therapy of pulmonary infections. This is clearly in contrast to other amino acids including arginine. Especially for patients suffering from cystic fibrosis, but to some extent also for other patients with pulmonary infections, this property of lysine may be of great value. In fact, many cystic fibrosis patients with pulmonary manifestations receive expectorants as adjuvant medication today. Therefore, the selection of lysine, or a salt or derivative of lysine, as a preferred basic excipient according to the invention follows both technical as well as physiological rationales.

When lysine is chosen as basic excipient, a recommended mass ratio of aztreonam to lysine is from about 2 : 1 to 1 : 1. In other words, if the solid composition contains about 100 mg of aztreonam, a preferred range for the amount of lysine to be incorporated is from about 50 to 100 mg. Especially preferred is the incorporation of about 60 to 75 mg of lysine, and most preferred is an incorporation of approximately 65 mg of lysine monohydrate per 100 mg of aztreonam. Alternatively, the corresponding relative amounts of aztreonam lysinate, optionally in combination with an additional amount of aztreonam acid, may be used.

Other than the basic excipient which is needed to at least partially neutralize aztreonam and render it soluble, the composition should contain as few other excipients as possible. As mentioned above, especially the use of insoluble and

polymeric excipients should be avoided as these materials are not easily cleared from the lungs. Preferred compositions do not contain polymers or insoluble excipients. As defined herein, an insoluble excipient is a therapeutically inactive material or substance with a water solubility which is commonly referred to as "very slightly soluble" or "practically insoluble".

It may be necessary, however, to incorporate an excipient to increase the wettability of the drug substance, such as a surfactant. At the same time, a surfactant could increase the spreading of the inhaled liquid in the lungs. Clearly, there are not many surfactants which are recommendable for the use in inhalable drug products. Among the preferred surfactants for the composition of the invention are Tween® 80, tyloxapol, phospholipids, and vitamin E TGPS, or mixtures thereof. As even these surfactants should be used carefully in inhalable products, it is recommended that their relative amount in the composition should be as low as possible, such as not more than about 0.2 % by weight, and more preferably not more than about 0.1 %. Most preferred are compositions which contain no more than about 0.05 % of surfactant.

In another embodiment, the invention provides a pharmaceutical kit for the preparation of an aerosolizable liquid for inhalation. Such a kit comprises a dry solid composition comprising an effective amount of aztreonam and a basic excipient, and an aqueous liquid composition. Again, the relative amounts of aztreonam, the basic excipient, and in this case also of the aqueous liquid composition, are selected to yield an aqueous solution having an aztreonam concentration of about 30 to 200 mg/ml and a pH of about 3.5 to 5.5 when the solid composition is dissolved in the liquid composition.

As used herein, a kit refers to a set of at least two compositions used for a specific purpose. In the present case, the purpose is the preparation of a liquid pharmaceutical composition for pulmonary administration. In most cases, such a liquid composition will resemble a solution, most preferably an aqueous solution. In some cases, however, the liquid may not be a solution in the strict physical sense, but rather a dispersion. As such, it may contain a dispersed colloidal material, suspended particles, dispersed liquid or semisolid droplets, liposomes,

and the like. In the present invention, it is preferred, however, that the liquid pharmaceutical composition which can be prepared by mixing the components of the kit is a solution.

The kit is preferably designed and formulated for the accommodation of one single dose of aztreonam. Thus, the complete dry solid composition should be mixed with, and dissolved in, the aqueous liquid composition of the kit to prepare an aerosolizable liquid for the inhalation of one dose of the drug substance.

The same principles and preferences as discussed above for the solid composition should also be applied to the embodiments of the kits. In fact, the solid composition of claim 1 represents a good example of a solid composition which is a component of a pharmaceutical kit according to the invention.

The amount of aztreonam contained in the solid composition of the kit preferably represents one single dose of the compound to be delivered to the respiratory system. On the other hand, there may be patients such as children who need less than the dose contained in the kit. In general, the aztreonam content is in the range of about 30 to 200 mg. A preferred content is about 100 mg.

Furthermore, the dry solid composition of the kit comprises any pharmaceutically acceptable basic excipient, or salt or derivative thereof; however, a preferred base is the amino acid lysine, or is derived from lysine. The particular advantages of lysin in the context of the present invention have been discussed further above. A basic excipient serves to at least partially neutralize aztreonam and thereby increase its solubility in water, but also to avoid the unphysiologically low pH resulting from the dissolution of aztreonam in water. When lysine is chosen as basic excipient, a recommended mass ratio of aztreonam to lysine is from about 2 : 1 to 1 : 1. In other words, if the solid composition of the kit contains about 100 mg of aztreonam, a preferred range for the amount of lysine or lysine derivative to be incorporated is from about 50 to 100 mg. Especially preferred is the incorporation of about 60 to 75 mg of lysine, and most preferred is an incorporation of approximately 65 mg of lysine monohydrate per 100 mg of

aztreonam. Alternatively, the corresponding relative amounts of aztreonam lysinate and aztreonam acid may be used.

The solid composition of the kit may also contain a surfactant to increase the wettability of the drug substance and thereby reduce the dissolution time of the composition. At the same time, a surfactant could increase the spreading of the inhaled liquid in the lungs. Among the preferred surfactants for the composition of the invention are Tween® 80, tyloxapol, phospholipids, and vitamin E TGPS, or mixtures thereof. As these surfactants should be used carefully in inhalable products, it is recommended that their relative amount in the composition should be as low as possible, such as not more than about 0.2 % by weight, more preferably not more than about 0.1 %. Most preferred are compositions which contain no more than about 0.05 % of surfactant.

A further excipient whose incorporation is highly recommended and preferred according to the invention is a salt containing chloride ions, such as sodium chloride or calcium chloride. It has been suggested that aerosolized aqueous liquids are much better tolerated by the lungs when they contain chloride ions, such as diluted saline. While in the prior art, the rationale for the incorporation of sodium chloride in inhalable preparations was typically to adjust the osmotic pressure of the inhalable liquid to physiological conditions, it is preferred in the present invention to incorporate a chloride even when the aerosolizable liquid is already hyperosmotic by virtue of its content of the drug substance and/or the basic excipient which is needed to render the drug substance better soluble.

The chloride can be incorporated either within the dry solid composition or the aqueous liquid composition of the kit. In a presently preferred embodiment, the chloride is part of the liquid composition. If the selected ratio of the amounts of aztreonam and of the basic excipient on the one hand, and of the liquid composition on the other hand, are selected to yield a hyperosmotic solution for inhalation upon the dissolution of the solid composition in the liquid composition, the amount of chloride to be incorporated should not exceed about 0.3 % (W/V) of the total mass of the solution for inhalation. More preferably, it should be below about 0.2 %. A useful way of incorporating a chloride is to provide the liquid

composition of the kit in the form of a sterile, diluted saline solution with a sodium chloride concentration of about 0.1 to 0.2 %.

In order to allow a rapid aerosolization and administration of the final solution for inhalation, the amount of liquid composition in the kit should be relatively small, and selected to allow the administration of the complete single dose of aztreonam within no more than about 5 to 15 minutes, and preferably no more than about 5 to 10 minutes. Therefore, the volume of the liquid composition should not exceed about 5 ml. More preferably, its volume is in the range of about 0.8 to 2 ml. In one embodiment, the volume of the liquid composition is approximately 1 ml. In a further embodiment, the relative amounts of aztreonam and the liquid composition are selected to yield a solution for inhalation with an aztreonam concentration of about 50 to 150 mg/ml, and more preferably about 85 to 115 mg/ml. In yet a further embodiment, the amount of aztreonam in the solid composition is about 100 mg, the basic excipient is about 60 to 70 mg of lysine, and the volume of the liquid composition is about 1 ml.

As mentioned above, the solid and the liquid compositions of the kit are adapted to be mixed with each other to form an aztreonam solution for inhalation whose pH is in the range of about 3.5 to 5.5. More preferably, the pH of the resulting solution is about 4.0 to 4.5. As is discussed in more detail further above, it seems that a relatively acidic pH, such as 4.0 to 4.5, is tolerated much better by the lungs than a very high osmolality, such as more than about 600 mOsmol/kg, which would result from further increasing the relative amount of the basic excipient in the solid composition. A physiologically ideal pH of about 6 to 7 at an osmolality of no more than about 600 mOsmol/kg, on the other hand, would require a reduced aztreonam concentration in the final solution for inhalation, which is not acceptable as this increases the volume to be administered and the time needed for inhaling a single dose of the drug substance.

In another embodiment, the compositions of the kit are selected and formulated in such a way that the aerosolizable aqueous solution which is formed by combining or mixing these compositions possesses a viscosity of about 1.5 to 2.0 mPas. As used herein, the viscosity is defined by its characterization with a

rotating cone-plate rheometer, such as the rheometer type RS-1 by Haake, Germany. A much higher viscosity could significantly reduce the output rate of commercially available nebulizers, which has been discussed in detail by Lintz et al., Influence of viscosity and surface tension on the nebulization efficiency of a jet (LC Plus®) and a vibrating membrane type nebulizer (e-Flow®), AAPS Annual Meeting 2001, which is incorporated herein by reference. A particularly preferred viscosity is from about 1.6 to 1.8 mPas. It was found that, in the case of aztreonam, this viscosity range allows a surprisingly large output rate in combination with the electronic vibrating membrane nebulizer e-Flow®, while the respirable fraction of the aerosol remains high.

Furthermore, the compositions of the kit are selected to yield an aerosolizable solution with a surface tension of about 50 to 73 mN/m. As used herein, the surface tension is defined according to the characterization method using a bubble point tensiometer, such as a Sita Online t60 by Sita Messtechnik, Germany. A preferred surface tension range is from about 60 to 70 mN/m. While a further reduction of the surface tension, such as below 50 mN/m, which can be achieved by the incorporation of a surfactant, or by the increase of the amount of surfactant, would generally tend to increase the rate of nebulization with many common nebulizers, the droplet size would also increase and lead to a lower respirable fraction of the aerosol (see also Lintz et al., ibid.). Therefore, the surface tension should preferably not be decreased below about 50 mN/m in the practice of the present invention.

In a further embodiment, the compositions of the kit are selected to yield an aerosolizable solution with an osmolality of about 300 to 650 mOsmol/kg, and more preferably of no more than about 600 mOsmol/kg. As was found by the inventors, this range represents a surprisingly good compromise between the physiological and pharmaceutical requirements. While an isoosmotic solution can only be reached when the concentration of aztreonam and/or the basic excipient are significantly reduced, such a solution would either have an unacceptably low pH or require a very long time to nebulize. As discussed above, one useful aspect of the selection of lysine as basic excipients, which is a preferred embodiment of the invention, is the fact that the osmotic activity of lysine is relatively low in

comparison with other basic excipients which could potentially be used, the latter representing strong electrolytes.

The aerosolizable liquid for inhalation prepared from the solid composition of the invention, or from the solid composition of the kit of the invention, may be aerosolized and inhaled with commercially available nebulizers, including jet nebulizers such as PARI LC Plus®, ultrasonic nebulizers, or vibrating disc nebulizers such as PARI eFlow™.

The kit itself can be designed according to several options. For instance, it may consist of a secondary package comprising a first closed container, such as a vial, containing the dry solid composition, and another closed container, such as a vial or an ampoule, containing the aqueous liquid composition. In view of the intended use, both compositions must be sterile, and both primary packaging systems must be designed to protect the compositions from microbial and other contaminants. In another embodiment, the kit may contain a primary packaging unit which holds both the solid and the liquid composition, but in separate chambers, such as blister chambers. The applicant's co-pending application PCT/EP02/11918 discloses several useful designs for pharmaceutical kits for the preparation of aerosolizable solutions for inhalation; the disclosure is incorporated herein by reference.

The kits and their components can be prepared by known methods, or by adapted methods based on known processes. For instance, the aqueous liquid composition may generally be manufactured in much the same way as other sterile solutions, such as injectable solutions. Unless the liquid composition comprises a sensitive compound, a preferred method of manufacture would include a step of sterilization after the preparation of the liquid and its filling into the primary packaging material. One of the useful sterilization methods for the liquid is heat sterilization under increased pressure.

It may, however, not be quite so straightforward to prepare the solid composition of the kit. As mentioned before, the solid composition should preferably be free of insoluble materials and polymeric excipients. Therefore, when

the solid composition is designed as a powder, as granules, or pellets, care must be taken to adapt the common pharmaceutical methods for making such formulations without some of the typical excipients used for these, such as insoluble fillers, polymeric binders, or antiadherents. For instance, the applicant's co-pending application EP02025006.4, whose disclosure is also incorporated herein by reference, describes some methods for making granules without these excipients, to enable the use of such granules for the preparation of inhalable solutions.

Alternatively, the solid composition of the invention, which may or may not be part of a kit, can be prepared by lyophilization, i.e. freeze drying. In order to carry out this method, at least these three steps are to be followed according to the invention: (a) Preparing an aqueous solution comprising aztreonam and a basic excipient capable of at least partially neutralizing the aztreonam; (b) filtering said aqueous solution using a filter capable of removing substantially all microbial and viral contaminants to yield a sterile filtrate; and (c) lyophilizing said sterile filtrate under aseptic conditions. The steps (a) to (c) are to be carried out in the given order, but further steps can be introduced before or after each of the steps.

In step (a), an aqueous solution comprising aztreonam and a basic excipient capable of at least partially neutralizing the aztreonam is prepared. In a similar fashion as already discussed further above, the phase "aztreonam and a basic excipient" is used herein to also include an aztreonam salt. For instance, it might not be necessary to prepare an aqueous solution using aztreonam acid and a base; instead, a solution of the aztreonam salt may be prepared directly, optionally comprising an additional amount of aztreonam acid. Also, the term "aqueous solution" is used in this context to include a suspension as well, because it is not an absolute requirement of the method of the invention that absolutely all of the aztreonam must be dissolved in step (a). Typically, however, at least a major part of the aztreonam will be dissolved.

Step (b), in which the solution prepared in step (a) is processed to undergo sterile filtration, is preferred over other options which lead to a sterile solid lyophilate. Both heat- and radiation-based sterilization methods may lead to a

significant degree of aztreonam degradation. Sterile filtration, on the other hand, is a commonly used process in the manufacture of sterile pharmaceutical solutions. It requires, however, that the subsequent processes are conducted under aseptical conditions until the composition is sealed from the environment within an appropriate container or primary packaging system.

Step (c) includes the aseptic freezing of the filtered solution provided in step (b). In order to avoid large amounts of crystalline material in the lyophilate, rapid freezing is preferred. In the case of aztreonam, the presence of crystals is undesirable because they increase the risk of instability. The presently most instable modification of the drug substance is the α-modification, which is formed, for instance, from other forms at or near the glass transition temperature of approximately 80°C. Step (c) further includes the sublimation of water and, if used, other solvents, such as volatile organic solvents including ethanol, acetone etc. The sublimation itself proceeds under vacuum at temperatures below the freezing point. Typically, lyophilization also includes a secondary drying phase which is conducted at room temperature or even elevated temperatures, under vacuum.

The invention will be further illustrated by the following examples which are, however, not intended to limit the scope of the invention.

Examples

Example 1

A dry, solid composition comprising aztreonam and lysine was prepared by lyophilization. More in detail, 50 g of aztreonam was suspended in sterile water for injection. A solution of lysine monohydrate in water (20 % W/V) was slowly added until pH 4.5 was reached, corresponding to approximately 39 g of lysine. By this time, the aztreonam had dissolved. The total mass was adjusted to about 780 g by adding sterile water. Subsequently, the bulk solution was filtered using a Sterivex (0.22 µm) filter cartridge. Of the filtered solution, aliquots of 5 ml were dosed into brown glass vials. The vials were then closed with rubber stoppers (position:

"open") and placed in a freeze dryer. Freezing was conducted for 9 hours at -40°C without vacuum. The primary drying phase was for 20 hours at -10°C and a pressure of 0.25 mbar, followed by a secondary drying phase at room temperature and 0.04 bar for 20 hours. After the completion of the freeze drying cycles, the rubber stoppers were set on the "closed" position, and the vials were fitted with aluminum crimp caps.

Example 2

A lyophilate having a volume of 1 ml containing 100 mg of aztreonam and 64 mg of lysine was prepared by a similar procedure as described in example 1. The lyophilate was combined to a kit with a vial containing 1 ml of a sterile sodium chloride solution (0.17 %). The lyophilate dissolved in the saline solution within about 1 second under agitation. The pH of the resulting solution was about 4.2.

Example 3

A lyophilate having a volume of 1 ml containing 100 mg of aztreonam and 72 mg of lysine was prepared by a similar procedure as described in example 1. The lyophilate was combined to a kit with a vial containing 1 ml of a sterile sodium chloride solution (0.17 %). The lyophilate dissolved in the saline solution within about 1 second under agitation. The pH of the resulting solution was about 5.5.

Example 4

A lyophilate having a volume of 1 ml containing 100 mg of aztreonam, 64 mg of lysine, and 0.5 mg of tyloxapol was prepared by a similar procedure as described in example 1. The lyophilate was combined to a kit with a vial containing 1 ml of a sterile sodium chloride solution (0.17 %). The lyophilate dissolved in the saline solution within less than 1 second even without agitation. The pH of the resulting solution was about 4.4.

Example 5

A lyophilate having a volume of 1 ml containing 100 mg of aztreonam and 64 mg of lysine was prepared by a similar procedure as described in example 1. The lyophilate was combined to a kit with a vial containing 1 ml of a sterile sodium chloride solution (0.17 %) which also contained 0.5 mg of Tween 80®. The lyophilate dissolved in the saline solution within about 1 second under agitation. The pH of the resulting solution was about 4.4.

Example 6

100.0 g of lysine-monohydrate were sieved through a 355µm sieve to remove clumps. 82.1 g of lysine-monohydrate were added to 112.5 g of aztreonam in the 1l mixing-bowl of a Diosna P1-6 high shear mixer. The powders were blended for 3 minutes (mixer: 500 rpm; chopper: 0 rpm). Blending was interrupted every minute in order to remove powder from the bowl's walls.

After blending was completed, 8 ml of purified water were slowly added to the mixture through an opening in the lid of the mixing bowl using a pump. During water addition, the mixer speed was kept at 500 rpm while the chopper speed was set to 1500 rpm. Mixing was performed for another 4 - 5 minutes. Thereafter, the wetted powder mixture was sieved through a 710 µm sieve and dried on trays at 40°C for 3 hours. When the granules were dissolved in water to form an aztreonam solution with a concentration of about 100 mg/ml, the resulting pH was 4.4.

CLAIMS

1. A solid pharmaceutical composition for the preparation of an aerosolizable liquid for inhalation, comprising an effective amount of aztreonam and a basic excipient, wherein the ratio of aztreonam to the basic excipient is selected to yield a solution with a pH of about 3.5 to 5.5 when dissolved in water at an aztreonam concentration of about 30 to 200 mg/ml.

2. The composition of claim 1, wherein the basic excipient is lysine or a lysine salt or derivative.

3. The composition of claim 2, wherein the ratio of aztreonam to lysine or the lysine salt or derivative is from 2:1 to 1:1.

4. The composition of any of the preceding claims, wherein aztreonam and the basic excipient are present as their combination in the form of a salt.

5. The composition of any of the preceding claims, further comprising a surfactant, such as Tween® 80, tyloxapol, a phospholipid, or vitamin E TPGS.

6. The composition of any of the preceding claims, being formulated and processed as a lyophilized solid single dosage unit.

7. The composition of any of claims 1 to 5, being formulated and processed as a powder or as granules.

8. The composition of any of the preceding claims, being substantially free of insoluble excipients.

9. The composition of any of the preceding claims, being substantially free of polymeric excipients.

10. A pharmaceutical kit for the preparation of an aerosolizable liquid for inhalation, comprising:

(a) a dry solid composition comprising an effective amount of aztreonam and a basic excipient, and

(b) an aqueous liquid composition,

wherein the relative amounts of aztreonam, the basic excipient, and the aqueous liquid composition are selected to yield an aqueous solution having an aztreonam concentration of about 30 to 200 mg/ml and a pH of about 3.5 to 5.5 when the solid composition is dissolved in the liquid composition.

11. The kit of claim 10, wherein the basic excipient is lysine or a lysine salt or derivate.

12. The kit of claim 10 or 11, wherein the solid composition comprises about 30 to about 200 mg of aztreonam.

13. The kit of any of claims 10 to 12, wherein the solid composition comprises about 100 mg of aztreonam.

14. The kit of claim 11, wherein the solid composition comprises about 0.5 to about 1.0 mg of lysine per mg of aztreonam.

15. The kit of claim 14, wherein the solid composition comprises about 0.6 to about 0.75 mg of lysine per mg of aztreonam.

16. The kit of any of claims 10 to 15, wherein the solid composition and/or the liquid composition further comprises a surfactant, such as Tween® 80, tyloxapol, a phospholipid, or vitamin E TPGS.

17. The kit of any of claims 10 to 16, wherein the solid composition and/or the liquid composition further comprises a chloride, such as sodium chloride or calcium chloride.

18. The kit of any of claims 10 to 17, wherein the volume of the liquid composition is from about 0.8 to about 2.0 ml.

19. The kit of any of claims 10 to 18, wherein both the solid and the liquid composition are sterile.

20. The kit of any of claims 10 to 19, wherein the relative amounts of aztreonam and of the aqueous liquid composition are selected to yield an aqueous solution having an aztreonam concentration of about 50 to about 150 mg/ml when the solid composition is dissolved in the liquid composition.

21. The kit of any of claims 10 to 20, wherein the relative amounts of aztreonam, the basic excipient, and the aqueous liquid composition are selected to yield an aqueous solution having a pH of about 4.0 to about 4.5 when the solid composition is dissolved in the liquid composition.

22. The kit of any of claims 10 to 21, wherein the dissolution of the solid composition in the liquid composition yields an aqueous solution having a viscosity of about 1.5 to about 2.0 mPas.

23. The kit of any of claims 10 to 22, wherein the dissolution of the solid composition in the liquid composition yields an aqueous solution having a surface tension of about 50 to about 73 mN/m.

24. The kit of any of claims 10 to 23, wherein the dissolution of the solid composition in the liquid composition yields an aqueous solution having an osmolality of about 300 to about 650 mOsmol/kg.

25. The kit of any of claims 10 to 24, wherein the solid composition and the liquid composition are accommodated in separate chambers of the same primary packaging unit or container.

26. Method for the preparation of the pharmaceutical composition of any of claims 1 to 9, comprising the steps of:

(a) preparing an aqueous solution comprising aztreonam and a basic excipient capable of at least partially neutralizing the aztreonam;

(b) filtering said aqueous solution using a filter capable of removing

substantially all microbial and viral contaminants to yield a sterile filtrate; and

(c) lyophilizing said sterile filtrate under aseptic conditions.

27. Method for the preparation of the solid composition of a kit according to any of claims 10 to 25, comprising the steps of:

(a) preparing an aqueous solution comprising aztreonam and a basic excipient capable of at least partially neutralizing the aztreonam;

(b) filtering said aqueous solution using a filter capable of removing substantially all microbial and viral contaminants to yield a sterile filtrate; and

(c) lyophilizing said sterile filtrate under aseptic conditions.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/14061

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/00 A61K31/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, EMBASE, MEDLINE, BIOSIS, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 070 024 A (SQUIBB & SONS INC) 19 January 1983 (1983-01-19) page 17; claims 1,5-9,11; examples 2,3,7 ---	1,4,10, 26,27
X	EP 0 297 580 A (SQUIBB & SONS INC) 4 January 1989 (1989-01-04) page 2; claims 1-6; examples 1-4; table 1 ---	1,4-27
X	US 4 675 398 A (ANDERSON CARL F ET AL) 23 June 1987 (1987-06-23) example 1 ---	1,26,27
X	WO 01 34128 A (UPJOHN CO ;BATTS DONALD H (US)) 17 May 2001 (2001-05-17) page 5 -page 6; claims 1,5,20; example 3 ---	1,10

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
17 July 2003	29/07/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Kardas-Llorens, E

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/14061

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 826 973 A (ANDERSON CARL F ET AL) 2 May 1989 (1989-05-02) Preparations A and B column 2; claims 1-4,7 ---	1
X	WO 02 051356 A (SALUS PHARMA INC) 4 July 2002 (2002-07-04) cited in the application page 17 -page 20; claims 1,7,8,26,27,30,36,38 page 31 page 39 -page 40 page 53 ---	1,4-27
A	LASHER SISSON T ET AL: "A PHARMACOKINETIC EVALUATION OF CONCOMITANT ADMINISTRATION OF LINEZOLID AND AZTREONAM" JOURNAL OF CLINICAL PHARMACOLOGY, LIPPINCOTT CO, HAGERSTOWN, MD, US, vol. 39, December 1999 (1999-12), pages 1277-1282, XP000991041 ISSN: 0091-2700 page 1280 -----	1-27

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 02/14061

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0070024 A	19-01-1983	AT 14016 T	15-07-1985
		AU 557096 B2	04-12-1986
		AU 8501082 A	20-01-1983
		CA 1181075 A1	15-01-1985
		DE 3264415 D1	01-08-1985
		EP 0070024 A1	19-01-1983
		IE 53109 B1	22-06-1988
		IL 66286 A	31-03-1986
		JP 1678482 C	13-07-1992
		JP 3043273 B	01-07-1991
		JP 58023689 A	12-02-1983
		NZ 201000 A	16-08-1985
		PH 19140 A	10-01-1986
		US 4946838 A	07-08-1990
		ZA 8204418 A	27-04-1983
EP 0297580 A	04-01-1989	AT 175965 T	15-02-1999
		CA 1339136 C	29-07-1997
		CN 1030238 A ,B	11-01-1989
		DE 3856297 D1	04-03-1999
		DE 3856297 T2	02-06-1999
		EP 0297580 A1	04-01-1989
		ES 2127178 T3	16-04-1999
		GR 3029873 T3	30-07-1999
		JP 1022874 A	25-01-1989
		JP 2701869 B2	21-01-1998
US 4675398 A	23-06-1987	AT 54147 T	15-07-1990
		CA 1268759 A1	08-05-1990
		DE 3672255 D1	02-08-1990
		EP 0212392 A1	04-03-1987
		JP 2031946 C	19-03-1996
		JP 7068243 B	26-07-1995
		JP 62042984 A	24-02-1987
WO 0134128 A	17-05-2001	AU 1572101 A	06-06-2001
		WO 0134128 A2	17-05-2001
US 4826973 A	02-05-1989	NONE	
WO 02051356 A	04-07-2002	WO 02051356 A2	04-07-2002
		US 2003055034 A1	20-03-2003