EXHIBIT 76

US 20040235807A1

EXHIBIT-7

(19) **United States**

(12) **Patent Application Publication** (10) **Pub. No.: US 2004/0235807 A1**

Weinrich et al. (43) **Pub. Date: Nov. 25, 2004**

(54) **FORMULATIONS INCLUDING A TOPICAL DECONGESTANT AND A TOPICAL CORTICOSTEROID SUITABLE FOR NASAL ADMINISTRATION AND METHOD FOR TREATING OBSTRUCTIVE SLEEP APNEA**

(76) Inventors: **Karl P. Weinrich**, Bridgewater, MA (US); **Leonard W. Kaplan**, Brookline, MA (US)

Correspondence Address:
REED & EBERLE LLP
800 MENLO AVENUE, SUITE 210
MENLO PARK, CA 94025 (US)

(21) Appl. No.: **10/443,672**

(22) Filed: **May 21, 2003**

Publication Classification

(51) **Int. Cl.**[7] **A61K 31/573**; A61K 31/137

(52) **U.S. Cl.** **514/171**; 514/649

(57) **ABSTRACT**

A pharmaceutical formulation is provided for nasal drug administration of a topically administrable decongestant, a topically administrable corticosteroid and a pharmaceutically acceptable carrier, and may optionally include further carriers, therapeutic extenders, and the like. Such formulations may also optionally further include a therapeutically active member selected from the group consisting of a topical antibiotic, a topical antihistamine (preferably a non-sedating antihistamine), a leukotriene D_4 antagonist, a 5-lipoxygenase inhibitor, and a FLAP antagonist, or a pharmaceutically acceptable salt thereof. In addition, methods for using the formulation to treat decongestant/corticosteroids-responsive conditions, diseases or disorders such as chronic obstructive nasal congestion and/or obstructive sleep apnea conditions, are provided, as are drug delivery devices and dosage forms for housing and/or dispensing the formulations.

FORMULATIONS INCLUDING A TOPICAL DECONGESTANT AND A TOPICAL CORTICOSTEROID SUITABLE FOR NASAL ADMINISTRATION AND METHOD FOR TREATING OBSTRUCTIVE SLEEP APNEA

TECHNICAL FIELD

[0001] This invention relates generally to pharmaceutical formulations, and more particularly relates to pharmaceutical formulations comprising at least one topical corticosteroid and at least one topical nasal decongestant (e.g., sympathomimetic amine), and one or more optional members selected from the group consisting of carriers, extenders and excipients. In addition, the invention relates to methods of using the described formulations and drug delivery devices containing the described formulations in the treatment of chronic nasal congestion and/or in the treatment of obstructive sleep apnea.

BACKGROUND ART

[0002] In a normal person, the nasal turbinates, small, shelf-like, structures composed of thin bone and covered by mucous membranes (mucosal), protrude into the nasal airway and help to warm, humidify and cleanse air as it is inhaled and before it reaches the lungs. Since the nasal airway is the normal breathing route during sleep, chronic enlargement (hypertrophy) of the nasal turbinates (caused by conditions such as chronic nasal congestion) can contribute to headaches and cause sleep disorders such as snoring and obstructive sleep apnea. Such chronic turbinates hypertrophy and nasal obstruction are commonly associated with chronic rhinitis (the inflammation of the mucosal lining of the nose). When the mucosal tissue becomes inflamed, the blood vessels inside the membrane swell and expand, causing the turbinates to become enlarged and obstruct the flow of air through the nose. According to several large populations surveys, approximately 20% of the population, or more than 50 million Americans, suffer from some type of chronic rhinitis.

[0003] Medications designed to treat the stuffy nose, sinus complaints and the common cold make up the largest segment of the over-the-counter drug market for the U.S. pharmaceutical industry, accounting for nearly $3.5 billion in sales. First-line medical treatment for the chronic stuffy nose and chronically enlarged turbinates associated with rhinitis mainly consists of a variety of antihistamines, decongestants, and topical and systemic corticosteroids. Surgery to reduce the size of the nasal turbinates with a concurrent reduction of symptoms is sometimes utilized, but this does not entirely cure such conditions in many patients. Post surgery continued swelling of the mucosal lining throughout the nasal passages (and deep in the sinuses) continues to aggravate the patients' condition with a return of symptoms and conditions. Accordingly, surgery often does not cure or give adequate chronic relief for the underlying condition.

[0004] Topical decongestants (as nasal sprays) are used to treat a chronic stuffy nose, but such use is not without serious drawbacks. Such topical decongestants act by constricting the blood vessels in swollen mucous membranes, forcing blood out so that the membranes shrink and air passages open. Typical commercial nasal sprays contain sympathomimetic compounds (decongestants), such as 0.05% oxymetazoline in Afrin® and the like. Common over-the-counter remedies contain phenylephrine hydrochloride, oxymetazoline hydrochloride, xylometazoline hydrochloride, and the like. These topical decongestants are generally considered to be harmful when used over long periods of time because they cause damage to nasal mucosal ciliary function, and they cause rebound mucosal thickening leading to nasal congestion. The manufacturers of certain over-the-counter remedies often warn that their products should not be used for more than three days. The use or abuse of these drugs can result in prolonged nasal obstruction ("rebound" can be worse than initial symptoms), where addictive use behavior can occur to avoid such uncomfortable rebound nasal congestion.

[0005] Several corticosteroid therapies, mostly in the form of a nasal spray or inhaler, have been developed to treat chronic nasal obstruction. Intranasal corticosteroid sprays are available only by prescription and they can be very effective, however, they are associated with side effects such as bleeding, drying and crusting. Patients must take care not to overuse corticosteroid preparations. Although the drugs are applied topically, some systemic absorption of the agent occurs, which can disrupt the body's steroid balance. Steroids can also be injected directly into the turbinates, however, their effectiveness usually lasts only three to six weeks. The anti-inflammatory effect of steroid sprays may produce a beneficial reaction in the nasal and sinus mucosa. However, such sprays are generally effective only in reducing inflammation, and only have inconsequential decongestant or physiological mucosal effects in mobilizing secretions or stimulating cells to evacuate secretions.

[0006] As mentioned above, chronic enlargement (hypertrophy) of the nasal turbinates (caused by conditions such as chronic nasal congestion) can cause sleep disorders such as snoring and obstructive sleep apnea. Obstructive sleep apnea (also referred to herein as "OSA") is a breathing disorder that occurs primarily during sleep with consequences that may persist throughout the waking hours in the form of sleepiness, thereby manifesting itself into substantial economic loss (e.g., thousands of lost man-hours) or employment safety factors (e.g., employee non-attentiveness during operation of heavy-machinery). Such sleep-related breathing disorders are characterized by repetitive reduction in breathing (hypopnea), periodic cessation of breathing (apnea), or a continuous or sustained reduction in ventilation. OSA is a significant public health burden. Such OSA disorder and related symptoms affects all races, ages and socioeconomic and ethnic groups. There is no known pharmacological treatment for OSA on the market that is generally successful.

[0007] In general, sleep apnea is defined as an intermittent cessation of airflow at the nose and mouth during sleep. By convention, apneas of at least 10 seconds in duration have been considered important, but in most individuals the apneas are 20-30 seconds in duration and may be as long as 2-3 minutes. While there is some uncertainty as to the minimum number of apneas that should be considered clinically important, by the time most individuals come to attention of the medical community they have at least 10 to 15 events per hour of sleep.

[0008] Sleep apneas have been classified into three types: central, obstructive, and mixed. In central sleep apnea the

neural drive to all respiratory muscles is transiently abolished. In obstructive sleep apneas, airflow ceases despite continuing respiratory drive because of occlusion of the oropharyngeal airway. Mixed apneas, which consist of a central apnea followed by an obstructive component, are a variant of obstructive sleep apnea. The most common type of apnea is OSA.

[0009] OSA syndrome has been identified in as many as 24% of working adult men and 9% of similar women, with peak prevalence in the sixth decade. Habitual heavy snoring, which is an almost invariant feature of OSA, has been described in up to 24% of middle aged men, and 14% of similarly aged women, with even greater prevalence in older subjects.

[0010] OSA syndrome's definitive event is the occlusion of the upper airway, frequently at the level of the oropharynx. The resultant apnea generally leads to a progressive-type asphyxia until the individual is briefly aroused from the sleeping state, thereby restoring airway patency and thus restoring airflow. An important factor that leads to the collapse of the upper airway in OSA is the generation of a critical sub-atmospheric pressure during the act of inspiration that exceeds the ability of the airway dilator and abductor muscles to maintain airway stability. Sleep plays a crucial role by reducing the activity of the muscles of the upper airways including the dilator and abductor muscles.

[0011] In individuals with OSA, in addition to chronic congestive nasal obstruction, the airway can be compromised structurally and be predisposed to occlusion. Obesity also frequently contributes to a reduction in size seen in the upper airways. The act of snoring, which is actually a high-frequency vibration of the palatal and pharyngeal soft tissues that results from the decrease in the size of the upper airway lumen, usually aggravates the narrowing via the production of edema in the soft tissues.

[0012] The recurrent episodes of nocturnal asphyxia and of arousal from sleep that characterize OSA lead to a series of secondary physiologic events, which in turn give rise to the clinical complications of the syndrome. The most common manifestations are neuro-psychiatric and behavioral disturbances that are thought to arise from the fragmentation of sleep and loss of slow-wave sleep induced by the recurrent arousal responses. Nocturnal cerebral hypoxia also may play an important role. The most pervasive manifestation is excessive daytime sleepiness. OSA is now recognized as a leading cause of daytime sleepiness and has been implicated as an important risk factor for such problems as motor vehicle accidents. Other related symptoms include intellectual impairment, memory loss, personality disturbances, and impotence.

[0013] The other major manifestations are cardio-respiratory in nature and are thought to arise from the recurrent episodes of nocturnal asphyxia. Most individuals demonstrate a cyclical slowing of the heart during the apneas to 30 to 50 beats per minute, followed by tachycardia of 90 to 120 beats per minute during the ventilatory phase. A small number of individuals develop severe bradycardia with asystoles of 8 to 12 seconds in duration or dangerous tachyarrhythmias, including unsustained ventricular tachycardia. OSA also aggravates left ventricular failure in patients with underlying heart disease. This complication is most likely due to the combined effects of increased left ventricular afterload during each obstructive event, secondary to increased negative intrathoracic pressure, recurrent nocturnal hypoxemia, and chronically elevated sympathoadrenal activity.

[0014] Currently, the most common and most effective treatment for adults with sleep apnea and other sleep-related breathing disorders are mechanical forms of therapy that deliver continuous positive airway pressure (also referred to herein as "CPAP"). Under CPAP treatment, an individual wears a tight-fitting plastic mask over the nose when sleeping. The mask is attached to a compressor, which forces air into the nose creating a positive pressure within the patient's airways. The principle of the method is that pressurizing the airways provides a mechanical "splinting" action, which prevents airway collapse and therefore prevents OSA. Although an effective therapeutic response is observed in most patients who undergo CPAP treatment, many patients cannot tolerate the apparatus or pressure and refuse treatment. Moreover, recent covert monitoring studies clearly demonstrate that long-term compliance with CPAP treatment is very poor.

[0015] A variety of upper airway and craniofacial surgical procedures have been attempted for treatment of OSA. Adenotonsillectomy appears to be an effective cure for OSA in many children, but upper airway surgery is rarely curative in adult patients with OSA. Surgical "success" is generally taken to be a 50% reduction in apnea incidence and there are no useful screening methods to identify the individuals that would benefit from the surgery versus those who would not derive a benefit.

[0016] Pharmacological treatments of several types have been attempted in patients with sleep apnea but, thus far, none have proven to be generally useful. A recent systematic review of these attempts is provided by Hudgel (1995) *J. Lab. Clin. Med.* 126:13-18. A number of compounds have been tested because of their expected respiratory stimulant properties. These include (1) acetazolamide, a carbonic anhydrase inhibitor that produced variable improvement in individuals with primary central apneas but caused an increase in obstructive apneas, (2) medroxyprogesterone, a progestin that has demonstrated no consistent benefit in OSA, and (3) theophylline, a compound usually used for the treatment of asthma, which may benefit patients with central apnea but appears to be of no use in adult patients with obstructive apnea.

[0017] Other attempted pharmacological treatment includes the administration of adenosine, adenosine analogs and adenosine reuptake inhibitors (U.S. Pat. No. 5,075,290 to Findley, et al.). Specifically, adenosine, which is a ubiquitous compound within the body and which levels are elevated in individuals with OSA, has been shown to stimulate respiration and is somewhat effective in reducing apnea in an animal model of sleep apnea.

[0018] Other possible pharmacological treatment options for OSA include agents that stimulate the brain activity or agents that are opioid antagonists. Specifically, since increased cerebral spinal fluid opioid activity has been identified in OSA, it is a logical conclusion that central stimulants or opioid antagonists would be a helpful treatment of OSA. In reality, doxapram, which stimulates the central nervous system and carotid body chemoreceptors, was found to decrease the length of apneas but did not alter

the average arterial oxygen saturation in individuals with OSA. The opioid antagonist naloxone, which is known to stimulate ventilation, was only slightly helpful in individuals with OSA.

[0019] Because OSA syndrome is strongly correlated with the occurrence of hypertension, agents such as angiotensin-converting enzyme (ACE) inhibitors may be of benefit in treating OSA individuals with hypertension but do not appear to be a viable treatment for OSA itself.

[0020] Finally, several agents that act on neurotransmitters and neurotransmitter systems involved in respiration have been tested in individuals with OSA. Most of these compounds have been developed as anti-depressant medications that work by increasing the activity of monoamine neurotransmitters, including norepinephrine, dopamine, and serotonin. Protriptyline, a tricyclic anti-depressant, has been tested in several small trials with variable results and frequent and significant side effects. As serotonin may promote sleep and stimulate respiration, tryptophan, a serotonin precursor and selective serotonin reuptake inhibitors have been tested in individuals with OSA. While a patent has been issued for the use of the serotonin reuptake inhibitor, fluoxetine (U.S. Pat. No. 5,356,934 to Robertson, et al.), initial evidence suggests that these compounds may yield measurable benefits in only approximately 50% of individuals with OSA. Therefore, in view of the fact that the only viable treatment for individuals suffering from sleep-related breathing disorders is a mechanical form of therapy (CPAP) for which patient compliance is low, and that hopes for pharmacological treatments have yet to come to fruition, there remains a need for simple pharmacologically-based treatments that would offer benefits to a broad base of individuals suffering from a range of sleep-related breathing disorders. There also remains a need for a viable treatment of sleep-related breathing disorders that would lend itself to a high rate of patient compliance.

[0021] In view of the above, current drugs only provide temporary symptomatic improvement and symptom reduction for chronic congestive nasal obstruction that can lead to OSA, but due to significant side effects must be rotated to avoid addition and subsequent rebound of symptoms. Surgery to reduce the size of the nasal turbinates is also sometimes utilized (as described above) to reduce symptoms in an attempt to treat sleep apnea, but this does not entirely cure such conditions in many patients. Post surgery continued swelling of the mucosal lining throughout the nasal passages and in the sinuses continues to aggravate the patients' condition with a return of symptoms, and thus, do not cure or give chronic relief for the underlying condition.

[0022] There is, accordingly, a need in the art to provide a composition for the effective, safe, and long-term treatment of OSA and/or chronic nasal obstruction that may be related to OSA, which reduces significant side effects and also reduces withdrawal rebound nasal congestion.

SUMMARY OF THE INVENTION

[0023] One primary aspect of the invention is a method for treating a patient suffering from a chronic condition, disease or disorder that is responsive to treatment with a decongestant/corticosteroid combination, comprising nasally administering to the patient a pharmaceutical formulation for nasal drug administration, wherein the formulation comprises: a therapeutically effective amount of a topically administrable decongestant; a therapeutically effective amount of a topically administrable corticosteroid; and a pharmaceutically acceptable carrier that is suitable for nasal drug administration.

[0024] Another aspect of the invention is a method for the treatment of a patient suffering from chronic nasal congestive obstruction or obstructive sleep apnea (OSA) with a topical decongestant/corticosteroid combination, comprising nasally administering to the patient a pharmaceutical formulation for topical drug administration as described above. This method may provide for the long-term treatment of such conditions.

[0025] Yet another aspect of the invention is a long-term treatment method for treating chronic nasal congestion and/or treating of OSA comprising daily administration of nasal pharmaceutical formulations that are adapted for such long-term administration (as described below), as well as drug delivery devices containing such formulations and means for daily administration in such methods.

[0026] Other aspects of the invention involve the methods described above, that provide for the administration of a pharmaceutical composition that comprises at least one topically administrable nasal sympathomimetic amine decongestant, which is a member selected from the group consisting of: oxymetazoline, xylometazoline, naphazoline, phenylephrine and pharmaceutically acceptable salts thereof.

[0027] Still another aspect of the invention is a method that includes the administration of a composition, as described above, and may optionally further include a therapeutically active agent selected from the group consisting of a topical antibiotic, a topical antihistamine (preferably a non-sedating antihistamine), a leukotriene D_4 antagonist, a 5-lipoxygenase inhibitor, and a 5-lipoxygenase-activating protein (FLAP) antagonist, or a pharmaceutically acceptable salt thereof.

[0028] Another aspect of the invention is a pharmaceutical composition for nasal drug administration comprising: a therapeutically effective amount of a topically administrable decongestant; a therapeutically effective amount of a topically administrable corticosteroid; and a pharmaceutically acceptable carrier that is suitable for nasal drug administration.

[0029] Still another aspect of the invention is a nasal or sinus drug delivery device, comprising: a topically administrable pharmaceutical formulation as described above, and a means for housing and dispensing unit dosages of the formulation into a patient's nasal passages and/or neighboring sinuses. A preferred drug delivery device comprises an aqueous extender solvent system, whereby each dose delivered has the ability to maintain a therapeutic effect for a period of more than 6 hours.

[0030] Still another aspect of the invention is a dosage form containing a topically administrable nasal pharmaceutical formulation as described above, and optionally a unit dose delivery system. The system may include a means for housing and dispensing metered unit dosages of the formulation into a patient's nasal passages and/or into the neighboring sinuses.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.