NAPADISYLATE SALT OF A MUSCARINIC M3 ANTAGONIST

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The present invention relates to a salt of a muscarinic antagonist, pharmaceutical composition containing it and its use in therapy.

Muscarinic receptors are a G-protein coupled receptor (GPCR) family having five family members M₁, M₂, M₃, M₄ and M₅. Of the five muscarinic subtypes, three (M₁, M₂ and M₃) are known to exert physiological effects on human lung tissue. Parasympathetic nerves are the main pathway for reflex bronchoconstriction in human airways and mediate airway tone by releasing acetylcholine onto muscarinic receptors. Airway tone is increased in patients with respiratory disorders such as asthma and chronic obstructive pulmonary disease (COPD), and for this reason muscarinic receptor antagonists have been developed for use in treating airway diseases. Muscarinic receptor antagonists, often called anticholinergics in clinical practice, have gained widespread acceptance as a first-line therapy for individuals with COPD, and their use has been extensively reviewed in the literature (e.g. Lee et al, Current Opinion in Pharmacology 2001,1, 223-229).

When used to treat respiratory disorders, muscarinic receptor antagonists are typically administered by inhalation. However, when administered by inhalation a significant proportion of the muscarinic receptor antagonist is often absorbed into the systemic circulation resulting in reported side effects such as dry mouth. Additionally, the majority of muscarinic antagonists have a relatively short duration of action requiring that they be administered several times a day. Such a multiple-daily dosing regime is not only inconvenient to the patient but also creates a significant risk of inadequate treatment due to patient non-compliance associated with the frequent repeat dosing schedule. There therefore remains a need for novel compounds that are capable of blocking muscarinic receptors. In particular, a need exists for new muscarinic antagonists that have high potency and reduced systemic side effects when administered by inhalation. Moreover, a need exists for new muscarinic antagonists that exhibit a long duration of action when dosed by inhalation, and which are amenable to either once or twice daily dosing.
In the manufacture of pharmaceutical formulations, it is important that the active compound is in a form in which it can be conveniently handled and processed in order to obtain a commercially-viable manufacturing process. In this connection, the chemical stability and the physical stability of the active compound are important factors. The active compound, and formulations containing it, must be capable of being effectively stored over appreciable periods of time, without exhibiting any significant change in the physico-chemical characteristics (e.g., chemical composition, density, hygroscopicity and solubility) of the active compound.

Furthermore, if the active compound is to be incorporated into a formulation for pulmonary administration, it is desirable if the active compound can be readily micronised to yield a powder with good flow properties and comprising a high fine crystalline particle fraction (i.e., a fraction in which the active compound particles have a mass median aerodynamic diameter of less than 10 µm (micrometer)). Such a fraction is capable of being carried deep into the lungs leading to faster and increased absorption of the active compound.

International Patent Application WO 2007/017669 (PCT/GB2006/002956) describes a novel class of muscarinic antagonist that display high potency to the M3 receptor. One such muscarinic antagonist described in PCT/GB 2006/002956 is 2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium bromide. The preparation of 2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium bromide described in PCT/GB2006/002956 yields an amorphous solid which is not crystalline and is thus not suitable for micronisation and pulmonary administration. It has now been found possible to prepare an alternative 2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium salt, which has good physico-chemical properties and which may be suitable for use in a dry powder formulation for pulmonary administration.

Thus, in accordance with the present invention, there is provided a salt which is a napadisylate (naphthalene-1,5-disulfonate) salt of 2-((R)-Cyclohexyl-hydroxy-phenyl-
methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium. In the present specification this salt may be referred to as the 'napadisylate salt'.

The salt of the present invention is herein referred to as [2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium napadisylate. The name [2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium was generated by the Autonom 2000 plug in for IsisDraw Version 2.5, as supplied by MDL Information Systems Inc., and denotes the structure depicted in Figure A. Stereochemistry was assigned according to the Cahn-Ingold-Prelog system.

Figure A

In an embodiment of the invention, the napadisylate salt has a cation/anion ratio of 2:1, i.e. it is [2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium hemi-naphthalene-1,5-disulfonate, as depicted in Figure B. In the present specification this salt may be referred to as the 'hemi-napadisylate salt'.

Figure B

The present invention encompasses solvates (e.g. hydrates) of the napadisylate salt.
In an embodiment of the invention, the napadisylate salt has crystalline properties and is preferably at least 50% crystalline, more preferably at least 60% crystalline, still more preferably at least 70% crystalline and most preferably at least 80% crystalline. Crystallinity can be estimated by conventional X-ray diffractometry techniques.

In another embodiment of the invention, the napadisylate salt is from 50%, 60%, 70%, 80% or 90% to 95%, 96%, 97%, 98%, 99% or 100% crystalline.

Three different physical forms of the napadisylate salt of the present invention have been isolated and characterised to date (Form 1, Form 2 and Form 3). All three are forms of hemi-napadisylate salt, i.e. [2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium hemi-naphthalene-1,5-disulfonate.

In the present specification, X-ray powder diffraction peaks (expressed in degrees 2\(\Theta\)) are measured using copper X-rays with a wavelength of 1.5406 Å. In the present specification unless otherwise stated the margin of error for X-ray powder diffraction peaks (expressed in degrees 2\(\Theta\)) is consistent with the United States Pharmacopeia general chapter on X-ray diffraction (USP941) - see the United States Pharmacopeia Convention. X-Ray Diffraction, General Test <941>. *United States Pharmacopeia*, 25th ed. Rockville, MD: United States Pharmacopeial Convention; 2002:2088-2089). In an embodiment of the invention, the margin of error for X-ray powder diffraction peaks (expressed in degrees 2\(\Theta\)) is (±0.1°).

Thus, the present invention also provides a salt form (Form 1) of [2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium hemi-naphthalene-1,5-disulfonate, which exhibits at least the following characteristic X-ray powder diffraction peaks (expressed in degrees 2\(\Theta\)):

(1) 5.6, 14.6, 16.7 and 18.0, or
(2) 5.6, 14.6, 16.7, 18.0, 19.4 and 20.4, or
(3) 5.6, 9.3, 13.6, 14.6, 16.7, 18.0, 19.4 and 20.4, or
(4) 5.6, 9.3, 13.6, 14.6, 16.7, 18.0, 19.4, 19.8, 20.4 and 20.8.
The present invention also provides a salt form (Form 1) of \[2-((R)-\text{Cyclohexyl-hydroxy-phenyl-methyl})-\text{oxazol-5-ylmethyl}]\text{-dimethyl-(3-phenoxy-propyl)-ammonium hemi-naphthalene-1,5-disulfonate},\] having an X-ray powder diffraction pattern comprising specific peaks at 5.6, 9.3, 9.9, 11.1, 11.7, 12.6, 13.6, 14.6, 16.7, 17.1, 17.4, 18.0, 19.1, 19.4, 19.8, 20.4, 20.8, 21.7, 23.6, 25.0, 25.6 and 26.0.

The present invention also provides a salt form (Form 1) of \[2-((R)-\text{Cyclohexyl-hydroxy-phenyl-methyl})-\text{oxazol-5-ylmethyl}]\text{-dimethyl-(3-phenoxy-propyl)-ammonium hemi-naphthalene-1,5-disulfonate},\] having an X-ray powder diffraction pattern which exhibits at least the following characteristic d-space values:

1. 15.9, 6.1, 5.3 and 4.9, or
2. 15.9, 6.1, 5.3, 4.9, 4.6 and 4.4 or
3. 15.9, 9.5, 6.5, 6.1, 5.3, 4.9, 4.6 and 4.4 or
4. 15.9, 9.5, 6.5, 6.1, 5.3, 4.9, 4.6, 4.5, 4.4 and 4.3.

Figure 1 shows an X-ray powder diffraction pattern of salt Form 1 of \[2-((R)-\text{Cyclohexyl-hydroxy-phenyl-methyl})-\text{oxazol-5-ylmethyl}]\text{-dimethyl-(3-phenoxy-propyl)-ammonium hemi-naphthalene-1,5-disulfonate}.\] The present invention also provides a salt form having an X-ray powder diffraction pattern substantially the same as that shown in Figure 1.

In an embodiment of the invention, salt Form 1 is hygroscopic.

The present invention also provides a salt form (Form 2) of \[2-((R)-\text{Cyclohexyl-hydroxy-phenyl-methyl})-\text{oxazol-5-ylmethyl}]\text{-dimethyl-(3-phenoxy-propyl)-ammonium hemi-naphthalene-1,5-disulfonate},\] which exhibits at least the following characteristic X-ray powder diffraction peaks (expressed in degrees 2Θ):

1. 5.3, 15.7, 16.5 and 26.4,
2. 5.3, 15.7, 16.5, 19.0, 21.2 and 26.4,
3. 5.3, 15.0, 15.7, 16.5, 17.6, 19.0, 21.2 and 26.4,
4. 5.3, 15.0, 15.7, 16.5, 17.6, 18.4, 19.0, 21.2 and 26.4.
The present invention also provides a salt form (Form 2) of [2-((R)-Cyclohexyl-hydroxyphenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium hemi-naphthalene-1,5-disulfonate, having an X-ray powder diffraction pattern comprising specific peaks at 5.3, 10.5, 15.0, 15.7, 16.5, 17.3, 17.6, 18.4, 19.0, 21.2, 26.4 and 29.5

Figure 2 shows an X-ray powder diffraction pattern of salt Form 2 of [2-((R)-Cyclohexyl-hydroxyphenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium hemi-naphthalene-1,5-disulfonate. The present invention also provides a salt form having an X-ray powder diffraction pattern substantially the same as that shown in Figure 2.

In an embodiment of the invention, salt Form 2 is anhydrous.

The present invention also provides a salt form (Form 3) of [2-((R)-Cyclohexyl-hydroxyphenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium hemi-naphthalene-1,5-disulfonate, which exhibits at least the following characteristic X-ray powder diffraction peaks (expressed in degrees 2Θ):

(1) 5.9, 17.3, 17.7 and 20.8, or
(2) 5.9, 13.9, 17.3, 17.7, 20.8 and 23.6, or
(3) 5.9, 11.6, 13.9, 17.3, 17.7, 18.8, 20.8 and 23.6, or
(4) 5.9, 11.6, 13.9, 14.9 17.3, 17.7, 18.8, 20.8, 21.8 and 23.6.
naphthalene-1,5-disulfonate, having an X-ray powder diffraction pattern comprising specific peaks at 5.9, 10.5, 11.6, 12.2, 13.9, 14.6, 14.9 17.3, 17.7, 18.8, 20.8, 21.8 and 23.6.

The present invention also provides a salt form (Form 3) of [2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]dimethyl-(3-phenoxy-propyl)-ammonium hemi-naphthalene-1,5-disulfonate, having an X-ray powder diffraction pattern which exhibits at least the following characteristic d-space values:

(1) 15.0, 5.1, 5.0 and 4.3, or
(2) 15.0, 6.4, 5.1, 5.0, 4.3 and 3.8, or
(3) 15.0, 7.6, 6.4, 5.1, 5.0, 4.7, 4.3 and 3.8, or
(4) 15.0, 7.6, 6.4, 5.9, 5.1, 5.0, 4.7, 4.3, 4.1 and 3.8.

Figure 3 shows an X-ray powder diffraction pattern of salt Form 3 of [2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]dimethyl-(3-phenoxy-propyl)-ammonium hemi-naphthalene-1,5-disulfonate. The present invention also provides a salt form having an X-ray powder diffraction pattern substantially the same as that shown in Figure 3.

In an embodiment of the invention, salt Form 3 is hydroscopic.
In an embodiment of the invention, salt Form 3 is hydrated.

The napadisylate salt of the present invention may be prepared as follows: A mixture of [2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]dimethyl-(3-phenoxy-propyl)-ammonium bromide (Example 8 in PCT/GB2006/002956 and Intermediate 6 as described in the experimental section of the present application) and naphthalene-1,5-disulfonate disodium salt are reacted in a suitable solvent (e.g. dichloromethane/water mixture) and stirred at a suitable temperature (e.g. 20 to 25 °C) for a period of time (e.g. 6 to 24 hours). The solids may then be collected and dried to yield [2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]dimethyl-(3-phenoxy-propyl)-ammonium hemi-naphthalene-1,5-disulfonate in amorphous form.

Salt Form 1 may for example be prepared by heating the amorphous form prepared as described above in toluene with stirring at approx. 60° C for approx. 48 hours and allowed
to cool to RT while stirring to afford the product as small platelets. Alternatively, salt Form 1 may be prepared by recrystallising the amorphous form from refluxing acetonitrile followed by hot filtration of the solution and allowing to cool to room temperature (20 to 25 °C). The solids may then be collected and dried to yield salt Form 1.

Salt Form 2 may for example be prepared by heating the amorphous form in anisole (approx. 154 °C) for approx. 3hrs then leaving to stand at RT for approx. 48hrs. The solids may then be collected and dried to yield salt Form 2. Alternatively, salt Form 2 may be prepared by recrystallising the amorphous form from chlorobenzene and slowly cooling to room temperature to afford the product as fine needles. The solids may then be collected and dried to yield salt Form 2. Alternatively, salt Form 2 may be prepared by stirring the amorphous form in toluene at approx. 80 °C for at least 60 hours to afford a fine powder. The solids may then be collected and dried to yield salt Form 2.

Salt Form 3 may for example be prepared by recrystallising the amorphous form from refluxing acetone/water mixture, hot filtration of the solution and allowing to cool to room temperature (20 to 25 °C). The solids may then be collected and dried to yield salt Form 3.

The napadisylate salt of the invention has activity as a pharmaceutical, in particular as an anticholinergic agent including a muscarinic receptor (M1, M2, and M3) antagonist, in particular a M3 antagonist. Diseases and conditions which may be treated with the salt include:
1. respiratory tract: obstructive diseases of the airways including: asthma, including bronchial, allergic, intrinsic, extrinsic, exercise-induced, drug-induced (including aspirin and NSAID-induced) and dust-induced asthma, both intermittent and persistent and of all severities, and other causes of airway hyper-responsiveness; chronic obstructive pulmonary disease (COPD); bronchitis, including infectious and eosinophilic bronchitis; emphysema; bronchiecstasy; cystic fibrosis; sarcoidosis; farmer's lung and related diseases; hypersensitivity pneumonitis; lung fibrosis, including cryptogenic fibrosing alveolitis, idiopathic interstitial pneumonias, fibrosis complicating anti-neoplastic therapy and chronic infection, including tuberculosis and aspergillosis and other fungal infections; complications of lung transplantation; vasculitic and thrombotic disorders of the lung
vasculature, and pulmonary hypertension; antitussive activity including treatment of chronic cough associated with inflammatory and secretory conditions of the airways, and iatrogenic cough; acute and chronic rhinitis including rhinitis medicamentosa, and vasomotor rhinitis; perennial and seasonal allergic rhinitis including rhinitis nervosa (hay fever); nasal polyposis; acute viral infection including the common cold, and infection due to respiratory syncytial virus, influenza, coronavirus (including SARS) and adenovirus;

2. **bone and joints:** arthritides associated with or including osteoarthritis/osteoarthrosis, both primary and secondary to, for example, congenital hip dysplasia; cervical and lumbar spondylitis, and low back and neck pain; rheumatoid arthritis and Still's disease; seronegative spondyloarthropathies including ankylosing spondylitis, psoriatic arthritis, reactive arthritis and undifferentiated spondarthropathy; septic arthritis and other infection-related arthropathies and bone disorders such as tuberculosis, including Potts' disease and Poncet's syndrome; acute and chronic crystal-induced synovitis including urate gout, calcium pyrophosphate deposition disease, and calcium apatite related tendon, bursal and synovial inflammation; Behcet's disease; primary and secondary Sjogren's syndrome; systemic sclerosis and limited scleroderma; systemic lupus erythematosus, mixed connective tissue disease, and undifferentiated connective tissue disease; inflammatory myopathies including dermatomyositis and polymyositis; polymyalgia rheumatica; juvenile arthritis including idiopathic inflammatory arthritides of whatever joint distribution and associated syndromes, and rheumatic fever and its systemic complications; vasculitides including giant cell arteritis, Takayasu's arteritis, Churg-Strauss syndrome, polyarteritis nodosa, microscopic polyarteritis, and vasculitides associated with viral infection, hypersensitivity reactions, cryoglobulins, and paraproteins; low back pain; Familial Mediterranean fever, Muckle-Wells syndrome, and Familial Hibernian Fever, Kikuchi disease; drug-induced arthalgias, tendonititides, and myopathies;

3. **pain and connective tissue remodelling of musculoskeletal disorders due to injury [for example sports injury] or disease:** arthritides (for example rheumatoid arthritis, osteoarthritis, gout or crystal arthropathy), other joint disease (such as intervertebral disc degeneration or temporomandibular joint degeneration), bone remodelling disease (such as osteoporosis, Paget's disease or osteonecrosis), polychondrititis, scleroderma, mixed connective tissue disorder, spondyloarthropathies or periodontal disease (such as periodontitis);
4. **skin**: psoriasis, atopic dermatitis, contact dermatitis or other eczematous dermatoses, and delayed-type hypersensitivity reactions; phyto- and photodermatitis; seborrhoeic dermatitis, dermatitis herpetiformis, lichen planus, lichen sclerosus et atrophica, pyoderma gangrenosum, skin sarcoma, discoid lupus erythematosus, pemphigus, pemphigoid, epidermolysis bullosa, urticaria, angioedema, vasculitides, toxic erythemas, cutaneous eosinophilias, alopecia areata, male-pattern baldness, Sweet's syndrome, Weber-Christian syndrome, erythema multiforme; cellulitis, both infective and non-infective; panniculitis; cutaneous lymphomas, non-melanoma skin cancer and other dysplastic lesions; drug-induced disorders including fixed drug eruptions;

5. **eyes**: blepharitis; conjunctivitis, including perennial and vernal allergic conjunctivitis; iritis; anterior and posterior uveitis; choroiditis; autoimmune; degenerative or inflammatory disorders affecting the retina; ophthalmitis including sympathetic ophthalmitis; sarcoidosis; infections including viral, fungal, and bacterial;

6. **gastrointestinal tract**: glossitis, gingivitis, periodontitis; oesophagitis, including reflux; eosinophilic gastro-enteritis, mastocytosis, Crohn's disease, colitis including ulcerative colitis, proctitis, pruritis ani; coeliac disease, irritable bowel syndrome, and food-related allergies which may have effects remote from the gut (for example migraine, rhinitis or eczema);

7. **abdominal**: hepatitis, including autoimmune, alcoholic and viral; fibrosis and cirrhosis of the liver; cholecystitis; pancreatitis, both acute and chronic;

8. **genitourinary**: nephritis including interstitial and glomerulonephritis; nephrotic syndrome; cystitis including acute and chronic (interstitial) cystitis and Hunner's ulcer; acute and chronic urethritis, prostatitis, epididymitis, oophoritis and salpingitis; vulvovaginitis; Peyronie's disease; erectile dysfunction (both male and female);

9. **allograft rejection**: acute and chronic following, for example, transplantation of kidney, heart, liver, lung, bone marrow, skin or cornea or following blood transfusion; or chronic graft versus host disease;

10. **CNS**: Alzheimer's disease and other dementing disorders including CJD and nvCJD; amyloidosis; multiple sclerosis and other demyelinating syndromes; cerebral atherosclerosis and vasculitis; temporal arteritis; myasthenia gravis; acute and chronic pain (acute, intermittent or persistent, whether of central or peripheral origin) including visceral pain, headache, migraine, trigeminal neuralgia, atypical facial pain, joint and bone pain,
pain arising from cancer and tumor invasion, neuropathic pain syndromes including diabetic, post-herpetic, and HIV-associated neuropathies; neurosarcoidosis; central and peripheral nervous system complications of malignant, infectious or autoimmune processes;

11. other auto-immune and allergic disorders including Hashimoto's thyroiditis, Graves' disease, Addison's disease, diabetes mellitus, idiopathic thrombocytopenic purpura, eosinophilic fasciitis, hyper-IgE syndrome, antiphospholipid syndrome;

12. other disorders with an inflammatory or immunological component; including acquired immune deficiency syndrome (AIDS), leprosy, Sezary syndrome, and paraneoplastic syndromes;

13. cardiovascular, atherosclerosis, affecting the coronary and peripheral circulation; pericarditis; myocarditis, inflammatory and auto-immune cardiomyopathies including myocardial sarcoid; ischaemic reperfusion injuries; endocarditis, valvulitis, and aortitis including infective (for example syphilitic); vasculitides; disorders of the proximal and peripheral veins including phlebitis and thrombosis, including deep vein thrombosis and complications of varicose veins;

14. oncology: treatment of common cancers including prostate, breast, lung, ovarian, pancreatic, bowel and colon, stomach, skin and brain tumors and malignancies affecting the bone marrow (including the leukaemias) and lymphoproliferative systems, such as Hodgkin's and non-Hodgkin's lymphoma; including the prevention and treatment of metastatic disease and tumour recurrences, and paraneoplastic syndromes; and,

15. gastrointestinal tract: Coeliac disease, proctitis, eosinopilic gastro-enteritis, mastocytosis, Crohn's disease, ulcerative colitis, microscopic colitis, indeterminant colitis, irritable bowel disorder, irritable bowel syndrome, non-inflammatory diarrhea, food-related allergies which have effects remote from the gut, e.g., migraine, rhinitis and eczema.

Accordingly, the present invention further provides \([2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium\) napadisylate as hereinbefore defined for use in therapy.
In another aspect, the invention provides the use of [2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium napadisylate as hereinbefore defined, in the manufacture of a medicament for use in therapy.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The terms "therapeutic" and "therapeutically" should be construed accordingly.

A further aspect of the invention provides a method of treating a disease state in a mammal suffering from, or at risk of, said disease, which comprises administering to a mammal in need of such treatment a therapeutically effective amount of [2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium napadisylate as hereinbefore defined.

The present invention also provides [2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium napadisylate for use in the treatment of chronic obstructive pulmonary disease (COPD) (such as irreversible COPD).

The present invention also provides the use of [2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium napadisylate as hereinbefore defined, in the manufacture of a medicament for use in the treatment of chronic obstructive pulmonary disease (COPD) (such as irreversible COPD).

The present invention also provides the use of [2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium napadisylate as hereinbefore defined, in the manufacture of a medicament for use in the treatment of asthma.

The present invention further provides a method of treating chronic obstructive pulmonary disease (COPD) (such as irreversible COPD), in a warm-blooded animal, such as man, which comprises administering to a mammal in need of such treatment an effective amount

In order to use a compound of the invention for the therapeutic treatment of a warm-blooded animal, such as man, said ingredient is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

For the above-mentioned therapeutic uses the dosage administered will, of course, vary with the mode of administration, the treatment desired and the disorder indicated but may typically be in the range from 0.001 mg/kg to 30 mg/kg.

The salt according to the invention may be used on its own but will generally be administered in the form of a pharmaceutical composition in which the [2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium napadisylate (active ingredient) is in association with a pharmaceutically acceptable adjuvant, diluent or carrier. Conventional procedures for the selection and preparation of suitable pharmaceutical formulations are described in, for example, "Pharmaceuticals - The Science of Dosage Form Designs", M. E. Aulton, Churchill Livingstone, 1988.

Depending on the mode of administration, the pharmaceutical composition may comprise from 0.05 to 99 %w (per cent by weight), more preferably from 0.05 to 80 %w, still more preferably from 0.10 to 70 %w, and even more preferably from 0.10 to 50 %w, of active ingredient, all percentages by weight being based on total composition.

The present invention also provides a pharmaceutical composition comprising [2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium napadisylate in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

The invention further provides a process for the preparation of a pharmaceutical composition of the invention which comprises mixing [2-((R)-Cyclohexyl-hydroxy-
phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium napadisylate with a pharmaceutically acceptable adjuvant, diluent or carrier.

The pharmaceutical compositions may be administered topically (e.g. to the skin or to the lung and/or airways) in the form, e.g., of creams, solutions, suspensions, heptafluoroalkane (HFA) aerosols and dry powder formulations, for example, formulations in the inhaler device known as the Turbuhaler®; or systemically, e.g. by oral administration in the form of tablets, capsules, syrups, powders or granules; or by parenteral administration in the form of solutions or suspensions; or by subcutaneous administration; or by rectal administration in the form of suppositories; or transdermally.

In an embodiment of the invention, the active ingredient is administered by inhalation. In a further embodiment, the active ingredient is administered by means of a dry powder inhaler. The inhaler may be a single or a multi dose inhaler, and may be a breath actuated dry powder inhaler.

When administered via inhalation the dose of the active ingredient may generally be in the range of from 0.1 µg to 10000 µg, 0.1 to 5000 µg, 0.1 to 1000 µg, 0.1 to 5000 µg, 0.1 to 200 µg, 5 to 200 µg, 0.1 to 100 µg, 0.1 to 50 µg, 5 µg to 500 µg, 5 to 1000 µg, 5 to 500 µg, 5 to 200 µg, 5 to 100 µg, 5 to 50 µg, 10 to 5000 µg, 10 to 1000 µg, 10 to 500 µg, 10 to 200 µg, 10 to 100 µg, 10 to 50 µg, 20 to 5000 µg, 20 to 1000 µg, 20 to 500 µg, 20 to 200 µg, 20 to 100 µg, 20 to 50 µg, 50 to 5000 µg, 50 to 1000 µg, 50 to 500 µg, 50 to 200 µg, 50 to 100 µg, 100 to 5000 µg, 100 to 1000 µg or 100 to 500 µg.

Dry powder formulations and pressurized HFA aerosols of the active ingredient may be administered by oral or nasal inhalation. For inhalation, the compound is desirably finely divided. The finely divided compound preferably has a mass median diameter of less than 10 µm, and may be suspended in a propellant mixture with the assistance of a dispersant, such as a C₈-C₂₀ fatty acid or salt thereof, (for example, oleic acid), a bile salt, a phospholipid, an alkyl saccharide, a perfluorinated or polyethoxylated surfactant, or other pharmaceutically acceptable dispersant.
One possibility is to mix the finely divided compound of the invention with a carrier substance, for example, a mono-, di- or polysaccharide, a sugar alcohol, or another polyol. Suitable carriers are sugars, for example, lactose, glucose, raffinose, melezitose, lactitol, maltitol, trehalose, sucrose, mannitol; and starch. Alternatively the finely divided compound may be coated by another substance. The powder mixture may also be dispensed into hard gelatine capsules, each containing the desired dose of the active compound.

Another possibility is to process the finely divided powder into spheres which break up during the inhalation procedure. This spheronized powder may be filled into the drug reservoir of a multidose inhaler, for example, that known as the Turbuhaler® in which a dosing unit meters the desired dose which is then inhaled by the patient. With this system the active ingredient, with or without a carrier substance, is delivered to the patient.

For oral administration the compound of the invention may be admixed with an adjuvant or a carrier, for example, lactose, saccharose, sorbitol, mannitol; a starch, for example, potato starch, corn starch or amylpectin; a cellulose derivative; a binder, for example, gelatine or polyvinylpyrrolidone; and/or a lubricant, for example, magnesium stearate, calcium stearate, polyethylene glycol, a wax, paraffin, and the like, and then compressed into tablets. If coated tablets are required, the cores, prepared as described above, may be coated with a concentrated sugar solution which may contain, for example, gum arabic, gelatine, talcum and titanium dioxide. Alternatively, the tablet may be coated with a suitable polymer dissolved in a readily volatile organic solvent.

For the preparation of soft gelatine capsules, the compound of the invention may be admixed with, for example, a vegetable oil or polyethylene glycol. Hard gelatine capsules may contain granules of the compound using either the above-mentioned excipients for tablets. Also liquid or semisolid formulations of the compound of the invention may be filled into hard gelatine capsules.
Liquid preparations for oral application may be in the form of syrups or suspensions, for example, solutions containing the compound of the invention, the balance being sugar and a mixture of ethanol, water, glycerol and propylene glycol. Optionally such liquid preparations may contain colouring agents, flavouring agents, saccharine and/or carboxymethylcellulose as a thickening agent or other excipients known to those skilled in art.

The invention will now be illustrated by the following non-limiting Examples. In the Examples the following Figures are presented:

Figure 1: X-ray powder diffraction pattern of salt Form 1 of [2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium hemi-naphthalene-1,5-disulfonate.

Figure 2: X-ray powder diffraction pattern of salt Form 2 of [2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium hemi-naphthalene-1,5-disulfonate.

Figure 3: X-ray powder diffraction pattern of salt Form 3 of [2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium hemi-naphthalene-1,5-disulfonate.

Figure 4: X-ray powder diffraction pattern of amorphous [2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium bromide

**General Experimental Details**

All reactions were carried out under an atmosphere of nitrogen unless specified otherwise.

NMR spectra were obtained on a Varian Unity Inova 400 spectrometer with a 5 mm inverse detection triple resonance probe operating at 400 MHz or on a Bruker Avance DRX 400 spectrometer with a 5 mm inverse detection triple resonance TXI probe operating at 400 MHz or on a Bruker Avance DPX 300 spectrometer with a standard 5 mm dual frequency probe operating at 300 MHz. Shifts are given in ppm relative to tetramethylsilane.
Where products were purified by column chromatography, 'flash silica' refers to silica gel for chromatography, 0.035 to 0.070 mm (220 to 440 mesh) (e.g. Fluka silica gel 60), and an applied pressure of nitrogen up to 10 p.s.i accelerated column elution. Where thin layer chromatography (TLC) has been used, it refers to silica gel TLC using plates, typically 3 x 6 cm silica gel on aluminium foil plates with a fluorescent indicator (254 nm), (e.g. Fluka 60778). All solvents and commercial reagents were used as received.

All compounds containing a basic centre(s), which were purified by HPLC, were obtained as the TFA salt unless otherwise stated.

Preparative HPLC conditions:
C18-reverse-phase column (100 x 22.5 mm i.d. Genesis column with 7 µm particle size). UV detection at 230 nm.

LC/MS Systems
The Liquid Chromatography Mass Spectroscopy (LC/MS) systems used:

LC-MS method 1
Waters Platform LCT with a C18-reverse-phase column (100 x 3.0 mm Higgins Clipeus with 5 µm particle size), elution with A: water + 0.1% formic acid; B: acetonitrile + 0.1 % formic acid. Gradient:

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Detection - MS, ELS, UV (100 µl split to MS with in-line UV detector at 254 nm)
MS ionisation method - Electrospray (positive ion)
LC-MS method 3
Waters Micromass ZQ with a C18-reverse-phase column (30 x 4.6 mm Phenomenex Luna 3 µm particle size), elution with A: water + 0.1% formic acid; B: acetonitrile + 0.1% formic acid. Gradient:

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Detection - MS, ELS, UV (100 µl split to MS with in-line UV detector)
MS ionisation method - Electrospray (positive and negative ion)

LC-MS method 4
Waters Micromass ZQ with a C18-reverse-phase column (100 x 3.0 mm Higgins Clipeus with 5 µm particle size), elution with A: water + 0.1% formic acid; B: acetonitrile + 0.1% formic acid. Gradient:

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Detection - MS, ELS, UV (100 µl split to MS with in-line UV detector at 254 nm)
MS ionisation method - Electrospray (positive ion)
X-Ray Powder Diffraction (XRPD) patterns were collected, on a high resolution Philips X-Pert MPD machine in reflection mode and 0-2θ configuration, over the scan range 2° to 40° 2θ with 100-second exposure per 0.03° increment. The X-rays were generated by a copper tube operated at 45kV and 40mA. The wavelengths of the direct beam X-rays was 1.5406 Å ($K_{\alpha}$) as a monochromator was used. The data was collected on zero background holders on which ~2mg of the compound was placed. The holder (provided by PANalytical) was made from a single crystal of silicon, which had been cut along a non-diffracting plane in the 2° to 40° 2θ range and then polished on an optically flat finish. The X-rays incident upon this surface were negated by Bragg extinction. Raw data were stored electronically and evaluation was performed on raw or smoothed diffraction patterns. XRPD were recorded at ambient temperature and relative humidity.

Differential scanning calorimetry (DSC) thermograms were measured using a TA Q1000 Differential Scanning Calorimeter, with aluminium pans and pierced lids. The sample weights varied between 0.5 to 5mg. The procedure was carried out under a flow of nitrogen gas (50ml/min) and the temperature studied from 25 to 300°C at a constant rate of temperature increase of 10°C per minute.

Thermogravimetric analysis (TGA) thermograms were measured using a TA Q500 Thermogravimetric Analyser, with platinum pans. The sample weights varied between 1 and 5mg. The procedure was carried out under a flow of nitrogen gas (60ml/min) and the temperature studied from 25 to 200°C at a constant rate of temperature increase of 10°C per minute.

GVS profiles were measured using a Dynamic Vapour Sorption DVS-I instrument. The solid sample ca. 1-5mg was placed into a glass vessel and the weight of the sample was recorded during a dual cycle step method (40 to 90 to 0 to 90 to 0% relative humidity (RH), in steps of 10% RH). GVS profiles were recorded at ambient temperature (25 °C).

Abbreviations used in the experimental section:

Aq = aqueous
DCM = dichloromethane
DMF = dimethylformamide
EtOAc = ethyl acetate
EtOH = ethanol
GVS = Gravimetric vapour sorption
MeOH = methanol
RT = RT
Rt = retention time
THF = tetrahydrofuran
Satd = saturated

The following intermediates 1-6 used in the preparation of [2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium napadisylate, were prepared as follows:

**Intermediate 1**: 2-Oxo-2-phenvI-\(N\)-prop-2-ynyl-acetamide

\[
\text{Oxalyl chloride (6.1 g, 48 mmol) was added to a solution of phenylglyoxylic acid (6.0 g, 40 mmol) and 3 drops of DMF in dry DCM (50 mL). The reaction mixture was stirred at RT for 3 h then the solvent was removed. The residue was taken up in dry DCM (50 mL) and the solution was cooled to 0 °C. A mixture of propargyl amine (2.2 g, 40 mmol) and triethylamine (4.05 g, 40 mmol) was added cautiously over a period of 10 min then the mixture was allowed to warm to RT. Stirring was continued for 2.5 h then water (10 mL) was added. The mixture was washed with 1 M HCl, sat. sodium hydrogencarbonate (aq.), then brine. The organic phase was then dried (Na\(_2\)SO\(_4\)) and the solvent was removed. The residue was crystallized from cyclohexane to afford the product as a light brown solid.}

Yield: 5.75 g, 76%. LC-MS (Method 3): Rt 2.47 min, m/z 188 [MH\(^+\)].

**Intermediate 2**: (5-Methyl-oxazol-2-yl)-phenyI-methanone.
Methane sulfonic acid (10 g, 104 mmol) was added drop wise to a solution of 2-oxo-2-phenyl-\( \text{V-} \)prop-2-ynyl-acetamide (Intermediate 1) (2.4 g, 12.83 mmol) in 1,4-dioxane (20 mL). The resultant solution was heated at 90 °C for 66 h. The reaction mixture was cooled and the solvent was removed. The dark residue was partitioned between DCM and water.

The DCM fraction was washed with 1 M HCl (2x), satd. sodium hydrogencarbonate solution (aq., 2x), then brine. The solution was dried (\( \text{Na}_2\text{SO}_4 \)) and the solvent was removed to give the crude product. Purification was achieved via column chromatography, eluting with cyclohexane/EtOAc (4:1). This afforded the product as an off-white solid.

Yield: 1.0 g, 41%. LC-MS (Method 3): Rt 2.94 min, \( m/z \) 188 [\( \text{MH}^+ \)].

**Intermediate 3: Cyclohexyl-fS-methyl-oxazoI-I-vD-phenyl-methanol**

A solution of (5-methyl-oxazol-2-yl)-phenyl-methanone (intermediate 2) (3.0 g, 16 mmol) in 32 mL dry THF at 0 °C under nitrogen was treated dropwise over 10 min with a 2 M solution of cyclohexylmagnesium chloride in diethyl ether (10 mL, 20 mmol). The resulting deep yellow solution was stirred at 0 °C for about 30 min during which time a precipitate was formed, and then at RT for 1.5 h. The reaction mixture was cooled to 0 °C again and treated cautiously with satd. ammonium chloride solution (aq.). The mixture was stirred at RT for 10 min then diluted with water (10 mL). The phases were separated and the organic phase was washed with brine. The combined aqueous phase was extracted with DCM and the combined organic phase was dried (\( \text{MgSO}_4 \)) and concentrated \textit{in vacuo} to give the crude product, which was triturated with ether, filtered off and dried.

Yield: 3.65 g, 84%. LCMS (Method 3): Rt 3.78 min, \( m/z \) 272 [\( \text{MH}^+ \)].

**Intermediate 4: (S-Bromomethyl-oxazol-Z-vD-cyclohexyl-phenyl-methanol.**
A solution of cyclohexyl-(5-methyl-oxazol-2-yl)-phenyl-methanol (Intermediate 3) (3.0 g, 11.1 mmol) in 1,2-dichloroethane (22 mL) was treated with iV-bromo-succinimide (2.16 g, 12.2 mmol) followed by 2,2'-azobis(2-methylpropionitrile) (0.18 g, 2.1 mmol). The mixture was heated to 80 °C for 2.5 h and then allowed to cool to RT. Satd. sodium hydrogen carbonate solution (aq.) was added and the phases were separated. The organic layer was washed with brine and the combined aqueous layers were extracted with DCM. The combined organic phase was dried (MgSO₄) and concentrated in vacuo to give the crude product as a brown oil. Purification was achieved via column chromatography eluting with 33-100% DCM/cyclohexane, followed by 25% EtOAc/DCM. Yield: 1.85 g, 48%: LCMS (Method 3): Rt 4.27 min, m/z 350, 352 [MH⁺].

Intermediate 5: CyclohexylS-dimethylaminomethyl-oxazol-Z-vD-phenyl-methanol

A solution of (5-bromomethyl-oxazol-2-yl)-cyclohexyl-phenyl-methanol (Intermediate 4) (3.2 g, 9.2 mmol) in THF (40 mL) was treated with a 2 M solution of dimethylamine in THF (40 mL, 80 mmol). A suspension formed after stirring for a few minutes. The reaction mixture was left at RT overnight and then the solid was filtered off and discarded. The filtrate was concentrated under reduced pressure and the residue was partitioned between DCM and satd. sodium hydrogen carbonate solution (aq.). The organic layer was dried (Na₂SO₄) and evaporated to afford the title compound as a solid. Yield: 2.74 g, 95%.

LC-MS (Method 1): Rt 6.57 min, m/z 315 [MH⁺].
The two enantiomers of cyclohexyl-(5-dimethylaminomethyl-oxazol-2-yl)-phenyl-methanol (Intermediate 5) (2.74 g) were separated by preparative chiral HPLC using 250x20 mm Chiralpak® IA column packed with amylase tris(3,5-dimethylphenyl-carbamate) immobilized on 5 µm silica gel. The column was eluted with 5% EtOH in heptane buffered with 0.1% diethylamine at 15 mL/min. The first eluting enantiomer (Rt 8.5 min) afforded (S)-cyclohexyl-(5-dimethylaminomethyl-oxazol-2-yl)-phenyl-methanol as a white solid (Yield: 0.73 g, 27%; LC-MS (Method 1): Rt 6.50 min, m/z 315 [MH+].

**Intermediate 5b**: (R)-cyclohexyl-(5-dimethylaminomethyl-oxazol-2-yl)-phenyl-methanol

![Intermediate 5b](image)

Yield: 1.04 g, 38%.

LC-MS (Method 1): Rt 6.48 min, m/z 315 [MH+].

**1H NMR** (CDCl₃): δ 1.10-1.39 (m, 7H), 1.62-1.76 (m, 3H), 2.25 (s, 6H), 2.29-2.35 (m, IH), 3.54 (dd ᴛ₀/₂, 2H), 3.70 (br.s, IH), 6.84 (s, IH), 7.24 (t, IH), 7.33 (t, 2H), 7.64 (d, 2H) ppm.

Intermediate 6: r2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl1-dimethyl-(3-phenoxy-propyl)-ammonium bromide
A solution of (R)-cyclohexyl-(5-dimethylaminomethyloxazol-2-yl)-phenyl-methanol (Intermediate 5a) (98 mg, 0.31 mg) and 3-phenoxypropyl bromide (740 mg, 3.44 mmol) in chloroform (1.5 mL) and acetonitrile (1.5 mL) was heated at 50 °C for 2 h. The RM was concentrated to dryness to afford a colourless viscous oil, which was triturated with diethyl ether to furnish a white gum. This was purified by column chromatography eluting with 2.5-25% MeOH/DCM to afford the product as a turbid viscous oil. Drying under vacuum at 45 °C for 1-2 days afforded a white solid.

Yield: 142 mg, 86%.

LC-MS (Method 1): Rt 8.41 min, m/z 449 [M+].

$^1$H NMR (CDCl$_3$): δ 0.61-1.16 (m, 3H), 1.21-1.37 (m, 4H), 1.59-1.74 (m, 3H), 2.32 (m, 3H), 3.32 (s, 3H), 3.33 (s, 3H), 3.61 (dd, 2H), 4.03 (t, 2H), 4.14 (br.s, 1H), 5.20 (dd, 2H), 6.85 (d, 2H), 6.98 (t, 1H), 7.19 (t, 1H), 7.26-7.30 (m, 4H), 7.55-7.58 (m, 3H) ppm.

An XRPD spectrum of [2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium bromide prepared as described herein above denotes that the material obtained is amorphous (Figure 4). The glass transition temperature $T_g$ of this amorphous form as determined by DSC was found to be 66 °C (onset) (±2 °C). Weight loss observed prior to melting by TGA was 3.4%. GVS determination showed a weight increase of approximately 10 % (%w/w) at 80% RH (±0.2%), GVS analysis showing deliquescence.
A mixture of [2-((R)-cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium bromide (Intermediate 6) (201 mg, 0.372 mmol), naphthalene-1,5-disulfonate disodium salt (68 mg, 0.21 mmol), DCM (2.8 mL), and water (2.8 mL) was stirred vigorously at RT overnight. The solids were collected by filtration, washed with DCM/water mixture, and dried under vacuum at 40 °C. The sample of napadisylate salt so obtained is hereinafter referred to as the amorphous form.

Yield: 208 mg, 94%.

LC-MS (Method 1): Rt 8.35 min, m/z 449 [M+].

$^1$H NMR (CD$_3$OD): δ 1.04-1.37 (m, 12H), 1.55-1.75 (m, 8H), 2.22 (m, 4H), 2.40 (m, 2H), 3.01 (s, 6H), 3.02 (s, 6H), 3.37 (m, 2H), 3.97 (m, 4H), 4.67 (s, 4H), 6.89 (d, 4H), 6.95 (t, 2H), 7.21 (t, 2H), 7.28 (m, 8H), 7.51 (m, 8H), 8.19 (d, 2H), 9.02 (d, 2H) ppm.

**Salt Form 1**

Amorphous form (as prepared herein above) was heated in toluene with stirring at 60° for 48 hours and allowed to cool to RT while stirring to afford the product as small platelets. The product was collected by filtration and dried under vacuum at 50 °C for 3 h.

The melting temperature of Form 1 was determined by DSC, during which testing Form 1 underwent dehydration and subsequently the dehydrated Form 1, totally or partially converted into an anhydrous form, melted at 225 °C ±2°C (onset). Water content as determined by TGA was 0.7 % (±0.2%). GVS determination gave a 3.1 % weight increase (%w/w) at 80 % RH (±0.5%).
An XRPD spectrum of Form 1 is presented in Figure 1.

Further quantities of Form 1 were prepared as follows: Amorphous form was crystallised from refluxing acetonitrile using a hot filtration of the solution and allowed to cool to RT while stirring to afford the product as small platelets. The product was collected by filtration and stirred in toluene at 60 °C for 19 h. The solids were collected by decanting the solvent and dried under vacuum at 50 °C for 3h. XRPD and DSC analysis were consistent with Form 1.

**Salt Form 2**

Amorphous form was heated in anisole at 154 °C for 3hrs then left to stand at RT for 48hrs. The solids were collected by decanting the solvent and dried under vacuum at 45 °C. The melting temperature of Form 2 as determined by DSC was found to be 227 °C ±2°C (onset). Water content as determined by TGA was 0.0 %. GVS determination gave a 0.7 % weight increase (%w/w) at 80 % RH (±0.2%).

An XRPD spectrum of Form 2 is presented in Figure 2.

Further quantities of Form 2 were prepared as follows: Amorphous form was crystallised from refluxing chlorobenzene and allowed to slowly cool to RT to afford the product as fine needles. The product was collected by filtration and dried under vacuum at RT overnight. XRPD and DSC analysis were consistent with Form 2.

Further quantities of Form 2 were prepared as follows: Amorphous form was stirred in toluene at 80 °C over for at least 60 hours. The solids were collected by decanting the solvent and dried under vacuum at 45 °C. XRPD and DSC analysis were consistent with Form 2.

**Salt Form 3**

Amorphous form was crystallised from refluxing acetone/water mixture using a hot filtration of the solution and allowed to cool to RT while stirring to afford the product as a white powder. The product was collected by filtration and dried under vacuum at RT overnight.
The melting temperature of Form 3 was determined by DSC, during which testing Form 3 underwent dehydration and subsequently the dehydrated Form 3, totally or partially converted into an anhydrous form, melted at 224 °C ±2°C (onset). Water content as determined by TGA was 2.1 % (±0.2%). GVS determination gave a 3.0 % weight increase (%w/w) at 80 % RH (±0.2%).

An XRPD spectrum of Form 3 is presented in Figure 3.

**Biological Activity of r2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl-dimethyl-(3-phenoxy-propyl)-ammonium hemi-naphthalene-1,5-disulfonate**

The inhibitory effects of compounds of the napadisylate salt were determined by a Muscarinic Receptor Radioligand Binding Assay. Radioligand binding studies utilising [³H]-N-methyl scopolamine ([³H]-NMS) and commercially available cell membranes expressing the human muscarinic receptors (M2 or M3) were used to assess the affinity of muscarinic antagonists for M2 and M3 receptors. Membranes in TRIS buffer were incubated in 96-well plates with [³H]-NMS and M3 antagonist at various concentrations for 3 hours. Membranes and bound radioligand were then harvested by filtration and allowed to dry overnight. Scintillation fluid was then added and the bound radioligand counted using a Canberra Packard Topcount scintillation counter.

The half-life of antagonists at each muscarinic receptor was measured using the alternative radioligand [³H]-QNB and an adaptation of the above affinity assay. Antagonists were incubated for 3 hours at a concentration 10-fold higher than their Ki, as determined with the [³H]-QNB ligand, with membranes expressing the human muscarinic receptors. At the end of this time, [³H]-QNB was added to a concentration 25-fold higher than its Kd for the receptor being studied and the incubation continued for various time periods from 15 minutes up to 180 minutes. Membranes and bound radioligand were then harvested by filtration and allowed to dry overnight. Scintillation fluid was then added and the bound radioligand counted using a Canberra Packard Topcount scintillation counter.

The rate at which [³H]-QNB is detected binding to the muscarinic receptors is related to the rate at which the antagonist dissociates from the receptor, i.e. to the half life of the
antagonists on the receptors. The napadisylate salt of the present invention displayed a M3 binding Ki, nM of 0.2.
1. A salt being [2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)-oxazol-5-ylmethyl]-
dimethyl-(3-phenoxy-propyl)-ammonium napadisylate.

2. A salt according to claim 1 which is [2-((R)-Cyclohexyl-hydroxy-phenyl-methyl)oxazol-5-ylmethyl]-dimethyl-(3-phenoxy-propyl)-ammonium hemi-naphthalene-1,5-
disulfonate.

3. A salt according to claim 2, which exhibits at least the following characteristic X-ray powder diffraction peaks (expressed in degrees 2Θ):
   (1) 5.6, 14.6, 16.7 and 18.0,
   (2) 5.6, 14.6, 16.7, 18.0, 19.4 and 20.4, or
   (3) 5.6, 9.3, 13.6, 14.6, 16.7, 18.0, 19.4 and 20.4, or
   (4) 5.6, 9.3, 13.6, 14.6, 16.7, 18.0, 19.4, 19.8, 20.4 and 20.8.

4. A salt according to claim 3 having an X-ray powder diffraction pattern substantially the same as that shown in Figure 1.

5. A salt according to claim 3 or claim 4, which is hygroscopic.

6. A salt according to claim 2, which exhibits at least the following characteristic X-ray powder diffraction peaks (expressed in degrees 2Θ):
   (1) 5.3, 15.7, 16.5 and 26.4,
   (2) 5.3, 15.7, 16.5, 19.0, 21.2 and 26.4,
   (3) 5.3, 15.0, 15.7, 16.5, 17.6, 19.0, 21.2 and 26.4,
   (4) 5.3, 15.0, 15.7, 16.5, 17.6, 18.4, 19.0, 21.2 and 26.4.

7. A salt according to claim 6 having an X-ray powder diffraction pattern substantially the same as that shown in Figure 2.
8. A salt according to claim 6 or claim 7, which is anhydrous.

9. A salt according to claim 2 which exhibits at least the following characteristic X-ray powder diffraction peaks (expressed in degrees 2θ):
   (1) 5.9, 17.3, 17.7 and 20.8 or
   (2) 5.9, 13.9, 17.3, 17.7, 20.8 and 23.6 or
   (3) 5.9, 11.6, 13.9, 17.3, 17.7, 18.8, 20.8 and 23.6 or
   (4) 5.9, 11.6, 13.9, 14.9 17.3, 17.7, 18.8, 20.8, 21.8 and 23.6.

10. A salt according to claim 9 having an X-ray powder diffraction pattern substantially the same as that shown in Figure 3.

11. A salt according to claim 9 or claim 10, which is hydrated.

12. A pharmaceutical composition comprising a salt according to any one of claims 1 to 11 in association with a pharmaceutically acceptable adjuvant, diluent or carrier.

13. A salt according to any one of claims 1 to 11 for use in therapy.

14. Use of a salt according to any one of claims 1 to 11 in the manufacture of a medicament for use in treating chronic obstructive pulmonary disease.
Figure 1: XRPD for Form 1

Figure 2: XRPD for Form 2
Figure 3: XRPD for Form 3

![Graph showing XRPD for Form 3]

Figure 4: XRPD of Amorphous Form (Bromide Salt)

![Graph showing XRPD of Amorphous Form (Bromide Salt)]
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D263/32 A61K31/421 A61P11/06

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)
C07D

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

Electronic database consulted during the international search (name of database and, where practical, search terms used)
EPO-Internal, WPI Data, EMBASE, BIOSIS, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>A</td>
<td>WO 97/30994 A (PFIZER RES &amp; DEV [IE]); PFIZER LTD [GB]; PFIZER [US]; MACKENZIE ALEXAND) 28 August 1997 (1997-08-28) claim 1</td>
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<td>P,X</td>
<td>WO 2007/017669 A (ARGENTA DISCOVERY LTD [GB]; RAY NICHOLAS CHARLES [GB]; BULL RICHARD JA) 15 February 2007 (2007-02-15) claim 1 examples</td>
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X Further documents are listed in the continuation of Box C

X See patent family annex

Date of the actual completion of the international search

13 June 2008

Date of mailing of the international search report

25/06/2008

Name and mailing address of the ISA/

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Authorized officer

Steendi jk, Martin
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<th>Category</th>
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