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Respiratory drug development compendium 2002

Prous Science is pleased to present the first in a series of brief accounts covering selected therapeutic groups that are complementary to the Annual Reviews. The objective of this article is to provide an overview of the current status of drugs in active development for respiratory indications. Information in this compendium includes company communications and data from Prous Science's Integrity® drug discovery portal. This month's compendium includes drugs for the treatment of allergic rhinitis (24), ARDS (5), asthma (48), COPD (23), cough (4), cystic fibrosis (13), pulmonary emphysema (5) and miscellaneous conditions (5). The Annual Review of Respiratory Drugs follows the compendium and offers updated information on the following drugs that have been published in previous issues of the journal: AWD-12-281, ciclesonide, cilomast, CPX, desloratadine, efletirizine, formoterol fumarate, fudosteine, iseganan hydrochloride, montelukast sodium, omalizumab, roflumilast, rupatadine fumarate, talniflumate, tecastemizole and tiotropium bromide.

A.I. Graul

Allergic Rhinitis

Background Information

Allergic rhinitis is an inflammation of the mucus membranes of the nose that occurs in response to an airborne antigen (allergen). Allergic rhinitis, also called allergic rhinoconjunctivitis, is characterized by frequent or repetitive sneezing, runny or congested nose and itchiness of the nose, eyes and throat. It may also be associated with other symptoms such as headache, impaired smell, postnasal drip, conjunctival symptoms (*e.g.*, itchy watery eyes), sinusitis and other complicating respiratory symptoms. Depending upon the time of exposure, allergic rhinitis can be classified as perennial, seasonal or occupational. Other forms of rhinitis can be classified as infectious, perennial nonallergic and miscellaneous (hormonal, drug-induced, mechanical and gustatory rhinitis). Allergic rhinitis is the sixth most prevalent chronic disease, affecting 10-20% of the general population.

Intervention at various points in the inflammatory cascade has been shown to be effective in controlling the symptoms of allergic rhinitis. Most currently marketed antiallergic drugs are histamine H_1 antagonists, although intranasal corticosteroids are highly effective in suppressing symptoms of nasal inflammation. Nonsteroidal antiinflammatory agents such as cromoglycate sodium inhibit the release of allergic mediators from mast cells and are useful in cases in which corticosteroids are contraindicated.

Histamine H_1 Antagonists

Antihistamines are typically prescribed as first-line therapy for allergic rhinitis. Compounds with this mechanism of action block the effects of histamine at H_1 receptors on postcapillary venule smooth muscle and thus prevent the decrease in vascular permeability, exudation and edema induced by histamine. They prevent symptoms associated with histamine release such as sneezing, rhinorrhea, nasal and conjunctival itching and lacrimation; they do not control symptoms of nasal congestion. Recent studies indicate that antihistamines may also have antiinflammatory activity, which may further explain their efficacy in this indication.

Three new antihistamines were introduced worldwide in 2001, the last year that any new antiallergic agents with this mechanism of action were launched. Two of the new antihistaminics – Sepracor's levocetirizine and desloratadine – are so-called Improved Chemical Entities (ICE™), meaning that they consist in the active isomers or active metabolites of previously marketed drugs. Thus **levocetirizine** is the active (*R*)-enantiomer of the previously marketed drug cetirizine, while **desloratadine** is an improved version of the second-generation antihistamine loratadine that does not block cardiac potassium channels and thus possesses a superior cardiovascular safety profile. The former is marketed by UCB as Xusal®, and the latter by Schering-Plough under the trade names Neoclarityn™ and Clarinex®. **Olopatadine hydrochloride** (Kyowa Hakko's Allelock®), another 2001 introduction, was previously marketed for the treatment of allergic conjunctivitis. A fourth product, **rupatadine fumarate** registered in Spain in 2001 by Uriach as Rupafin®, is a dual-acting antihistamine and PAF antagonist.

On March 7, 2002, the U.S. Food and Drug Administration (FDA) issued a "not approvable" letter for Sepracor's New Drug Application (NDA) for Soltara™ (**tecastemizole**). In October 2002, Sepracor met with the FDA to discuss initiation of additional preclinical and clinical studies of Soltara. Contingent upon favorable results of proposed preclinical and clinical studies, Sepracor expects to include approximately 10 additional preclinical and 10 additional clinical studies as part of a resubmission of the Soltara™ NDA.

Several other new antihistamines are in development, as shown in Table I.

Table I: Newer antihistamines marketed and in development for allergic rhinitis.

Drug Name	Source	Status
Desloratadine	Sepracor/Schering-Plough	Launched-2001 (Germany, U.K.)
Levocetirizine	Sepracor/UCB	Launched-2001 (Germany)
Olopatadine Hydrochloride	Kyowa Hakko	Launched-2001 (Japan)
Rupatadine Fumarate	Uriach	Registered-2001 (Spain)
Efleterizine	UCB	Phase III
Tecastemizole	Sepracor	Phase III
Bilastine	FAES	Phase II
TAK-427	Takeda	Phase II
UCB-35440	UCB	Phase I

Corticosteroids

Ciclesonide is an ester prodrug, new-generation inhaled nonhalogenated corticosteroid with potent local antiinflammatory properties that is essentially devoid of oral bioavailability. **Ciclesonide** (B-9207-015, BY-9010, Alvesco®) is in phase I development at Altana as a nasal spray formulation for the treatment of seasonal and allergic rhinitis.

An inhalable formulation of the steroid compound **NS-126** is being codeveloped by Nippon Shinyaku and SSP in Japan for the treatment of allergic rhinitis and of bronchial asthma. The compound is in phase II testing for both indications.

Leukotriene CysLT$_1$ (LTD$_4$) Receptor Antagonists

Leukotrienes are generally classified in two subclasses: the cysteinyl-leukotrienes LTC$_4$ (CysLT$_2$), LTD$_4$ (CysLT$_1$) and LTE$_4$ and the dihydroxy-leukotriene LTB$_4$ (BLT). Peptidoleukotrienes are responsible for the biological responses characteristic of allergic rhinitis and asthma, *i.e.*, prolonged bronchoconstriction, coronary artery vasoconstriction and numerous other biological responses. The pharmacological activities of peptidoleukotrienes include smooth muscle contraction, myocardial depression, increased vascular permeability and enhanced mucus production.

The established antiasthmatic agent **montelukast sodium** (marketed by Merck & Co. as Singulair™ since 1997) is scheduled to be introduced in early 2003 for a new indication: treatment of seasonal allergic rhinitis (hay fever) in adults and children as young as 2 years of age. It is in phase III testing as a fixed-dose combination with loratadine (Claritin™); the combination therapy is being codeveloped with Schering-Plough.

Another LTD$_4$ receptor antagonist designated **MCC-847** is in phase II clinical testing in Japan at Mitsubishi Pharma. It is targeted for the treatment of both allergic rhinitis and asthma.

Adenosine A$_2$ Receptor Agonists

Adenosine, a ubiquitous autacoid with a wide spectrum of biological activities, has been shown to suppress leukotriene biosynthesis in human neutrophils via the inhibition of agonist-induced arachidonic acid release. Adenosine A$_{2A}$ receptor agonists and other agents that modulate the biosynthesis, metabolism and transport of adenosine have been proposed as novel agents for the treatment of inflammatory disease, including allergic rhinitis.

The adenosine A$_2$ receptor agonist **GW-328267** is in phase II testing at GlaxoSmithKline for the treatment of allergic rhinitis.

Phosphodiesterase Type 4 Inhibitors

A selective phosphodiesterase type 4 (PDE4) inhibitor with potent bronchodilator activity, **AWD-12-281** is under development at elbion in collaboration with GlaxoSmithKline for the treatment of allergic rhinitis, COPD and bronchial asthma. It is in phase II as an intranasal suspension for the indication of allergic rhinitis. Under the terms of an agreement signed in July 2002, GSK will have exclusive worldwide development, registration, manufacturing and commercialization rights and will assume all responsibilities and costs.

Cytokine Modulators

A high-affinity human IgG4 monoclonal antibody that neutralizes eotaxin1, **CAT-213** is under development at Cambridge Antibody Technology. Its ability to inhibit the major stimulus that attracts eosinophils into tissues suggests a potential mechanism for treating severe allergic disorders wherein eosinophils may cause tissue damage. CAT-213 entered phase I/II testing in November 2001 as a nasal formulation for the treatment of severe allergic disorders.

Anti-IgE Therapy

Anti-IgE therapy, one of the newest therapeutic approaches to allergic rhinitis, is designed to treat the underlying immune and inflammatory response initiated by IgE antibodies in atopic patients. Anti-IgEs inhibit or neutralize free IgE as well as downregulating the production of IgE by B cells. For reasons not yet fully understood, the production of IgE in allergic patients is abnormally high and the IgE produced has increased binding specificity for those allergens to which the individual is sensitized. Long-term treatment with anti-IgE therapy appears to be required, since IgE appears to be synthesized continuously.

In June 2002, the anti-IgE monoclonal antibody **omalizumab** (Xolair™) was approved for the first time in Australia, where it will be supplied as an s.c. injectable formulation for the treatment of allergic rhinitis and moderate allergic asthma in adults and adolescents. It is in phase III in the U.S. for the treatment of allergic asthma and seasonal allergic rhinitis in adults and children. ALTO safety study results have been completed and were scheduled to be incorporated into a BLA application to the FDA at the end of 2002. The product is the result of a collaborative effort by Genentech, Novartis and Tanox.

Mast Cell Activation Inhibitors

Rigel's **R-112** has entered phase I clinical testing in the U.S. for the treatment of allergic rhinitis. The randomized, double-blind, placebo-controlled, crossover study, being conducted at the National Jewish Medical and Research Center, will assess R-112 in 20 patients with documented allergies. Preliminary findings are expected in mid-2003. The experimental compound is directed at mast cells and has the potential to block all components of the mast cell response; it targets mast cells after they have been activated by IgE and prevents mediator release. Easily administered by nasal spray, R-112 may also have application in the treatment of other allergic diseases of the respiratory system. R-112 first entered the clinic in the U.K. in September 2002. In the initial safety study in healthy volunteers, no significant adverse events were noted.

$P2Y_2$ Receptor Agonists

A synthetic dinucleotide $P2Y_2$ receptor agonist, **INS-37217** (dCp4U) is undergoing phase III clinical evaluation at Inspire Pharmaceuticals as a nasal spray formulation for the treatment of perennial allergic rhinitis. INS-37217 Intranasal is designed to enhance mucosal hydration and mucociliary clearance in airways tissue by activating $P2Y_2$ receptors on the mucosal surface. This novel approach could provide significant benefit to patients without the disadvantages associated with antihistamines and corticosteroids.

Integrin Receptor Antagonists

In asthma and other inflammatory respiratory disorders, numerous inflammatory cells – including eosinophils, neutrophils, mast cells and lymphocytes – are found to infiltrate the mucosal layer. Most of the cells are believed to be recruited from the bloodstream, transmigrating through endothelial barriers. Leukocyte extravasation is a multistep process in which different molecules (selectins, integrins and chemokines) are involved. Several adhesion molecules and chemokines as well as their counterparts are thought to play an important role in regulating the local influx of immune and inflammatory cells.

At this time only one integrin antagonist is reported to be in active development for the indication of allergic rhinitis. **GW-559090** is in phase I testing at GlaxoSmithKline for both allergy and asthma.

Immune-Targeted Therapy

A killed *Mycobacterium vaccae* suspension with long-term protective antiinflammatory activity, **SRP-299** is in development at SR Pharma for the treatment of allergic rhinitis, asthma and atopic dermatitis. The mechanism of action of SRP-299 results in the accumulation of allergen-specific regulatory T cells, which then selectively downregulate the Th2 response without inducing a Th1 response. The drug is currently in phase I/II testing for allergic rhinitis.

Specific Immunotherapy

The peptide allergen desensitization (PAD) technology-based vaccine against cat-induced allergies, **Cat-PAD**™, which is comprised of a mixture of T-cell-specific peptide epitopes selected on the basis of MHC binding, is in development at PowderJect Pharmaceuticals. Phase I testing commenced in 2000. Phase II testing is expected to begin in 2004. In May 2002, PowderJect acquired 100% of the share capital of Circassia Limited, the biotechnology company responsible for the early development of Cat-PAD™.

A conjugate of purified ragweed allergen (Amb a 1) linked to an immunostimulatory polynucleotide DNA sequence (ISS), **AIC** (Amb a 1-ISS conjugate) is in phase II/III clinical development at Dynavax Technologies. Trials are under way in both Canada and the U.S. evaluating AIC as a subcutaneous formulation for the treatment of allergic rhinitis in adults with an allergy to ragweed. Dynavax entered into a strategic alliance with Stallergenes in November 1999, granting the latter an option to acquire commercial rights in Europe for the technologies

based on ISS linked to allergens for the treatment of seasonal allergies.

Miscellaneous Agents

A novel, potent antiallergy and antiinflammatory agent and mediator release inhibitor, **andolast** (CR-2039) is in phase IIb clinical testing at Rotta for the treatment of asthma and other atopic allergic diseases.

A potent inhibitor of the inducible form of nitric oxide synthase (iNOS), **GW-274150** has progressed to phase I clinical testing at GlaxoSmithKline for the treatment of both allergic rhinitis and asthma.

Adult (Acute) Respiratory Distress Syndrome (ARDS)

Background Information

Adult (acute) respiratory distress syndrome (ARDS) is the rapid onset of progressive malfunction of the lungs, usually associated with the malfunction of other organs due to the inability to take up oxygen. The condition is characterized by extensive lung inflammation and small blood vessel injury in all affected organs. ARDS is commonly precipitated by trauma, sepsis (systemic infection), diffuse pneumonia and shock. It may occur following extensive surgery or as a result of certain blood abnormalities. Less common causes include drowning and inhalation of toxic gases. In half of all cases, onset occurs within 24 hours of the original illness or injury; in nearly all, it occurs within three days. The incidence of ARDS has been difficult to determine, partly due to the variety of causes, but it is a common problem in hospital intensive care units. Various published estimates have ranged from 1.5 to 71 cases per 100,000 population. Earlier estimates suggested that approximately 150,000 Americans are affected each year.

There are many experimental therapies that show promise for the treatment of ARDS. These include replacement surfactant (a natural soapy substance that keeps the lung air sacs open) and the use of antiinflammatory agents.

Surfactants

HL-10 is a natural freeze-dried surfactant isolated from minced pig lungs, containing phospholipids as well as the surfactant proteins SP-B and SP-C. HL-10 is in phase II testing at Leo Pharma for the treatment of acute respiratory distress syndrome; trials are underway in Europe and Canada.

Another pulmonary surfactant compound, Altana's **lusupultide** (recombinant surfactant protein C, rSPC-Surfactant, Venticute™), is in phase III testing in the U.S. and Europe as a potential treatment for ARDS.

The first humanized peptide-based surfactant to mimic human surfactant protein B, **sinapultide** (KL4, RWJ-45652, lucinactant, Surfaxin™) is the subject of an expanded alliance between Discovery Laboratories and Esteve for the development, marketing and sale of the drug throughout Europe and in South and Central America. Sinapultide is in phase III testing for the prevention and treatment of idiopathic respiratory distress syndrome in premature infants and the treatment of meconium aspiration syndrome in full-term newborns, and in phase II for the treatment of acute respiratory distress syndrome in adults. The product has fast-track designation in the U.S., and orphan drug status in the U.S. and Europe.

Human Neutrophil Elastase Inhibitors

A highly specific and potent member of a group of human neutrophil elastase (hNE) inhibitors, **EPI-hNE-4** (DX-890) was derived from the second Kunitz-type domain of inter-inhibitor protein (ITI-D2). The product was engineered by Dyax and is being codeveloped by Debiopharm and H3 Pharma. EPI-hNE-4 is in preclinical testing for the ARDS indication; it is in phase III for the treatment of cystic fibrosis (see below).

Miscellaneous Agents

ALS-886, an antiinflammatory compound licensed from Baxter and under development at Advanced Life Sciences, has been shown to be effective in reducing microvascular permeability commonly seen in acute lung injury and sepsis. The molecular mechanism by which ALS-886 may be exerting tissue damage-sparing properties is currently under investigation. An IND has been filed in the U.S.

Asthma

Background Information

Asthma is a chronic inflammatory airway disease characterized by elevated bronchial tone, hypersecretion of airway mucus that may lead to bronchial obstruction, hyperplasia of the airways smooth muscle and mucous glands, subepithelial fibrosis, submucosal edema and inflammation of the respiratory wall. In susceptible individuals the inflammation causes recurrent episodes of wheezing, breathlessness, chest tightness and cough (termed exacerbations or attacks), particularly at night or early in the morning. These symptoms are usually associated with widespread but variable airflow obstruction that is at least partly reversible, either spontaneously or

Table II: New β_2-adrenoceptor agonists in development for asthma.

Drug Name	Source	Status
AeroDose Albuterol Inhalar	AeroGen	Phase II
AIR-Albuterol	Alkermes	Phase II
MSI-Albuterol	Sheffield	Phase II
QAB-149	Novartis	Phase II
NCX-950	NicOx	Phase I/II

with treatment. More than 50 million people worldwide, including a projected 17 million in the U.S. alone, suffer from asthma. Furthermore, evidence indicates that asthma is increasing in both prevalence and severity.

The treatment of asthma has a dual focus: the short-term treatment of acute symptoms with bronchodilators, together with the prevention or eventual reversal of chronic inflammation using antiinflammatory drugs.

β_2-Adrenoceptor Agonists

β_2-Adrenoceptor agonists are the most widely used class of asthma medications. These drugs stimulate specific β-adrenergic receptors located in the plasma membrane, altering adenylyl cyclase and increasing intracellular levels of cyclic 3',5'-adenosine monophosphate (cAMP). cAMP is responsible for the relaxation of smooth muscle during bronchodilation, increased ciliary beat frequency and decreased mucus viscosity.

Short-acting inhaled β_2-agonists such as albuterol are extremely effective in providing quick relief from exacerbations. The newer long-acting β_2-adrenoceptor agonists such as salmeterol and formoterol, when used in combination with inhaled corticosteroids, are useful in preventing exacerbations, especially nocturnal symptoms, in patients with moderate or severe persistent asthma.

Several new formulations of marketed β_2-adrenoceptor agonists as well as new compounds are in development for asthma at this time, as indicated in Table II. The major advantage of these products is the incorporation of improved inhalation devices. For example, AeroGen's **AeroDose™**device is a small, portable hand-held inhaler utilizing the company's proprietary aerosol generator technology to aerosolize liquids. Alkermes' **AIR™** pulmonary drug delivery technology is designed to provide several hours of therapeutic benefit from a single administration, based on the principal that relatively large, low-density drug particles can be inhaled into the lungs with high efficiency from simple inhaler devices. Sheffield's proprietary **MSI** delivery system incorporates a small, portable, hand-held nebulizer (manufactured by Siemens). The system is designed to overcome the difficulty both children and the elderly often experience in coordinating the use of a traditional metered-dose inhaler (MDI).

NCX-950, a patented NO-donating salt of the β_2-adrenoceptor agonist salbutamol, is in development at NicOx as an inhalable formulation for the treatment of asthma.

Corticosteroids

Ciclesonide is an ester prodrug, new-generation inhaled nonhalogenated corticosteroid with potent local antiinflammatory properties that is essentially devoid of oral bioavailability. **Ciclesonide** (B-9207-015, BY-9010, Alvesco®) is awaiting registration in Australia, Canada and Europe for the treatment of bronchial asthma.

An inhalable formulation of the steroid compound **NS-126** is being co-developed by Nippon Shinyaku and SSP in Japan for the treatment of allergic rhinitis and of bronchial asthma. The compound is in phase II testing for both indications.

Histamine H_1 Antagonists

Kyowa Hakko launched the dual-acting histamine H_1 antagonist/mediator release inhibitor **olopatadine hydrochloride** (Allelock®) in Japan in 2001 as an oral treatment for asthma. The compound has been marketed by Alcon (under the brand name Patanol®) since 1997 as an eye drop solution for the treatment of allergic conjunctivitis.

A new antiasthmatic histamine H_1 receptor antagonist with 5-lipoxygenase inhibitory activity, **UCB-35440** is in development at UCB. The combined antihistamine and antileukotriene properties are expected to provide a unique, synergistic approach in the treatment of airway allergies, including asthma. In July 2002, UCB announced the commencement of clinical trials for the treatment of allergic rhinitis and asthma.

Leukotriene $CysLT_1$ (LTD_4) Receptor Antagonists

Mitsubishi Pharma is conducting phase II trials in Japan of the leukotriene $CysLT_1$ (LTD_4) antagonist **MCC-847** for the treatment of allergic rhinitis and asthma.

Another potent and selective leukotriene $CysLT_1$ (LTD_4) receptor antagonist, Menarini's **MEN-91507**, is in phase I for the treatment of mild and moderate asthma.

Table III: PDE4 inhibitors in development for the treatment of asthma..

Drug Name	Source	Status
Roflumilast	Altana/Pharmacia/Tanabe Seiyku	Phase III
KW-4490	Kyowa Hakko	Phase II
Undisclosed PDE4 Inhibitor	Merck & Co./Celltech	Phase II
AWD-12-281	elbion/GlaxoSmithKline	Phase I/II
Ono-6126	Ono	Phase I

Drugs Acting on Adenosine Receptors

Adenosine, a ubiquitous autacoid with a wide spectrum of biological activities, has been shown to suppress leukotriene biosynthesis in human neutrophils via the inhibition of agonist-induced arachidonic acid release. Adenosine A_{2A} receptor agonists and other agents that modulate the biosynthesis, metabolism and transport of adenosine have been proposed as novel agents for the treatment of inflammatory disease, including asthma.

An ADORA1 expression inhibitor and the first of a new class of respiratory drugs called respirable antisense oligonucleotides (RASONs), **EPI-2010** was formulated by EpiGenesis to inhibit the production of the adenosine A_1 receptor in the cells lining the lung. The compound is being developed by EpiGenesis in the U.S. and by licensees Taisho in Japan and Chiesi in Europe for a variety of respiratory diseases. It is in phase II in the U.S. and Europe for the prevention and chronic treatment of bronchial asthma and in phase I in Japan.

Phosphodiesterase Type 4 Inhibitors

Phosphodiesterases are a family of enzymes responsible for the metabolism and inactivation of the intracellular second messengers cyclic AMP and cyclic GMP. The isoenzyme phosphodiesterase 4 (PDE4), expressed predominantly in inflammatory cells (*e.g.*, mast cells, eosinophils, T lymphocytes and macrophages) and structural cells (*e.g.*, sensory nerves and epithelial cells) of the lung, specifically catalyzes the breakdown of cAMP. Extensive preclinical studies have provided evidence that selective inhibitors of PDE4 may represent a new therapeutic approach for asthma and other atopic diseases as well as COPD. PDE4 inhibitors have been reported to combine bronchodilatory and antiinflammatory activity, concomitant with modulation of the neuronal control of the lung.

Table III presents new PDE4 inhibitors in development for the treatment of asthma.

Leukocyte-Selective Antiinflammatory Drugs (LSAIDs)

A synthetic polyhydroxylated steroid codeveloped by InflaZyme and Aventis Pharma as one of a new class of antiinflammatory compounds known as LSAIDS (leukocyte selective antiinflammatory drugs), **IPL-576092** is in development as an oral formulation for the treatment of asthma and other respiratory diseases. Phase II has been completed. Despite promising results, InflaZyme and Aventis plan to advance the next-generation LSAID IPL-512602 instead of IPL-576092.

The oral, second-generation LSAID **IPL-512602** is in development at InflaZyme in collaboration with Aventis Pharma for the treatment of asthma. Phase I trials began in the U.K. in September 2001, and results were announced in November 2002. Phase II testing is expected to begin in the first half of 2003. Under the terms of the agreement, InflaZyme is responsible for the development of IPL-512602 until the completion of these trials, at which time Aventis will have the opportunity to acquire exclusive worldwide rights (nonexclusive in Canada) to an oral formulation. Aventis will also begin preclinical studies on the new indication of allergic rhinitis, to be conducted in parallel with the asthma program.

IPL-550260, a novel, small-molecule antiinflammatory compound based on a molecule originally isolated from a sea sponge by researchers at the Universities of British Columbia and Alberta, is also being codeveloped by InflaZyme and Aventis as a therapeutic agent for the treatment of asthma. Phase Ib trials are under way in the U.K.

Tachykinin Receptor Antagonists

Tachykinins have a variety of effects on the lungs and, along with eicosanoids, are among the most potent bronchoconstricting agents known. They mediate a variety of pulmonary responses including cough and airway hyperresponsiveness, and have been implicated in the pathogenesis of inflammatory lung diseases and the process of pulmonary wall remodeling. The NK_2 receptor is the principal receptor mediating airway smooth muscle contraction in humans.

A glycosylated bicyclic peptide with potent, selective and competitive tachykinin NK_2 receptor antagonism, **nepadutant** is in phase II development at Menarini for the treatment of bronchial asthma.

The tachykinin NK_1, NK_2 and NK_3 receptor antagonist **CS-003** is being developed at Sankyo for the treatment of both asthma and COPD. The drug is in phase I in Japan and phase II in Europe.

Immune-Targeted Therapy

Decreased exposure to major diseases such as tuberculosis has been fingered by many researchers as a culprit in the increased incidence of asthma in industrialized countries. The intranasal administration of *Mycobacterium bovis* Bacillus Calmette Guerin (BCG) has been demonstrated to inhibit airway eosinophilia in a model of atopic asthma in mice. BCG and other mycobacterial fractions are potent inducers of the Th1 immune response, leading to suppression of Th2 responses such as lung eosinophilia. Although much research into delivery methods, definition of the necessary components of BCG and mechanism of action are required, this may one day become a promising method of treating atopic asthma. At least two agents in development are based on this hypothesis.

A killed *Mycobacterium vaccae* suspension with long-term protective antiinflammatory activity, **SRP-299** is in development at SR Pharma for the treatment of asthma. The mechanism of action of SRP-299 results in the accumulation of allergen-specific regulatory T cells which then selectively down-regulate the Th2 response without inducing a Th1 response. Recruitment for a phase II, multicenter trial sponsored by Sakai Chemical Industries Co. Ltd. Is expected to be completed at the end of the first quarter of 2003. SR Pharma has exclusively licensed the product to Sakai for allergic disorders in Japan.

The *Mycobacterium vaccae* derivative **AVAC™** is under codevelopment by SR Pharma and Genesis for the treatment of asthma. AVAC™ is in phase I testing.

DNA Immunostimulatory Sequences

DNA immunostimulatory sequences (ISS) are cytosine and guanosine dinucleotide repeat motifs with adjuvant properties. The CpG sequences are able to decrease Th2 response by increasing Th1 cytokine production.

ISS-1018, an inhalable immunostimulatory DNA sequence formulation from Dynavax Technologies, is in phase I testing in the U.K. for the treatment of asthma. A phase IIa efficacy trial in asthmatic patients is planned if a favorable outcome is achieved.

Cytokines and Cytokine Modulators

A biosynthetic humanized IgG_1 monoclonal antibody directed at the α-chain of the human IL-2 receptor (CD25), **daclizumab** (Zenapax™) is under phase II development at Protein Design Labs in the U.S. for the treatment of chronic asthma. This product has been marketed for some years for the prevention of organ transplant rejection.

A potent and specific anti-IL-5 monoclonal antibody, **mepolizumab** (SB-240563) is under phase II development at GlaxoSmithKline for the treatment of steroid-sparing asthma.

A potent dual IL-4 and IL-13 antagonist, **Interleukin-4/Interleukin-13 Cytokine Trap** is in development at Regeneron in the U.S. for the treatment of adults with mild to moderate asthma. Assessment via dose escalation studies will evaluate the potential benefit of blocking the actions of both cytokines simultaneously. Phase I testing commenced in October 2002.

A fully humanized IL-4 receptor antagonist monoclonal antibody, **pascolizumab** (SB-240683) was formulated by GlaxoSmithKline and is under development at Protein Design Labs for the treatment of moderate to severe asthma. Currently in phase II testing.

Interferon gamma-1b (Actimmune™) is an important immunomodulatory and pleiotropic cytokine produced primarily by activated T lymphocytes and natural killer cells. Under license from InterMune, Mondobiotech is conducting European phase II trials evaluating the efficacy of interferon gamma-1b for the treatment of asthma. Actimmune™ is marketed by InterMune for the treatment of chronic granulomatous disease and of severe, malignant osteopetrosis.

Anti-IgE Therapy

In patients with allergic asthma, the antibody immunoglobulin E (IgE) is at the top of the allergic cascade. Exposure to an allergen in a susceptible individual causes T lymphocytes to become activated and send a signal to B lymphocytes, initiating the production of IgE antibodies. For every allergen, specific IgE antibodies are produced within a few weeks after the first exposure. Some IgE antibodies bind to FcεRI receptors on mast cells and basophils while others remain free, floating in the bloodstream. Mast cells and basophils in the skin and mucosal layers of the respiratory tract contain the inflammatory mediators that cause the symptoms of allergic rhinitis and allergic asthma: histamine, leukotrienes and prostaglandins. These mediators are released every time that an allergen crosslinks mast cell-bound IgE via the process of degranulation. Reexposure to an allergen causes mast cells in the nose and sinuses to become activated by IgE antibodies, releasing inflammatory mediators and causing symptoms of allergic asthma.

Anti-IgE therapy, one of the newest therapeutic approaches to allergic rhinitis and asthma, is designed to treat the underlying inflammatory response initiated by IgE antibodies in atopic patients. Anti-IgEs inhibit or neutralize free IgE, blocking its interaction with mast cells and basophils, as well as downregulating the production of IgE by B cells and downregulating FcεRI on inflammatory cells.

In June 2002, the anti-IgE monoclonal antibody **omalizumab** (Xolair™) was approved for the first time in Australia, where it will be supplied as an s.c. injectable formulation for the treatment of allergic rhinitis and moderate allergic asthma in adults and adolescents. It is in

Table IV: Cell adhesion inhibitors in development for asthma.

Drug Name	Source	Mechanism of Action	Status
Bimosiamose	Revotar	E-, P- and L-selectin inhibitor	Phase II
GW-559090	GlaxoSmithKline	Integrin antagonist	Phase II
R-411	Roche	$\alpha_4\beta_1$ integrin (VLA-4) receptor antagonist	Phase II
IDEC-152	Idec/Seikagaku	Anti-CD23 MAb	Phase I/II
RBx-7796	Ranbaxy	$\alpha_4\beta_1$ integrin (VLA-4) receptor antagonist	Phase I
TR-14035	Tanabe Seiyaku/GlaxoSmithKline	$\alpha_4\beta_1$ and $\alpha_4\beta_7$ integrin receptor antagonist	Phase I

phase III in the U.S. for the treatment of allergic asthma and seasonal allergic rhinitis in adults and children. ALTO safety study results have been completed and were scheduled to be incorporated into a BLA application to the FDA at the end of 2002. The product is the result of a collaborative effort by Genentech, Novartis and Tanox.

Cell Adhesion Inhibitors

In bronchial asthma, numerous inflammatory cells, including eosinophils, neutrophils, mast cells and lymphocytes, are found to infiltrate the mucosal layer. Most of the cells are believed to be recruited from the bloodstream, transmigrating through endothelial barriers. Leukocyte extravasation is a multistep process in which different molecules (selectins, integrins and chemokines) are involved. Several adhesion molecules and chemokines as well as their counterparts are thought to play an important role in regulating the local influx of immune and inflammatory cells, and have emerged as an interesting target for asthma therapy.

A small molecule E-, P- and L-selectin inhibitor with novel antiinflammatory properties, **bimosiamose** (TBC-1269) is Revotar's primary candidate agent for asthma. The company initiated phase II testing in June 2002 for the treatment of pediatric asthma.

An anti-CD23 monoclonal antibody product with both antiallergy and antiasthmatic properties, **IDEC-152** (gomiliximab) is in development at Idec in the U.S., Europe and Asia for the treatment of patients with allergic asthma. The product entered phase I/II testing in the U.S. in the first quarter of 2002, and is in preclinical testing in Asia and Europe. Idec has recently extended its collaborative research agreement with Seikagaku to support the complete clinical development of IDEC-152, whereby Seikagaku will share costs through the filing of a BLA.

These and other cell adhesion inhibitors in development for asthma are presented in Table IV.

Miscellaneous Agents

The nonsteroidal antiinflammatory drug **talniflumate** (Lomucin™) was developed by Bagó (which markets the drug as an antiinflammatory agent in Argentina) and was licensed to Genaera as an oral formulation for the treatment of asthma and cystic fibrosis. Based on the discovery of the *hCLCA1* gene, which regulates abnormal mucus production, talniflumate blocks hCLCA1-dependent mucus overproduction and enables the opening of airways to facilitate the easing of breathing in patients with respiratory diseases. Talniflumate is in phase II in the U.S. and Mexico for the treatment of asthma. It is also in development for cystic fibrosis (see below).

A novel, potent antiallergy and antiinflammatory agent and mediator release inhibitor, **andolast** (CR-2039) is in phase IIb clinical testing at Rotta for the treatment of asthma and other atopic allergic diseases.

A synthetic, injectable formulation of dehydroepiandrosterone sulfate, **prasterone sulfate** (PB-005, Inflarest™), is in development at Pharmadigm in the U.S. as an adjunctive intravenous therapy for the management of inflammatory response in acute asthma.

Table V summarizes the status of these and other miscellaneous agents in active development for the treatment of asthma.

Chronic Obstructive Pulmonary Disease (COPD)

Background Information

Chronic obstructive pulmonary disease (COPD) is an all-inclusive term that refers to a set of symptoms including chronic cough, expectoration, exertional dyspnea and a significant, progressive reduction in airflow that may or may not be partly reversible. In patients with the disorder, poor gas exchange in the lungs leads to decreased oxygen levels in the blood, increased levels of carbon dioxide and shortness of breath. Chronic airflow obstruction in COPD is complicated by the loss of lung elasticity resulting from enzymatic destruction of the lung parenchyma. Rather than a single pathologic condition, COPD is actually an umbrella term encompassing chronic obstructive bronchitis and emphysema; some classifications also include asthmatic bronchitis. As emphysema and obstructive bronchitis share similar symptoms and frequently coexist, the term COPD is generally employed. COPD is now the fourth most common cause of morbidity and mortality in the United States, and the WHO estimates that COPD as a single cause of death worldwide shares fourth and fifth places with HIV/AIDS.

Table V: Miscellaneous antiasthma agents.

Drug Name	Source	Mechanism of Action	Status
Andolast	Rotta	Mediator release inhibitor	Phase II
KCO-912	Novartis	Potassium channel opener	Phase II
ME-3301	Meiji Seika	Not known	Phase II
OPC-6535	Otsuka	Antioxidant	Phase II
Prasterone Sulfate	Pharmadigm	Not known	Phase II
S-3013	Lilly/Shionogi	Secretory phospholipase A_2 inhibitor	Phase II
S-5751	Shionogi	Prostaglandin D_2 (PGD_2) receptor antagonist	Phase II
Talniflumate	Genaera	Nonsteroidal antiinflammatory drug	Phase II
AVE-0547	Aventis	Not known	Phase I/II
E-4931	Esteve	Not known	Phase I
GW-274150	GlaxoSmithKline	Inducible nitric oxide synthase (iNOS) inhibitor	Phase I

Table VI: Bronchodilators for the treatment of COPD.

Drug Name	Source	Mechanism of Action	Status
Formoterol Fumarate	Novartis/Schering Plough/AstraZeneca	β_2-Adrenoceptor agonist	Launched-2001
Tiotropium Bromide	Boeringher Ingelheim/Pfizer	Muscarinic receptor antagonist	Launched-2002
(*R*,*R*)-Formoterol	Sepracor	β_2-Adrenoceptor agonist	Phase II
AD-237	Arakis	Not known	Phase II
AeroDose Ipratropium Inhaler	AeroGen	Muscarinic receptor antagonist	Phase II
QAB-149	Novartis	β_2-Adrenoceptor agonist	Phase II

Various pharmacological approaches are used to treat COPD, including bronchodilators (β_2-adrenoceptor agonists, anticholinergic agents, xanthines), corticosteroids, expectorants and long-term oxygen therapy, as well as smoking cessation therapy, cardiovascular drugs, *etc.*

Bronchodilators

Within the bronchodilator class, topical anticholinergic agents appear to be more effective than short-acting β_2-adrenoceptor agonists. Anticholinergic agents block muscarinic receptors in airways, including M_1 receptors on parasympathetic ganglia, M_2 receptors on presynaptic cholinergic nerve terminals and M_3 receptors on smooth muscle. It has been speculated that selective blockade of muscarinic M_1 or M_3 receptors should decrease cholinergic tone of the lung, while blockade of muscarinic M_2 receptors could enhance it.

In addition to their bronchodilating effects, anticholinergic agents have significant impact on quality of life. They improve sleep quality and exercise performance and reduce dyspnea, mucous hypersecretion and nocturnal desaturation. Sustained efficacy is associated with long-term use of compounds in this class, without associated tachyphylaxis or receptor downregulation. Furthermore, they have a very favorable side effect profile. For this reason, anticholinergic drugs are considered first-line therapy for COPD in many countries including the U.S.

The most significant advance in the area of bronchodilating agents has been the recent development of longer-acting, more potent nonselective muscarinic antagonists such as tiotropium bromide, which is administered just once daily, whereas existing anticholinergics such as ipratropium bromide must be taken three times daily. Tiotropium is characterized by its novel property of kinetic selectivity: it dissociates rapidly from M_2 receptors but slowly from M_1 and M_3 receptors. **Tiotropium bromide** (Spiriva®) was launched by Boehringer Ingelheim for the first time in 2002 in The Netherlands and the Philippines. Spiriva® was approved in Europe through the mutual recognition procedure in April 2002. An NDA was submitted in the U.S. in December 2001, and other submissions are pending worldwide. The product is copromoted worldwide by Pfizer.

β_2-Adrenoceptor agonists used in the treatment of COPD include fenoterol hydrobromide, salmeterol xinafoate and salbutamol sulfate. In any case, the bronchodilator activity of β_2-adrenoceptor agonists is generally less pronounced in COPD than in asthma.

Table VI presents recently marketed bronchodilating agents together with compounds in active development for the treatment of COPD.

Phosphodiesterase Type 4 (PDE4) Inhibitors

Phosphodiesterases are a family of enzymes responsible for the metabolism and inactivation of the intracellular second messengers cyclic AMP and cyclic GMP. The isoenzyme phosphodiesterase 4 (PDE4), found in

Table VII: PDE4 inhibitors in development for COPD.

Drug Name	Source	Status
Cilomilast	GlaxoSmithKline	Phase III
Roflumilast	Altana/Pharmacia/Tanabe Seiyaku	Phase III
Arofylline	Almirall Prodesfarma	Phase II
Undisclosed PDE4 Inhibitor	Merck & Co./Celltech	Phase II
AWD-12-281	elbion/GlaxoSmithKline	PhaseI/II
IC-485	Icos	Phase I
Ono-6126	Ono	Phase I

immune and inflammatory cells in the lung, specifically catalyzes the breakdown of cAMP. Extensive preclinical studies have provided evidence that selective inhibitors of PDE4 may represent a new therapeutic approach for COPD. PDE4 inhibitors have been reported to combine bronchodilatory and antiinflammatory activity, concomitant with modulation of the neuronal control of the lung.

Several phosphodiesterase inhibitors are in active development at this time for the COPD indication, as seen in Table VII.

Lipoxygenase Inhibitors

A 5-lipoxygenase inhibitor and 4-aryl-4-hydroxytetrahydropyran derivative, **AZD-4407** (ZD-4407) has antiallergic, antiinflammatory and cytoprotective properties and is undergoing phase I evaluation at AstraZeneca as a potential treatment for COPD.

Tachykinin Receptor Antagonists

The tachykinin NK_1, NK_2 and NK_3 receptor antagonist, **CS-003** is being developed at Sankyo for the treatment of COPD and asthma. It is in phase I in Japan and phase II in Europe.

A potent, selective, competitive and orally active tachykinin NK_3 receptor antagonist, **talnetant** (SB-223412) is being developed by GlaxoSmithKline for the treatment of COPD, as well as for use as an antitussive agent. Phase II trials are under way in the U.S.

Combination Therapy

A single medication is generally insufficient to provide adequate control of COPD symptoms and/or optimum improvement of functional capacity. Combination therapy therefore has an important role in the treatment of patients with stable COPD. For example, the benefits obtained with an anticholinergic in combination with a β_2-adrenoceptor agonist are consistently superior to those obtained with either agent alone, while enabling dose reduction of the individual components and thus reducing adverse effects. There has been significant interest in recent years in the development of new products combining complementary drugs in a single formulation.

A combined formulation incorporating the long-acting β_2-adrenoceptor agonist **salmeterol xinafoate** and the inhaled corticosteroid **fluticasone propionate** (Seretide™, Advair™) has been developed by GlaxoSmithKline for the treatment of COPD. Applications have been filed to market the product in the E.U. both as a dry powder inhaler and as a non-CFC metered dose inhaler, and in the U.S. as a dry powder inhaler. An FDA Advisory Committee recommended approval of the dry powder inhaler formulation (Advair™ Diskus™) in January 2002. This product has been available since 1999 for the treatment of asthma.

Another combined formulation incorporating the inhaled corticosteroid **budesonide** and the β_2 agonist **formoterol fumarate** (Symbicort™ Turbuhaler™) has been developed by AstraZeneca for the treatment of COPD. Symbicort™ Turbuhaler™ is awaiting approval in the E.U., and in phase III development in the U.S. This product has been available since 2000 for the treatment of asthma.

Mucoregulators

One of the characteristic features of chronic bronchitis is the presence of a persistent, mucus-producing cough without an obvious alternative explanation. Clinical trials have shown that chronic bronchitis patients have impaired mucociliary clearance. Failure to effectively clear mucus from the airways results in retention of secretions and leads to a cycle of inflammation, infection and eventual airway obstruction.

Heavy cigarette smokers typically have increased mucus secretion, regardless of the presence of airway obstruction. However, the hypersecretion of mucus has been linked to an accelerated decrease in FEV_1 and provides an environment conducive to bacterial growth and subsequent infection, making the control of this symptom an important factor in the effective management of COPD. Several class of mucoregulatory agents, including mucolytics, surfactants, potassium channel openers and P2Y2 agonists, have been studied for the management of patients with COPD.

DCF-987 (Usherdex-4), a dextran-based compound that acts as both a mucolytic agent and a bacterial adhesion inhibitor, is being developed by BCY Life Sciences for the treatment of COPD and cystic fibrosis. The company is conducting phase I trials in Canada for the treatment of COPD. DCF-987 is also being developed for the treatment of cystic fibrosis, as discussed below.

ML-03 (HP-3), a proprietary form of calf thymus DNA, is in phase II testing at Milkhaus Laboratory for the treatment of COPD; it is also in development for cystic fibrosis (see below).

Miscellaneous Agents

In addition to the major drug classes listed above, a few other pharmaceutical products are known to be in active development for COPD, although their mechanisms of action are unclear or have not yet been disclosed.

As part of its Performance Enhanced Medicine (PEM) program, Arakis and SkyePharma are developing **AD-313** as a treatment for COPD. AD-313, currently in phase II testing, is an inhaled formulation of a currently marketed drug. Its use as a disease modifier in COPD is a previously unexploited pharmacological application, providing a new use and delivery route for this well accepted molecule. AD-313 works by a completely novel mechanism of action to inhibit tissue destruction.

MondoBIOTECH-811 (MBD-811) is in development at Mondobiotech for various indications. The company has commenced phase II trials with the compound in the indication primary pulmonary hypertension, and is planning additional phase II trials in the indications COPD and sarcoidosis.

The nuclear receptor antagonist **R-667** is in phase II clinical development at Roche for the treatment of pulmonary emphysema.

Treatment of COPD-Associated Wasting

Severe weight loss and wasting often accompanies advanced-stage chronic obstructive pulmonary disease. Anywhere from 25% to 50% of patients with COPD are reported to suffer malnutrition.

The growth hormone-releasing factor analogue **TH-9507** is in phase II development at Theratechnologies for the treatment of muscle wasting in patients with COPD. Theratechnologies and Sakai Chemical Industry entered into a licensing agreement in 2002, which gives Sakai the option to codevelop and market the compound in Japan. It is currently in preclinical status there with Sakai, who will be responsible for all funding of the Japanese clinical development of TH-9507, as well as for regulatory approvals in that country.

Cystic Fibrosis

Background Information

Cystic fibrosis (CF) is a chronic, progressive and usually fatal autosomal recessive multisystem disease characterized by a wide range of symptoms and complications that vary in severity. It primarily affects the exocrine glands in the digestive and respiratory systems, although the sweat glands and reproductive system are often also involved. The disease was first recognized in the 1930s in very young children and involved pancreatic insufficiency that culminated in early death due to malnutrition and lung disease. According to the Cystic Fibrosis Foundation, there are approximately 30,000 children and adults with CF in the U.S. and about 70,000 patients worldwide; in the U.S., some 2,500 babies are born each year with cystic fibrosis.

The treatment of cystic fibrosis varies depending on the stage of disease and the organs involved. Daily baseline therapy, which is primarily aimed at improving secretion clearance, decreasing inflammation and controlling infection, is initiated at time of diagnosis and maintained throughout life. Eventually, even with diligent effort on the part of the practitioner and patient, severe pulmonary dysfunction almost inevitably develops. Double-lung transplantation is a potentially life-saving alternative, although very few patients receive donor organs.

Antibacterial Agents

The thick, sticky mucus that builds up in the respiratory tracts of patients with cystic fibrosis provides an ideal breeding ground for microorganisms. The microorganisms that are most problematic to CF patients are virtually innocuous in healthy individuals. The most common bacteria affecting CF patients is *Pseudomonas aeruginosa*; other important pathogens include *Haemophilus influenzae, Burkholderia cepacia, Staphylococcus aureus* and *Xanthomonas maltophilia*. Once they become established in the smaller airways, bacteria are difficult to clear in CF patients, even with antibiotic therapy. Chronic infection causes a vicious cycle: infection causes lung inflammation, which leads to more mucus secretion. Additional mucus buildup and lung damage cause further lung obstruction and encourage the growth of more bacteria. Recurrent *Pseudomonas* infection is the major cause of gradual lung damage, respiratory failure and eventually death among patients with CF.

A lanthiomine-containing, 19-residue polycyclic peptide antibiotic produced by *Streptoverticillium griseoverticillatum*, **duramycin** (MOLI-1901, PA-48009) is in development at MoliChem Medicines in the U.S. and E.U. as an aerosol formulation for the treatment of cystic fibrosis. It is believed that duramycin may normalize the mucus composition in the lung by activating an alternative chloride and water channel that is present in the lung lining cells of CF patients. Phase II testing began in the U.S. in

May 2002. The trial, conducted at John Hopkins Children's Hospital, is evaluating the pulmonary delivery and deposition of duramycin into the lungs of CF patients by inhalation. It will also study the possible action of duramycin on mucociliary clearance. A follow-on study aims to assess the duration of action of the treatment.

Iseganan hydrochloride (IB-367), a 17 amino acid-long synthetic protegrin antimicrobial peptide with a broad spectrum of activity against Gram-positive and Gram-negative bacteria, is in phase I clinical testing at IntraBiotics. The product has been developed as an aerosol formulation for the treatment of respiratory infections associated with cystic fibrosis.

DCF-987 (Usherdex-4), a dextran-based compound that acts as a mucolytic agent and bacterial adhesion inhibitor, is being developed at BCY Life Sciences for the treatment of COPD and cystic fibrosis. Permission for phase II trials for the treatment of bacterial exacerbations in patients with cystic fibrosis was granted in September 2002 by Health and Welfare Canada's Therapeutic Production Directorate (TPD), which will be funded, at least in part, by a grant from the Western Life Sciences Venture Fund.

A stable histatin-derivative with proven activity against bacterial isolates, **P-113D** (Histatin-P-113D) was developed as a pulmonary spray by Demegen and has recently been granted orphan drug status by the FDA for the treatment of lung infections in subjects with cystic fibrosis. An IND has been filed in the U.S., although preclinical toxicology evaluations are required before human trials can commence.

Agents for Improving Lung Secretion Clearance

Individuals with CF are born with anatomically and functionally normal lungs. However, via mechanisms that are not fully understood, a brutal triad of airway mucus thickening, infection and inflammation results in progressive pulmonary dysfunction. Several classes of drugs have been studied for the improvement of lung secretion clearance in CF, including elastase inhibitors, DNAse, $P2Y_2$ agonists and α_1-antitrypsin.

The human neutrophil elastase inhibitor **EPI-hNE-4** (DX-890), derived from the second Kunitz-type domain of inter-inhibitor protein (ITI-D2), was engineered by Dyax and is being codeveloped by Debiopharm and H3 Pharma. Phase II trials are underway in Europe for the treatment of cystic fibrosis.

ML-03 (HP-3) is a product based on calf thymus DNA, administered as a sublingual drop containing a very small amount of DNA. The drug clears respiratory and gastrointestinal congestion by preventing the formation of mucus, rather than by breaking it up after it has been formed. ML-03 is in phase II testing at Milkhaus Laboratory for the treatment of cystic fibrosis in patients aged 6 to 21 years.

The synthetic dinucleotide $P2Y_2$ receptor agonist **INS-37217** (dCp4U) is undergoing phase II development at Inspire Pharmaceuticals as an inhaled formulation for the treatment of cystic fibrosis in adult and pediatric patients.

Recombinant α_1-antitrypsin (TgAAT) is a human blood protein produced using transgenic technology, which targets neutrophil elastase. It is being developed by PPL Therapeutics in collaboration with Bayer as an aerosol formulation for the treatment of cystic fibrosis. It is in phase II testing in the U.S. for this indication.

Inhibitors of Mucus Overproduction

A nonsteroidal antiinflammatory drug, **talniflumate** (MSI-1995, Lomucin™) was developed by Bagó and licensed to Genaera as an oral formulation for the treatment of asthma and cystic fibrosis. Based on the discovery of the *hCLCA1* gene, which regulates abnormal mucus production, talnuflumate blocks hCLCA1-dependent mucus overproduction and enables the opening of airways to facilitate the easing of breathing in patients with respiratory diseases. The drug is in preclinical testing for the treatment of patients with cystic fibrosis. In 2001, Genaera received a grant from the Cystic Fibrosis Foundation to develop the compound.

Agents for Improving Pulmonary Inflammation

The specific, long-acting and orally active leukotriene BLT (LTB_4) receptor antagonist **amelubant** (BIIL-284) is in phase II testing at Boehringer Ingelheim for the treatment of cystic fibrosis. It was granted orphan drug status in the U.S. in January 2002 for this indication and subsequently granted orphan medicinal product designation in July 2002 by the European Agency for the Evaluation of Medicinal Products (EMEA).

Agents for Improving CFTR Protein Function

The cystic fibrosis transmembrane regulator (CFTR) protein is embedded in the membranes of several cell types in the body and plays a pivotal role in the pathogenesis of cystic fibrosis. CFTR levels are highest in the epithelial cells lining the internal surfaces of the pancreas, sweat glands, salivary glands, intestines and reproductive organs, as well as in the submucosal glands of the airways – precisely the organs and tissues that are most affected in patients with CF. The most straightforward role of the CFTR involves its function as a chloride channel, regulating the flow of chloride ions in both directions. In addition to serving as a chloride channel itself, CFTR also acts as a channel regulator, influencing the function of other chloride channels and of sodium channels located nearby on the cell membrane. Several approaches to improving the function of the faulty CFTR protein are under investigation.

SciClone's **CPX** (DPCPX) is an adenosine A_1 receptor antagonist that repairs the defect in the CFTR protein

responsible for the excess production of mucus in patients with CF. The drug improves impaired chloride ion transport and enables the defective CFTR to reach the epithelial cell membrane. CPX is in phase II testing in the U.S. as an oral formulation for the treatment of cystic fibrosis in patients 12 years and older. The drug has orphan drug status in the U.S. and European Union.

Genistein has angiogenesis and EGF receptor inhibitory activity and has also demonstrated estrogen receptor agonism. The U.S. National Institutes of Health is conducting a phase I trial evaluating genistein in combination with phenylbutyrate for the treatment of cystic fibrosis.

Gene Therapy

AAV-CF is the world's first clinically studied application of an adeno-associated virus vector (AAV) technology. It is an AAV that contains a normal copy of the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which it delivers to the airways of patients, and is in development at Targeted Genetics in the U.S. as an aerosol formulation for the treatment of cystic fibrosis. Phase II testing was initiated in November 2001. The Celltech Group collaborated on the development and commercialization of AAV-CF until full rights to the program were returned to Targeted Genetics at the end of 2002. The company may retain North American rights and partner the program in other territories.

Congenital Deficiency of α_1-Proteinase Inhibitor/Emphysema

Many respiratory diseases including α_1-antitrypsin (AAT) congenital deficiency (hereditary emphysema), cystic fibrosis and COPD are characterized by an imbalance of AAT elastase in the lung. AAT, also known as α_1-proteinase inhibitor, is a human blood protein whose prime physiological target is neutrophil elastase. An abundance of elastase is thought to contribute to damage of the pulmonary epithelium. Administration of supplemental AAT is therefore expected to alleviate the deleterious effects of elastase in the lung in these diseases. Severe AAT deficiency (hereditary emphysema) is thought to affect around 150-200,000 individuals in U.S. and Europe.

A human plasma-derived α_1-proteinase inhibitor, **Aralast™** is in development at Alpha Therapeutic as an augmentation therapy for the treatment of patients with clinically evident emphysema and congenital deficiency of α_1-proteinase inhibitor. FDA approval to market Aralast™ was granted in December 2002. Baxter Healthcare has been selected as the exclusive distributor, and will launch the product on behalf of Alpha Therapeutic.

Recombinant α_1-antitrypsin (TgAAT) is a human blood protein produced using transgenic technology that targets neutrophil elastase. It is being developed by PPL Therapeutics in collaboration with Bayer as an aerosol formulation for the treatment of pulmonary emphysema in patients with a congenital AAT deficiency. Current status: Phase II trials are being conducted in Australia, Canada, Europe, New Zealand and the U.S. for the indication of pulmonary emphysema. The drug received orphan drug status in 2001 in the E.U. for hereditary emphysema.

Aventis Behring has filed for U.S. regulatory approval to market an i.v. injection formulation of Prolastin™ (**α_1-antitrypsin [human]**, α_1-proteinase inhibitor [human]) for the treatment of congenital emphysema caused by α_1-antitrypsin deficiency. In collaboration with Inhale, Aventis Behring is also conducting phase I testing of an inhalation formulation of the same product. Prolastin has been marketed since 1987 as a Replacement therapy in the α_1-proteinase inhibitor congenital deficiency state.

A proprietary aerosol formulation of hyaluronic acid, **ETX-100** is being developed by Exhale Therapeutics to protect lung elastin fibers from the degrading effects of elastase enzymes. Phase I have been initiated in the Netherlands for the treatment of genetic emphysema associated with α_1-antitrypsin deficiency. ETX-100 received orphan drug status in July 2002 from the FDA for the treatment of this disorder.

Cough

Fudosteine, a mucoactive cysteine derivative from SSP, was launched for the first time in Japan in late 2001 as an expectorant agent for use in patients with chronic respiratory diseases (bronchial asthma, chronic bronchitis, bronchiectastasis, *etc.*). The product is marketed by SSP (as Cleanal®) in conjunction with Welfide (as Spelear®).

A potent, selective, competitive and orally active tachykinin NK_3 receptor antagonist, **talnetant** (SB-223412) is being evaluated by GlaxoSmithKline as an antitussive agent in phase II trials.

The selective opioid delta receptor antagonist **TRK-851** is being codeveloped in Japan by Mitsubishi Pharma and Toray as an oral antitussive agent. It is expected to suppress cough associated with a variety of chronic and acute respiratory diseases, and to induce fewer adverse reactions than narcotic antitussive agents. TRK-851 is in phase I clinical trials.

Idiopathic Pulmonary Fibrosis

Idiopathic Pulmonary Fibrosis (IPF) is a disease characterized by progressive scarring or fibrosis of the lungs, which leads to the loss of pulmonary function and ulti-

mately death. The cause of IPF is unknown, and currently there is no FDA-approved or effective treatment for this fatal disease, which affects more than 75,000 patients in the United States alone.

Interferon gamma-1b (Actimmune™) is an immunomodulatory and pleiotropic cytokine produced primarily by activated T lymphocytes and natural killer cells. It is being developed by Intermune in the U.S. and by mondo-BIOTECH in Europe as an injectable formulation for the treatment of idiopathic pulmonary fibrosis (IPF). The drug is currently in phase II testing in Europe, and recently completed phase III in the U.S. Actimmune™ is marketed for the treatment of osteopetrosis and chronic granulomatous disease.

Sarcoidosis

Sarcoidosis is a disease associated with inflammation, a response of cells to injury. The cause of injury to cells affected by sarcoidosis is unknown. The disease can appear suddenly and disappear. Or it can develop gradually and go on to produce symptoms that come and go, sometimes for a lifetime. As sarcoidosis progresses, small lumps, or granulomas, appear in the affected tissues. In the majority of cases, these granulomas clear up, either with or without treatment. In the few cases where the granulomas do not heal and disappear, the tissues tend to remain inflamed and become scarred (fibrotic). It can affect almost any organ, but usually starts in the lungs or lymph nodes. Sarcoidosis is not contagious and is rarely fatal.

MondoBIOTECH-811 (MBD-811) is in development at Mondobiotech for various indications. The company has commenced phase II trials with the compound in the indication primary pulmonary hypertension, and is planning additional phase II trials for COPD and sarcoidosis.

Miscellaneous Respiratory Indications

A nonsteroidal antiinflammatory drug with cyclooxygenase-inhibitory activity, **zaltoprofen** is being codeveloped by Nippon Chemiphar and Zeria for the treatment of acute upper respiratory tract inflammation. The product is awaiting approval in Japan for this indication; it will be marketed as Peon™ by Zeria and as Soleton™ by Nippon Chemiphar. Zaltoprofen has been available since 1993 for the treatment of arthritis.

A multicomponent phytopharmaceutical extracted from North American ginseng (*Panax quinquefolium*) and developed by CV Technologies using the company's ChemBioPrint™ technology, **CVT-E002** (COLD-FX™) is in development for the treatment of respiratory illnesses in adults during the influenza season. Upon successful completion of phase II testing, the company will seek a partner to license the drug for phase III development, drug approval and marketing.

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Drug	Source	Indication	Phase
AAV-CF	Targeted Genetics/Celltech	Cystic fibrosis	II
AD-237	Arakis/Vectura	COPD	II
AD-313	Arakis/SkyePharma	COPD	II
AeroDose Albuterol Inhaler	AeroGen	Asthma	II
AeroDose Ipatropium Inhalar	AeroGen	COPD	II
AIC	Dynavax	Allergic rhinitis	II/III
AIR-Albuterol	Alkermes	Asthma	II
α_1-Antitrypsin (Transgenic)	PPL Therapeutics/Bayer	Cystic fibrosis	II
	PPL Therapeutics/Bayer	Pulmonary emphysema	II
α_1-Proteinase Inhibitor IV	Aventis Behring	Pulmonary emphysema	Prereg
ALS-886	Advanced Life Sciences	ARDS	IND
Amelubant	Boehringer Ingelheim	Cystic fibrosis	II
Andolast	Rotta	Allergic rhinitis	II
	Rotta	Asthma	II
Aralast™	Alpha Therapeutic/Baxter	Pulmonary emphysema	R-2002
Arofylline	Almirall Prodesfarma	COPD	II
AVAC™	SR Pharma/Genesis	Asthma	I
AVE-0547	Aventis Pharma	Asthma	I/II
AWD-12-281[1]	elbion/GlaxoSmithKline	Allergic rhinitis	II
	elbion/GlaxoSmithKline	Asthma	I/II
	elbion/GlaxoSmithKline	COPD	I/II
Bilastine	FAES	Allergic rhinitis	II
Bimosiamose	Revotar Biopharmaceuticals	Asthma	II
CAT-213	Cambridge Antibody Technology	Allergic rhinitis	I/II
Cat-PAD	Powder Ject	Allergic rhinitis	I
Ciclesonide[1]	Altana/Teijin	Allergic rhinitis	I
	Altana/Aventis	Asthma	Prereg
Cilomilast[1]	GlaxoSmithKline	COPD	III
CPX[1]	SciClone	Cystic fibrosis	II
CS-003	Sankyo	Asthma	II
	Sankyo	COPD	II
CVT-E002	CV Technologies	Rhinitis	II
Daclizumab[2]	Protein Design Labs	Asthma	II
DCF-987	BCY LifeSciences	COPD	I
	BCY LifeSciences	Cystic fibrosis	I
Desloratadine[1]	Schering-Plough	Allergic rhinitis	L-2001
Duramycin	MoliChem Medicines	Cystic fibrosis	II
E-4931	Esteve	Asthma	I
Efletirizine[1]	UCB	Allergic rhinitis	III
EPI-2010	EpiGenesis/Taisho/Chiesi	Asthma	II
EPI-hNE-4	Debiopharm/H3 Pharma	ARDS	II
	Debiopharm/H3 Pharma	Cystic fibrosis	II
ETX-100	Exhale Therapeutics	Pulmonary emphysema	I
Formoterol Fumarate[1,2]	Novartis/Schering Plough/AstraZeneca	COPD	L-2001
(*R*,*R*)- Formoterol	Sepracor	COPD	III
Fudosteine[1]	SSP/Mitsubishi Pharma	Cough	L-2001
Genistein	NIH/Yamanouchi	Cystic fibrosis	I
GW-274150	GlaxoSmithKline	Allergic rhinitis	I
	GlaxoSmithKline	Asthma	I
GW-328267	GlaxoSmithKline	Allergic rhinitis	II
GW-559090	GlaxoSmithKline	Allergic rhinitis	II
	GlaxoSmithKline	Asthma	II
HL-10	Leo	ARDS	II
IC-485	Icos	COPD	I
IDEC-152	IDEC/Seikagaku	Asthma	I/II
IL-4/IL-13 Trap	Regeneron	Asthma	I
INS-37217	Inspire Pharmaceuticals	Allergic rhinitis	III
	Inspire Pharmaceuticals	Cystic fibrosis	II
Interferon gamma1b[2]	Mondobiotech/InterImmune	Asthma	II
	Mondobiotech/InterImmune	Idiopathic pulmonary fibrosis	II
IPL-512602	InflaZyme/Aventis Pharma	Asthma	I
IPL-550260	InflaZyme/Aventis Pharma	Asthma	I
IPL-576092	InflaZyme/Aventis Pharma	Asthma	II
Iseganan Hydrochloride[1]	IntraBiotics	Cystic fibrosis	I
ISS-1018	Dynavax	Asthma	I

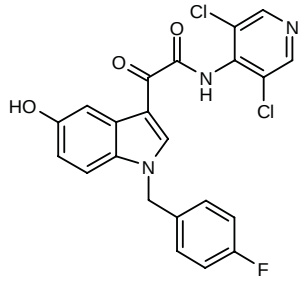
Continuation

Annual Review 2002: Respiratory Drugs

Drug	Source	Indication	Phase
KCO-912	Novartis	Asthma	II
KW-4490	Kyowa Hakko	Asthma	II
Levocetirizine	UCB/Sepracor	Allergic rhinitis	L-2001
Lusupultide	Altana	ARDS	III
MCC-847	Mitsubishi Pharma	Allergic rhinitis	II
	Mitsubishi Pharma	Asthma	II
ME-3301	Meiji Seika	Asthma	II
MEN-91507	Menarini	Asthma	I
Mepolizumab	GlaxoSmithKline	Asthma	II
ML-03	Milkhaus	COPD	II
	Milkhaus	Cystic fibrosis	II
mondoBIOTECH-811	Mondobiotech	COPD	I
	Mondobiotech	Sarcoidosis	I
Montelukast Sodium[1,2]	Merck & Co.	Allergic rhinitis	Prereg
MSI-Albuterol	Sheffield	Asthma	II
NCX-950	NicOx	Asthma	I/II
Nepadutant	Menarini	Asthma	II
NS-126	SSP/Nippon Shinyaku	Allergic rhinitis	II
	SSP/Nippon Shinyaku	Asthma	II
Olopatadine Hyrochloride[2]	Kyowa Hakko	Allergic rhinitis	L-2001
	Kyowa Hakko	Asthma	L-2001
Omalizumab[1]	Genentech/Novartis/Tanox	Allergic rhinitis	R-2002
	Genentech/Novartis/Tanox	Asthma	R-2002
Ono-6126	Ono	Asthma	I
	Ono	COPD	I
OPC-6535	Otsuka	Asthma	II
P-113D	Demegen	Cystic fibrosis	IND
Pascolizumab	Protein Design Labs	Asthma	II
Prasterone Sulfate	Pharmadigm	Asthma	II
QAB-149	Novartis	Asthma	II
	Novartis	COPD	II
R-112	Rigel	Allergic rhinitis	I
R-411	Roche	Asthma	II
R-667	Roche	Pulmonary emphysema	II
RBx-7796	Ranbaxy	Asthma	I
Roflumilast[1]	Altana/Pharmacia/Tanabe Seiyaku	Asthma	III
	Altana/Pharmacia	COPD	III
Rupatadine Fumarate[1]	Uriach	Allergic rhinitis	R-2001
S-3013	Shionogi	Asthma	II
S-5751	Shionogi	Asthma	II
Seretide/Advair[2]	GlaxoSmithKline	COPD	Prereg
Sinapultide	Discovery Laboratories	ARDS	III
SRP-299	SR Pharma/Sakai	Allergic rhinitis	I/II
	SR Pharma/Sakai	Asthma	I/II
Symbicort[2]	AstraZeneca	COPD	Prereg
TAK-427	Takeda	Allergic rhinitis	II
Talnetant	GlaxoSmithKline	COPD	II
	GlaxoSmithKline	Cough	II
Talniflumate[1,2]	Genaera	Asthma	II
	Genaera	Cystic fibrosis	II
Tecastemizole[1]	Sepracor	Allergic rhinitis	III
TH-9507	Theratechnologies	COPD	II
Tiotropium Bromide[1]	Boehringer Ingelheim/Pfizer	COPD	L-2002
TR-14035	Tanabe Seiyaku/GlaxoSmithKline	Asthma	I
TRK-851	Mitsubishi Pharma/Toray	Cough	I
UCB-35440	UCB	Allergic rhinitis	I
	UCB	Asthma	I
Undisclosed PDE4 Inhibitor	Merck & Co./Celltech	Asthma	II
	Merck & Co./Celltech	COPD	II
Zaltoprofen[2]	Nippon Chemiphar/Zeria	Upper respiratory inflammation	Prereg
ZD-4407	AstraZeneca	COPD	I

[1]Previously published in Drugs of the Future. [2]Launched for another indication.

AWD-12-281



AWD-12-281 (GW-842470) is a phosphodiesterase type 4 (PDE4) inhibitor currently in phase I/II clinical evaluation at elbion and GlaxoSmithKline for the treatment of asthma, chronic obstructive pulmonary disease and allergic rhinitis, and experimental studies have indicated its potential in the treatment of allergic dermatitis.

AWD-21-281 has been assessed for its effects on airways mucus secretion and lung neutrophilia in animal models in comparison to other PDE4 inhibitors. AWD-12-281 (10 mg/kg i.p.; 119%) was more effective than cilomilast (10 mg/kg i.p.; 50%) and roflumilast (1 mg/kg i.p.; 44%) in enhancing phenol red secretion into tracheal lumen of mice, a measure of airways mucus secretion. Although it was less effective than the other PDE4 inhibitors in reducing lipopolysaccharide (LPS)-induced lung neutrophilia in rats following oral administration (37% inhibition at 30 mg/kg *vs*. 60% inhibition at 1 mg/kg), it was the most potent compound tested when given topically (ID_{50} = 0.02 mg/kg by intrapulmonary administration). Intrapulmonary administration to pigs dose-dependently inhibited LPS-induced lung neutrophilia and the increase in IL-8 levels in bronchoalveolar lavage fluid (BALF). AWD-12-281 may thus have potential in the treatment of chronic obstructive pulmonary disease (COPD) (1).

Results from a study examining the effects of AWD-12-281 and steroids in a pig model of COPD were reported. Pigs were administered LPS to induce neutrophil migration into the BALF and were treated with AWD-12-281, dexamethasone or beclomethasone dipropionate given i.v. 0.5 h prior to inhalation of LPS or intratracheally (i.t.) 1 h before LPS. At a dose of 4 mg i.t., AWD-12-281 reduced lung neutrophilia at 4 and 6 h by 86% and 65%, respectively, compared to controls. Beclomethasone at 0.4 mg i.t. produced 73% and 65% inhibition, respectively, and dexamethasone 0.28 mg/kg i.v. suppressed neutrophilia by 80% and 90%, respectively, at these time points. Topically applied AWD-12-281 thus appears to have potential in the treatment of COPD and other inflammatory airways disorders (2).

When given before or after ovalbumin challenge in rats, AWD-12-281 inhibited the migration of eosinophils into the bronchoalveolar space. Intratracheal administration of the agent (0.05 and 5.0 mg/kg) was well tolerated (3).

Cilomilast and AWD-12-281 were tested in a model of allergic dermatitis in mice. Toluene-2,4-diisocyanate was administered topically to the ear of sensitized BALB/c mice which had previously been treated or not with cilomilast or AWD-12-281. Mice not previously treated with either compound showed significant ear swelling after challenge. Both cilomilast and AWD-12-281 inhibited this swelling for up to 48 h after challenge through inhibition of IL-1β secretion. The authors suggested that the PDE4 inhibitors may be strong modulators of allergic responses of the skin with potential in the treatment of chronic allergic dermatitis (4).

The therapeutic efficacy and safety margin of AWD-12-281 were compared to other PDE4 inhibitors in pigs and ferrets. The results confirmed a strong antiinflammatory effect in the lung for AWD-12-281 and lower emetic potential compared to rolipram, cilomilast, RPR-73401 and roflumilast. In ferrets, AWD-12-281 inhibited LPS-induced neutrophilia with ID_{50} values of 2.4 mg/kg i.p. and approximately 10 mg/kg p.o., and emesis was first seen only at higher doses (15 mg/kg i.p., 40 mg/kg p.o.). In pigs, neutrophilia was inhibited at a dose of 1 mg/kg i.v. and emesis was first seen at a dose of 9 mg/kg i.v. (30 mg/kg p.o.) (5).

Results from *in vitro* experiments using liver preparations from rats, dogs and humans and *in vivo* studies involving the administration of single oral and i.v. doses in rats and dogs showed that AWD-12-281 is mainly metabolized by glucuronidation. Oral bioavailability was less than 3%. Following i.v. and oral dosing in both species, more than 97% was excreted as unchanged compound in the feces. Experiments using bile-cannulated rats confirmed that the agent was metabolized via hepatic glucuronidation with excretion of glucuronide into bile (6).

1. Poppe, H., Marx, D., Heer, S., Ugerland, U., Hoefgen, N., Szelenyi, I. *Effects of a selective PDE4-inhibitor AWD 12-281 in comparison with SB 207499 and roflumilast on trancheal phenol red secretion in mice and LPS-induced neutrophilia in BAL in Lewis rats and domestic pigs.* Am J Respir Crit Care Med 2001, 163(5, Suppl.): A994.

2. Poppe, H., Sims, G., Helm, K.P., Rundfeldt, C. *The selective PDE4-inhibitor AWD 12-281 inhibits LPS-induced neutrophilia in domestic pig lung, an animal model of COPD: Comparison with steroids.* Eur Respir J 2001, 18(Suppl. 33): Abst P1085.

3. Kuss, H., Höfgen, N., Arzneimittelwerk, R. *Inhibition of late phase eosinophilia in allergen challenged Brown Norway rats with AWD 12-281, a new selective PDE4-inhibitor, and local tolerability in rat lungs*. 98th Int Conf Am Thorac Soc (May 17-22, Atlanta) 2002, Abst A24.

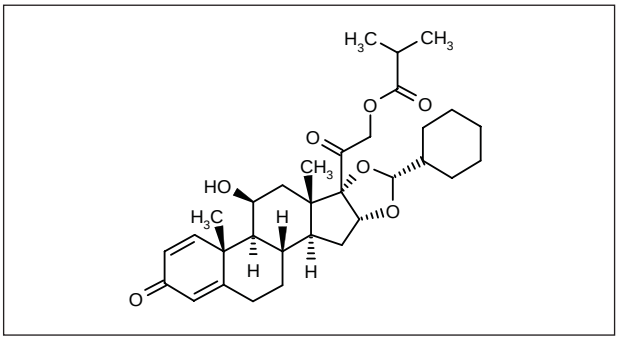
4. Baumer, W., Gorr, G., Hoppmann, J., Ehinger, A.M., Ehinger, B., Kietzmann, M. *Effects of the phosphodiesterase 4 inhibitors SB 207499 and AWD 12-281 on the inflammatory reaction in a model of allergic dermatitis*. Eur J Pharmacol 2002, 446(1-3): 195.

5. Kuss, H., Höfgen, N. *AWD 12-281, a new selective PDE4-inhibitor with a high safety margin: Separation of anti-inflammatory and emetic effects in ferrets and domestic pigs*. Eur Respir J 2002, 20(Suppl. 38): Abst P3859.

6. Gasparic, A., Schupke, H., Olbrich, M., Krone, D., Peter, G., Hempel, R., Kronbach, T. *O-Glucuronidation as major metabolic pathway of the phosphodiesterase 4 inhibitor AWD 12-281 in vitro and in vivo*. 14th Int Symp Microsomes Drug Oxid (July 22-26, Sapporo) 2002, Abst P23-C-46.

Original monograph - Drugs Fut 2002, 27(2): 111.

Ciclesonide



Ciclesonide (BY-9010, BY-9207-015, Alvesco®) is a site-activated, inhaled corticosteroid for the treatment of asthma developed at Altana Pharma. Filings for approval have been made in the E.U., Australia, Switzerland and Canada, and in the U.S., where it is licensed to Aventis for development and marketing, an NDA submission is scheduled for 2003. A cooperation agreement has also been concluded with Teijin in Japan, Taiwan and Korea (1-3).

Studies on the *in vitro* antiinflammatory activity of ciclesonide demonstrated that it is more active than the *S*-epimer against LPS-stimulated TNF-α release in human cells and whole blood. The active metabolite was even more effective and compared favorably with budesonide and fluticasone propionate (4).

Ciclesonide, its active metabolite and fluticasone have been compared in rats with airways eosinophilia induced by Sephadex or allergen challenge. Although intratracheal ciclesonide was less potent than fluticasone in inhibiting eosinophilia, it was also much less potent in inducing femoral hypoplasia, suggesting an improved therapeutic ratio compared to fluticasone in the treatment of asthma (5).

In *in vivo* studies using rat models of inflammation, ciclesonide proved to be equieffective to budesonide and to have a superior safety profile in terms of thymus and adrenal involution and body weight loss, suggesting an improved therapeutic ratio for ciclesonide (6).

Preclinical studies provided further evidence that ciclesonide is activated on site following direct delivery to the lungs, resulting in greater local antiinflammatory activity than the active metabolite. Although the active metabolite displayed 100-fold higher binding affinity for the human glucocorticoid receptor (K_i = 0.31 nM *vs*. 37 nM), inhaled ciclesonide was more potent than inhaled active metabolite in two models of airways inflammation. In sensitized Brown-Norway rats, the ED_{50} values for ciclesonide and the active metabolite for inhibiting antigen-induced eosinophilia in lung tissue were 0.49 and 1.0 mg/kg, respectively, and the respective values for inhibition of airways lumen eosinophilia were 0.75 and 1.97 mg/kg. In the Sephadex-induced lung edema model in rats, ciclesonide and active metabolite gave respective ED_{50} values of 0.72 and 1.08 mg/kg (7).

Occupation of glucocorticoid receptors by ciclesonide and its active metabolite was determined in an *ex vivo* rat receptor binding model. Receptor occupancy was similar for both compounds in lung and spleen, but was significantly greater in lung than in kidney or brain upon intratracheal administration (8).

In actively sensitized rats, ciclesonide (1, 3.29 and 6.19 μg/kg) dose-dependently attenuated allergen-induced early and late airways responses, infiltration of inflammatory cells into bronchoalveolar lumen and airways hyperresponsiveness. Ciclesonide and its active metabolite also maintained inhibition of cytokine production in human alveolar epithelial cells treated with glucocorticoids followed by a wash with medium and then TNF-α and IL-1β stimulation (9).

The population pharmacokinetics/pharmacodynamics of ciclesonide and its active metabolite have been estimated using data from phase I studies. The results indicated that the active metabolite is associated with negligible cortisol suppression and may therefore have a better therapeutic index compared to other inhaled corticosteroids (10).

The pharmacokinetics of ciclesonide were investigated in a randomized, crossover study in 6 healthy male volunteers. Subjects received a single oral dose of radiolabeled ciclesonide 6.9 mg and a single i.v. dose of 0.64 mg with a minimum washout of 2 weeks. Oral absorption of ciclesonide was low, and the drug demonstrated almost complete first-pass metabolism. The results indicated that the amount of drug swallowed after inhalation does not alter systemic concentrations (11).

The pharmacokinetics and pharmacodynamics of ciclesonide were assessed in a randomized, open, crossover study. Healthy male volunteers (n=12) were given inhaled placebo plus inhaled ciclesonide 800 μg on the following day in one period and i.v. placebo plus i.v.

Table I: Clinical studies of ciclesonide (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Healthy volunteers	Double-blind, crossover	Ciclesonide, 800 μg od inhal AM x 7 d Ciclesonide, 800 μg od inhal PM x 7 d Ciclesonide, 400 μg bid inhal x 7 d Placebo	12	Independently of the time of dosing, inhalation of 800 μg od of ciclesonide did not lead to suppression of cortisol levels	17, 18
Asthma, COPD	Randomized, double-blind, crossover	Ciclesonide, 400 μg od inhal AM x 2 wk Budesonide, 400 μg od inhal AM x 2 wk	16	Ciclesonide 400 μg or budesonide 400 μg daily for short-term treatment of patients with mild asthma had similar potency in attenuating airway responsiveness to AMP and in reducing the concentration of exhaled nitric oxide as a marker of airway inflammation	19
Asthma, COPD	Randomized, double-blind, crossover	Ciclesonide, 400 μg od inhal x 7 d Ciclesonide, 800 μg od inhal x 7 d Ciclesonide, 800 μg bid inhal x 7 d Fluticasone, 500 μg bid inhal x 7 d Fluticasone, 1000 μg bid inhal x 7 d	26	Fluticasone but not ciclesonide suppressed cortisol secretion and all active treatments decreased hyper-responsiveness to adenosine	25
Asthma, COPD	Randomized, double-blind, multicenter	Ciclesonide, 100 μg od inhal x 12 wk (n=120) Ciclesonide, 400 μg od inhal x 12 wk (n=115) Placebo (n=125)	360	Ciclesonide at doses of 100 μg and 400 μg od showed efficacy and was safe in asthmatic patients	27
Asthma, COPD	Randomized, double-blind	Ciclesonide, 800 μg/d x 12 wk → Ciclesonide, 800 [min] μg/d x 4 wk → individualized dose x 40 wk Ciclesonide, 200 μg/d x 12 wk → Ciclesonide, 800 [min] μg/d x 4 wk → individualized dose x 40 wk Placebo x 12 wk → Ciclesonide, 800 [min] μg/d x 4 wk → individualized dose x 40 wk	329	Ciclesonide was safe and significantly improved FEV_1, regardless of the dose administered in the double-blind period	30
Asthma, COPD	Randomized, double-blind, multicenter	Ciclesonide, 200 μg od inhal AM x 8 wk (n=88) Ciclesonide, 200 μg od inhal PM x 8 wk (n=80)	209	Ciclesonide 200 μg od was effective in the treatment of mild to moderate asthma as assessed by lung function, symptoms, use of rescue medication and number of asthma exacerbations	31

ciclesonide 800 μg on the following day in the other period. The results indicated a high rate of pulmonary deposition for the active metabolite and no suppression of cortisol in serum (12).

In randomized, open, crossover studies in healthy volunteers, the bioequivalence of different dosing regimens of ciclesonide was demonstrated: 4 puffs of ciclesonide 200 μg with the 200-μg metered-dose inhaler, 8 puffs of 100 μg ciclesonide with the 100-μg metered-dose inhaler and 16 puffs of 50 μg ciclesonide via the 50-μg metered-dose inhaler (13, 14).

Two-dimensional planar scintigraphy and 3D SPECT scintigraphy were used to assess pulmonary deposition of ^{99}m-Tc-labeled ciclesonide after administration of 50 μg to 6 healthy volunteers inhaling 1 puff and 2 healthy volunteers inhaling 10 puffs. The drug was administered with a metered-dose inhaler. Imaging revealed that, on average, more than 50% of ciclesonide was deposited in the lungs (15, 16).

A placebo-controlled, randomized, double-blind, crossover study in 12 healthy male adults assessed three dosage regimens of ciclesonide (800 μg in the morning, 800 μg in the evening and 400 μg b.i.d. for 7 days) administered via metered-dose inhalers on the circadian serum cortisol rhythm. Results indicated that ciclesonide was safe and had no clinically relevant effect on the hypothalamic-pituitary-adrenal axis, with serum cortisol displaying a typical circadian pattern posttreatment (17, 18). The results of these studies and some of the following studies are summarized in Table I.

Inhalation of 400 μg ciclesonide for 2 weeks was as effective as inhalation of 400 μg budesonide for 2 weeks in reducing both airways responsiveness to inhaled AMP and airways inflammation in nonsmoking patients with mild asthma (19).

The oropharyngeal deposition of ciclesonide and its active metabolite was compared to that of fluticasone propionate in a study in patients with asthma administered the drugs (800 μg ciclesonide, 1000 μg fluticasone propionate) using HFA-based metered-dose inhalers. The results indicated significantly reduced oropharyngeal deposition of ciclesonide compared to fluticasone, which may result in reduced local side effects (20).

A double-blind, randomized, parallel-group study compared the efficacy and safety of 2 doses of ciclesonide (400 and 800 μg b.i.d.) in patients with moderate to severe asthma pretreated with beclomethasone dipropionate (800-2000 μg/day) or equivalent. A total of 365 patients were enrolled to receive either dose over 12 weeks. Morning peak expiratory flow (PEF) increased 5%

in both groups and mean daily symptom scores significantly decreased to a similar extent on both doses. The use of rescue medication was also decreased on both doses and only 4 and 2 patients on 800 and 1600 μg/day ciclesonide, respectively, withdrew due to lack of efficacy. Both doses were well tolerated, with a similar increase in serum and 24-h urinary cortisol (21, 22).

Morning and evening inhalation of ciclesonide was compared in 209 asthma patients given 200-μg doses of the drug for 8 weeks. In this double-blind study, ciclesonide significantly improved asthma control, irrespective of the time of administration (23).

Ciclesonide (400 or 800 μg once daily and 800 μg b.i.d.) was compared to fluticasone propionate (500 and 1000 μg b.i.d.) in 26 asthma patients in a randomized, double-blind, placebo-controlled, crossover trial. Urinary cortisol production was significantly suppressed with fluticasone compared to ciclesonide. Similar reductions in hyperresponsiveness to adenosine were seen with all treatments (24, 25).

A multicenter, randomized, double-blind, placebo-controlled clinical trial was conducted to evaluate ciclesonide for the treatment of asthma. Doses of 100 or 400 μg ciclesonide or placebo were assigned to 360 patients for 12 weeks. Ciclesonide significantly increased morning PEF compared to placebo. Forced expiratory volume in 1 s (FEV_1) values were also increased with ciclesonide but decreased with placebo, and the difference between either dose of ciclesonide and placebo was significant. The active treatment was well tolerated (26, 27).

A study in 329 asthma patients compared ciclesonide (200 or 800 μg/day) and placebo over 12 weeks following a 2-week baseline period during which patients used beclomethasone dipropionate (400-800 μg/day) or equivalent. Both doses of ciclesonide were significantly superior to placebo. Those on ciclesonide showed stable morning PEF, FEV_1 and FVC (forced vital capacity) values, in contrast to the decreases seen on placebo. No significant difference in serum and 24-h urinary cortisol levels compared to placebo was observed on ciclesonide and both doses were well tolerated. The 12-week, double-blind, randomized part of the study was followed by an open treatment period with ciclesonide for up to 1 year. The treatment was safe and significantly improved FEV_1 (28-30).

Inhalation of 200 μg of ciclesonide for 8 weeks improved spirometry variables, symptoms and number of exacerbations in patients with asthma. Similar improvement rates were found regardless of the time of inhalation (morning or evening), although morning PEF tended to improve more when ciclesonide was administered in the evening (31).

1. *Ciclesonide to be codeveloped and copromoted by Aventis and Altana for asthma*. DailyDrugNews.com (Daily Essentials) March 29, 2001.

2. *Byk files for approval of ciclesonide for asthma in Canada*. DailyDrugNews.com (Daily Essentials) June 13, 2002.

3. *Altana reports decisive progress in development of roflumilast and ciclesonide*. DailyDrugNews.com (Daily Essentials) Aug 29, 2001.

4. Stoeck, M., Hatzelmann, A., Belvisi, M.G., Foster, M.L., Bundschuh, D.S. *In vitro anti-inflammatory activity of the new glucocorticoid ciclesonide in human cells*. Eur Respir J 2001, 18(Suppl. 33): Abst P679.

5. Belvisi, M.G., Bundschuh, D.S., Stoeck, M., Wicks, S., Underwood, S., Battram, C.H., Webber, S.E., Haddad, E.-B., Foster, M.L. *Pre-clinical in vivo assessment of ciclesonide, a novel corticosteroid for the treatment of asthma*. Eur Respir J 2001, 18(Suppl. 33): Abst P682.

6. Bundschuh, D.S., Marx, D., Hatzelmann, A., Beume, R., Haefner, D., Hochhaus, G., Montoro, F., Riedel, R., Stoeck, M. *Pre-clinical anti-inflammatory activity and safety profile of the novel glucocorticoid ciclesonide*. Eur Respir J 2001, 18(Suppl. 33): Abst 1013.

7. Belvisi, M., Bundschuh, D., Stoeck, M., Wicks, S., Underwood, S., Battram, C., Webber, S., Haddad, E.-B. *Ciclesonide, a novel "on site activated" inhaled corticosteroid with potent anti-inflammatory actions in the airways*. J Allergy Clin Immunol 2002, 109(1, Part 2): Abst 59.

8. Hochhaus, G., Talton, J.D., Stoeck, M. *Pulmonary targeting of ciclesonide and its active metabolite as determined in an ex-vivo rat receptor-binding assay*. Eur Respir J 2002, 20(Suppl. 38): Abst P3865.

9. Nonaka, T., Sugiyama, H., Taneda, M., Kishimoto, T., Horiuchi, H., Sakuma, Y., Hoshina, K., Kamimura, T. *Effect of a novel inhaled glucocorticoid, ciclesonide, on an allergen-induced asthmatic response in rats and its prolonged anti-inflammatory activity in vitro*. Eur Respir J 2002, 20(Suppl. 38): Abst P652.

10. Rohatagi, S., Arya, V., Zech, K., Barret, J.S., Hochhaus, G., Jensen, B.K. *Population pharmacokinetics/pharmacodynamics of ciclesonide*. J Allergy Clin Immunol 2002, 109(1, Part 2): Abst 716.

11. Nave, R., Bethke, T.D., van Marle, S.P., Zech, K. *Pharmacokinetics of ^{14}C-ciclesonide after oral and intravenous administration in healthy subjects*. Eur Respir J 2002, 20(Suppl. 38): Abst P745.

12. Nave, R., Bethke, T.D., Seiberling, M., Steinijans, V.W., Zech, K. *Pharmacokinetics and pharmacodynamics of ciclesonide and its active principle after inhalative and intravenous administration in healthy subjects*. Eur Respir J 2002, 20(Suppl. 38): Abst P749.

13. Drollmann, A., Bethke, T.D., Nave, R., Zech, K., Hauns, B., Steinijans, V.W., Wurst, W. *Bioequivalence of two ciclesonide dosing regimen (4 puffs of 200 μg vs. 8 puffs of 100 μg using a MDI)*. Eur Respir J 2002, 20(Suppl. 38): Abst P1914.

14. Bethke, T.D., Drollmann, A., Hauns, B., Nave, R., Zech, K., Steinijans, V.W., Wurst, W. *Bioequivalence of two ciclesonide dosing regimens (4 puffs of 200 μg vs.16 puffs of 50 μg using a MDI)*. Eur Respir J 2002, 20(Suppl. 38): Abst P748.

15. Bethke, T.D., Boudreau, R.J., Hasselquist, B.E., Davidson, P., Leach, C.L., Drollmann, A., Hauns, B., Wurst, W. *High lung deposition of ciclesonide in 2D- and 3D-imaging*. Eur Respir J 2002, 20(Suppl. 38): Abst P746.

16. Drollmann, A., Hasselquist, B.E., Boudreau, R.J., Leach, C.L., Davidson, P., Hauns, B., Bethke, Th. *Ciclesonide shows high lung deposition in 2D and 3D-imaging*. 98th Int Conf Am Thorac Soc (May 17-22, Atlanta) 2002, Abst A40.

17. Weinbrenner, A., Hüneke, D., Zschiesche, M., Engel, G., Timmer, W., Steinijans, V.W., Bethke, T., Wurst, W., Drollman, A., Kaatz, H.J., Siegmund, W. *Circadian rhythm of serum cortisol after repeated inhalation of the new topical steroid ciclesonide*. J Clin Endocrinol Metab 2002, 87(5): 2160.

18. Drollmann, A., Weinbrenner, A., Hüneke, D., Ziesche, M., Engel, G., Bethke, T., Steinijans, V., Wurst, W., Siegmund, W. *Repeated inhalation of the new topical steroid ciclesonide does not lead to suppression of endogenous cortisol release in healthy subjects*. Eur Respir J 2001, 18(Suppl. 33): Abst P680.

19. Kanniess, F., Richter, K., Böhme, S., Jörres, R.A., Magnussen, H. *Effect of inhaled ciclesonide on airway responsiveness to inhaled AMP, the composition of induced sputum and exhaled nitric oxide in patients with mild asthma*. Pulm Pharmacol Ther 2001, 14(2): 141.

20. Richter, K., Nielsen-Gode, D., Biberger, C., Nave, R., Magnussen, H. *Oropharyngeal deposition of inhaled ciclesonide and fluticasone propi-*

onate in patients with asthma. 21st Congr Eur Acad Allergol Clin Immunol (June 1-5, Naples) 2002, Abst 1121.

21. O'Connor, B.J., Sips, P., Biberger, C., Steinijans, V.W., Wurst, W. *Management of moderate to severe bronchial asthma by ciclesonide: A 12-week study*. 21st Congr Eur Acad Allergol Clin Immunol (June 1-5, Naples) 2002, Abst 1120.

22. O'Connor, B., Sips, P., Engelstatter, R., Steinijans, V.W., Wurst, W. *Management of moderate to severe bronchial asthma by ciclesonide: A 12-week trial*. 98th Int Conf Am Thorac Soc (May 17-22, Atlanta) 2002, Abst G75.

23. Postma, D.S., Schlosser, N., Sevette, C., Martinat, Y., Aumann, J., Kafe, H. *Morning and evening administration of inhaled ciclesonide is equally effective in treatment of asthma*. Eur Respir J 2002, 20(Suppl. 38): Abst P1913.

24. Pauwels, R.A., Derom, E., Van De Velde, V., Marissens, S., Vincken, W. *Effects of inhaled ciclesonide and fluticasone propionate on cortisol secretion and PC20 for adenosine in asthma patients*. 98th Int Conf Am Thorac Soc (May 17-22, Atlanta) 2002, Abst G84.

25. Derom, E., Van De Velde, V., Marissens, S., Vinken, W., Pauwels, R.A. *Efficacy and systemic effects of ciclesonide and fluticasone in asthma patients*. Eur Respir J 2001, 18(Suppl. 33): Abst 1015.

26. Engelstatter, R., Langdon, C., Bethke, T., Rathgeb, F., Steinijans, V.W., Wurst, W. *Efficacy of ciclesonide after twelve-week treatment of bronchial asthma*. 98th Int Conf Am Thorac Soc (May 17-22, Atlanta) 2002, Abst G70.

27. Drollmann, A., Langdon, C., Engelstätter, R., Rathgeb, F., Steinijans, V.W., Wurst, W. *Ciclesonide is effective in the treatment of bronchial asthma*. Eur Respir J 2001, 18(Suppl. 33): Abst P681.

28. Chapman, K.R., D'Urzo, A.D., Oedekoven, C., Steinijians, V.W., Wurst, W. *Ciclesonide vs placebo: Effect on lung function in asthma patients after 12 weeks of treatment*. 21st Congr Eur Acad Allergol Clin Immunol (June 1-5, Naples) 2002, Abst 1119.

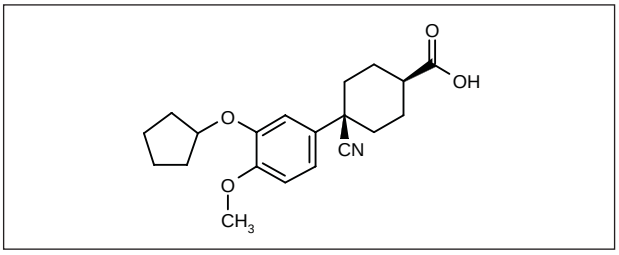
29. Chapman, K.R., D'Urzo, A.D., Oedekoven, C., Steinijans, V.W., Wurst, W. *Effects of ciclesonide versus placebo on lung function after 12 weeks of treatment in patients with asthma*. 98th Int Conf Am Thorac Soc (May 17-22, Atlanta) 2002, Abst G74.

30. Chapman, K.R., Patel, P., Boulet, L.P., D'Urzo, A.D., Alexander, M., Mehra, S., Oedekoven, C. *Efficacy and long-term safety of ciclesonide in asthmatic patients as demonstrated in a 52 week long study*. Eur Respir J 2002, 20(Suppl. 38): Abst 2328.

31. Postma, D.S., Sevette, C., Martina, Y., Schlösser, N., Aumann, J., Kafé, H. *Treatment of asthma by the inhaled corticosteroid ciclesonide given either in the morning or evening*. Eur Respir J 2001, 17(6): 1083.

Original monograph - Drugs Fut 2001, 26(11): 1033.

Cilomilast



Cilomilast (SB-207499, Ariflo™) is a PDE4 inhibitor in phase III clinical trials at GlaxoSmithKline as a new treatment for COPD (1).

An *in vitro* study using bronchial epithelial cells (BEC) and sputum cells (SC) isolated from 10 COPD patients examined the efficacy of cilomilast (10 μM) on TNF-α, IL-8 and GM-CSF (granulocyte-macrophage colony-stimulating factor) release. TNF-α was significantly decreased from 139 ± 59 pg/ml to 97 ± 50 pg/ml in BEC and from 1485 ± 440 pg/ml to 1080 ± 354 pg/ml in SC. GM-CSF was significantly reduced from 546 ± 230 pg/ml to 302 ± 149 pg/ml in SC. The agent had no significant effect on IL-8 release from either cell type. Results indicate that cilomilast may be effective in resolving COPD-associated neutrophil inflammation (2).

Results from an *in vitro* study using human polymorphonuclear neutrophils (PMNs) pretreated with TNF-α (100 U/ml for 15 min) and activated with fMLP (10 nM for 30 min) showed that cilomilast (10 nM-100 μM) significantly and concentration-dependently inhibited migration and extracellular proteolysis by PMNs. The agent (10 μM) inhibited PMN polarization in response to fMLP and actin (by 61.2 ± 1.2%). Polymorphonuclear neutrophil release and cell-surface expression of human leukocyte elastase were also significantly inhibited by 46.3 ± 4.4% and 63.8 ± 2.5%, respectively, with 1 μM cilomilast (3). Treatment of neutrophils with mediators associated with inflammation in COPD (IL-8, fMLP and cigarette smoke) caused a decrease in cell deformability. Treatment with cilomilast (0.3 μM) plus PGE_2 (0.05 μM) reversed these effects, and cilomilast alone concentration-dependently inhibited fMLP-stimulated O_2^- release (4).

Another *in vitro* study using human PMNs showed that cilomilast selectively and significantly inhibited agonist-induced neutrophil effector functions such as oxidative burst (> 90%), adhesion (60%) and exocytosis of primary and secondary granules (50%) and fMLP-induced chemotaxis (50%). The agent (up to 10 μM) had no effect on phagocytosis of IgG-opsonized red blood cells or serum-opsonized zymosan, or on bacterial killing (5, 6).

Results from an *in vitro* study showed that cilomilast suppressed the growth of human acute lymphoblastic leukemia cells (EC_{50} = 100-200 μM), as well as the growth of REH and CEM cells. It was also shown to increase the sensitivity of a highly dexamethasone-resistant subclone of CEM cells to the glucocorticoid, but it had no effect on the dexamethasone sensitivity of REH cells. Synergistic inhibition of the growth of CEM-CCRF leukemia cells was observed when cilomilast was combined with forskolin (7).

In a study to assess the *in vitro* activity of rolipram and cilomilast (both 10 μM) on fibroblast responses, both drugs inhibited the chemotaxis of human fetal lung

fibroblasts (HFL-1) toward fibronectin and also the contraction of 3-dimensional collagen gels. The results indicate the potential of these agents to inhibit the onset of progressive fibrosis (8).

The effect of cilomilast (10 μM) and several comparator phosphodiesterase inhibitors on the ability of HFL-1 fibroblasts (cultured with TNF-α and/or neutrophil elastase) to degrade extracellular matrix was also evaluated using a 3-dimensional gel culture system. In contrast to amrinone and zaprinast, cilomilast inhibited the degradation of gels, an effect that was facilitated by blocking the release of the matrix metalloproteinases MMP-1 and MMP-9 and by preventing the conversion of MMP-1 to its active form. Cilomilast may therefore have potential for the treatment of emphysema and other conditions featuring excessive tissue damage (9).

The effects of cilomilast and RPR-73401 were examined using the toluene-2,4-diisocyanate (TDI)-induced mouse ear swelling test. Animals were treated topically with either agent (20 μl of 3% in acetone/DMSO) 2 h before TDI rechallenge. Both agents significantly reduced ear swelling, IL-1β and IL-4 content of ear skin and elevated plasma TNF-α at 1 and 6 h after rechallenge. Although RPR-73401 had no effect, cilomilast significantly inhibited the TDI-induced increase in peptidoleukotriene synthesis (10).

The activity of cilomilast was evaluated in a murine model of sublethal intranasal influenza infection followed by subsequent challenge with *Streptococcus pneumoniae* after viral clearance (day 9). Untreated mice predisposed with the sublethal influenza challenge required 4 $\log_{10}$ fewer bacterial organisms to produce a lethal infection. Mice treated with cilomilast doses of 10 and 30 mg/kg showed increased resistance to a secondary bacterial challenge, increasing the LD_{50} from 47 cfu/mouse for diluent controls to 303 cfu/mouse and 269 cfu/mouse, respectively (11).

Injection of IL-8 in rabbits caused a dose-related trapping of indium-labeled neutrophils in the pulmonary circulation, which was markedly reduced by treatment with cilomilast (10 mg/kg i.v.) (12).

Immunosuppression with the PDE4 inhibitors cilomilast, rolipram and roflumilast, as well as ciclosporin, was evaluated in a rat model of heterotopic tracheal transplantation. Assessment of epithelial integrity showed that the epithelium was completely lost until day 21 in animals receiving the PDE4 inhibitors. Monocyte/macrophage infiltration during the acute phase was significantly inhibited by cilomilast, to the same degree as ciclosporin; rolipram and roflumilast were not as effective as ciclosporin. A significant increase in monocytes and macrophages was seen in the chronic phase after treatment with ciclosporin, but not with PDE4 inhibitors. Rolipram was less potent and cilomilast and roflumilast more potent than ciclosporin in blocking cell proliferation. Among the PDE4 inhibitors, only cilomilast significantly inhibited luminal obliteration, although it was not as effective as ciclosporin. While the PDE4 inhibitors did not appear appropriate for immunosuppression after lung transplantation, cilomilast and roflumilast may be useful in blocking immune cell and fibroblast proliferation leading to obliterative bronchiolitis (13).

The comparative antiinflammatory activity of cilomilast and rolipram (both 0.3 or 10 mg/kg p.o. 2 h prior to challenge) was assessed using a rat model of LPS-induced pulmonary inflammation. Pretreatment with either drug resulted in dose-dependent antiinflammatory activity, but no effect on the pulmonary production of TNF-α or IL-1β was observed. Furthermore, their activity was not related to either IL-10 or endogenous catecholamine or corticosteroid production. Results support the continued development of these drugs for the treatment of respiratory diseases (14).

Cilomilast and AWD-12-281 were tested in a model of allergic dermatitis in mice. Toluene-2,4-diisocyanate (TDI) was administered topically to the ear of sensitized BALB/c mice which had previously been treated or not with cilomilast or AWD-12-281. Mice not previously treated with either compound showed significant ear swelling after challenge. Both cilomilast and AWD-12-281 inhibited this swelling for up to 48 h after challenge through inhibition of IL-1β secretion. The authors suggested that the PDE4 inhibitors may be strong modulators of allergic responses of the skin, with potential in the treatment of chronic allergic dermatitis (15).

Results from a study in rabbits showed that administration of cilomilast (10 mg/kg i.v. 1 min before LPS) inhibited LPS-induced pulmonary trapping of [^{111}In]-labeled polymorphonuclear leukocytes (16).

Data from 5 studies, including single- and multiple-dose studies, were used to evaluate the tolerability and pharmacokinetics of orally administered cilomilast in healthy young and elderly volunteers. Results showed that cilomilast was rapidly absorbed and pharmacokinetics were proportional to dose after single and repeated doses up to and including 15 mg, which were well tolerated. Better tolerability was reported following the ingestion of food, and this was optimal for repeated doses up to 30 mg twice daily after meals. No dose adjustment was required in the elderly, a favorable factor in the treatment of COPD (17).

The disposition of cilomilast (15 mg b.i.d. for 1 week) was investigated in subjects with mild, moderate and severe renal impairment and in healthy subjects. The half-life and unbound AUC of the drug increased with increasing renal impairment, as did the incidence and severity of gastrointestinal adverse events. It was concluded that cilomilast should not be administered to patients with severe renal impairment (18).

Data from 5 prospective pharmacokinetic studies in 96 healthy volunteers were assessed to determine the absolute oral bioavailability of cilomilast. The absolute bioavailability was 100% and pharmacokinetic parameters were not affected by time of dosing or coadministration with food or antacid (19).

A randomized, double-blind, placebo-controlled, multiple-dose, crossover study conducted in 18 subjects showed that no pharmacokinetic or pharmacodynamic

Table II: Clinical studies of cilomilast (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Healthy volunteers	Crossover	Cilomilast, 15 g bid x 9 d Placebo	16	Cilomilast had no clinically important effects on gut transit times in healthy volunteers	23
Healthy volunteers	Randomized, double-blind, crossover	Cilomilast, 15 g bid x 7d Placebo	12	Cilomilast had no significant effects on esophageal motility in healthy volunteers	24
COPD	Open	Cilomilast, 15 mg bid x 6 mo Placebo		Cilomilast reduced the risk and rate of chronic obstructive pulmonary disease exacerbations	27
COPD	Randomized, double-blind	Cilomilast, 15 mg bid x 24 wk (n=431) Placebo (n=216)	647	Compared with placebo, cilomilast decreased the number of exacerbations and thus the use of healthcare resources (physician visits, ER/urgent care visits and hospitalizations) in patients with chronic obstructive pulmonary disease. This reduced the exacerbation costs per treated patient and the costs per exacerbation	33
COPD	Randomized, double-blind, multicenter	Cilomilast, 15 mg bid x 24 wk (n=1374) Placebo (n=684)	2058	The rate of exacerbations in patients with chronic obstructive pulmonary disease was significantly reduced with cilomilast compared to placebo, therefore increasing the patients' quality of life	34
COPD	Randomized	Cilomilast, 15 mg po bid x 6 mo (n=353) Placebo (n=188)	541	Cilomilast effectively improved lung function in smoking and nonsmoking chronic obstructive pulmonary disease patients	37

interaction occurred when cilomilast (15 mg p.o. b.i.d.) was coadministered with theophylline (individualized dosing to achieve steady-state plasma levels of 10-15 μg/ml) for 4 days. Combination treatment was well tolerated and no significant changes in supine or erect blood pressure, ECG intervals or morphology, hand tremor or tachycardia were observed. No differences were seen in the Q-Tc interval in subjects treated with cilomilast alone or in combination with theophylline (20, 21).

A randomized, double-blind, placebo-controlled, parallel-group study in 38 healthy men investigated over a period of 28 days the effect of steady-state concentrations of cilomilast (15 mg twice daily) on warfarin-induced (5 mg/day on days 1 and 2, followed by dose titration) anticoagulation. The pharmacodynamics of warfarin were not affected by coadministration of cilomilast, as indicated by the 90% confidence interval for the cilomilast/placebo ratio on day 24 falling within the 25% equivalence range (22).

A study was performed in 16 subjects given a breakfast of baked beans on bread before the administration of cilomilast 15 mg b.i.d. for 9 days or placebo. No clinically relevant effect on gut transit times was seen for cilomilast, with average decreases in orocecal and whole-gut transit times of 0.37 and 2.96 h, respectively, compared to placebo (23). The results of this study and some of the following studies are summarized in Table II.

In a double-blind, randomized, placebo-controlled, crossover study, 12 healthy volunteers received cilomilast (15 mg b.i.d.) or placebo for 7 days. The results showed that cilomilast had no significant effect on the amplitude, duration or velocity of propagation of esophageal contractions or on lower esophageal sphincter pressure. One subject experienced vomiting (24).

The tolerability and steady-state pharmacokinetics of coadministered cilomilast (15 mg b.i.d.) and digoxin (375 μg once daily) were evaluated in a double-blind, crossover study in 16 healthy adults. Following a 5-day open-label phase with cilomilast alone, two consecutive 14-day testing periods were implemented with coadministration during the first and digoxin alone during the second period. Steady-state concentrations of cilomilast had no significant effect on the steady-state AUC_{0-24} or C_{min} of digoxin, with 90% confidence interval values for these endpoints falling within the range of equivalence (0.80-1.25). Likewise, digoxin did not appear to affect cilomilast steady-state pharmacokinetics, suggesting that this combination could be of benefit to elderly COPD patients (25).

The effect of cilomilast on inflammatory cells in sputum from patients with COPD was examined in 65 patients who were randomized to receive 12 weeks of treatment with placebo or cilomilast 15 mg b.i.d. Analysis of sputum samples demonstrated a 14.9% reduction in the percentage of neutrophils on cilomilast (4.0%

decrease from baseline) compared to placebo (10.9% increase from baseline), associated with an 11.4% increase in macrophages. Other cellular and biochemical indices were not significantly altered by cilomilast and the treatment was well tolerated (26).

A randomized, placebo-controlled study with a 1-month run-in period conducted in 647 patients with stable COPD (FEV_1 = 30-70%; 15% or less response to a β_2-agonist) showed the efficacy of cilomilast (15 mg b.i.d. p.o. for 6 months) in reducing exacerbations and improving lung function and health status. Treatment with cilomilast reduced exacerbations, including acute worsening of COPD (level 1), acute worsening requiring additional treatment as an outpatient (level 2), and acute worsening requiring hospitalization (level 3). Treatment with cilomilast significantly decreased the risk of all levels by 39% and levels 2 and 3 by 45% as compared to placebo. Regarding lung function, treated patients showed a significant average improvement in FEV_1 of 40 ml as compared to placebo; an 80-ml difference was observed between treated and placebo groups at the end of treatment. Treated patients also exhibited significant improvements as compared to placebo in FVC (mean difference = 110 ml), clinic trough FEV_6 (mean difference = 90 ml) and clinic trough FEF_{25-75} (mean forced expiratory flow at 25-75% forced vital capacity; mean difference = 40 ml/s). Finally, a significant reduction of 4.1 points in St. George's Respiratory Questionnaire (SGRQ) scores which was maintained throughout the 6-month dosing period was observed in treated patients. Significant improvements in symptom (–5.1 points), impact (–3.7 points) and activity (–4.1 points) SGRQ subscales were observed with treatment. Cilomilast-treated patients also displayed significant improvements in SF-36 physical function (difference of 3.6 points over placebo) and general health perception scores at week 24 (27-31).

Patients (n=21) with COPD were enrolled in a placebo-controlled, double-blind study of treatment with cilomilast 15 mg as a single dose or cilomilast plus salbutamol 400 μg and/or ipratropium 80 μg. Single-dose cilomilast did not produce acute bronchodilatation, suggesting that improvements in lung function upon long-term treatment with the drug are due to another mechanism (32).

The results of 3 multicenter, double-blind, placebo-controlled studies showed that cilomilast administered at a dose of 15 mg b.i.d. for 24 weeks significantly decreased the rate of exacerbations in patients with COPD as compared to placebo. In a cost-effectiveness analysis, treatment with cilomilast was associated with a lower utilization of available healthcare resources (*e.g.*, emergency room visits and hospitalization), lower exacerbation costs per patient and lower direct costs per exacerbation (33, 34).

Patients with COPD (n=145) were randomized to cilomilast 15 mg b.i.d. or placebo for 12 weeks in a multicenter, double-blind trial evaluating trapped pulmonary gas volume and hyperinflation. Compared with placebo, cilomilast reduced prealbuterol trapped gas volume, pre- and postalbuterol residual volume and prealbuterol thoracic gas volume at functional residual capacity, and improved prealbuterol PEF and postalbuterol FEV_1 (35).

The reductions in inflammatory markers in COPD following treatment with cilomilast (15 mg b.i.d.) were evaluated in a randomized, placebo-controlled, 10-week study in 59 patients. Cilomilast reduced CD8+ and CD68+ cells and Poisson regression indicated reduced levels of CD4+ cells and neutrophils as well. Gene expression of IL-8 and TNF-α was not affected (36).

A randomized, placebo-controlled phase III clinical trial determined the effects of cilomilast at a dose of 15 mg p.o. b.i.d. for 6 months on the FEV_1 values of smoking and nonsmoking patients with COPD. The results revealed that cilomilast was more effective than placebo in improving FEV_1 in these patients, regardless of their previous smoking habits (37).

Cilomilast 5, 10 or 15 mg b.i.d. or placebo was assigned to patients with COPD in a 6-week, randomized study. The 15-mg dose demonstrated potential as maintenance therapy for the condition by significantly improving FEV_1 compared to placebo (38).

A multicenter, randomized, placebo-controlled phase III trial conducted in 2,058 patients with COPD (FEV_1 = 30-70%; 15% or less response to a β_2-agonist) confirmed the safety and efficacy of cilomilast (15 mg p.o. b.i.d. for 6 months). Fewer adverse events were observed in the cilomilast group as compared to placebo. Acute exacerbation of COPD (30.7% *vs*. 38.9% on placebo) was the most common adverse event and the gastrointestinal side effects seen in the cilomilast group were only mild to moderate and self-limited. No significant effects were observed on Holter and 12-lead ECGs, vital signs and laboratory parameters (39).

1. *GlaxoSmithKline updates R&D activities – merger makes way for robust pipeline*. DailyDrugNews.com (Daily Essentials) March 1, 2001.

2. Chipappara, G., Merendino, A.M., Chimenti, L., Riccobono, L., Mirabella, F., La Rocca, A.M., Weck, P.K., Bonsignore, G., Vignola, A.M. *Cilomast (Ariflo®) reduces TNF-α and GM-CSF release by airway cells isolated from COPD subjects*. Am J Respir Crit Care Med 2001, 163(5, Suppl.): A278.

3. Owen, C.A., Barnette, M.S., Campbell, E.J., Weck, P.K. *Cilomilast (Ariflo®) inhibits neutrophil pro-inflammatory activities*. Am J Respir Crit Care Med 2001, 163(5, Suppl.): A348.

4. Drost, E.M., Ouziaux, L., Donaldson, K., MacNee, W. *Cilomilast, a second generation phosphodiesterase 4 inhibitor, in combination with PGE_2 attenuates fMLP, IL-8 and cigarette smoke-induced effects on the mechanical and functional properties of neutrophils*. Eur Respir J 2001, 18(Suppl. 33): Abst P1086.

5. Malus, E., Cherapanov, V., Arora, A., Sjolin, C., Downey, G.P. *Selective inhibition of neutrophil function by the phosphodiesterase 4 inhibitor SB 207499*. Am J Respir Crit Care Med 2001, 163(5, Suppl.): A993.

6. Downey, G.P., Malus, E., Cherapanov, V., Arora, A., Loeve, C. *The phosphodiesterase 4 inhibitor SB 207499 selectively inhibits neutrophil functions*. Eur Respir J 2001, 18(Suppl. 33): Abst P332.

7. Kato, G.J., Bugayenko, A. *Ariflo, an inhibitor of PDE4 phosphodiesterase, suppresses the growth of human acute lymphoblastic leukemia cells and augments glucocorticoid sensitivity*. Blood 2001, 98(11, Part 1): Abst 1281.

8. Kohyama, T., Liu, X., Wen, F.-Q., Zhu, Y.K., Wang, H., Kim, H.J., Takizawa, H., Cieslinski, L.B., Barnette, M.S., Rennard, S.I. *PDE4 inhibitors attenuate fibroblast chemotaxis and contraction of native collagen gels*. Am J Respir Cell Mol Biol 2002, 26(6): 694.

9. Kohyama, T., Liu, X.D., Zhu, Y.K., Wen, F.Q., Wang, H.J., Fang, Q.H., Kobayashi, T., Rennard, S.I. *Phosphodiesterase 4 inhibitor cilomilast inhibits fibroblast-mediated collagen gel degradation induced by tumor necrosis factor-alpha and neutrophil elastase*. Am J Respir Cell Mol Biol 2002, 27(4): 487.

10. Baumer, W., Ehinger, A.M., Gorr, G., Hoppmann, J., Telser, E., Kietszmann, M. *Effects of SB 207499 and RPR 73401 on inflammatory mediators in a model of allergic dermatitis*. Naunyn-Schmied Arch Pharmacol 2001, 363(4, Suppl.): Abst 327.

11. DeMarsh, P.L., Sucoloski, S.K., Tal-Singer, R., Wells, G., Dillon, S.B., Woodnutt, G. *Effect of cilomilast, an orally active, selective PDE4 inhibitor in a murine viral/bacterial co-infection model*. Am J Respir Crit Care Med 2001, 163(5, Suppl.): A381.

12. Jones, H., Paul, W., Page, C. *The selective phosphodiesterase 4 inhibitor, cilomilast, inhibits interleukin-8-induced pulmonary neutrophil accumulation in the rabbit*. Eur Respir J 2001, 18(Suppl. 33): Abst P336

13. Schade, I., Roth-Eichhorn, S., Kasper, M., Kuss, H., Plötze, K., Funk, R.H.W., Schüler, S. *Benefit of phosphodiesterase 4 inhibitors as supplemental therapy after lung transplantation concerning their antiproliferative effects: An experimental study using a heterotopic rodent model*. Transplantation 2002, 74(3): 326.

14. Spond, J., Chapman, R., Fine, J., Jones, H., Kreutner, W., Kung, T.T., Minnicozzi, M. *Comparison of PDE4 inhibitors, rolipram and SB 207499 Ariflo), in a rat model of pulmonary neutrophilia*. Pulm Pharmacol Ther 2001, 14(2): 157.

15. Baumer, W., Gorr, G., Hoppmann, J., Ehinger, A.M., Ehinger, B., Kietzmann, M. *Effects of the phosphodiesterase 4 inhibitors SB 207499 and AWD 12-281 on the inflammatory reaction in a model of allergic dermatitis*. Eur J Pharmacol 2002, 446(1-3): 195.

16. Jones, H., Paul, W., Page, C. *Effect of the phosphodiesterase (PDE) 4 inhibitor, Ariflo, on polymorphonuclear leukocyte (PMN) trapping in rabbit pulmonary circulation*. Am J Respir Crit Care Med 2001, 163(5, Suppl.): A993.

17. Zussman, B.D., Benincosa, L.J., Webber, D.M., Clark, D.J., Cowley, H., Kelly, J., Murdoch, R.D., Upward, J., Wyld, P., Port, A., Fuder, H. *An overview of the pharmacokinetics of cilomilast (Ariflo®), a new, orally active phosphodiesterase 4 inhibitor, in healthy young and elderly volunteers*. J Clin Pharmacol 2001, 41(9): 950.

18. Zussman, B., Kelly, J., Rost, K., Clark, D., Ritchie, S., Bullman, S., Muxlow, A. *The effect of renal impairment on the disposition of cilomilast, a novel and selective oral PDE4 inhibitor*. 98th Int Conf Am Thorac Soc (May 17-22, Atlanta) 2002, Abst C99.

19. Zussman, B.D., Davie, C.C., Kelly, J., Murdoch, R.D., Clark, D.J., Schofield, J.P., Walls, C., Birrell, C., Webber, D., Quinlan, J., Ritchie, S.Y., Carr, A. *Bioavailability of the oral selective phosphodiesterase 4 inhibitor cilomilast*. Pharmacotherapy 2001, 21(6): 653.

20. Kelly, J., Schofield, J.P., Murdoch, R.D., Webber, D., Zussman, B. *The safety of cilomilast (Ariflo®) co-administration with oral theophylline: Cardiovascular profile*. Am J Respir Crit Care Med 2001, 163(5, Suppl.): A79.

21. Kelly, J., Murdoch, R.D., Schofield, J.P., Webber, D., Zussman, B. *The pharmacokinetic and tolerability profile of cilomilast (Ariflo®), unaffected by co-administration of theophylline*. Am J Respir Crit Care Med 2001, 163(5, Suppl.): A278.

22. Kelly, J., Murdoch, R.D., Clark, D.J., Webber, D.M., Fuder, H. *Warfarin pharmacodynamics unaffected by cilomilast*. Ann Pharmacother 2001, 35(12): 1535.

23. Walls, C.M. et al. *Cilomilast (Ariflo), a selective PDE4 inhibitor does not affect gut transit times of healthy volunteers*. Gut 2001, 49(Suppl. 3): Abst 1528.

24. Houghton, L.A., Atkinson, W., Whorwell, P.J., Morris, J., Isaac, L.M., Cooper, S.M. *Effect of cilomilast (Ariflo®), a selective phosphodiesterase-4 (PDE-4) inhibitor on oesophageal motility in man*. Gut 2001, 49(Suppl. 3): Abst 1304.

25. Zussman, B.D., Kelly, J., Murdoch, R.D., Clark, D.J., Schubert, C., Collie, H. *Cilomilast: Pharmacokinetic and pharmacodynamic interactions with digoxin*. Clin Ther 2001, 23(6): 921.

26. Rennard, S.I., Edelson, J.D., Robinson, C.B. et al. *Cilomilast reduces the percentage of sputum neutrophils in patients with chronic obstructive pulmonary disease (COPD)*. Chest 2001, 120(4, Suppl.): 151S.

27. Kelsen, S.G., Rennard, S.I., Chodosh, S., Schryver, B., Vleisides, C., Zhu, J. *COPD exacerbation in a 6-month trial of cilomilast (Ariflo®) a potent, selective phosphodiesterase 4 inhibitor*. 98th Int Conf Am Thorac Soc (May 17-22, Atlanta) 2002, Abst 316.

28. Ramsdell, J., Edelson, J.D., Compton, C., Vleisides, C., Amit, O., Kelsen, S., Strek, M., Rennard, S.I., Chodosh, S. *Cilomilast, a potent, selective inhibitor of phosphodiesterase 4, improves small airway function in patients with chronic obstructive pulmonary disease: Results of a 6-month trial*. Eur Respir J 2001, 18(Suppl. 33): Abst P673.

29. Edelson, J.D., Compton, C., Nieman, R., Robinson, C.B., Amrit, O., Bagchi, I., Strek, M., Rennard, S.I., Kelsen, S. *Cilomilast (Ariflo®) a potent, selective phosphodiesterase 4 inhibitor, reduces exacerbations in COPD patients: Results of a 6-month trial*. Am J Respir Crit Care Med 2001, 163(5, Suppl.): A771.

30. Edelson, J.D., Compton, C., Nieman, R. et al. *Cilomilast (Ariflo®) improves health status in patients with COPD: Results of a 6-month trial*. Am J Respir Crit Care Med 2001, 163(5, Suppl.): A277.

31. Edelson, J.D., Compton, C., Nieman, R., Robinson, C.B., Schryver, B., Amit, O., Kelsen, S., Strek, M., Rennard, S.I. *Cilomilast (Ariflo®), a potent, selective inhibitor of phosphodiesterase 4, improves lung function in COPD patients: Results of a 6-month trial*. Am J Respir Crit Care Med 2001, 163(5, Suppl.): A277.

32. Grootendorst, D.C., Gauw, S.A., Kelly, J., Murdoch, R.D., Sterk, P.J., Rabe, K.F. *First-dose bronchodilating effect of phosphodiesterase-4 (PDE-4) inhibition by cilomilast (Ariflo) with or without co-administration of salbutamol and/or ipratropium in COPD patients*. Eur Respir J 2001, 18(Suppl. 33): Abst P334.

33. Borker, R.D., Stanford, R.H., Reisner, C., Fischer, T., Morris, A., Zhu, F., Barnhart, F. *Direct cost savings associated with the use of cilomilast in patients with chronic obstructive pulmonary disease*. Chest 2002, 122(4, Suppl.): Abst S128.

34. Reisner, C., Fischer, T., Morris, A., Zhu, J., Barnhart, F. *Cilomilast reduces exacerbations in COPD patients*. Chest 2002, 122(4, Suppl.): Abst S148.

35. Zamel, N., McClean, P., Zhu, J., Schryver, B., Madan, A., Robinson, C.B., Faiferman, I. *Effect of cilomilast (Ariflo®) on trapped gas volume and indices of hyperinflation in patients with chronic obstructive pulmonary disease*. 98th Int Conf Am Thorac Soc (May 17-22, Atlanta) 2002, Abst 309.

36. Gamble, E., Pavord, I.D., Vignola, A.M., Kroegel, C., Morell, F., Hansel, T.T., Compton, C., Troy, S., Edelson, J.D., Amit, O., Tat, T., Rabe, K.F., Barnes, N.C., Jeffery, P.K. *Cilomilast (Ariflo®), a novel treatment for COPD, reduces the key inflammatory cells in bronchial biopsies*. 98th Int Conf Am Thorac Soc (May 17-22, Atlanta) 2002, Abst 311.

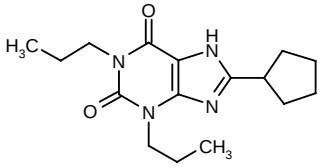
37. Zhu, J., Anderson, K.M., Vleisides, C., Watt, R., Schlenker-Herceg, R. *The positive effect of cilomilast on lung function in patients with chronic obstructive pulmonary disease (COPD) is independent of patients smoking status*. Eur Respir J 2002, 20(Suppl. 38): Abst P3876.

38. Compton, C.H. et al. *Cilomilast, a selective phosphodiesterase-4 inhibitor for treatment of patients with chronic obstructive pulmonary disease: A randomized, dose-ranging study*. Lancet 2001, 358(9278): 265.

39. Compton, C.H., Edelson, J.D., Cedar, E., Nieman, R., Robinson, C.B., Vleisides, C., Amit, O. *Cilomilast (Ariflo®) 15 mg bid safety in a 6-month clinical trial program*. Am J Respir Crit Care Med 2001, 163(5, Suppl.): A909.

Original monograph - Drugs Fut 1998, 23(6): 607.

CPX



SciClone's small-molecule protein repair therapy for the oral treatment of cystic fibrosis, CPX, is currently in phase II trials in the U.S.; the drug has been assigned orphan drug status by the FDA and the European authorities. In preclinical studies sponsored by the NIH, CPX improved impaired chloride ion transport and enabled the defective cystic fibrosis transmembrane regulator (CFTR) protein to reach the epithelial cell membrane (trafficking) (1).

In vitro studies were undertaken to pharmacologically correct a defect in the CFTR protein implicated in abnormal protein secretion in airways gland cells and mucus secretions in cystic fibrosis (CF). The drugs CPT and CPX corrected the defective β-adrenergic stimulation of mucin secretion in CFTR antibody-inhibited submandibular gland cells, suggesting a possible therapeutic role for these drugs in the treatment of CF (2).

Transient hypoxia impaired the synaptic plasticity and the performance of rats in the water maze task. Intralateral cerebroventricular injections of CPX prevented this impairment and may prevent functional interruption due to hypoxic episodes or chronic hypoxia related to respiratory dysfunction (3).

A multicenter, single-dose phase I trial investigated the safety, pharmacokinetics and efficacy of CPX (1, 3, 10, 30, 100, 300 and 1000 mg) in 37 patients with mild CF. Adverse events were minimal, variability in absorption was observed and single doses had no effect on nasal transepithelial potential difference or sweat chloride outcomes (4).

1. *SciClone's CPX for cystic fibrosis assigned orphan drug status in E.U.* DailyDrugNews.com (Daily Essentials) May 23, 2001.

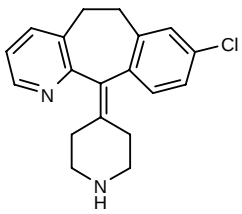
2. McPherson, M.A., Pereira, M.M.C., Russell, D., McNeilly, C.M., Morris, R.M., Stratford, F.L.L., Dormer, R.L. *The CFTR-mediated protein secretion defect: Pharmacological correction*. Pflug Arch Eur J Physiol 2001, 443(Suppl. 1): S121.

3. Sun, M.-K., Xu, H., Alkon, D.L. *Pharmacological protection of synaptic function, spatial learning, and memory from transient hypoxia in rats*. J Pharmacol Exp Ther 2002, 300(2): 408.

4. McCarty, N.A., Standaert, T.A., Teresi, M. et al. *A phase I randomized, multicenter trial of CPX in adult subjects with mild cystic fibrosis*. Pediatr Pulmonol 2002, 33(2): 90.

Original monograph - Drugs Fut 2000, 25(10): 1011.

Desloratadine



Desloratadine (Clarinex® in the U.S. and Aerius™, Neoclarityn™ or Azomyr in the E.U.) is a once-daily, nonsedating histamine H_1 receptor antagonist developed by Sepracor and licensed to Schering-Plough for marketing. The compound was initially approved for seasonal allergic rhinitis and chronic idiopathic urticaria, and indications were subsequently broadened to include perennial allergic rhinitis. The product is available in several formulations, including a rapidly disintegrating tablet and syrup (1-13).

In vitro experiments demonstrated that desloratadine interacts with P-glycoprotein significantly less than loratadine, indicating that it should have more predictable pharmacokinetics when used to treat allergic diseases (14).

Scientists have found that the transport of desloratadine, a P-glycoprotein substrate, is inhibited by ketoconazole, a known inhibitor of P-glycoprotein. Therefore the potential for drug-drug interactions between these agents exists (15).

The effect of desloratadine on peptidoleukotriene LTC_4 release from nasal polyp tissue from 8 aspirin-sensitive patients and 8 aspirin-tolerant patients was evaluated. Incubation of nasal polyp cells with desloratadine significantly inhibited LTC_4 generation induced by calcium ionophore in aspririn-sensitive polyp tissue but not in aspirin-tolerant tissue (16).

The effects of loratadine and desloratadine on cytokine release and adhesion receptor expression were investigated in the human mast cell line HMC-1. Desloratadine more potently inhibited IL-8 and TNF-α and more potently downregulated expression of CD11a (17).

A recent report summarized the preclinical efficacy of desloratadine as a novel histamine H_1 receptor antago-

nist. The agent was 25-50 times more potent than terfenadine, fexofenadine, cetirizine, loratadine, ebastine and mizolastine in binding to the human H_1 receptor expressed in CHO cells. The rank order for inhibiting histamine-induced calcium flux from CHO cells was desloratadine (pA_2 = 0.4 nM), mizolastine, terfenadine, cetirizine, ebastine, loratadine and fexofenadine. Desloratadine was 10-fold more potent than loratadine in suppressing histamine-induced increases in nasal microvascular permeability in a guinea pig nasal challenge model. The antiallergic properties of desloratadine were also discussed. The agent (0.1 μM) inhibited the production of IL-4 and IL-13 *in vitro* from ionomycin- or anti-IgE-stimulated human basophils; expression of IL-4 mRNA was also inhibited with treatment. Desloratadine (5 mg/kg) decreased acute bronchospasm and airways resistance in allergic cynomolgus monkeys. Antigen-induced cough was inhibited (ED_{50} = 0.3 mg/kg) in guinea pigs allergic to inhaled albumin. The safety of the agent was also evaluated, with studies showing that doses up to 300 mg/kg produced no behavioral, neurological or autonomic effects in mice. Studies in rats, guinea pigs and monkeys demonstrated that high doses of desloratadine did not affect heart rate, blood pressure or ECG; the agent (10 μM) had no effect on cardiac K^+ HERG channels. Results in guinea pigs showed that desloratadine does not interfere with subsequent [^{3}H]-pyrilamine binding to brain H_1 receptors, suggesting that the agent would not have sedative effects (18).

The pharmacokinetics of desloratadine were summarized. The agent can be administered once daily due to its long half-life of 21-24 h. No dose adjustments were required in patients with renal or hepatic failure, or when administered with food or grapefruit juice. The pharmacokinetics of the agent were not altered by race or sex. The C_{max} and AUC of desloratadine were slightly increased when given in combination with the cytochrome P-450 inhibitors ketoconazole and erythromycin, although no significant accumulation of the agent was observed. High doses (45 mg/day for 10 days) resulted in elevated plasma desloratadine levels but were not accompanied by significant adverse events; in particular, there was no effect on the corrected Q-T interval even when administered in combination with ketoconazole or erythromycin (19).

A randomized, placebo-controlled study in 90 healthy volunteers evaluated the pharmacokinetics and safety of coadministration of desloratadine (5 mg once daily) or fexofenadine (60 mg b.i.d.) with azithromycin (500-mg loading dose, then 250 mg once daily for 4 days). Results revealed only minimal changes in mean C_{max} and AUC values for the combination of desloratadine and azithromycin, whereas coadministration of fexofenadine and azithromycin resulted in substantial increases in these parameters. All drug combinations were well tolerated, with headache being the most frequent adverse event reported in 20 subjects (20, 21).

Pharmacokinetic studies of desloratadine administered with grapefruit juice, ketoconazole, erythromycin and food have shown that, unlike fexofenadine and loratadine, desloratadine is not subject to drug-drug and drug-food interactions. It has also been found that desloratadine is not an inhibitor of or substrate for the MDR-1 gene-mediated transport system (22).

Two open-label, single-dose trials examined desloratadine syrup 0.5 mg/ml in healthy children (n=18 in each study). Pharmacokinetic analysis revealed that doses of 1.25 mg given to children between 2 and 5 years of age and 2.5 mg given to children between 6 and 11 years of age resulted in a similar amount of drug exposure to that in adults taking the recommended 5-mg dose (23).

A randomized, placebo-controlled trial in 54 healthy volunteers examined coadministration of desloratadine and fluoxetine. Patients were assigned to 3 treatment groups: 1) desloratadine 5 mg p.o. on day 1, followed by a 4-day washout period, then fluoxetine 20 mg/day p.o. for 30 days with desloratadine 5 mg/day p.o., also given on the last 7 days; 2) desloratadine 5 mg p.o. on day 1, followed by a 4-day washout period, then placebo for 30 days with desloratadine 5 mg/day p.o., also given on the last 7 days; 3) placebo on day 1, followed by a 4-day washout period, then fluoxetine 20 mg/day p.o. for 30 days with placebo, also given on the last 7 days. No potential for drug interactions between the agents was found (24).

Two multicenter, double-blind, randomized, parallel-group, placebo-controlled trials have examined the efficacy and tolerability of once-daily desloratadine (5 mg) during the spring and fall allergy seasons in patients with SAR at least 12 years of age. The spring study enrolled 172 and 174 patients, respectively, in the desloratadine and placebo groups, and the fall study 164 patients in each group, who were treated for 14 days. The primary efficacy variable in both studies was the change from baseline in the average reflective am/pm total symptom score (TSS), a sum of individual nasal and non-nasal symptom scores. This treatment regimen of desloratadine was associated with significant improvement in TSS compared to placebo in both studies as early as the second day and sustained over the 2-week treatment period; the average reduction on desloratadine in the spring study was 28% *versus* 12.5% on placebo, and the average reduction in the fall was 30% *versus* 22%. Adverse events were mild to moderate and similar in both groups, the most frequent being headache. Neither group showed clinically significant sedation or ECG changes from baseline. These data support the use of this once-daily regimen of desloratadine for the treatment of SAR in adolescents and adults (25).

Patients (n=278) with seasonal allergic rhinitis (SAR) and asthma were administered desloratadine 5 mg or placebo in a multicenter, double-blind study. Desloratadine was well tolerated and significantly relieved asthma and SAR symptoms. Patients taking desloratadine also reduced their use of inhaled β_2-agonists compared with placebo. Pulmonary function was maintained

Table III: Clinical studies of desloratadine (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Asthma, seasonal allergic rhinitis	Randomized, double-blind, multicenter	Desloratadine, 5 mg po od Placebo	278	Desloratadine was well tolerated and provided significant relief of asthma in patients with seasonal allergic rhinitis and asthma	26
Perennial allergic rhinitis	Randomized, double-blind, multicenter	Desloratadine, 5 mg po od x 4 wk (n=337) Placebo (n=339)	676	Desloratadine was effective for the relief of symptoms of perennial allergic rhinitis	30
Allergic rhinitis	Randomized, double-blind, multicenter	Desloratadine/Pseudoephedrine, 5 mg/240 mg po od [combination tablet] x 15 d (n=336) Desloratadine, 5 mg po od x 15 d (n=340) Pseudoephedrine, 240 mg po od x 15 d (n=342)	1018	Desloratadine/pseudoephedrine fixed dose combination tablets provided significantly greater relief from moderate severe nasal congestion in seasonal allergic rhinitis compared with component monotherapy	32
Seasonal allergic rhinitis	Randomized	Desloratadine OR, 5 mg sd (n=81) Diphenhydramine OR, 50 mg sd (n=84) Placebo (n=83)	248	Treatment with desloratadine improved seasonal allergic rhinitis symptoms similar to diphenhydramine without adversely affecting cognitive performance	35
Allergic rhinitis	Crossover	Desloratadine, 5 mg od x 5 d Nasal challenges with diluent and allergen (100, 1000, 10000 SQ-U)	24	Acute allergen challenges produced dose-dependent nasal mucosal output of fucose and desloratadine had symptom-reducing effects and prevented acute allergen-induced mucus secretion in patients with allergic rhinitis	37
Idiopathic urticaria	Randomized, double-blind, multicenter	Desloratadine, 5 mg po od x 6 wk (n=95) Placebo (n=95)	190	Desloratadine was well tolerated and effective with a rapid onset of action and reduced interference with sleep and daily activities providing a significant improvement in chronic idiopathic urticaria over a 6-week period	38-41, 43
Idiopathic urticaria	Pooled/ meta-analysis	Desloratadine, 5-20 mg po od Placebo	2346	Desloratadine provided significant improvement in chronic idiopathic urticaria and other allergic inflammatory disorders with a placebo-like safety profile. No effects were seen on ECG, including QTc interval, and there was no cognitive or psychomotor impairment when administered with ethanol	44

(26, 27). These results and results from some of the following studies are summarized in Table III.

The efficacy of once-daily desloratadine as a decongestant was demonstrated in SAR patients. Treatment not only improved symptoms, but also improved patient ratings of nasal congestion (28).

In a randomized, double-blind, placebo-controlled, crossover trial in 47 patients, the effects of desloratadine (5 mg) on nasal airflow and the symptoms of SAR were assessed in response to grass pollen. The drug was well tolerated, nasal obstruction was less pronounced and symptom severity scores were significantly reduced compared with placebo (29).

Treatment of perennial allergic rhinitis (PAR) with desloratadine was investigated in a multicenter, randomized, double-blind, placebo-controlled trial in which 676 patients received either placebo or desloratadine 5 mg for 4 weeks. Adverse events were comparable to placebo, and desloratadine provided relief and improved rhinitis symptoms from the first dose throughout the course of treatment (30).

In a randomized, double-blind, placebo-controlled study, 45 SAR patients received placebo or desloratadine 20 mg daily for 4 weeks during the ragweed pollen season. Examination of inflammatory markers indicated that desloratadine influences allergic inflammation through mechanisms other than blockade of histamine H1 receptors (31).

A multicenter, randomized, double-blind study investigated treatment of 1,018 patients with SAR with desloratadine 5 mg, pseudoephedrine 240 mg or a combination of desloratadine 5 mg/pseudoephedrine 240 mg once daily for 15 days. The combination tablet was significantly better in reducing nasal congestion than either agent alone (32).

Once-daily administration of desloratadine at doses ranging from 1.5 mg to 20 mg for 2 weeks was well tolerated and showed similar efficacy in improving the

average morning and evening total symptoms scores of patients with SAR (33).

A double-blind, crossover study established that the recommended doses of desloratadine (5 mg once daily) and fexofenadine (180 mg once daily) administered for 2 weeks were equally effective in improving nasal peak flow and nasal symptoms in 49 patients with SAR (34).

A randomized, placebo-controlled study assessed the CNS effects of single doses of desloratadine 5 mg (n=81), diphenhydramine 50 mg (n=84) or placebo (n=83) in patients with SAR. Desloratadine significantly improved SAR symptoms without affecting cognitive performance on neuropsychological tests. Diphenhydramine also improved SAR symptoms but was associated with significant impairment of cognitive performance and sedation (35).

A placebo-controlled, crossover study was conducted with desloratadine 5 mg given for 5 days to 24 allergic rhinitis patients examined out of season. Nasal challenges were given on day 5. Desloratadine reduced nasal symptoms and the acute mucinous secretion and plasma exudation found in nasal lavage fluids (36, 37).

In a multicenter, randomized, double-blind, placebo-controlled trial in 190 patients with moderate to severe chronic idiopathic urticaria, 6 weeks of treatment with desloratadine 5 mg once daily demonstrated superiority to placebo in controlling pruritus and total symptoms. Significant improvements in sleep and reductions in interference with daily activities in desloratadine-treated patients were also observed. Benefit was seen within 24 h and maintained throughout the study; adverse events were similar to those for placebo (38-43).

The safety of desloratadine at up to 4 times the recommended daily dose of 5 mg was determined according to pooled data from several placebo-controlled phase II/III trials conducted in a total of 2,346 evaluable patients. The incidence of adverse events was similar in both desloratadine and placebo groups. The most common adverse event was headache (4% and 5% in desloratadine and placebo groups, respectively) and no cardiovascular events or effects on CNS, hepatic or renal function were observed with treatment. Desloratadine alone or in combination with ketoconazole or erythromycin had no effect on ECGs even when administered at 9 times the recommended dose. Results indicate that the agent is not a substrate for P-glycoprotein. Results from these studies also showed the efficacy of desloratadine as a treatment for improving signs and symptoms of chronic idiopathic urticaria, allergic rhinitis and other allergic inflammatory disorders (44).

The use of antiallergic drugs for the treatment of mental and vascular disorders, particularly depression, alcoholism, weight control, sexual dysfunction, panic and obsessive-compulsive disorder, migraine, stroke, orthostatic hypotension, gastrointestinal stasis, nausea, dizziness and jet lag has been claimed. Preferred compounds are nonsedating or low-sedating antihistamines such as loratadine or its metabolite desloratadine. It is believed that they exert their effects by interacting with the 5-HT_7 receptor, as demonstrated in a binding assay where desloratadine gave a K_i value of 204 nM for displacement of [^{3}H]-LSD (45).

1. *NDA submitted to FDA for rapidly disintegrating desloratadine tablets*. DailyDrugNews.com (Daily Essentials) Dec 29, 2000.

2. *Clarinex approved by FDA for perennial allergic rhinitis and chronic idiopathic urticaria*. DailyDrugNews.com (Daily Essentials) Feb 14, 2002.

3. *Clarinex tablets now available in U.S. pharmacies for SAR*. DailyDrugNews.com (Daily Essentials) Jan 25, 2002.

4. *Clarinex cleared by FDA for SAR symptom relief, will be launched next month*. DailyDrugNews.com (Daily Essentials) Dec 27, 2001.

5. *Schering-Plough seeks FDA approval of broader Clarinex indication; first launches in E.U.* DailyDrugNews.com (Daily Essentials) April 18, 2001.

6. *Year 2000 progress highlighted by Sepracor*. DailyDrugNews.com (Daily Essentials) Feb 2, 2001.

7. *New indications approved for desloratadine in E.U.* DailyDrugNews.com (Daily Essentials) June 7, 2002.

8. *Schering-Plough's Aerius/NeoClarityn approved in E.U. for treatment of seasonal allergic rhinitis*. DailyDrugNews.com (Daily Essentials) Jan 18, 2001.

9. *Desloratadine approved in the E.U. for symptoms of chronic idiopathic urticaria*. DailyDrugNews.com (Daily Essentials) Aug 13, 2001.

10. *EMEA recommends approval for desloratadine syrup and rapidly disintegrating tablets*. DailyDrugNews.com (Daily Essentials) Jan 10, 2002.

11. *CPMP recommends expansion of desloratadine indication to indoor and outdoor allergies*. DailyDrugNews.com (Daily Essentials) March 8, 2002.

12. *CPMP issues approvable letter for use of desloratadine in CIU*. DailyDrugNews.com (Daily Essentials) May 11, 2001.

13. *Schering-Plough submits two new applications for desloratadine in the E.U.* DailyDrugNews.com (Daily Essentials) Jan 22, 2001.

14. Wang, E.J., Casciano, C.N., Clement, R.P., Johnson, W.W. *Evaluation of the interaction of loratadine and desloratadine with P-glycoprotein*. Drug Metab Dispos 2001, 29(8): 1080.

15. Hwang, K., Correll, M., Offord, S.J. *Evaluation of desloratadine for absorption drug-drug interactions with ketoconazole*. J Allergy Clin Immunol 2001, 107(2, Part 2): Abst 504.

16. Lewandowska, A., Kowalski, M.L., Wozniak, J., Kornatowski, T., Jankowski, T., Jankowski, A., Makowska, J., Dubuske, L.M. *Inhibitory activity of desloratadine on LTC_4 release by nasal polyp tissue from aspirin-sensitive patients*. J Allergy Clin Immunol 2002, 109(1, Part 2): Abst 253.

17. Babina, M., Lippert, U., Henz, B.M. *Comparative effects of loratadine and desloratadine on cytokine release and adhesion molecule expression by human leukemic mast cells (HMC-1)*. J Allergy Clin Immunol 2002, 109(1, Part 2): Abst 761.

18. Kreutner, W., Hey, J.A., Anthes, J.C., Barnett, A. *Preclinical efficacy and antiallergic profile of desloratadine, A potent next-generation histamine H_1-receptor antagonist with additional antiallergic properties*. 59th Annu Meet Am Acad Dermatol (March 2-7, Washington DC) 2001, Abst P452.

19. Henz, B.M. *The pharmacologic profile of desloratadine: A review*. Allergy 2001, 56(Suppl. 65): 7.

20. Gupta, S., Banfield, C., Kantesaria, B., Marino, M., Clement, R., Affrime, M., Batra, V. *Pharmacokinetic and safety profile of desloratadine and fexofenadine when coadministered with azithromycin: A randomized, placebo-controlled, parallel-group study*. Clin Ther 2001, 23(3): 451.

21. Gupta, S., Banfield, C., Lim, J., Marino, M., Clement, R.P., Affrime, M.B. *Unlike fexofenadine, the pharmacokinetics of desloratadine are minimally altered by coadministration with azithromycin*. J Allergy Clin Immunol 2001, 107(2, Part 2): Abst 524.

22. Rachelefsky, G.S., Salmun, L.M., Banfield, C. *Predictability of desloratadine: Lack of clinical interaction with food and concomitant medications*. J Allergy Clin Immunol 2001, 107(2, Part 2): Abst 534.

23. Banfield, C., Gupta, S., Affrime, M., Batra, V. *Pharmacokinetic equivalence of pediatric dosages of desloratadine syrup in children and standard 5-mg desloratadine tablets in adults*. J Allergy Clin Immunol 2002, 109(1, Part 2): Abst 278.

24. Banfield, C., Gupta, S., Kantesaria, B., Marino, M., Batra, V., Cayen, M.N., Affrime, M.B. *No drug interaction between fluoxetine and desloratadine, a new nonsedating once-daily antihistamine*. J Allergy Clin Immunol 2001, 107(2, Part 2): Abst 529.

25. Meltzer, E.O., Prenner, B.M., Nayak, A. *Efficacy and tolerability of once-daily 5 mg desloratadine, an H_1-receptor antagonist, in patients with seasonal allergic rhinitis - Assessment during the spring and fall allergy seasons*. Clin Drug Invest 2001, 21(1): 25.

26. Corren, J. et al. *Desloratadine reduces the use of inhaled β_2-agonists and improves asthma symptoms in patients with seasonal allergic rhinitis and asthma*. J Allergy Clin Immunol 2001, 107(2, Part 2): Abst 535.

27. Baena Cagnani, C.E. *Desloratadine activity in concurrent seasonal allergic rhinitis and asthma*. Allergy 2001, 56(Suppl. 65): 21.

28. Bachert, C. *Decongestant efficacy of desloratadine in patients with seasonal allergic rhinitis*. Allergy 2001, 56(Suppl. 65): 14.

29. Horak, F., Stubner, U.P., Zieglmayer, R., Harris, A.G. *Effect of desloratadine versus placebo on nasal airflow and subjective measures of nasal obstruction in subjects with grass pollen-induced allergic rhinitis in an allergen-exposure unit*. J Allergy Clin Immunol 2002, 109(6): 956.

30. Dubuske, L.M. et al. *Once-daily desloratadine reduces the symptoms of perennial allergic rhinitis for at least 4 weeks*. J Allergy Clin Immunol 2001, 107(2, Part 2): Abst 525.

31. Cyr, M.M., Baatjes, A.J., Hayes, L.M., Crawford, I., Denburg, J.A. *The effect of desloratadine on eosinophil/basophil progenitors and other inflammatory markers in seasonal allergic rhinitis: A placebo-controlled randomized study*. J Allergy Clin Immunol 2002, 109(1, Part 2): Abst 329.

32. Schenkel, E., Corren, J., Murray, J.J. *Fixed-dose desloratadine and pseudoephedrine relieves moderate/severe nasal congestion in patients with seasonal allergic rhinitis*. J Allergy Clin Immunol 2002, 109(1, Part 2): Abst 279.

33. Salmun, L.M., Lorber, R. *24-Hour efficacy of once-daily desloratadine therapy in patients with seasonal allergic rhinitis [ISRCTN32042139]*. BMC Fam Pract 2002, 3(1): 14.

34. Wilson, A.M., Haggart, K., Sims, E.J., Lipworth, B.J. *Effects of fexofenadine and desloratadine on subjective and objective measures of nasal congestion in seasonal allergic rhinitis*. Clin Exp Allergy 2002, 32(10): 1504.

35. Wilken, J., Kane, R. *Vigilance and cognitive functioning during treatment of seasonal allergic rhinitis (SAR): A comparison of diphenhydramine (DPH) and desloratadine (DL)*. J Allergy Clin Immunol 2002, 109(1, Part 2): Abst 272.

36. Greiff, L., Persson, C.G.A., Andersson, M. *Desloratadine reduces allergen challenge-induced mucinous secretion and plasma exudation in allergic rhinitis*. Ann Allergy Asthma Immunol 2002, 89(4): 413.

37. Greiff, L., Persson, C.G.A., Andersson, M. *Allergen challenge-induced mucinous secretion in allergic rhinitis and its attenuation by desloratadine*. J Allergy Clin Immunol 2002, 109(1, Part 2): Abst 252.

38. Hein, R., Gauger, A., Breneman, D., Guerrero, R., Rikken, G., Ring, J. *Rapid onset and durability of response of desloratadine in the treatment of chronic idiopathic urticaria*. 59th Annu Meet Am Acad Dermatol (March 2-7, Washington DC) 2001, Abst P448.

39. Monroe, E.W., Raimer, S., Bronsky, E., Rikken, G. *Efficacy and safety of desloratadine in the treatment of chronic idiopathic urticaria*. 59th Annu Meet Am Acad Dermatol (March 2-7, Washington DC) 2001, Abst P450.

40. Ring, J., Hein, R., Gauger, A. et al. *Once-daily desloratadine improves the signs and symptoms of chronic idiopathic urticaria: A randomized, double-blind, placebo-controlled study*. Int J Dermatol 2001, 40(1): 72.

41. Miller, B.H., Patel, P., Bernstein, D., Rikken, G. *Therapy with desloratadine for chronic idiopathic urticaria reduces interferences with sleep and daily activities*. 59th Annu Meet Am Acad Dermatol (March 2-7, Washington DC) 2001, Abst P449.

42. Ring, J., Hein, R., Gauger, A. *Desloratadine in the treatment of chronic idiopathic urticaria*. Allergy 2001, 56(Suppl. 65): 28.

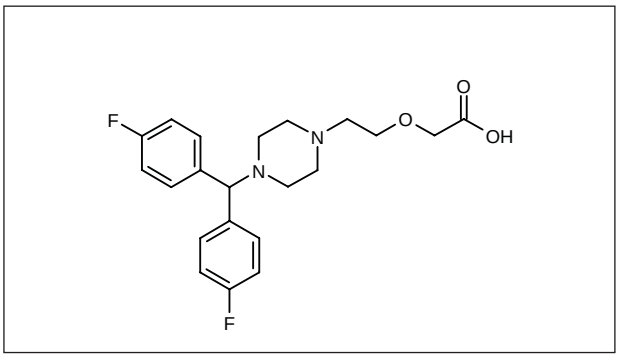
43. Gauger, A., Ring, J., Hein, R. *Desloratadine improves symptoms of chronic idiopathic urticaria and reduces interference with sleep and daily activities*. Allergy 2001, 56(Suppl. 68): Abst 454.

44. Banfield, C., Affrime, M., Lorber, R. *Desloratadine, a novel H_1-receptor antagonist, has a placebo-like safety profile*. 59th Annu Meet Am Acad Dermatol (March 2-7, Washington DC) 2001, Abst P451.

45. Binder, G. et al. (Schering Corp.). *Methods for the treatment of mental disorders*. US 6140337, WO 0113905.

Original monograph - Drugs Fut 2000, 25(4): 339.

Efletirizine

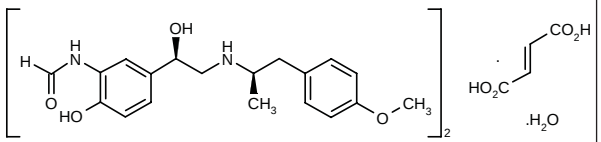


Efletirizine (UCB-28754) is a histamine H_1 receptor antagonist developed by UCB and shown to have an excellent efficacy and safety profile. It is currently in phase III clinical evaluation for allergic rhinitis (1).

1. *UCB presents R&D overview.* DailyDrugNews.com (Daily Essentials) June 21, 2002.

Original monograph - Drugs Fut 1997, 22(6): 626.

Formoterol Fumarate



A fast- and long-acting bronchodilator, the β_2-adrenoceptor agonist formoterol fumarate, developed originally at Yamanouchi, is currently marketed in many countries worldwide for the treatment of asthma by AstraZeneca under the names Oxis® Turbuhaler® and Oxeze® Turbuhaler® (or Turbohaler®), and by Novartis (overseas)/Schering-Plough (U.S.) under the name Foradil® Aerolizer®. The U.S. FDA cleared formoterol fumarate inhalation powder (Foradil® Aerolizer®) in 2001 for long-term administration in the maintenance treatment of bronchoconstriction in patients with COPD, including chronic bronchitis and emphysema. AstraZeneca recently announced that the mutual recognition procedure has been successfully completed for Oxis® Turbuhaler® in the E.U., with Sweden acting as the reference member state, for the maintenance therapy of COPD.

Numerous clinical studies have been reported over the last 2 years describing the use of formoterol in patients with asthma (1-28). The results of some of these studies and the 2 that follow are summarized in Table IV.

Formoterol as maintenance and rescue therapy was assessed in a randomized, double-blind, 6-month trial in 657 patients with COPD. Patients received formoterol 9 μg b.i.d. plus terbutaline 0.5 mg rescue, formoterol 9 μg b.i.d. and formoterol 4.5 μg rescue, or placebo b.i.d. plus terbutaline 0.5 mg rescue. The FEV_1 was significantly improved in all patients receiving formoterol maintenance therapy, regardless of baseline FEV_1 or reversibility. Significant additional benefits were seen with formoterol rescue therapy in those patients with the lowest reversibility and the highest level of airflow obstruction (29, 30).

Rescue medication for patients with stable COPD with formoterol was assessed in a randomized, double-blind, placebo-controlled study. Formoterol 12 and 24 μg (via Turbuhaler®) was compared with salbutamol 400 and 800 μg (via pMDI) in 16 patients. The active treatments and placebo were inhaled as single doses on 5 separate days. No significant difference was seen in the onset of bronchodilatation between the treatment groups (31).

Patients with stable COPD (n=40) were randomized to treatment with formoterol 24 μg, salbutamol 400 μg or placebo in a double-blind, crossover study. Similar and near-maximal bronchodilatation was seen with both formoterol and salbutamol at 5 min (32).

Single doses of formoterol (9 and 18 μg) and salbutamol (100 and 200 μg) were administered to 20 patients with reversible chronic airways obstruction (intrinsic asthma or COPD) in a randomized, double-blind, crossover study. Formoterol (via Turbuhaler®) demonstrated an onset of action equivalent to salmeterol via pMDI. No adverse events were observed during the study (33).

A multicenter, randomized, double-blind, placebo-controlled, crossover trial compared bronchodilatation with single-dose formoterol (dry powder 12 and 24 μg) and single-dose salmeterol (50 and 100 μg) in 47 patients with COPD. Formoterol 12 μg was significantly superior to salmeterol 50 μg with regard to onset of action. Bronchodilatation was significantly greater with the formoterol doses than with placebo (34).

A randomized, double-blind, placebo-controlled, crossover trial was conducted to compare the effects of formoterol (4, 5, 9 or 18 μg b.i.d. via Turbohaler®), ipratropium bromide (80 μg t.i.d. via pMDI with spacer) and placebo on exercise capacity in 34 patients with COPD. Treatments were given for 1 week. Compared with placebo, both active treatments significantly improved exercise capacity and lung function, as measured by an incremental cycle ergometer test, and had similar adverse event profiles. Also, a negative dose-response relationship with formoterol was unexpectedly discovered (35).

Formoterol (4.5, 9 or 18 μg b.i.d.) was administered to 692 patients with COPD for 12 weeks in a multicenter, randomized, double-blind, placebo-controlled trial. Formoterol at doses of 4.5 μg and higher significantly improved FEV_1 compared with placebo and the higher doses reduced symptoms and increased the number of symptom-free days (36).

1. Palmqvist, M., Arvidsson, P., Beckman, O., Peterson, S., Lotvall, J. *Onset of bronchodilation of budesonide/formoterol vs. salmeterol/fluticasone in single inhalers*. Pulm Pharmacol Ther 2001, 14(1): 29.

2. Vilsvik, J., Ankerst, J., Palmqvist, M., Persson, G., Schaanning, J., Schwabe, G., Johansson, A. *Protection against cold air and exercise-induced bronchoconstriction while on regular treatment with Oxis®*. Respir Med 2001, 95(6): 484.

3. Nielsen, K.G., Bisgaard, H. *Bronchodilation and bronchoprotection in asthmatic preschool children from formoterol administered by mechanically actuated dry-powder inhaler and spacer*. Am J Respir Crit Care Med 2001, 164(2): 256.

4. Zetterstrom, O., Buhl, R., Mellem, H., Perpiñá, M., Hedman, J., O'Neill, S., Ekström, T. *Improved asthma control with budesonide/formoterol in a single inhaler, compared with budesonide alone*. Eur Respir J 2001, 18(2): 262.

5. Rosenhall, L., Heinig, J.H., Lindqvist, A., Leegaard, J., Stahl, E., Bergqvist, P.B.F. *Budesonide/formoterol (Symbicort®) is well tolerated and effective in patients with moderate persistent asthma*. Int J Clin Pract 2002, 56(6): 427.

6. Ind, P., Haughney, J., Price, D., Rosen, J.-P., Kennelly, J. *4-Month adjustable or fixed maintenance treatment with budesonide/formoterol in a single inhaler reduces symptom severity*. Eur Respir J 2002, 20(Suppl. 38): Abst P378.

Table IV: Clinical studies of formoterol (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Asthma, COPD	Randomized, open	Budesonide/formoterol, bid inhal x 16 wk [adjustable doses] (n=782) Budesonide/formoterol, bid inhal x 16 wk [fixed doses] (n=771)	1553	Important and similar quality of life improvements were seen in both treatment groups within 4 weeks and lasted throughout the study. Patients on the adjustable dosing schedule had a lower mean number of daily inhalations	6, 7
Asthma, COPD	Randomized, open, multicenter	Formoterol, 4.5 µg x 6 mo (n=9064) Salbutamol, 200 µg x 6 mo (n=9060)	18124	In patients graded as mild, moderate or severe, formoterol significantly reduced the incidence of exacerbations compared with salbutamol. Formoterol tended to reduce exacerbations across age groups as well, with significant differences seen in adults and elderly patients	9, 10, 12-15
Asthma, COPD	Randomized, open, multicenter	Formoterol, 4.5 µg x 6 mo (n=1099) Salbutamol, 200 µg x 6 mo (n=1141)	2240	The addition of formoterol reliever to formoterol maintenance therapy was safe and reduced the risk of exacerbations compared with salbutamol reliever therapy in patients with asthma	11
Asthma, COPD	Randomized, open, multicenter	Formoterol, 12 µg bid x 1 mo Previous treatment	6155	Formoterol was well tolerated and improved PEF, days without symptoms and rescue salbutamol use	16
Asthma, COPD	Randomized, open	Formoterol, 12 µg (n=18) Formoterol, 24 µg (n=16) Fenoterol, 100 µg (n=18) Fenoterol, 200 µg (n=20)	71	A similar onset of action was observed with both agents, although the bronchodilating effect of formoterol was higher in the first 5 min	17
Asthma, COPD	Randomized, double-blind	Formoterol, 18 µg inhal at 0 min → 18 µg inhal at 30 min → 18 µg inhal at 60 min Salbutamol, 800 µg inhal [spacer] at 0 min → 800 µg inhal [spacer] at 30 min → 800 µg inhal [spacer] at 60 min	88	At 4 h formoterol and salbutamol were equally safe and effective as rescue therapy in emergency room patients with acute severe asthma	18, 20
Asthma, COPD	Randomized, double-blind	Formoterol, 18 µg inhal at 0 min → 18 µg inhal at 30 min Salbutamol, 800 µg inhal [spacer] at 0 min → 800 µg inhal [spacer] at 30 min	78	Increases in FEV_1 at 45 min, maximum FEV_1 increases and the average FEV_1 over 4 h were similar in both treatment groups in patients with asthma	19
Asthma	Randomized, double-blind, multicenter	Budesonide, 80 µg bid inhal x 12 wk + Formoterol, 4.5 µg bid inhal x 12 wk (n=148) Budesonide, 100 µg bid inhal x 12 wk (n=138)	286	The combination of budesonide plus formoterol was well tolerated and, compared to budesonide alone, induced a quicker improvement in PEF and FEV_1 in children with moderate persistent asthma	23
Asthma, COPD	Open	Formoterol, 12 µg + Budesonide, 200 µg Formoterol, 12 µg + Budesonide, 400 µg Salmeterol, 50 µg bid + Fluticasone, 100 µg bid Salmeterol, 50 µg bid + Fluticasone propionate, 250 µg bid	211	Among asthma patients receiving flexible budesonide/formoterol treatment, a signficantly lower median incidence of mild exacerbations was seen, although severe exacerbations were similar between groups	24
Asthma	Randomized, multicenter	Fluticasone, 250 µg bid inhal x 12 wk + Salmeterol, 50 µg bid inhal x 12 wk (n=212) Budesonide, 800 µg bid inhal x 12 wk + Formoterol, 12 µg bid inhal x 12 wk (n=216)	428	The combination of fluticasone propionate plus salmeterol was more effective than the combination of budesonide plus formoterol in reducing the symptoms of patients with asthma	25
Healthy volunteers	Randomized, double-blind, crossover	Formoterol, 12 µg sd Formoterol, 24 µg sd Albuterol, 180 µg sd Placebo	23	Formoterol was significantly more effective than albuterol in preventing exercise-induced bronchoconstriction in children	26

Continuation

Table IV (Cont.): Clinical studies of formoterol (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
COPD	Randomized, double-blind	Formoterol, 9 µg bid + Terbutaline, 0.5 mg PRN (n=215) Formoterol, 9 µg bid + Formoterol, 4.5 µg PRN (n=225) Placebo + Terbutaline, 0.5 mg PRN (n=217)	657	FEV_1 was significantly improved in all patients receiving formoterol maintenance therapy, regardless of baseline FEV_1 or reversibility. Significant additional benefits were seen with formoterol reliever therapy in those with the lowest reversibility and the highest level of airflow obstruction in COPD patients	29, 30

7. Ind, P., Haughney, J., Rosen, J.-P., Kennelly, J. *Managed adjustable dosing of budesonide/formoterol combination is similarly well tolerated to fixed dosing*. Eur Respir J 2002, 20(Suppl. 38): Abst P380.

8. Haughney, J., Price, D., Rosen, J.-P., Kennelly, J. *Adjustable maintenance treatment with budesonide/formoterol combination rapidly improves and maintains quality of life in asthma patients*. Eur Respir J 2002, 20(Suppl. 38): Abst P379.

9. Pauwels, R.A., Campbell, M., Villasante, C., Huang, S., Lindh, A., Petermann, W., Schwabe, G., Tornling, G., Bengtsson, T., Sears, M.R. *Formoterol Turbuhaler compared with salbutamol as reliever medication in asthma: Outcomes from the RELIEF study in patients across different severities and age groups*. Eur Respir J 2002, 20(Suppl. 38): Abst P395.

10. Lindgren, B., Sears, M.R., Campbell, M., Villasante, C., Huang, S., Lindh, A., Petermann, W., Svensson, K., Berggren, F., Pauwels, R.A. *Total costs according to reliever use of formoterol Turbuhaler in asthma: Results from the RELIEF worldwide randomised effectiveness study, stratified by maintenance medication levels*. Eur Respir J 2002, 20(Suppl. 38): Abst P390.

11. Pauwels, R.A., Campbell, M., Villasante, C., Huang, S., Lindh, A., Petermann, W., Schwabe, G., Tornling, G., Naya, I., Sears, M.R. *Formoterol Turbuhaler compared with salbutamol as reliever medication in asthma: An exploratory analysis of the RELIEF study in patients using formoterol as maintenance therapy*. Eur Respir J 2002, 20(Suppl. 38): Abst P392.

12. Sears, M.R., Pauwels, R.A., Campbell, M., Villasante, C., Huang, S., Lindh, A., Petermann, W., Ottosson, A., Anderson, A., Elnertz, S.-A. *Safety of formoterol Turbuhaler used as reliever in asthma: Relationship with age and baseline treatment including regular long-acting β_2-agonists (the RELIEF study)*. Eur Respir J 2002, 20(Suppl. 38): Abst P394.

13. Sears, M.R., Pauwels, R.A., Campbell, M., Villasante, C., Huang, S., Lindh, A., Petermann, W., Ottosson, A., Anderson, A., Elnertz, S.-A. *Safety of formoterol Turbuhaler when used as a reliever therapy in asthma (the RELIEF study)*. Eur Respir J 2002, 20(Suppl. 38): Abst P393.

14. Pauwels, R.A., Campbell, M., Villasante, C., Huang, S., Lindh, A., Petermann, W., Schwabe, G., Lindmark, B., Bengtsson, T., Sears, M.R. *Formoterol Turbuhaler compared with salbutamol as reliever medication in asthma: A worldwide, randomised, effectiveness trial (RELIEF study)*. Eur Respir J 2002, 20(Suppl. 38): Abst P391.

15. Lindgren, B., Sears, M.R., Campbell, M., Villasante, C., Huang, S., Lindh, A., Petermann, W., Svensson, K., Berggren, F., Pauwels, R.A. *Cost-effectiveness of formoterol Turbuhaler versus salbutamol as reliever therapy in asthma: Results from the RELIEF worldwide randomised effectiveness study*. Eur Respir J 2002, 20(Suppl. 38): Abst P389.

16. Brambilla, C., Le Gros, V., Bourdeix, I. *Efficacy of formoterol 12 µg dry powder capsules in 6,155 asthmatic patients poorly controlled with salmeterol or on-demand salbutamol (EFORA study)*. Eur Respir J 2002, 20(Suppl. 38): Abst P736.

17. Stitsenko, I.A. *Formoterol (Aerolizer) in acute asthma exacerbation*. Eur Respir J 2002, 20(Suppl. 38): Abst P438.

18. Charoenratanakul, S., Boonsawat, W., Pothiratana, C., Sawanyawisuth, K., Seearamrungruang, T., Bengtsson, T., Brander, R., Selroos, O. *Formoterol Turbuhaler as a rescue therapy was as effective and safe as salbutamol by pMDI and spacer in patients with acute severe asthma*. Eur Respir J 2002, 20(Suppl. 38): Abst P436.

19. Rubinfeld, A., Scicchitano, R., Hunt, A., Thompson, P.J., Van Nooten, A., Hedlund, M., Horstedt, A.S., Brander, R. *Formoterol Turbuhaler is effective and safe compared with salbutamol by pMDI and spacer as reliever therapy in patients with acute severe asthma*. Eur Respir J 2002, 20(Suppl. 38): Abst P437.

20. Juniper, E.F., Charoenratanakul, S., Boonsawat, W., Mork, A.-C., Slahl, E. *Treatment of acute severe asthma with formoterol Turbuhaler provides a similar effect on patients' well-being as salbutamol by pMDI plus spacer*. Eur Respir J 2002, 20(Suppl. 38): Abst P410.

21. Eliraz, A., Ramirez-Rivera, A., Ferranti, P. et al. *Similar efficacy following four weeks treatment of asthmatics with formoterol 12 µg b.d. delivered by two different dry powder inhalers: Differences in inhaler handling*. Int J Clin Pract 2001, 55(3): 164.

22. Schlimmer, P. *Single-dose comparison of formoterol (Oxis®) Turbuhale® 6 µg and formoterol Aerolizer® 12 µg in moderate to severe asthma: A randomised, crossover study*. Pulm Pharmacol Ther 2002, 15(4): 369.

23. Tal, A., Simon, G., Vermeulen, J.H., Petru, V., Cobos, N., Everard, M.L., de Boeck, K. *Budesonide/formoterol in a single inhaler versus inhaled corticosteroids alone in the treatment of asthma*. Pediatr Pulmonol 2002, 34(5): 342.

24. Kaik, G., Kottakis, I., Anagnostopoulou, O., Sichletidis, L., Bachlitzanakis, N., D'Amato, M., Zucchi, L., Cruz, A.A., Pizzichini, M., Vieira, J.R., Beard, M., Davis, M.M., Overend, T. *Sequential flexible therapy with formoterol (Foradil) plus budesonide (Miflonide) versus a fixed combination of salmeterol and fluticasone (Seretide) in asthma self-management*. Eur Respir J 2002, 20(Suppl. 38): Abst P2407.

25. Rance, L., Musin, A. *Asthma management costs in Canada are lower with combination fluticasone propionate/salmeterol (250/50 µg BID) in a single inhaler than with budesonide 800 µg BID plus formoterol 12 mcg BID via separate inhalers*. Chest 2002, 122(4, Suppl.): Abst S6.

26. Peralman, D., Milgrom, H., Andriano, K., Feldman, J., Ziehmer, B. *Comparison of formoterol (Aerolizer®), albuterol (MDI) and placebo in the prevention of exercise-induced bronchospasm in pediatric patients*. Chest 2002, 122(4, Suppl.): Abst P209.

27. Gessner, C., Bräutigan, M., Müller, A., Stenglein, S:, Schauer, J. *Miflonide/Foradil in comparison to other combined antiinflammatory and antiobstructive therapy regimens - A German multicenter study*. 98th Int Conf Am Thorac Soc (May 17-22, Atlanta) 2002, Abst H40.

28. Chuchalin, A.G., Ovcharenko, S.I., Goriachnika, L.A., Sidorenko, I.V., Tsoi, A.N. *The safety and efficacy of formoterol (Oxis® Turbuhaler®) plus budesonide (Pulmicort®)) Turbuhaler in mild to moderate asthma: A comparison with budesonide turbuhaler alone and current non-corticosteroid therapy in Russia*. Int J Clin Pract 2002, 56(1): 15.

29. Bogdan, M., Eliraz, A., McKinnon, C., Nihlen, U., Radeczky, E., Soliman, S., Osmanliev, D. *Formoterol Turbuhaler is an effective maintenance and maintenance plus reliever therapy in patients with chronic obstructive pulmonary disease (COPD) irrespective of the level of lung*

function impairment and reversibility. Eur Respir J 2002, 20(Suppl. 38): Abst P1578.

30. Eliraz, A., Bengtsson, T., Bogdan, M., Coenen, P.D.M., Johanson, G., Osmanilev, D., Soliman, S., Tornling, G. *Formoterol Turbuhaler is effective and safe as maintenance or maintenance plus reliever therapy in patients with chronic obstructive pulmonary disease (COPD).* Eur Respir J 2002, 20(Suppl. 38): Abst P1580.

31. Cazzola, M., Centanni, S., Regorda, C., Di Marco, F., de Perna, F., Carlucci, P., Boveri, B., Santus, P. *Onset of action of single doses of formoterol administered via Turbuhaler in patients with stable COPD*. Pulm Pharmacol Ther 2001, 14(1): 41.

32. Benhamou, D., Cuvelier, A., Muir, J.F., Leclerc, V., Le Gros, V., Kottakis, J., Bourdeix, I. *Rapid onset of bronchodilation in COPD: A placebo-controlled study comparing formoterol (Foradil(R) Aerolizer™) with salbutamol (Ventodisk™)*. Respir Med 2001, 95(10): 817.

33. Cazzola, M., Grella, E., Matera, M.G., Mazzarella, G., Marisco, S.A. *Onset of action following formoterol Turbuhaler® and salbutamol pMDI in reversible chronic airway obstruction*. Pulm Pharmacol Ther 2002, 15(2): 97.

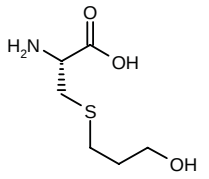
34. Kottakis, J., della Cioppa, G., Creemers, J. et al. *Faster onset of bronchodilation with formoterol than with salmeterol in patients with stable, moderate to severe COPD: Results of a randomized, double-blind clinical study*. Can Respir J 2002, 9(2): 107.

35. Liesker, J.J.W., van de Velde, V., Meysman, M. et al. *Effects of formoterol (Oxis® Turbuhaler®) and ipratropium on exercise capacity in patients with COPD*. Respir Med 2002, 96(8): 559.

36. Aalbers, R., Ayres, J., Backer, V. et al. *Formoterol in patients with chronic obstructive pulmonary disease: A randomized, controlled, 3-month trial*. Eur Respir J 2002, 19(5): 936.

Original monograph - Drugs Fut 1977, 2(10): 639.

Fudosteine



Fudosteine is an expectorant which was launched in 2001 in Japan by SSP as Cleanal® and by Mitsubishi Pharma as Spelear® for patients with chronic respiratory diseases, including bronchial asthma, chronic bronchitis, bronchiectasis, pulmonary tuberculosis, pulmonary emphysema, atypical mycobacterial disease and pneumoconiosis.

Oral fudosteine (500 mg/kg) did not affect the normal mucociliary transport (MCT) rate in quails, but it dose-dependently blocked cigarette smoke-induced impairment of the MCT rate when topically applied to the tracheal mucosa. It was suggested that fudosteine might play a role in the defense against irritant gases in the respiratory tract (1).

1. Takahashi, K., Kai, H., Mizuno, H., Koda, T., Miyata, T. *Effect of fudosteine, a new cysteine derivative, on mucociliary transport*. J Pharm Pharmacol 2001, 53(6): 911.

Original monograph - Drugs Fut 1998, 23(4): 374.

Iseganan Hydrochloride

L-Arginyl-glycyl-glycyl-L-leucyl-L-cysteinyl-L-tyrosyl-L-cysteinyl-L-arginyl-glycyl-L-arginyl-L-phenylalanyl-L-cysteinyl-L-valyl-L-cysteinyl-L-valyl-glycyl-L-argininamide cyclic *S*-3.5-*S*-3.14:S-3.7-*S*-3.12-bis(disulfide) hydrochloride

Iseganan hydrochloride (protegrin IB-367) is a synthetic analogue of a naturally occurring antimicrobial peptide that defends mammals from bacterial infection. The protegrins are rapidly bactericidal and iseganan appears to kill bacteria by integrating with and disrupting the integrity of bacterial cell membranes.

Developed by IntraBiotics, iseganan is currently undergoing phase I evaluation for the treatment of respiratory infections associated with CF (as aerosol) and phase II/III trials for the prevention of ventilator-associated pneumonia (as rinse and gel) in the U.S. Trials evaluating iseganan for reducing the severity of oral mucositis were discontinued in the U.S. and the E.U. in September 2002 based on disappointing results from a phase III trial in patients undergoing high-dose chemotherapy (1-4).

IntraBiotics has released data from phase I trials on the use of iseganan in CF patients. To date, there has been no sign of bacterial resistance to iseganan and it could therefore have potential use in CF patients who build up resistance to antibiotics that are inhaled for ease of breathing. The phase I trial involved the administration of up to 5 doses of iseganan twice daily for 3 days. The data indicated that inhalation of iseganan over the 3-day period was safe. The main side effect reported was mild

cough, which lessened over the treatment period. Wheezing and chest tightness were also reported. IntraBiotics intends to proceed to phase II trials to evaluate the effect of a 2-week administration of iseganan on the reduction of microorganisms in patients' lungs when adequate financial resources become available (5).

Data from IntraBiotics' phase IIa clinical trial evaluating the safety and efficacy of iseganan oral solution for reducing oral bacteria as an approach to preventing ventilator-associated pneumonia (VAP) were reported last year. There are no currently approved antimicrobial therapies for VAP. The results showed iseganan to be well tolerated and to significantly reduce the mean number of oral microorganisms in mechanically ventilated patients. The company is planning a pivotal trial to test iseganan for the prevention of VAP (6-8).

In a phase III trial in 323 patients receiving radiotherapy for head and neck cancer, iseganan prevented ulcerative oral mucositis, reduced the severity of peak stomatitis and reduced mouth pain, throat pain and dysphagia. The only adverse event reported was esophagitis, which was generally mild in severity and self-limited (9).

1. *IntaBiotics' Protegrin IB-367 rinse meets secondary but not primary endpoints*. DailyDrugNews.com (Daily Essentials) April 30, 2001.

2. *Iseganan fails to meet primary endpoint in ulcerative oral mucositis phase III trial*. DailyDrugNews.com (Daily Essentials) Oct 2, 2002.

3. *IntraBiotics completes patient enrollment in phase III Protegrin IB-367 Rinse study*. DailyDrugNews.com (Daily Essentials) Jan 17, 2001.

4. Cella, D., Fuchs, H., Miller, C., Hurd, D., Wingard, J.R., Fleming, T., Sonis, S., Anaissie, E., Martin, P.J., Giles, F.J. *Evaluation of pain associated with oral mucositis (OM) using an 11-point Likert scale by patients receiving myeloablative chemotherapy*. Blood 2001, 98(11, Part 1): Abst 805.

5. *Inhaled iseganan safe in cystic fibrosis patients*. DailyDrugNews.com (Daily Essentials) Nov 5, 2001.

6. *IntraBiotics presents promising results for iseganan in treating ventilator-associated pneumonia*. DailyDrugNews.com (Daily Essentials) Oct 11, 2001.

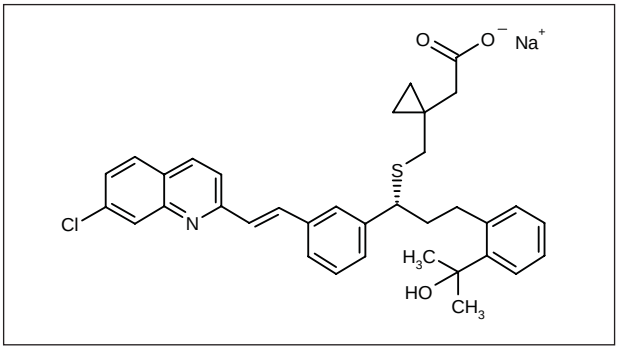
7. *Protegrin IB-367 shows antimicrobial activity, good safety in phase IIa for prevention of VAP*. DailyDrugNews.com (Daily Essentials) March 12, 2001.

8. *Protegrin IB-367 phase I results in ventilator-associated pneumonia reported*. DailyDrugNews.com (Daily Essentials) Feb 15, 2001.

9. Trotti, A., Garden, A.S., Warde, P. et al. *Phase III trial of iseganan HCl oral solution (iseganan) for reducing oral mucositis severity in patients receiving radiotherapy for head and neck malignancies (PROMPT-RT)*. Proc Am Soc Clin Oncol 2002, 21(Part 1): Abst 908.

Original monograph - Drugs Fut 2002, 27(3): 234.

Montelukast Sodium



The leukotriene receptor antagonist montelukast sodium (Singulair®) is marketed by Merck & Co. for the chronic treatment and prevention of asthma in adults and pediatric patients 12 months of age or over, and was just approved by the FDA for the relief of symptoms of SAR in adults and children as young as 2 years of age.

Montelukast was assessed in 6 children with both asthma and migraine in a prospective, open-label trial. All patients were administered montelukast at a dose of 5 mg at night for 24 weeks and showed a decrease in asthma attacks without significant side effects. Moreover, headache frequency was reduced from 3-8 attacks per month during the 4 weeks before treatment to 1-3 attacks per month during the first 8 weeks and to 0-2 attacks per month by the end of the study. According to this small study, montelukast is a safe and effective treatment for comorbid asthma and migraine (1).

The combination of montelukast and rofecoxib was evaluated in a prospective, open-label study in which 33 patients with migraine without aura were enrolled to receive rofecoxib 12.5 mg/day and montelukast 10 mg/day for 12 weeks. Twenty-five of the 31 evaluable patients experienced at least a 50% reduction in migraine frequency. The mean number of migraine attacks was reduced from 6.4 attacks per month at study entry to 2.3 attacks per month at the end of the study. Transient adverse events were reported by 2 patients but did not lead to withdrawal. Long-term use for up to 40 more weeks was not associated with either an increase in side effects or a decrease in response rate (2).

Patients with continuing asthma symptoms and/or impaired lung function despite the use of inhaled corticosteroids and additional medications were entered in a double-blind, randomized, placebo-controlled, crossover study of add-on therapy with montelukast. Although the antiinflammatory effect of this relatively new class of asthma medications has been reported to be inferior to that of inhaled corticosteroids, the additional bronchodilating effect of montelukast together with its approved indication (add-on therapy for asthma not controlled by inhaled corticosteroids and β_2-agonists) led a group of

investigators to examine its potential as add-on therapy in 100 such difficult-to-treat outpatients at a dose of 10 mg for 14 days. However, no additional benefit was seen in these patients, as evaluated by symptom scores, rescue inhaled β_2-agonists or PEF measurements, and no evidence for a subgroup of responding patients was obtained (3).

A total of 21 patients with SAR were included in a crossover study and randomized to receive either 400 μg of inhaled plus 200 μg of intranasal budesonide once daily or 10 mg of montelukast plus 10 mg of cetirizine once daily. Both treatments improved the nasal symptoms of SAR (4).

In a population of 12 asthmatic patients with SAR, a once-daily dose of 10 mg montelukast was as effective as a once-daily combination of 400 μg of inhaled plus 200 μg of intranasal budesonide in reducing total rhinitis symptoms after 2 weeks of treatment. Only budesonide had a significant effect on the nasal symptoms of the patients (5).

A subgroup analysis of the COMPACT (Clinical Observation of Montelukast as a Partner Agent for Complementary Therapy) trial, which was conducted to determine the potential of montelukast sodium as complementary therapy in the management of asthma, compared the efficacy of a combination of 800 μg/day of inhaled budesonide plus 10 mg/day of oral montelukast with that of 1600 μg/day of budesonide alone in 889 adult asthmatics previously treated with 800 μg/day of budesonide. Both treatments were found to be effective in improving the lung function of the patients, together with other symptoms such as nocturnal awakening, rescue use of beta-agonists, daytime symptoms and percentage of asthma-free days. The combination of montelukast and the inhaled corticosteroid had a faster onset of action in terms of improvement in morning PEF rate (6).

Researchers analyzed economic data from a 12-week, randomized, double-blind trial comparing inhaled fluticasone propionate/salmeterol 100/50 μg b.i.d. and fluticasone propionate 100 μg b.i.d. plus montelukast 10 mg once daily in 247 asthmatic patients. The fluticasone propionate/salmeterol regimen was found to be the most cost-effective treatment (7, 8).

A crossover study revealed that 2-week intranasal administration of 200 μg mometasone furoate once daily was as effective as a 2-week combination of a daily oral dose of 10 mg montelukast and 10 mg cetirizine in improving peak nasal flow, nasal blockage and total nasal symptoms of patients with SAR (9).

A multicenter, randomized, double-blind, placebo- and active-controlled trial was undertaken to assess the efficacy and tolerability of montelukast for the treatment of SAR. Male and female subjects received montelukast 10 mg (n=348), loratadine 10 mg (n=602) or placebo (n=352) once daily for 2 weeks. Montelukast was safe and well tolerated and improved both daytime symptoms (nasal congestion, rhinorrhea, nasal pruritus and sneezing), nighttime symptoms and quality-of-life parameters (10).

Montelukast alone (10 mg once daily) or combined with loratadine (10 mg once daily) was as effective as loratadine monotherapy (10 mg once daily) in improving the clinical symptoms and quality of life of patients with SAR after 2 weeks of treatment (11).

A daily dose of 200 μg of fluticasone propionate administered as an aqueous nasal spray was more effective than montelukast alone (10 mg once daily), a combination of montelukast with loratadine (10 mg once daily) or placebo in preventing the nighttime symptoms of SAR after 2 weeks of treatment. The daytime symptoms of the disease were better prevented by fluticasone propionate or the combination treatment than placebo or montelukast alone (12).

Pediatric patients with cat-induced asthma (n=18) were enrolled in a randomized, double-blind, crossover study in which they were given montelukast 5 mg/day or placebo for 1 week before a cat allergen challenge. Compared with placebo, montelukast reduced lower respiratory tract symptom scores and significantly extended the challenge length (13).

A retrospective analysis of 8 children with eosinophilic inflammatory lesions in the gastrointestinal tract revealed positive results with montelukast treatment (5-10 mg/day). All patients had failed diet restrictions or oral cromolyn therapy. However, they showed marked improvement following 2-3 weeks of montelukast therapy. All patients have remained asymptomatic at a mean follow-up of 1 year (14).

Once-daily administration of 120 mg of fexofenadine for 2 weeks was as effective as once-daily administration of 10 mg of montelukast plus 10 mg of loratadine for 2 weeks in improving the nasal symptoms and peak inspiratory flow of patients with SAR (15).

Data from 6 randomized, double-blind trials in which asthma patients received either fluticasone propionate 88 μg b.i.d., zafirlukast 20 mg b.i.d., montelukast 10 mg once daily or placebo indicated that the most effective of these treatments in improving pulmonary function was low-dose fluticasone propionate, regardless of asthma duration prior to treatment (16-18).

Combinations of a PDE4 inhibitor such as roflumilast and a leukotriene antagonist, particularly montelukast, have been claimed for the treatment of bronchial and respiratory disorders (19).

1. de Souza Carvalho, D., Fragoso, Y.D., Coelho, F.M., Pereira, M.M. *Asthma + migraine in childhood and adolescence: Prophylactic benefits with leukotriene receptor antagonist*. Cephalalgia 2001, 21(4): Abst P2-I17.

2. Freitag, F.G., Diamond, S., Diamond, M.L., Urban, G. *Preventative treatment of migraine headache with rofecoxib and montelukast*. Cephalalgia 2001, 21(4): Abst P2-I18.

3. Robinson, D.S., Campbell, D., Barnes, P.J. *Addition of leukotriene antagonists to therapy in chronic persistent asthma: A randomised double-blind placebo-controlled trial*. Lancet 2001, 357(9273): 2007.

4. Wilson, A.M., Sims, E.J., Orr, L.C., Coutie, W.J.R., White, P.S., Gardiner, Q., Lipworth, B.J. *Effects of topical corticosteroid and combined mediator blockade on domiciliary and laboratory measurements of nasal function in seasonal allergic rhinitis*. Ann Allergy Asthma Immunol 2001, 87(4): 344.

5. Wilson, A.M., Dempsey, O.J., Sims, E.J., Lipworth, B.J. *A comparison of topical budesonide and oral montelukast in seasonal allergic rhinitis and asthma*. Clin Exp Allergy 2001, 31(4): 616.

6. Hernandez, D., Namenyi, M. , Fiterman, J. et al. *Adding montelukast versus doubling the budesonide dose in persistent asthma: A subgroup analysis of the COMPACT study*. Eur Respir J 2002, 20(Suppl. 38): Abst P2406.

7. Leibman, C.W., Stanford, R., Emmett, A., Dorinsky, P.M., Rickard, K.A. *Cost-effectiveness of fluticasone/salmeterol combination versus fluticasone + montelukast in the treatment of persistent asthma*. 98th Int Conf Am Thorac Soc (May 17-22, Atlanta) 2002, Abst C9.

8. Stanford, R.H., Borker, R., Dorinsky, P., Pepsin, P., Kalberg, C., Emmett, A., Rickard, K. *The costs and efficacy of fluticasone propionate/salmeterol combination versus montelukast in the treatment of adults with persistent asthma*. Chest 2002, 122(4, Suppl.): Abst P422.

9. Wilson, A.M., Orr, L.C., Sims, E.J., Lipworth, B.J. *Effects of monotherapy with intra-nasal corticosteroid or combined oral histamine and leukotriene receptor antagonists in seasonal allergic rhinitis*. Clin Exp Allergy 2001, 31(1): 61.

10. Philip, G., Malmstrom, K., Hampel Jr., F.C., Weinstein, S.F., Laforce, C.F., Ratner, P.H., Reiss, T.F., Malice, M.P. *Montelukast for treating seasonal allergic rhinitis: A randomized, double-blind, placebo-controlled trial performed in the spring*. Clin Exp Allergy 2002, 32(7): 1020.

11. Nayak, A.S., Philip, G., Lu, S., Malice, M.-P., Reiss, T.F. *Efficacy and tolerability of montelukast alone or in combination with loratadine in seasonal allergic rhinitis: A multicenter, randomized, double-blind, placebo-controlled trial performed in the fall*. Ann Allergy Asthma Immunol 2002, 88(6): 592.

12. Pullerits, T., Praks, L., Ristioja, V., Lotvall, J. *Comparison of a nasal glucocorticoid, antileukotriene, and a combination of antileukotriene and antihistamine in the treatment of seasonal allergic rhinitis*. J Allergy Clin Immunol 2002, 109(6): 949.

13. Phipatanakul, W., NowakWegrzyn, A., Eggleston, P.A., VanNatta, M., Kesavan, J., Schuberth, K., Wood, R.A. *The efficacy of montelukast in the treatment of cat allergen-induced asthma in children*. J Allergy Clin Immunol 2002, 109(5): 794.

14. Vanderhoof, J.A., Young, R.J. *Efficacy of montelukast in the treatment of children with eosinophilic gastrointestinal disease*. Dig Dis Week (May 19-22, San Francisco) 2002, Abst 616.

15. Wilson, A.M., Orr, L.C., Coutie, W.J.R., Sims, E.J., Lipworth, B.J. *A comparison of once daily fexofenadine versus the combination of montelukast plus loratadine on domiciliary nasal peak flow and symptoms in seasonal allergic rhinitis*. Clin Exp Allergy 2002, 32(1): 126.

16. Donohue, J.F., Srebro, S., Edwards, L., Kalberg, J.F., Goode-Sellers, S., Rickard, K. *Comparison of pulmonary function results based on asthma duration: Low-dose fluticasone vs. zafirlukast vs. montelukast*. Chest 2001, 120(4, Suppl.): 224S.

17. Crim, C., Edwards, L., Srebro, S., Rickard, K. *Changes in asthma staging with low-dose fluticasone propionate (FP), montelukast (MON), and zafirlukast (ZAF)*. Chest 2001, 120(4, Suppl.): 223S.

18. Crim, C., Edwards, L., Rickard, K., Kalberg, C. *An evalution of asthma control using asthma instability measures in patients receiving fluticasone or montelukast*. Chest 2001, 120(4, Suppl.): 224S.

19. Chang, Y. (Merck & Co., Inc.). *Method of treatment with a combination of a PDE_4 inhibitor and a leukotriene antagonist*. WO 0238155.

Original monograph - Drugs Fut 1997, 22(10): 1103.

Omalizumab

Genentech, Novartis and Tanox have codeveloped a novel anti-IgE therapy for the treatment of allergic asthma and rhinitis. Omalizumab (rhuMAb-E25, Xolair™) is a humanized monoclonal antibody that binds to circulating IgE and prevents it from attaching to mast cells. Without this attachment, the presence of an allergen does not cause the release of chemical mediators such as histamine and leuko-trienes, which lead to the symptoms and inflammation of allergic asthma.

Omalizumab received its first approval in Australia in June for the treatment of moderate allergic asthma in adults and adolescents, and submissions are under review in the U.S., the E.U., Switzerland and New Zealand (1-5).

Experiments were conducted with segments of human isolated bronchi incubated with normal serum, normal serum plus 60, 120 or 180 mg/ml omalizumab, asthmatic serum or asthmatic serum plus 60, 120 or 180 mg omalizumab. Omalizumab concentration-dependently inhibited nonspecific hyperresponsiveness induced by passive sensitization and a significant decrease in mast cell degranulation was also observed (6).

Children (n=91) with SAR and sensitized to birch and grass pollen were treated with specific immunotherapy for birch or grass pollen and s.c. omalizumab or placebo for 24 weeks during the pollen season. Isolated leukocytes were then stimulated with grass and birch pollen allergens or with PHA. Omalizumab and specific immunotherapy for birch or grass pollen reduced symptom load compared with placebo, and significantly reduced leukotreine release *in vitro* after stimulation with birch or grass allergens (7). The results of this study and some of those that follow are summarized in Table VI.

A randomized, double-blind, placebo-controlled trial enrolled 546 allergic asthma patients who were treated with omalizumab 150-300 mg monthly, 225-375 mg twice monthly or placebo. After 28 weeks, 88% of patients continued treatment in a 26-week extension. The treatment was safe and well tolerated, allowed reduction of beclomethasone treatment and other asthma medications, and reduced the incidence of asthma exacerbation episodes (8).

In a randomized, double-blind, placebo-controlled trial, 525 patients with moderate to severe allergic asthma under control with inhaled corticosteroids were administered s.c. omalizumab (at least 0.016 mg/kg monthly) or placebo for 28 weeks. Long-term treatment with omalizumab was well tolerated, sustained disease control, prevented exacerbations and reduced the intake of beclomethasone (9).

Data were reported from a double-blind trial involving 246 patients with severe asthma optimally controlled on daily doses of 1000-2000 μg inhaled fluticasone. The ini-

Table V: Clinical studies of omalizumab (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Allergic conjunctivitis, seasonal allergic rhinitis	Randomized, multicenter	Omalizumab, sc [dose adjusted to baseline IgE and body weight] + Specific immunotherapy for birch pollen (prior to and during the pollen season) (n=22) Omalizumab, sc [dose according to baseline IgE and body weight] + Specific immunotherapy for grass pollen (prior to and during the pollen season) (n=23) Placebo + Specific immunotherapy for birch pollen (prior to and during the pollen season) (n=22) Placebo + Specific immunotherapy for grass pollen (prior to and during the pollen season) (n=24)	91	Omazilumab and specific immunotherapy for birch or for grass pollen reduced symptom loads compared with placebo, and significantly reduced leukotreine release *in vitro* after stimulation with birch or grass allergens	7
Asthma, COPD	Randomized, double-blind, multicenter	Omalizumab, 150-300 or 225-375 mg 1x/2 wk [depending on weight and serum IgE] sc 1x/4 wk x 54 wk Placebo	546	Long-term treatment with omalizumab was safe and well tolerated, and showed a sustained reduction of exacerbations and steroid medication in patients with previously inadequately controlled allergic asthma	8
Asthma, COPD	Randomized, double-blind	Omalizumab, ≥ 0.016 mg/kg/IgE IU/ml sc 1x/1 mo + Beclomethasone dipropionate [stable doses during 16 wk and reduced progressively for 12 wk] x 28 wk + follow-up for further 5 mo (n=245) Placebo + Beclomethasone dipropionate [stable doses during 16 wk and reduced progressively for 12 wk] x 28 mo + follow-up for further 5 mo (n=215)	525	Omalizumab was safe and effective in reducing inhaled corticosteroid usage and preventing asthma exacerbations in moderate to severe allergic asthma	9
Asthma, COPD	Randomized, double-blind, multicenter	Omalizumab, >0.016 mg/kg/IgE IU/ml sc 1x/2-4 wk + Fluticasone propionate, 1369 [mean] µg/d inhal [reduced by 250 µg/d q2 wk @ 16 wk over the next 12 wk] x 32 wk Placebo + Fluticasone propionate, 1369 [mean] µg/d inhal [reduced by 250 µg/d q2 wk @ 16 wk over the next 12 wk]	246	Omalizumab was safe, well tolerated and effective in allowing a reduction in fluticasone propionate dose, improving FEV_1 and quality of life in severe allergic asthma	10-12, 14-16
Perennial allergic rhinitis	Randomized, double-blind, multicenter	Omalizumab, 150-300 mg [or 225-375 mg sc 1x/2 wk depending on baseline serum total IgE and body weight] sc 1x/4 wk x 16 wk (n=144) Placebo (n=145)	289	Omalizumab was well tolerated and effective in perennial allergic rhinitis	17
Allergic conjunctivitis, seasonal allergic rhinitis	Randomized, double-blind, multicenter	Omalizumab, 150-300 mg 1x/4 wk or 225-375 mg 1x/2wk [dose adjusted to baseline IgE and bodyweight] sc x 24 wk + Specific immunotherapy (ALK-Abello) for birch/grass pollen (4 mo prior to pollen season) Placebo + Specific immunotherapy (ALK-Abello) for birch/grass pollen (4 mo prior to pollen season)	225	Omalizumab was safe and effective in reducing allergic mediators in nasal secretion, symptoms and rescue medication requirement when compared with specific immunotherapy alone in birch and grass pollen-induced seasonal allergic rhinoconjuntivitis	18
Asthma, COPD	Randomized, double-blind, multicenter, pooled/ meta-analysis	Omalizumab, >0.016 mg/kg sc 1-2x/mo x 28 wk Placebo	767	Omalizumab reduced hospitalizations due to serious asthma exacerbations in both adults and children	20

Continuation

Table V (Cont.): Clinical studies of omalizumab (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Seasonal allergic rhinitis	Randomized, double-blind, multicenter	Omalizumab, 50 mg sc 1x/3 wk x 4 doses (n=137) Omalizumab, 150 mg sc 1x/3 wk x 4 doses (n=134) Omalizumab, 300 mg sc 1x/3 wk x 4 doses (n=129) Placebo x 4 doses (n=136)	536	Omalizumab decreased serum free IgE levels and improved symptoms of seasonal allergic rhinitis in a dose-dependent manner	21
Asthma, COPD	Randomized, double-blind, multicenter	Omalizumab, 0.016 mg/kg/IgE IU/ml 1x/4 wk + Beclomethasone dipropionate, 500-1000 μg/d x 16 wk Placebo + Beclomethasone dipropionate, 500-1000 μg/d	35	Omalizumab was effective in allergic asthma	23
Airway obstruction, asthma	Randomized, double-blind, multicenter	Omalizumab, ≥ 0.016 mg/kg/IgE IU/ml [adjusted to serum free IgE and body weight at baseline] sc 1x/1mo + Beclomethasone dipropionate, 420-1008 μg/d [stable doses during 16 wk and reduced by 25% q2 wk from 16-28 wk] x 28 wk (n=542) Placebo + Beclomethasone dipropionate, 420-1008 μg/d [stable doses during 16 wk and reduced by 25% q2 wk from 16-28 wk] x 28 wk (n=529)	1071	Omalizumab was safe, well tolerated and effective in reducing inhaled corticosteroids, decreasing asthma exacerbations and improving quality of life in patients with allergic asthma relative to placebo. It was associated with fewer exacerbations and greater reductions in inhaled steroids	25
Asthma, COPD	Randomized, double-blind, multicenter, pooled/ meta-analysis	Studies I/II: Omalizumab, >0.016 mg/kg/IgE IU/ml sc 1x/2-4 wk + Beclomethasone dipropionate, 420-1008 μg/d x 52 wk [tapered after 16 wk over 8 wk] x 52 wk (n=542) Placebo + Beclomethasone dipropionate, 420-1008 μg/d [tapered after 16 wk over 8 wk] x 52 wk (n=529) Study III: Omalizumab, >0.016 mg/kg/IgE IU/ml sc 1x/2-4 wk x 52 wk + Beclomethasone dipropionate, 420-1008 μg/d [tapered after 16 wk over 8 wk] x 28 wk (n=225) Placebo + Beclomethasone dipropionate, 420-1008 μg/d [tapered after 16 wk over 8 wk] x 28 wk (n=109)	1405	Omalizumab reduced the risk of serious asthma exacerbations requiring hospitalization in moderate to severe allergic asthma	26
Asthma	Randomized, double-blind, multicenter, pooled/ meta-analysis	Studies I/II: (Studies 008 and 009) Omalizumab, >0.016 mg/kg/IgE IU/ml sc 1x/2-4 wk + inhaled corticosteroids [tapered after 16 wk over 12 wk] x 52 wk Placebo + inhaled corticosteroids [tapered after 16 wk over 12 wk] x 52 wk Study III: (Study 011) Omalizumab, >0.016 mg/kg/IgE IU/ml sc 1x/2-4 wk + inhaled corticosteroids [tapered after 16 wk over 16 wk] x 32 wk Placebo + inhaled corticosteroids [tapered after 16 wk over 16 wk] x 76 wk	1412	Omalizumab was well tolerated and effective in improving asthma exacerbation episodes and quality of life when administered to patients at high risk for serious asthma-related morbidity and mortality	27, 28
Asthma, allergic rhinitis	Pooled/ meta-analysis	Omalizumab x 1 [max] y (n=1763) Placebo (n=1278)	3041	Omalizumab was not associated with a higher risk of immunological reactions in patients with allergic asthma/rhinitis	29, 30

tial dose of fluticasone was maintained over 16 weeks and then gradually reduced over 12 weeks to the minimum level required for disease control, and patients received placebo or omalizumab during this time and for a further 4 weeks, for a total of 32 weeks. Omalizumab allowed a significantly greater reduction in corticosteroid dose compared to placebo while maintaining the same level of asthma control. The daily dose of fluticasone could be reduced to 500 μg or less in 60.3% of those on omalizumab versus 45.8% of those on placebo. No increase in exacerbation rates, worsening of symptoms or additional use of emergency medication (β_2-agonists) was seen on omalizumab, whereas these parameters worsened on placebo. Improvement in quality of life was also reported by the patients in the omalizumab group. Moreover, a follow-up study indicated that cessation of omalizumab is unlikely to result in sudden loss of disease control (10-16).

A multicenter, double-blind trial in 289 patients showed that omalizumab was also effective and safe in the treatment of moderate to severe PAR. In this trial, patients received placebo or omalizumab by s.c. injection every 2 or 4 weeks over 16 weeks. As compared to placebo, omalizumab was associated with increased improvement in symptoms affecting the nose, antihistamine use and quality of life. Rhinitis was considered controlled in almost 30% of the patients given omalizumab *versus* < 10% of those given placebo (17).

A study conducted in 225 children suffering from seasonal allergic rhinoconjunctivitis induced by birch and grass pollen found that the addition of omalizumab to specific immunotherapy significantly decreased the levels of inflammatory mediators in nasal secretions. This decrease was closely correlated with the improvement in symptoms and the reduced need for rescue medication (18).

Investigators analyzed a subgroup of patients at high risk for asthma-related death enrolled in 3 randomized, double-blind, placebo-controlled studies of add-on therapy with omalizumab. Treatment included s.c. omalizumab given every 2 or 4 weeks at a 4-weekly dose of at least 0.016 mg/kg/IgE. Omalizumab treatment produced a reduction of 55% in significant asthma exacerbation episodes and improved disease control in these patients. Omalizumab also significantly reduced hospitalizations due to serious asthma exacerbations (19, 20).

A randomized, placebo-controlled trial found that omalizumab provides clinical benefit and reduces serum free IgE levels in subjects with ragweed-induced SAR. The study was conducted at 25 outpatient centers across the U.S. and recruited 536 patients aged 12-75 years who had had moderate to severe ragweed-induced SAR for at least 2 years. Patients were randomized to receive one of three possible doses of omalizumab or placebo subcutaneously before the start of the ragweed season. Injections were repeated every 3 or 4 weeks throughout the pollen season, depending on IgE levels. Patients who received the highest dose of omalizumab (300 mg) had significantly lower nasal symptom scores than those who received placebo, and nasal symptom scores were significantly associated with IgE levels and need for rescue antihistamine use. Adverse events were similar in both the active and placebo treatment groups. The findings show that in patients with SAR, omalizumab reduces IgE levels and affords dose-dependent improvement in clinical symptoms (21).

A double-blind, placebo-controlled phase III study was conducted to assess the safety and tolerability of omalizumab in patients with moderate to severe asthma. Long-term omalizumab treatment in 254 patients was found to have a safety and tolerability profile similar to that of placebo (229 patients) (22).

A trial in 35 patients with allergic asthma confirmed the beneficial effects of omalizumab on asthma symptoms, β_2-agonist use and mediator release (23).

Data from 3 double-blind phase III trials in Europe and the U.S. involving 1,071 adolescents or adults and 334 children, all with moderate to severe allergic asthma despite treatment with inhaled corticosteroids, have been reported. After 1 year of treatment, only 2 of 542 adolescent and adult patients receiving omalizumab had been hospitalized for severe exacerbations *versus* 13 of 529 on placebo. Similar results were obtained for children, no omalizumab-treated patients being hospitalized for serious asthma exacerbations over 28 weeks *versus* 5 patients in the placebo group. This improved control was reflected in significantly greater improvements in PEF rate, overall quality of life and mean nocturnal and total asthma symptom scores with omalizumab compared with placebo. The greatest benefit was seen in patients receiving high doses of inhaled steroids, those with poor control and those with poor lung function. Greater reductions in inhaled steroid doses and reduced asthma exacerbations were seen in omalizumab-treated subjects (24-28).

A meta-analysis that included the safety data from 8 phase IIB/III clinical trials found that omalizumab had a safety profile very similar to that of placebo in patients with allergic asthma/rhinitis. The most frequent adverse events in placebo- and omalizumab-treated patients were viral infections, headache, upper respiratory tract infections, sinusitis and pharyngitis. Most adverse events were mild or moderate, and the percentage of serious adverse events was low (2.6% and 2.8% for omalizumab and placebo, respectively). No evidence of serum sickness, serum sickness-like syndrome or anti-omalizumab antibodies was found during the treatment. These data support the clinical use of omalizumab in the treatment of IgE-mediated allergic diseases of the airways (29, 30).

1. *Australia first to approve Xolair*. DailyDrugNews.com (Daily Essentials) June 21, 2002.

2. *Tanox updates product developments, looks ahead to 2001*. DailyDrugNews.com (Daily Essentials) Feb 2, 2001.

3. *Xolair BLA amendment will be submitted in the second quarter of 2002*. DailyDrugNews.com (Daily Essentials) Nov 5, 2001.

4. *FDA requests further data on Xolair, delaying approval*. DailyDrugNews.com (Daily Essentials) July 11, 2000.

5. *Update on Xolair BLA review by FDA*. DailyDrugNews.com (Daily Essentials) March 9, 2001.

6. Tunon-de-Lara, J.M., Berger, P., Molimard, M., Le Gros, V., Hultsch, T. *Omalizumab (Xolair, rhuMAb-E25) anti-IGE monoclonal antibody inhibits passive sensitization-induced hyperresponsiveness*. Am J Respir Crit Care Med 2001, 163(5, Suppl.): A858.

7. Kopp, M.V., Reggelin, U., Brauburger, J., Riedinger, F., Ihorst, G., Zielen, S., Kamin, W., von Berg, A., Friedrichs, F., Hamelmann, E., Wahn, U., Joachim, K. *Combined effect of anti-IgE (omalizumab) and specific immunotherapy (SIT) on in vitro release of leukotrienes (LT) and the cytokines IL-4 and interferon-gamma (IFN)*. Eur Respir J 2002, 20(Suppl. 38): Abst 3682.

8. Soler, M., Buhl, R., Bensch, G. et al. *Omalizumab (Xolair®, rhuMAb-E25) treatment reduces inhaled corticosteroid use in moderate/severe allergic asthma*. Am J Respir Crit Care Med 2001, 163(5, Suppl.): A858.

9. Lanier, R., Busse, W., Corren, J., Chervinsky, P., Bernstein, J., McAlary, M., Gupta, N., Fowler-Taylor, A., Rohane, P. *Long-term improvement in asthma control and exacerbation frequency is achieved with omalizumab (Xolair®) in patients with moderate-to-severe asthma*. Am J Respir Crit Care Med 2001, 163(5, Suppl.): A858.

10. Holgate, S., Chuchalin, A., Herbert, J. et al. *Omalizumab improves asthma-specific quality of life in patients with severe allergic asthma*. Eur Respir J 2001, 18(Suppl. 33): Abst P348.

11. Holgate, S., Chuchalin, A., Herbert, J. et al. *Omalizumab (rhuMAb-E25) improves asthma-specific quality of life in patients with severe allergic asthma*. Am J Respir Crit Care Med 2001, 163(5, Suppl.): A858.

12. Holgate, S., Chuchalin, A., Herbert, J. et al. *Omalizumab (Xolair®, rhuMAb-E-25), a novel therapy for severe allergic asthma*. Am J Respir Crit Care Med 2001, 163(5, Suppl.): A812.

13. Hebert, J., Yang, W., D'Urzo, A., Fox, H., Thirlwell, J. *No rebound worsening after cessation of omalizumab therapy in patients with severe allergic asthma*. Chest 2001, 120(4, Suppl.): 163S.

14. Chung, K.F., Hogate, S., O'Brien, J., Fox, H., Thirlwell, J. *Inhaled corticosteroid dose-reducing effect of omalizumab in patients with controlled, severe asthma according to usage of inhaled long-acting beta-agonists*. J Allergy Clin Immunol 2002, 109(1, Part 2): Abst 726.

15. Holgate, S., Chung, K.F., Bousquet, J., Fox, H., Surrey, K. *Greatest benefit from omalizumab treatment in patients with more severe asthma*. 21st Congr Eur Acad Allergol Clin Immunol (June 1-5, Naples) 2002, Abst 24.

16. Holgate, S., Chuchalin, A., Herbert, J., Lotvall, J., Chung, F., Bousquet, J., Kersjens, H., Fox, H., Thirlwell, J., Della Cioppa, G. *Omalizumab, a novel therapy for severe allergic asthma*. Eur Respir J 2001, 18(Suppl. 33): Abst P346.

17. Casale, T., Chervinsky, P., Busse, W., Nayak, A., Tripathy, I., Fowler Taylor, A., Gupta, N., Shen, H. *Omalizumab in the treatment of perennial allergic rhinitis*. Eur Respir J 2001, 18(Suppl. 33): Abst P349.

18. Bez, C., Ersfeld, Y., Schubert, R. et al. *Combined effect of omalizumab (rhuMAb-E25, Xolair®) and specific immunotherapy on nasal inflammation*. 98th Int Conf Am Thorac Soc (May 17-22, Atlanta) 2002, Abst C109.

19. Bousquet, J., Hogate, S., Fox, H., Liu, J., Castellsague, J. *Efficacy of omalizumab in allergic asthma patients at high-risk for asthma-related death*. J Allergy Clin Immunol 2002, 109(1, Part 2): Abst 460.

20. Buhl, R., Soler, M., Fox, H., Ashby, M., McAlary, M., Cooper, J., Rohane, P., Johnson, C., Fick, R. *Omalizumab (Xolair®, rhuMAb-E-25), decreases hospitalizations due to serious asthma exacerbations*. Am J Respir Crit Care Med 2001, 163(5, Suppl.): A858.

21. Casale, T.B., Condemi, J., LaForce, C. et al. *Effect of omalizumab on symptoms of seasonal allergic rhinitis. A randomized controlled trial*. JAMA - J Am Med Assoc 2001, 286(23): 2956.

22. Matz, J., Wolfe, J., Shapiro, G., Champain, K., Thirwell, J., Fox, H., Della Cioppa, G. *Omalizumab is safe and well tolerated for long-term treatment in patients with moderate-severe allergic asthma*. Chest 2001, 120(4, Suppl.): 170S.

23. Noga, O., Hanf, G., Kirchhof, E., Buettner, C., Kunkel, G. *Treatment with omalizumab (rhuMAb-E25), a monoclonal anti-IgE antibody induces effective changes in subjects with allergic asthma*. Eur Respir J 2001, 18(Suppl. 33): Abst P345.

24. Wenzel, S., Bousquet, J., Freeman, P., Fox, H. *Factors predictive of response to omalizumab therapy in patients with moderate-to-severe allergic asthma*. J Allergy Clin Immunol 2002, 109(1, Part 2): Abst 458.

25. Busse, W.W., Corren, J., Lanier, B.Q., Everhard, F., Surrey, K., Kirchdoerfer, L. *Omalizumab improves asthma-specific quality of life (QoL): An analysis of data from 1071 patients*. J Allergy Clin Immunol 2002, 109(1, Part 2): Abst 891.

26. Buhl, R., Corren, J., Busse, W. et al. *Omalizumab, a recombinant humanised monoclonal anti-IgE antibody, decreases the risk of serious asthma exacerbations requiring hospitalisation in patients with moderate-to-severe allergic asthma*. Eur Respir J 2001, 18(Suppl. 33): Abst P347.

27. Bousquet, J., Holgate, S., Wenzel, S., Fox, H., Gupta, N. *Omalizumab is well tolerated in patients at high risk of serious asthma-related morbidity and mortality*. 21st Congr Eur Acad Allergol Clin Immunol (June 1-5, Naples) 2002, Abst 1054.

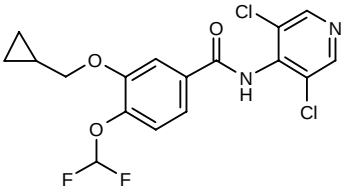
28. Holgate, S., Bousquet, J., Wenzel, S., Fox, H., Liu, J. *Omalizumab improves disease control in patients at high risk of serious asthma-related morbidity and mortality*. 98th Int Conf Am Thorac Soc (May 17-22, Atlanta) 2002, Abst A33.

29. Schoenwetter, W., Gupta, N., Liu, J., Van As, A. *Omalizumab, an anti-immunoglobulin E antibody, is well tolerated in patients with allergic diseases of the airways*. Chest 2002, 122(4, Suppl.): Abst P118.

30. Johansson, S.G.O., Gupta, N., Van As, A. *Omalizumab, an anti-immunoglobulin E antibody, is not associated with an increased risk of immunological reactions*. Eur Respir J 2002, 20(Suppl. 38): Abst P741.

Original monograph - Drugs Fut 2002, 27(6): 537.

Roflumilast



Roflumilast (BY-217) is an orally active, selective PDE4 inhibitor developed at Altana Pharma and recently licensed to Pharmacia for codevelopment for the treatment of respiratory diseases, including asthma and COPD, in the U.S., Europe and other markets. Pharmacia will coordinate the development in the U.S., while Altana will do the same in Europe. The companies will jointly launch and promote roflumilast in the U.S., Europe and other markets. Altana also recently signed a development and commercialization agreement with Tanabe Seiyuaku for Japan. Roflumilast is the first PDE4 inhibitor to achieve proof of concept in both asthma and COPD. The agent is currently in phase III trials for both conditions in Europe and phase II and III trials, respectively, for COPD and asthma in the U.S. (1-3).

Roflumilast and its major metabolite roflumilast-*N*-oxide were at least as effective as piclamilast, rolipram or cilomilast *in vitro* in inhibiting activation of human neutrophils, eosinophils, monocytes, monocyte-derived macrophages, dendritic cells and CD4+ T-cells, and they were clearly more effective *in vivo* in inhibiting antigen-induced lung eosinophilia in Brown-Norway rats and LPS-induced TNF-α production in rats following oral administration (4-7).

In studies in a sensitized Brown-Norway rat model of allergic asthma, intragastric roflumilast was shown to inhibit airways hyperresponsiveness to acetylcholine and to adenosine following antigen challenge (8, 9).

Roflumilast 0.3-3 mg/kg p.o. dose-dependently inhibited airways hyperresponsiveness, neutrophil influx and TNF release in ovalbumin-sensitized, allergen-challenged rats (10).

Immunosuppression with the PDE4 inhibitors rolipram, cilomilast and roflumilast, as well as ciclosporin, was evaluated in a rat model of heterotopic tracheal transplantation. Assessment of epithelial integrity showed that the epithelium was completely lost until day 21 in animals receiving the PDE4 inhibitors. Monocyte/macrophage infiltration during the acute phase was significantly inhibited by cilomilast and to the same degree as with ciclosporin. Rolipram and roflumilast were not as effective as ciclosporin. A significant increase in monocytes and macrophages was seen in the chronic phase after treatment with ciclosporin, but not with PDE4 inhibitors. Rolipram was less potent and cilomilast and roflumilast more potent than ciclosporin in blocking cell proliferation. Among the PDE4 inhibitors, only cilomilast significantly inhibited luminal obliteration, although it was not as effective as ciclosporin. While the PDE4 inhibitors did not appear appropriate for immunosuppression after lung transplantation, cilomilast and roflumilast may be useful in blocking immune cell and fibroblast proliferation leading to obliterative bronchiolitis (11).

Researchers evaluated the effect of smoking on the pharmacokinetics of roflumilast and its major metabolite roflumilast-*N*-oxide. In the study, 24 subjects received a single oral dose of roflumilast 500 μg and the pharmacokinetics in smokers and nonsmokers were compared. It was found that smoking did not affect the pharmacokinetics of roflumilast or the metabolite (12).

An open, randomized, crossover study in 12 healthy volunteers investigated the effect of food intake on the pharmacokinetics of a single oral dose of roflumilast 500 μg. The AUC values of roflumilast and the major metabolite roflumilast-*N*-oxide were similar in the fasted state and after intake of a fat-rich breakfast, although food intake reduced the C_{max} of roflumilast (13, 14).

The pharmacokinetics of roflumilast were found not to be affected by age in an open study in 12 healthy middle-aged subjects. A single oral dose of 500 μg was considered to be safe and well tolerated (15).

The pharmacokinetics of roflumilast and its active metabolite roflumilast-*N*-oxide were assessed in 12 healthy subjects and in 12 patients with severe renal impairment. Subjects received a single oral dose of roflumilast 500 μg. The results indicated that roflumilast dose adjustments were not necessary in patients with severe renal impairment (16, 17).

Administration of a daily dose of 500, 750 and 1000 μg of roflumilast to 18 healthy volunteers revealed that the compound followed linear pharmacokinetics at this dose range, with a $t_{1/2}$ estimated to be between 13.7 and 14.7 h (18, 19).

No pharmacokinetic interactions between roflumilast, its major metabolite roflumilast-*N*-oxide and budesonide or salbutamol were observed in open, randomized, crossover studies in healthy male volunteers (20, 21).

The cardiovascular safety of roflumilast (500 μg/day orally for 5 days) was examined in a double-blind randomized, placebo-controlled, crossover trial in 12 healthy volunteers. The results demonstrated no influence on cardiovascular function at therapeutic doses of roflumilast (22).

A total of 25 subjects with a history of allergic rhinitis but asymptomatic at screening took part in a randomized, double-blind, placebo-controlled trial of roflumilast 500 μg once daily for 9 days, with washout periods of at least 14 days between treatment periods. Assessments following allergen provocation showed that roflumilast provided

Table VI: Clinical studies of roflumilast (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Asthma, COPD	Randomized, double-blind, multicenter	Roflumilast, 100 μg od po x 12 wk (n=229) Roflumilast, 250 μg od po x 12 wk (n=228) Roflumilast, 500 μg od po x 12 wk (n=233)	690	Roflumilast improved asthma control in a dose-dependent manner, increasing FEV_1 and PEF values after 12 weeks of treatment	24
Asthma	Randomized, double-blind	Roflumilast, 500 μg od po x 12 wk (n=207) Beclomethasone dipropionate, 200 μg bid inhal x 12 wk (n=214)	421	Once-daily roflumilast was as effective as twice-daily beclomethasone dipropionate in improving lung function in asthma patients, as assessed using FEV_1, FVC and PEF measurements and asthma symptom scores	25
COPD	Randomized, double-blind, multicenter	Roflumilast, 250 μg od po x 26 wk (n=175) Roflumilast, 500 μg od po x 26 wk (n=169) Placebo (n=172)	516	Roflumilast administered at daily doses of 250 and 500 μg was safe, well tolerated and effective in improving FEV_1 and FVC and decreasing the probability of exacerbations in patients with chronic obstructive pulmonary disease	26-28
Asthma	Randomized, double-blind, crossover	Roflumilast, 250 μg od po x 7-10 d Roflumilast, 500 μg od po x 7-10 d Placebo	23	Compared with placebo, roflumilast dose-dependently decreased both early and late asthmatic responses in patients with mild asthma	29

effective antiallergic therapy, with improvements in rhinal airflow, itching and rhinorrhea (23).

In a multicenter, randomized, double-blind study, 690 asthma patients were given roflumilast 100, 250 or 500 μg once daily for 12 weeks after a placebo run-in period pf 1-3 weeks. The treatment produced dose-dependent increases in FEV_1 and PEF (24, 25). The results of these studies and some that follow are summarized in Table VI.

A double-blind, randomized trial compared the efficacy of 500 μg/day of roflumilast with 200 μg b.i.d. of inhaled beclomethasone dipropionate in 421 symptomatic asthma patients. Both treatments were found to be equally effective, improving lung function and asthma symptoms of the patients to an identical degree (26).

The efficacy of roflumilast in the treatment of asthma was investigated in a double-blind, randomized, placebo-controlled clinical trial. Administration of daily doses of 250 or 500 μg of roflumilast to mild asthma patients for 7-10 days resulted in a dose-dependent inhibition of the early and late asthmatic reactions (27).

A double-blind, randomized, placebo-controlled, crossover study was conducted to determine the efficacy and safety of roflumilast in the treatment of exercise-induced asthma. Sixteen male patients received either placebo or 500 μg/day of roflumilast for 28 days followed by crossover to the other treatment after a washout period of at least 14 days. The results of the study show that roflumilast improved lung function throughout the treatment period, with a mean percentage decrease in FEV_1 after exercise 41% lower than that found with placebo after 28 days. The median LPS-induced TNF-α levels in whole blood *ex vivo* decreased by 21% on roflumilast but remained the same with placebo, suggesting that treatment with roflumilast inhibits inflammatory cell activation. No clinically significant safety problems were detected during treatment with roflumilast, and most adverse events reported were mild, transient and disappeared spontaneously without having to discontinue the medication. Overall, roflumilast appears to be an effective and safe therapeutic option in the treatment for exercise-induced asthma (28).

New data were reported on the efficacy of roflumilast in patients with COPD who were randomized to receive 250 or 500 μg/day of roflumilast or placebo for 26 weeks. Compared to placebo, patients treated with roflumilast showed an increase in FEV_1, morning PEF and FVC, together with a lower probability of experiencing an exacerbation. Roflumilast was well tolerated, with a similar incidence of adverse events in the placebo and roflumilast treatment groups (49% for placebo and roflumilast 250 mcg and 48% for roflumilast 500 μg). The most frequent adverse events associated with roflumilast were mild to moderate headache (2%), nausea (2%) and diarrhea (1%). No severe or serious adverse events were reported, suggesting that roflumilast was both safe and well tolerated in this population of patients (29-31).

Combinations of a PDE4 inhibitor such as roflumilast and a leukotriene antagonist, particularly montelukast, have been claimed for the treatment of bronchial and respiratory disorders (32).

1. *Altana and Pharmacia to codevelop and comarket roflumilast for respiratory conditions*. DailyDrugNews.com (Daily Essentials) April 26, 2002.

2. *Altana and Tanabe Seiyaku to develop and commercialize roflumilast in Japan*. DailyDrugNews.com (Daily Essentials) Nov 20, 2002.

3. *Altana reports decisive progress in development of roflumilast and ciclesonide.* DailyDrugNews.com (Daily Essentials) Aug 29, 2001.

4. Hatzelmann, A., Schudt, C. *Anti-inflammatory and immunomodulatory potential of the novel PDE4 inhibitor roflumilast in vitro*. J Pharmacol Exp Ther 2001, 297(1): 267.

5. Bundschuh, D.S., Barsig, J., Beume, R., Eltze, M., Schudt, C., Wollin, L., Hatzelmann, A. *In vitro and in vivo anti-inflammatory activity of the novel PDE4 inhibitor roflumilast*. Eur Respir J 2001, 18(Suppl. 33): Abst P338.

6. Bundschuh, D.S., Eltze, M., Barsig, J., Wollin, L., Hatzelamm, A., Beume, R. *In vivo efficacy in airway disease models of roflumilast, a novel orally active PDE4 inhibitor*. J Pharmacol Exp Ther 2001, 297(1): 280.

7. Bundschuh, D.S., Barsig, J., Beume, R., Eltze, M., Schudt, C., Wollin, L., Hatzelmann, A. *Antiinflammatory and immunomodulatory potential of roflumilast, a novel PDE4 inhibitor*. Am J Respir Crit Care Med 2001, 163(5, Suppl.): A431.

8. Wollin, L., Barsig, J., Bundschuch, D.S., Beume, R. *Inhibition by roflumilast of airway hyperresponsiveness to adenosine and pulmonary neutrophil accumulation 3h after allergen challenge in rats*. Am J Respir Crit Care Med 2001, 163(5, Suppl.): A432.

9. Hoymann, H.G., Wollin, L., Krug, N., Hohfeld, J., Beume, R. *Inhibition by roflumilast of airway hyperresponsiveness to acetylcholine 48h after allergen challenge in rats*. Am J Respir Crit Care Med 2001, 163(5, Suppl.): A431.

10. Wollin, L., Barsig, J., Bundschuh, D.S., Marx, D., Beume, R. *Inhibition by roflumilast of airway hyperresponsiveness to adenosine and pulmonary inflammation in allergen challenged Brown-Norway rats*. Eur Respir J 2001, 18(Suppl. 33): Abst P337.

11. Schade, I., Roth-Eichhorn, S., Kasper, M., Kuss, H., Plötze, K., Funk, R.H.W., Schüler, S. *Benefit of phosphodiesterase 4 inhibitors as supplemental therapy after lung transplantation concerning their antiproliferative effects: An experimental study using a heterotopic rodent model*. Transplantation 2002, 74(3): 326.

12. Hünnemeyer, A., Hauns, B., Drollmann, A., David, M., Zech, K., Bethke, T., Wurst, W., Gulden, B. *Pharmacokinetics of roflumilast and its active metabolite, roflumilast-N-oxide, is not influenced by smoking*. 98th Int Conf Am Thorac Soc (May 17-22, Atlanta) 2002, Abst C91.

13. Hauns, B., Bethke, T., Hünnemeyer, A., Hartmann, M., Wurst, W., Zech, K., Gulden, B. *Influence of food intake on the pharmacokinetics of roflumilast and its active metabolite roflumilast-N-oxide*. 98th Int Conf Am Thorac Soc (May 17-22, Atlanta) 2002, Abst C95.

14. Drollmann, A., Huennemayer, A., Hartmann, M., Hauns, B., Zech, K., Bethke, T.D. *Pharmacokinetic characteristics of roflumilast and its active metabolite roflumilast N-oxide are not affected by food intake*. Eur Respir J 2002, 20(Suppl. 38): Abst P747.

15. Manegold, A., Huennemayer, A., Zech, K., Hauns, B., David, M., Bethke, T.D., Wurst, W. *Phamacokinetics of roflumilast and its active metabolite roflumilast N-oxide in middle aged and young subjects*. Eur Respir J 2002, 20(Suppl. 38): Abst P744.

16. Bethke, T., Hartmann, M., Zech, K., David, M., Weimar, C., Wurst, W., Gulden, B. *No dose adjustment of roflumilast in patients with severe renal impairment*. 98th Int Conf Am Thorac Soc (May 17-22, Atlanta) 2002, Abst C90.

17. Drollmann, A., Hartmann, M., Zech, K., David, M., Weimar, C., Bethke, T.D. *Patients with severe renal impairment do not require dose adjustment of roflumilast*. Eur Respir J 2002, 20(Suppl. 38): Abst P743.

18. Manegold, A., Hauns, B., David, M., Zech, K., Bethke, T.D., Wurst, W. *Pharmacokinetic characteristics of roflumilast administered in gradually increasing doses of 500 µg to 1000 µg are dose-linear in healthy subjects*. Eur Respir J 2002, 20(Suppl. 38): Abst P742.

19. Bethke, T., Hauns, B., Zech, K., David, M., Wurst, W., Gulden, B. *Dose linearity of roflumilast: A new selective PDE4 inhibitor*. 98th Int Conf Am Thorac Soc (May 17-22, Atlanta) 2002, Abst C94.

20. Hünnemeyer, A., Bethke, T., David, M., Westphal, K., Wurst, W. *No interaction of roflumilast and its active metabolite, roflumilast-N-oxide, with inhaled budesonide*. 98th Int Conf Am Thorac Soc (May 17-22, Atlanta) 2002, Abst C93.

21. Weimar, C., Bethke, T., Wetphal, K., Zech, K., Siegmund, W., Wurst, W. *Roflumilast and its active metabolite, roflumilast-N-oxide, do not interact with inhaled salbutamol*. 98th Int Conf Am Thorac Soc (May 17-22, Atlanta) 2002, C89.

22. Bethke, T.D., Hartmann, M., Baumgartner, A., Eichberger, C., Hauns, B., Wurst, W. *The new PDE4 inhibitor roflumilast does not influence cardio-vascular function*. Am J Respir Crit Care Med 2001, 163(5, Suppl.): A431.

23. Schmidt, B.M.W., Kusma, M., Feuring, M., Timmer, W.E., Neuhauser, M., Bethke, T., Stuck, B.A., Hormann, K., Wehling, M. *The phosphodiesterase 4 inhibitor roflumilast is effective in the treatment of allergic rhinitis*. J Allergy Clin Immunol 2001, 108(4): 530.

24. Leichtl, S., Schmid-Wirlitsch, C., Bredenbröker, D., Rathgeb, F., Wurst, W., Gulden, B. *Dose-related efficacy of once-daily roflumilast, a new, orally active, selective phosphodiesterase 4 inhibitor, in asthma*. 98th Int Conf Am Thorac Soc (May 17-22, Atlanta) 2002, Abst A23.

25. Leichtl, S., Schmid-Wirlitsch, C., Bredenbroker, D., Rathgeb, F., Wurst, W. *Roflumilast, a new, orally active, selective phosphodiesterase 4 inhibitor, is effective in the treatment of asthma*. Eur Respir J 2002, 20(Suppl. 38): Abst P1908.

26. Albrecht, A., Leichtl, S., Bredenbroker, D., Bethke, T., Wurst, W. *Comparison of roflumilast, a new, orally active, selective phosphodiesterase 4 inhibitor, with beclomethasone dipropionate in asthma controls*. Eur Respir J 2002, 20(Suppl. 38): Abst P1911.

27. van Schalkwyk, E.M., van Heerden, K., Bredenbroker, D., Leichtl, S., Wurst, W., Venter, L., Bardin, P.G. *Dose-dependent inhibitory effect of roflumilast, a new, orally active, selective phosphodiesterase 4 inhibitor, on allergen-induced early and late asthmatic reaction*. Eur Respir J 2002, 20(Suppl. 38): Abst P751.

28. Timmer, W., Leclerc, V., Birraux, G., Neuhäuser, M., Hatzelmann, A., Bethke, T., Wurst, W. *The new phosphodiesterase 4 inhibitor roflumilast is efficacious in exercise-induced asthma and leads to suppression of LPS-stimulated TNF-alpha ex vivo*. J Clin Pharmacol 2002, 42(3): 297.

29. Bredenbröker, D., Syed, J., Leichtl, S., Rathgeb, F., Wurst, W. *Roflumilast, a new orally active phosphodiesterase 4 inhibitor, is effective in the treatment of chronic obstructive pulmonary disease*. Eur Respir J 2002, 20(Suppl. 38): Abst 2330.

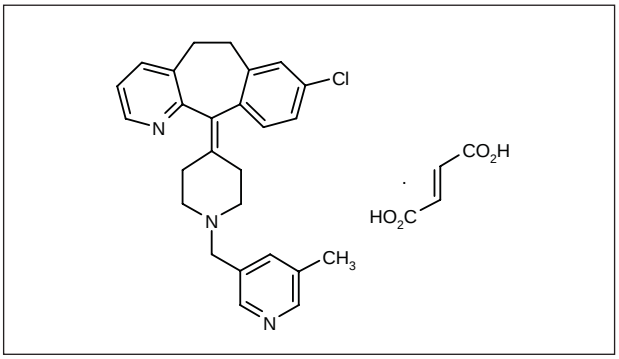
30. Bredenbröker, D., Syed, J., Leichtl, S., Rathgeb, F., Wurst, W., Gulden, B. *Safety of once-daily roflumilast, a new, orally active, selective phosphodiesterase 4 inhibitor, in patients with COPD*. 98th Int Conf Am Thorac Soc (May 17-22, Atlanta) 2002, Abst C92.

31. Leichtl, S., Syed, J., Bredenbröker, D., Rathgeb, F., Wurst, W. *Roflumilast, a new, orally active, selective phosphodiesterase 4 inhibitor, is safe and well tolerated in patients with chronic obstructive pulmonary disease*. Eur Respir J 2002, 20(Suppl. 38): Abst P1907.

32. Chang, Y. (Merck & Co., Inc.). *Method of treatment with a combination of a PDE4 inhibitor and a leukotriene antagonist*. WO 0238155.

Original monograph - Drugs Fut 2000, 25(12): 1261.

Rupatadine Fumarate



Uriach's rupatadine fumarate (UR-12592, Rupafin), an orally active, nonsedating histamine H_1 receptor and PAF antagonist, was launched in Spain in 2001 for the treatment of allergic rhinitis.

A study in guinea pigs with histamine-, PAF- or ovalbumin-induced experimental conjunctivitis demonstrated the efficacy of topical rupatadine (0.0005-0.1% solution) as compared to loratadine and levocabastine (0.001-0.1% solution). Treatment was administered ocularly 15 min prior to exposure to histamine, PAF or ovalbumin. Rupatadine was well tolerated and significantly and dose-dependently prevented histamine-induced conjunctivitis. Loratadine at doses of 0.01% or higher also prevented histamine conjunctivitis, and levocabastine (0.001%) was the most active agent. Treatment with rupatadine also prevented PAF-induced conjunctivitis at doses of 0.05 and 0.1%, whereas loratadine and levocabastine had no significant effects. Similarly, although levocabastine had no effect, rupatadine (0.03-0.1%) inhibited ovalbumin-induced conjunctivitis (1).

The efficacy and safety of rupatadine and ebastine were compared in a multicenter, randomized, double-blind, placebo-controlled study in outpatients with SAR. Patients were randomized to rupatadine 10 mg/day, ebastine 10 mg/day or placebo once daily for 2 weeks. Statistically significant differences were found between rupatadine and placebo for mean daily total symptom score. The lowest mean daily symptom scores were found with rupatadine, while for ebastine and placebo these values were only statistically significant for runny nose. Both ebastine and rupatadine were significantly better than placebo according to patient and investigator assessments. Both agents were well tolerated, with headache being the most common adverse event reported overall (2).

Pooled analysis of data from 10 clinical studies involving over 2,000 subjects with SAR and PAR was conducted in order to better define the effects of rupatadine fumarate. The results supported previous data indicating effective doses of 10 and 20 mg for optimal symptomatic improvement. Furthermore, no influence of gender or age on the effects of the drug could be discerned (3).

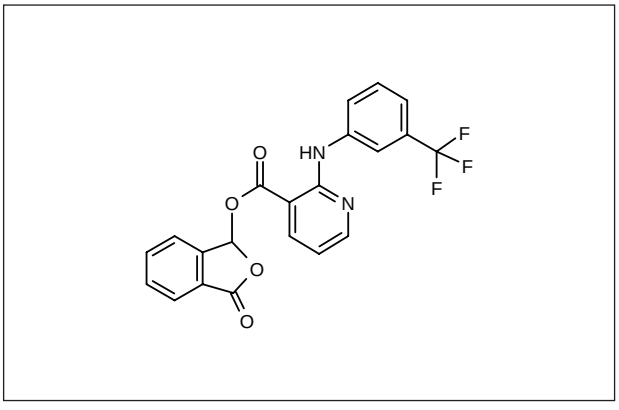
1. Merlos, M., Ferrando, R., Giral, M., Ramis, I., Forn, J. *Effect of topical rupatadine in experimental conjunctivitis in guinea pigs: Macroscopic evaluation of ocular lesions.* J Allergy Clin Immunol 2001, 107(2, Part 2): Abst 1016.

2. Izquierdo, I., Lurigados, C., Pérez, I., Forn, J. *Rupatadine exhibits a better profile than ebastine in patients with seasonal allergic rhinitis.* Allergy 2001, 56(Suppl. 68): Abst 635.

3. Perez, I., De la Cruz, G., Villa, M., Izquierdo, I. *Rupatadine in allergic rhinitis: Pooled analysis of efficacy data*. 21st Congr Eur Acad Allergol Clin Immunol (June 1-5, Naples) 2002, Abst 784.

Original monograph - Drugs Fut 1996, 21(10): 1032.

Talniflumate



Talniflumate (Ba-7602-06, MSI-1995, Solmagen®, Lomucin™) was discovered, developed and has been marketed by Bago in Argentina and selected other countries for almost 20 years as an antiinflammatory agent. The compound was subsequently shown to block the human calcium-activated chloride channel hCLCA1, which regulates abnormal mucus production. Genaera holds exclusive rights to talniflumate as an oral mucoregulator in all major markets, including the U.S., Europe and Japan, and is developing it for the treatment of mucus overproduction in asthma and cystic fibrosis patients.

Genaera is currently conducting a phase II trial of talniflumate in CF patients in Ireland. The double-blind, placebo-controlled, randomized trial is evaluating tolerance and the preliminary efficacy of talniflumate oral tablets on respiratory symptoms and pulmonary function in CF patients. Of the 60 patients to be enrolled, 40 will receive talniflumate for 30 days and 20 will receive placebo. Results are expected in the first half of 2003. The clinical development of talniflumate in the CF indication is supported by an initial Therapeutics Development Grant of up to USD 1.7 million from Cystic Fibrosis Foundation Therapeutics, the nonprofit drug development affiliate of the Cystic Fibrosis Foundation. Genaera also announced positive results from its first clinical study of talniflumate in asthma. The open-label, single-center, randomized study evaluated 63 patients with chronic asthma, of whom 42 received talniflumate and 21 ibuprofen. The gastrointestinal and respiratory tolerance of talniflumate oral tablets in these patients was assessed, along with the preliminary effects on symptoms and pulmonary function. As the primary outcome, talniflumate was well tolerated, with a trend for improved gastrointestinal tolerance compared to ibuprofen and no serious adverse events. There were no significant differences in the effects on asthma symptoms compared to ibuprofen. Patients with moderate asthma experienced a positive efficacy trend, as demonstrated by increased residual volume at baseline. In these patients, representing half of the enrolled participants, talniflumate significantly decreased residual volume by 28%, compared to 13% with ibuprofen. This trend may be a result of talniflumate's mucoregulatory activity causing decreased mucus production and opening of small airways (1-4).

1. *Genaera provides Lomucin update in cystic fibrosis and asthma*. DailyDrugNews.com (Daily Essentials) Oct 25, 2002.

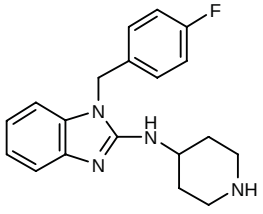
2. Urueta, J., Desai, A., Holroyd, K., Solomon, S., Levitt, R., Petrone, M: *Open-label, randomized tolerability study of mucoregulator MSI-1995 (Lomucin™) in chronic moderate asthma*. 98th Int Conf Am Thorac Soc (May 17-22, Atlanta) 2002, Abst H13.

3. *Genaera initiates first clinical trial for Lomucin*. DailyDrugNews.com (Daily Essentials) Aug 24, 2001.

4. *Genaera receives Cystic Fibrosis Foundation grant to develop Lomucin*. DailyDrugNews.com (Daily Essentials) Sept 27, 2001.

Original monograph - Drugs Fut 1979, 4(6): 448.

Tecastemizole



Sepracor's NDA for the nonsedating antihistamine tecastemizole (formerly norastemizole, Soltara™), submitted in March 2001 seeking clearance for use as a capsule formulation in the treatment of allergic rhinitis, was deemed not approvable in early 2002 by the FDA. The FDA raised issues relating to safety, particularly as regards the cardiovascular system, and to the possibility of accumulation in target organs following prolonged exposure. The NDA was supported by data from 7 large-scale allergic rhinitis studies, over 30 smaller clinical trials and numerous preclinical studies. The clinical studies included over 3,700 subjects with SAR and PAR administered tecastemizole at doses of 2-300 mg. Sepracor is also developing a tecastemizole/pseudoephedrine combination for the treatment of allergic rhinitis, as well as syrup and rapidly dissolving tablet formulations (1-5).

The pharmacokinetics of single oral doses of tecastemizole were investigated in healthy subjects, those between 6 and 11 years of age receiving 5 or 15 mg and adults receiving 30 mg. All doses were well tolerated and exhibited predictable behavior. The 15-mg dose provided comparable exposure to the 30-mg dose given to adults (6).

An 8-week study evaluated the pharmacokinetics of tecastemizole 30 mg in healthy adults aged 18-55 years. Steady state was reached by 14 days, with a $t_{1/2}$ of 30-40 h (7).

The results of a pharmacokinetic study of a single oral dose of tecastemizole (90 mg) in subjects with mild to moderate or moderate to severe hepatic or renal insufficiency indicated that dose adjustments of the drug should not be necessary in these patients (8, 9).

A pharmacokinetic study evaluated single doses of tecastemizole (30 mg) given alone or concomitantly with erythromycin (500 mg) for 7 days in healthy adult volunteers. The pharmacokinetics of erythromycin were not affected by tecastemizole, while tecastemizole pharmacokinetic parameters increased somewhat with erythromycin coadministration. No tecastemizole dose adjustment was deemed necessary, however, when the drugs are administered together (10).

The cardiovascular safety of tecastemizole was assessed in a randomized, open-label, dose-escalation study in which healthy volunteers received single doses of 30, 150 and 250 mg or 90, 200 and 300 mg. A multiple-dose phase also involved 10 subjects who received tecastemizole 300 mg for 14 days. No dose- or

concentration-dependent effects on Q-Tc interval were seen at doses higher than the therapeutic dose and at high plasma exposures (11).

A double-blind, placebo-controlled, ascending-dose study compared the effects of single morning doses of tecastemizole (25, 50 or 100 mg) and placebo on histamine-induced wheal and flare reactions. All doses of tecastemizole produced maximum inhibition of the responses to histamine of 90-100% compared to placebo. The onset of activity was 0.5-1 h, with peak activity seen at about 4 h and lasting for at least 8 h. The intermediate and high doses of tecastemizole were associated with inhibition of histamine-induced flare for up to 24 h. All doses were safe (12).

A multicenter, randomized, double-blind study in an outdoor setting compared single doses of tecastemizole 30 mg to placebo in 885 subjects with pollen allergies. Already at the first timepoint (measured 20 min after dosing) tecastemizole decreased total, nasal and non-nasal symptom scores by 43%, 25% and 100%, respectively, over placebo. Tecastemizole was still more effective than placebo at 8 h postdose, with average reductions from baseline in total, nasal and non-nasal symptom scores of 53%, 47% and 55%, respectively, *versus* respective values of 39%, 34% and 41% on placebo. No differences were seen in the number or severity of adverse events (13).

A double-blind, randomized, placebo-controlled, parallel-group study examined multiple doses of tecastemizole (15, 30 or 45 mg once daily for 2 weeks) or placebo in subjects with SAR. The greatest improvement in total symptom score compared to placebo was obtained on the dose of 30 mg, and this dose also significantly reduced non-nasal symptoms compared to placebo over the entire treatment period and trough total symptom score at week 1. Nasal symptoms were significantly improved on all doses of tecastemizole compared to placebo. At the dose of 30 mg, tecastemizole was associated with significantly fewer adverse events than placebo, with no significant differences in various safety parameters among the other treatment groups (14).

Tecastemizole (30 mg once daily) was compared to placebo in a multicenter, double-blind, randomized study in patients with SAR who completed daily diary cards at 12 and 24 h after each dose. Significant improvement in total symptom score compared to placebo was seen at 12 h after the first dose of the antihistamine. For the duration of the study, trough total symptom score at 24 h after the previous dose was also significantly decreased from baseline on tecastemizole compared to placebo. Significantly greater efficacy was also seen for tecastemizole for reduction in total symptom score, nasal total symptom score, trough nasal total symptom score, non-nasal total symptom score and trough non-nasal total symptom score. No significant adverse events were seen, and fewer subjects reported sedation on tecastemizole (0.5%) compared to placebo (4.3%) (15).

1. *Soltara moves into formal review at the FDA*. DailyDrugNews.com (Daily Essentials) May 10, 2001.

2. *Sepracor pharmaceutical products portfolio update*. DailyDrugNews.com (Daily Essentials) Jan 8, 2001.

3. *Year 2000 progress highlighted by Sepracor*. DailyDrugNews.com (Daily Essentials) Feb 2, 2001.

4. *Sepracor submits norastemizole NDA for treatment of allergic rhinitis*. DailyDrugNews.com (Daily Essentials) March 13, 2001.

5. *FDA finds Soltara not approvable*. DailyDrugNews.com (Daily Essentials) March 8, 2002.

6. Baumgartner, R., Carpio, J., Maier, G. *Comparison of tecastemizole pharmacokinetics in healthy adult and pediatric subjects*. Annu Meet Am Coll Allergy Asthma Immunol (Nov 12-17, Chicago) 2001, Abst 11.

7. Maier, G., Goldwater, D.R., Jensen, D., Smith-Remillard, A. *Steady state pharmacokinetic study of tecastemizole in healthy subjects*. Annu Meet Am Coll Allergy Asthma Immunol (Nov 12-17, Chicago) 2001, Abst P35.

8. Albrecht, J., Maier, G. *Pharmacokinetics of tecastemizole in subjects with mild-to-severe hepatic impairment*. Annu Meet Am Coll Allergy Asthma Immunol (Nov 12-17, Chicago) 2001, Abst P37.

9. Swan, S., Maier, G., Miller, P.J. *Pharmacokinetics of tecastemizole in subjects with mild-to-severe renal impairment*. Annu Meet Am Coll Allergy Asthma Immunol (Nov 12-17, Chicago) 2001, Abst P38.

10. Goldwater, D.R., Maier, G., Jauch, B.M. *Pharmacokinetics of tecastemizole administered concomitantly with erythromycin*. Annu Meet Am Coll Allergy Asthma Immunol (Nov 12-17, Chicago) 2001, Abst P39.

11. Ferguson, C., DeGraw, S., Wilson, A., Tripp, K., Vaickus, L. *Human cardiac safety of tecastemizole: No evidence of QT prolongation despite high plasma concentrations*. Annu Meet Am Coll Allergy Asthma Immunol (Nov 12-17, Chicago) 2001, Abst P36.

12. Degraw, S.S., Baumgartner, R.A. *Tecastemizole induces a rapid and sustained inhibition of wheal and flare reactions*. J Allergy Clin Immunol 2002, 109(1, Part 2): Abst 274.

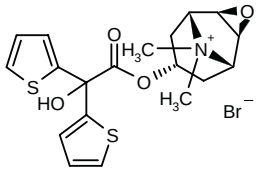
13. Ratner, P., Hampel, F.C., Baumgartner, R.A. *Tecastemizole produces rapid and sustained symptom reduction in seasonal allergic rhinitis*. J Allergy Clin Immunol 2002, 109(1, Part 2): Abst 285.

14. Meltzer, E.O. et al. *Tecastemizole effectively reduces total and nasal allergic symptoms*. J Allergy Clin Immunol 2002, 109(1, Part 2): Abst 275.

15. Corren, J. et al. *Tecastemizole 30 mg effectively reduces the symptoms of allergic rhinitis*. J Allergy Clin Immunol 2002, 109(1, Part 2): Abst 273.

Original monograph - Drugs Fut 1998, 23(9): 966.

Tiotropium Bromide



Tiotropium bromide (Spiriva®), the first once-daily inhaled therapy for COPD, was launched by Boehringer Ingelheim and its global copromotion partner Pfizer last year in The Netherlands, Finland, Sweden, Germany, Denmark and the Philippines as a bronchodilator for the maintenance treatment of COPD. Tiotropium has been approved throughout the E.U., with The Netherlands acting as the reference member state following its approval there in October 2001, and it has also been registered in New Zealand, Slovakia and Mexico. An NDA for the product was submitted in the U.S. in December 2001 and an FDA advisory committee subsequently issued a positive recommendation. The product is also undergoing regulatory review in Japan, where it will be copromoted by Nippon Boehringer Ingelheim and Pfizer (1-8).

Similar pharmacokinetic parameters have been reported for the anticholinergic drugs tiotropium and ipratropium in rats after administration of a single i.v. dose of 7-8 mg/kg. Both drugs showed similar concentration-time profiles, with a very high volume of distribution and a rapid clearance rate. Similar results were reported in dogs after a single dose of 0.08 mg/kg of tiotropium by i.v. bolus or 0.106 mg/kg/h of ipratropium i.v. over 3 h. Intratracheal administration of either drug was associated with lower but more persistent plasma levels, and although both drugs were absorbed orally, the absorption rates were much higher in dogs than in rats (46% and 38% in dogs, and 6% and 12% in rats, respectively, for tiotropium and ipratropium) (9).

A randomized, double-blind clinical trial compared the effects of tiotropium (18 μg by once-daily inhalation) and placebo administered for 6 weeks to 187 patients with COPD. Tiotropium was found to reduce dyspnea during activities of daily living and during cycle ergometer exercise. It was significantly better than placebo in reducing static lung hyperinflation, which in turn may contribute towards the improvement in dyspnea (10, 11).

A total of 31 patients with a mean FEV_1 value of 38% of predicted were allocated to receive either tiotropium 18 μg once daily or ipratropium 40 μg 4 times daily for 1 week. The analysis of the FEV_1 and FVC of the patients 1 h before and up to 6 h after inhalation of the first morning dose revealed that tiotropium increased the values of both parameters. The steady-state FEV_1 was reached after 2 days of treatment, whereas improvements in the FVC were still found after 1 week (12).

A double-blind, randomized, parallel-group study showed that tiotropium has a marked effect on aerosol distribution patterns in COPD. Controlled inhalation of 5 μM inert ^{99m}Tc-radioaerosol particles was followed by radioaerosol imaging in 37 COPD patients. Patients were given either tiotropium (18 μg once daily) or placebo for 3 weeks, at which time inhalation and imaging were repeated. The percentage improvement produced by tiotropium compared to placebo was significant in 3 aerosol indices: FEV_1 (+11.8 ± 12.5% *vs.* –6.1 ± 16.5%), penetration index (+29.3 ± 47.8% *vs.* –16.2 ± 37%) and alveolar deposition at 48 h (+24 ± 41% *vs.* –13.1 ± 28.7%) (13).

Results from double-blind, randomized, placebo-controlled studies showed that tiotropium inhaled daily for 1 year favorably influenced FEV_1 levels in 921 COPD patients. The baseline mean FEV_1 for both treatment and control groups was 1.01 ± 0.42 l. Results from spirometry performed at baseline and again predose at the end of the 12-month study yielded changes in FEV_1 values of 0.11 l (+10.9%) and –0.04 l (–4.0%), respectively, on tiotropium and placebo. The changes in day 8 predose FEV_1 values compared to last predose values were –0.01 l (–0.9%) and –0.04 l (–4.0%), respectively, and changes in the 3-h postdose values on day 8 were –0.04 l (–3.2%) and –0.05 l (–4.9%) for tiotropium and placebo, respectively (14). Tiotropium-treated patients did not experience the decline in health status seen in placebo-treated patients. The difference in health status between the two groups of patients widened over the course of the study (15). The benefits of treatment with tiotropium disappeared after withdrawal of the treatment. The improvement in dyspnea, health status and rescue use of β-adrenoceptor agonists compared to placebo mostly disappeared by 3 weeks of follow-up after discontinuation of tiotropium. It was suggested that evaluation of withdrawal may be useful in assessing clinical efficacy of chronic therapies (16). PEF rates prior to an exacerbation were unchanged in the patients administered tiotropium and only moderate changes were observed in the placebo group. Although the PEF rate results indicated that tiotropium improved lung function, the parameter appears to have only limited use in detecting exacerbations in COPD (17). The Transition Dyspnea Index (TDI) was used to compare the effects of placebo and tiotropium on the breathlessness of the patients. After 1 year of treatment, the changes in the TDI correlated with those found in FEV_1, physician's global evaluation and dyspnea diary scores, suggesting that the TDI is a valid tool to measure changes in breathlessness associated with tiotropium therapy (18). Tiotropium was also effective in increasing FEV_1 compared to placebo in patients with different frequencies of exacerbations. The results indicated that

an increasing frequency of exacerbations is associated with a lower baseline FEV_1 and a higher rate of FEV_1 decline over time. It was suggested that reducing the frequency of exacerbations may result in a reduced rate of decline in FEV_1 in COPD (19). The impact of exacerbations on health-related quality of life (HRQL), as measured on the St. George's Respiratory Questionnaire (SGRQ), was reduced in tiotropium-treated patients as compared to controls (20). Other data from these studies showed that nocturnal symptoms were associated with markers of disease severity (lower FEV_1, increased dyspnea and lower HRQL scores) and that tiotropium helped to improve symptoms as compared to placebo (21). Results from these studies and some that follow are summarized in Table VII.

A randomized, placebo-controlled, double-blind trial in COPD patients showed that tiotropium once daily in the morning or evening improves sleep-related oxygen desaturation (SaO_2) during rapid eye movement (REM) sleep without impairing sleep quality. Sleep disturbance was observed in all patients (n=94), with no significant differences between morning and evening groups. Patients in both treatment groups demonstrated higher morning spirometry values and fewer exacerbations (1/64) than placebo patients (3/30). Of the 49 patients with acceptable sleep data, both morning and evening groups showed significantly higher SaO_2 levels during REM sleep (+2.31% and +2.13%, respectively) as compared to placebo (22).

The effects of tiotropium on regional ventilatory responses in COPD patients were shown to be greater than those detectable by standard spirometry in a double-blind, randomized, parallel-group study. Patients received either tiotropium 18 μg once daily for 3 weeks (n=18) or placebo (n=19). Quantitative analysis did not show a statistically significant overall enhancement from drug treatment, although patients with poor peak flow experienced significant improvement as compared to those with higher peak flow (23).

Parallel to 2 double-blind, randomized, controlled trials in 519 patients with COPD, the impact of tiotropium and ipratropium on healthcare resource utilization and overall costs was analyzed. The results demonstrated reductions in the number of exacerbations, improved quality of life and consistently reduced healthcare utilization for patients treated with tiotropium compared to ipratropium, suggesting that the higher cost of the new drug may be balanced by lower healthcare costs (24).

Healthcare resource use and exacerbations were examined in 1,207 patients with COPD treated with tiotropium 18 μg/day, salmeterol 50 μg b.i.d. or placebo for 6 months. Patients taking either tiotropium or salmeterol had fewer days in hospital compared with placebo. Tiotropium, however, was superior to salmeterol in the number of hospitalizations per patient, the number of patients requiring hospitalization, the number of unscheduled physician visits and the days patients were unable to perform daily activities (25). Tiotropium significantly delayed the time to the first exacerbation compared with placebo and signficantly fewer exacerbations per patient year were seen in tiotropium-treated *versus* placebo-treated patients. Tiotropium-treated patients also tended to have fewer exacerbations leading to hospitalizations than patients receiving salmeterol or placebo (26).

A retrospective analysis of two 6-month, randomized, placebo-controlled trials in patients with COPD in which tiotropium 18 μg/day or salmeterol 50 μg b.i.d. were assigned evaluated only the subgroup of patients (n=524) who received inhaled steroids before the studies. In these patients, tiotropium was superior to salmeterol in terms of FEV_1 and FVC, as well as measures of dyspnea, exacerbations and quality of life (27).

A total of 623 patients suffering from COPD were included in a 6-month, multicenter, double-blind, randomized, placebo-controlled clinical trial aimed at comparing the effects and safety of tiotropium bromide 18 μg once daily with salmeterol 50 μg b.i.d. While both agents improved FEV_1 and FVC values, the effect of salmeterol declined over 6 months, while that of tiotropium did not. The quality of life and dyspnea symptoms of the patients improved significantly more with tiotropium than with salmeterol (28, 29).

Results of a study comparing tiotropium with ipratropium in patients with COPD showed that more patients in the tiotropium (18 μg once daily) group than in the ipratropium (40 μg q.i.d.) group achieved clinically relevant improvement in dyspnea (31% *vs*. 18%). Moreover, lung function on tiotropium as assessed by trough FEV_1 was approximately 150 ml above that observed with ipratropium at the end of the study. Health-related quality of life as measured by the SGRQ showed sustained improvement over 1 year on tiotropium compared to ipratropium, with more patients in the tiotropium group achieving clinically meaningful improvement in key measures after 1 year of treatment (52% *vs*. 35%). Tiotropium was also associated with a significant reduction in the frequency of exacerbations of 24% over 1 year compared to ipratropium. The only adverse event consistently reported more frequently with tiotropium was dry mouth (12.1% *vs*. 6.1%), which was generally mild and transient (30).

Results from two 1-year placebo-controlled trials supported the use of once-daily tiotropium in the maintenance treatment of COPD patients. In these studies, lung function (predose FEV_1) at 1 year improved by 12% over baseline in the tiotropium group compared to a decline of 2% in the placebo group. Significant improvements in dyspnea were also seen on tiotropium compared to placebo. Exacerbations were reduced by 20% over the placebo group, resulting in a 44% reduction in COPD-related hospitalizations. Moreover, as measured by the SGRQ, 49% of patients treated with tiotropium achieved clinically significant improvement in health-related quality of life compared with only 30% of those treated with placebo. The only adverse event consistently reported as possibly related to tiotropium and more frequently than on placebo was dry mouth (16% *vs*. 2.7%) (31).

A retrospective analysis of phase I studies has revealed that tiotropium bromide may be useful in the

Table VII: Clinical studies of tiotropium bromide (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
COPD	Double-blind, pooled/meta-analysis	Tiotropium, 18 μg od x 1 y (n=518) Placebo (n=328)	846	Tiotropium was more effective than placebo in inducing broncho-dilation in patients with chronic obstructive pulmonary disease irrespective of the degree of severity and frequency of exacerbations	5, 20, 30
COPD	Randomized, double-blind	Tiotropium, 18 μg od inhal x 6 wk (n=96) Placebo (n=91)	187	Tiotropium was effective in reducing the degree of dyspnea during exercise and also in performing daily activities in patients with chronic obstructive pulmonary disease	10, 11
COPD	Randomized, double-blind	Tiotropium, 18 μg od inhal x 3 wk (n=18) Placebo (n=19)	37	In addition to the effects detected by spirometry, tiotropium had effects on ventilatory distribution in patients with chronic obstructive pulmonary disease	13, 23
COPD	Randomized, double-blind, pooled/meta-analysis	Tiotropium, 18 μg od inhal x 1 y (n=550) Placebo (n=371)	921	Tiotropium for 1 year was more effective than placebo in improving lung function dyspnea, health status and rescue use of β-agonists in patients with mild chronic obstructive pulmonary disease irrespective of gender and frequency of exacerbations. Those changes could not be maintained after discontinuation of treatment, despite the use of other therapies	14-19, 21 31, 32, 34
COPD	Randomized, double-blind	Tiotropium AM x 4 wk Tiotropium PM x 4 wk Placebo	95	Tiotropium was effective in improving saturation of oxygen during REM sleep without impairing sleep quality, irrespective of the time of administration	22
COPD	Randomized, double-blind	Tiotropium Ipratropium	519	Tiotropium was more effective than ipratropium in reducing the number of exacerbations and improving quality of life in patients with chronic obstructive pulmonary disease	24
COPD		Tiotropium, 18 μg od inhal x 6 mo (n=402) Salmeterol, 50 μg od inhal x 6 mo (n=405) Placebo (n=400)	1207	Tiotropium was more effective than salmeterol and placebo in improving lung function and health-related quality of life as well as healthcare resource utilization in patients with chronic obstructive pulmonary disease	25, 26
COPD	Randomized, pooled/meta-analysis	Tiotropium, 18 μg od inhal x 6 mo (n=253) Salmeterol, 50 μg od inhal x 6 mo (n=271) Placebo	524	Tiotropium was more effective than salmeterol in improving lung function, dyspnea, exacerbations and quality of life in patients with chronic obstructive pulmonary disease	27
COPD	Randomized, double-blind	Tiotropium, 18 μg od inhal x 6 mo (n=209) Salmeterol, 50 μg od inhal x 6 mo (n=213) Placebo (n=201)	623	Inhaled tiotropium was safe and more effective than salmeterol in improving FEV_1 values, dyspnea and quality of life in patients suffering from chronic obstructive pulmonary disease. Tolerance to salmeterol but not tiotropium was seen after 6 months of treatment with a decrease in broncho-dilatory effects	28, 29
Airways obstruction	Randomized, double-blind, multicenter	Tiotropium, 18 μg od inhal x 1 y (n=356) Ipratropium, 40 μg qid inhal x 1 y (n=179)	535	Tiotropium was more effective than ipratropium in obstructive pulmonary disease	30
COPD	Double-blind, multicenter	Tiotropium, 18 μg od inhal AM x 6 wk Tiotropium, 18 μg od inhal PM x 6 wk		Tiotropium had no effects on heart rate or cardiac rhythm in patients with chronic obstructive pulmonary disease treated for 6 weeks	33

treatment of mild COPD. Assessment using the Gold spirometric criteria revealed that tiotropium administered once daily for 8 days improved morning predose FEV_1 by 14.7%, peak postdose FEV_1 by 46.3%, morning predose FVC by 11.8% and peak postdose FVC by 32.1%. Both the Transition Dyspnea Index and the health status of the patients also improved after 1 year of treatment. Tiotropium may become a useful maintenance treatment for patients with COPD so mild that it is generally not treated with bronchodilators (32).

The cardiac effects of treatment with tiotropium 18 μg once daily for COPD were assessed by 24-h ECG monitoring in 103 patients included in a multicenter, double-blind study. Patients were given tiotropium in the morning or in the evening or placebo for 6 weeks, with Holter studies at baseline and at the end of treatment. The results showed that tiotropium had no adverse effects on heart rate or cardiac rhythm in these patients (33).

The efficacy of tiotropium compared to placebo in both male and female COPD patients was confirmed in a 1-year study. The changes in baseline FEV_1, dyspnea and health status (assessed by SGRQ scores) as compared to last predose (12 months later) were significantly different and consistent across gender: FEV_1 (+11.8% *vs.* –3.7% for men; +10.7% *vs.* –4.8% for women); dyspnea (+1.2% *vs.* +0.5% for men; +1.3% *vs.* –0.1% for women); and SGRQ (–2.9% *vs.* 0% for men; –4.3% *vs.* –1.3% for women) (34).

Data from 1-year, placebo-controlled studies of tiotropium (18 μg once daily) in 846 patients with COPD indicated that long-term improvement can occur despite nonsignificant short-term improvement in FEV_1. In both tiotropium and placebo groups, acute improvement in FEV_1 (at least 12% or 200 ml) was associated with superior baseline spirometry and less dyspnea, and with superior long-term improvement over the course of the year. However, the long-term improvement in FEV_1 on tiotropium was greater than for placebo, regardless of the acute response (35).

1. *Spiriva approved in E.U. under mutual recognition procedure.* DailyDrugNews.com (Daily Essentials) April 19, 2002.

2. *Spiriva launched for COPD in The Netherlands and the Philippines.* DailyDrugNews.com (Daily Essentials) June 5, 2002.

3. *FDA advisory committee recommends approval of Spiriva.* DailyDrugNews.com (Daily Essentials) Sept 10, 2002.

4. *Japanese filing for Spiriva announced.* DailyDrugNews.com (Daily Essentials) July 29, 2002.

5. Kesten, S., Flanders, J.S., Menjoge, S.S., Serby, C.W. *Maintenance of bronchodilation following tiotropium in patients with mild, moderate, and severe COPD in 1-year placebo-controlled clinical trials.* Chest 2001, 120(4, Suppl.): 170S.

6. *Boehringer Ingelheim and Pfizer to comarket Spiriva for COPD.* DailyDrugNews.com (Daily Essentials) April 17, 2001.

7. *Boehringer Ingelheim submits U.S. NDA for Spiriva in chronic obstructive pulmonary disease.* DailyDrugNews.com (Daily Essentials) Dec 20, 2001.

8. *First approval granted for Spiriva in The Netherlands for treatment of COPD.* DailyDrugNews.com (Daily Essentials) Oct 19, 2001.

9. Leusch, A. et al. *Pharmacokinetics and tissue distribution of the anticholinergics tiotropium and ipratropium in the rat and dog.* Biopharm Drug Dispos 2001, 22(5): 199.

10. Magnussen, H., O'Donnell, D.E., Casaburi, R., Kesten, S., Gerken, F., Fluge, T. *Spiriva (tiotropium) reduces lung hyperinflation in COPD.* 98th Int Conf Am Thorac Soc (May 17-22, Atlanta) 2002, Abst 313.

11. O'Donnell, D.E., Magnussen, H., Aguilaniu, B., Make, B., Fluege, T., Hamilton, A. *Spiriva® (tiotropium) reduces exertional dyspnea in COPD.* 98th Int Conf Am Thorac Soc (May 17-22, Atlanta) 2002, Abst 809.

12. van Noord, J.A. et al. *Pharmacodynamic steady state of tiotropium in patients with chronic obstructive pulmonary disease.* Eur Respir J 2002, 19(4): 639.

13. Hasani, A., Dilworth, J.P., Agnew, J.E., Begent, L., Mier, A., Sarno, M., Lee, A., Harrison, A. *Effect of tiotropium on distribution pattern of aerosol particles deposited in the lung.* Am J Respir Crit Care Med 2001, 163(5, Suppl.): A277.

14. Anzueto, A., Menjoge, S.S., Kesten, S. *Changes in FEV_1 over time in one-year clinical trials of tioptropium in COPD.* Am J Respir Crit Care Med 2001, 163(5, Suppl.): A280.

15. Spencer, S., Jones, P.W. *Decline in health status over one year is eliminated by tiotropium.* 98th Int Conf Am Thorac Soc (May 17-22, Atlanta) 2002, Abst 317.

16. Briggs, D.D. Jr., Witek, T.J. Jr., Menjoge, S.S., Kesten, S. *Evaluating the efficacy of chronic therapy with tiotropium in COPD through discontinuation of treatment.* Eur Respir J 2002, 20(Suppl. 38): Abst P1589.

17. Friedman, M., Menjoge. S.S., Kesten, S., Witek, T.J. Jr. *An evaluation of PEFR as a predictor of COPD exacerbations in large one year COPD clinical trials.* Am J Respir Crit Care Med 2001, 163(5, Suppl.): A768.

18. Witek, T.J. Jr. et al. *The Transition Dyspnea Index (TDI) in assessing improvements in breathlessness following tiotropium (TIO).* Am J Respir Crit Care Med 2001, 163(5, Suppl.): A60.

19. Pauwels, R.A., Menjoge, S.S., Kesten, S. *COPD exacerbations and decline in FEV_1: The role of tiotropium.* Am J Respir Crit Care Med 2001, 163(5, Suppl.): A770.

20. Jones, P.W., Koch, P., Menjoge, S.S., Witek, T.J. Jr. *The impact of COPD exacerbations (EXAC) on health related quality of life (HRQL) is attenuated by tiotropium (TIO).* Am J Respir Crit Care Med 2001, 163(5, Suppl.): A771.

21. Kotch, A., Menjoge, S.S., Serby, C.W., Kesten, S. *Nocturnal symptoms and severity of disease in COPD.* Am J Respir Crit Care Med 2001, 163(5, Suppl.): A906.

22. McNicholas, W.T., Calverley, P.M.A., Edwards, C., Lee, A. *Effects of anticholinergic therapy (tiotropium) on REM-related desaturation (SaO_2) and sleep quality in patients with COPD.* Am J Respir Crit Care Med 2001, 163(5, Suppl.): A280.

23. Hasani, A., Agnew, J.E., Dilworth, J.P., Creer, D., Mier, A., Sarno, M., Lee, A., Harrison, A. *Effect of tiotropium on lung ventilatory distribution in COPD patients.* Am J Respir Crit Care Med 2001, 163(5, Suppl.): A282.

24. Oostenbrink, J.B., Rutten-van Molken, M.P.M.H., Anton, S.F., Hoenderdos, E. *Costs and consequences of tiotropium compared to ipratropium in patients with COPD.* Chest 2001, 120(4, Suppl.): 148S.

25. Bateman, E.D., Jenkins, C., Korducki, L., Kesten, S. *Tiotropium (TIO) improves health care resource utilization (HRU) and patient disability in patients with COPD.* 98th Int Conf Am Thorac Soc (May 17-22, Atlanta) 2002, Abst K38.

26. Friedman, M., Morera, G., Menjoge, S., Kesten, S. *Reduced COPD exacerbations with tiotropium.* 98th Int Conf Am Thorac Soc (May 17-22, Atlanta) 2002, Abst 315.

27. Hodder, R.V., White, R.J., Menjoge, S.S., Kesten, S. *Effectiveness of tiotropium or salmeterol in COPD patients receiving inhaled steroids.* 98th Int Conf Am Thorac Soc (May 17-22, Atlanta) 2002, Abst 316.

28. Donohue, J.F., Rea, H.H., Menjoge, S.S., Kesten, S. *Alterations in bronchodilator effectiveness over six months with tiotropium and salmeterol.* 98th Int Conf Am Thorac Soc (May 17-22, Atlanta) 2002, Abst 314.

29. Donohue, J.F., van Noord, J.A., Bateman, E.D., Langley, S.J., Lee, A., Witek, T.J. Jr., Kesten, S., Towse, L. *A 6-month, placebo-controlled study comparing lung function and health status changes in COPD patients treated with tiotropium or salmeterol.* Chest 2002, 122(1): 47.

30. Vincken, W., van Noord, J.A., Greefhorst, A.P.M., Bantje, T.A., Kesten, S., Korducki, L., Cornelissen, P.J.G. *Improved health outcomes in patients with COPD during 1 yr's treatment with tiotropium.* Eur Respir J 2002, 19(2): 209.

31. Casaburi, R., Mahler, D.A., Jones, P.W., Wanner, A., San Pedro, G., ZuWallack, R.L., Menjoge, S.S., Serby, C.W., Witek, T. Jr. *A long-term evaluation of once-daily inhaled tiotropium in chronic obstructive pulmonary disease.* Eur Respir J 2002, 19(2): 217.

32. Briggs, D. Jr., Bhattacharya, S., Kesten, S. *Tiotropium is effective in patients with Gold stage I disease (mild COPD).* Chest 2002, 122(4, Suppl.): Abst P287.

33. Langley, S., Towse, L., Kesten, S., Calverley, P.M. *Heart rate and rhythm analysis from Holter monitoring in COPD patients receiving tiotropium.* 98th Int Conf Am Thorac Soc (May 17-22, Atlanta) 2002, Abst C74.

34. Weisman, I.M., Menjoge, S.S., Serby, C.W., Kesten, S. *Influence of gender on outcomes in large COPD clinical trials.* Am J Respir Crit Care Med 2001, 163(5, Suppl.): A281.

35. Tashkin, D.P., Menjoge, S.S., Kesten, S. *Is an acute FEV_1 improvement of 12% and 200 ml predictive of long-term improvements with bronchodilators in patients with COPD?* Am J Respir Crit Care Med 2001, 163(5, Suppl.): A280.

Original monograph - Drugs Fut 2000, 25(7): 693.