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(54) **INHALABLE FORMULATIONS FOR TREATING PULMONARY HYPERTENSION AND METHODS OF USING SAME**

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(57) **ABSTRACT**

The present invention is directed to an inhalable formulation for the treatment of pulmonary hypertension in a mammal (e.g., humans), wherein the formulation comprises at least one hypertension reducing agent, including but not limited to an angiotensin converting enzyme inhibitor, angiotensin receptor blocker, beta-blocker, calcium-channel blocker or vasodilator, or any combination thereof. The formulations of the present invention may be a solution or suspension, and preferably are suitable for administration via nebulization. The present invention is also directed to a method and kit for treating a mammal suffering from pulmonary hypertension.

INHALABLE FORMULATIONS FOR TREATING PULMONARY HYPERTENSION AND METHODS OF USING SAME

I. FIELD OF THE INVENTION

[0001] The present invention relates to an inhalable formulation for the treatment of pulmonary hypertension, and methods of treating the same in mammals, including humans. The formulation of the present invention comprises a hypertension reducing agent, wherein the hypertension reducing agent may include an angiotensin-converting enzyme inhibitor ("ACEI"), angiotensin receptor blocker ("ARB"), beta adrenergic blocking agent ("beta-blockers"), calcium-channel blocker or vasodilator, or any combination thereof. Preferably, the formulation of the present invention is suitable for administration via nebulization. The present invention also relates to a prepackaged kit for treating pulmonary hypertension containing the formulation of the present invention.

II. BACKGROUND OF THE INVENTION

[0002] Pulmonary hypertension is a disorder of the lung in which the pressure in the pulmonary artery (the blood vessel that leads from the heart to the lungs) rises above normal levels. If left untreated, pulmonary hypertension may become life threatening. Symptoms of pulmonary hypertension include shortness of breath with minimal exertion, fatigue, chest pain, dizzy spells fainting, and other symptoms. Pulmonary hypertension is frequently misdiagnosed and has often progressed to late stage by the time it is accurately diagnosed. Moreover, pulmonary hypertension has been historically chronic and incurable with a poor survival rate.

[0003] When pulmonary hypertension occurs in the absence of a known cause, it is referred to as primary pulmonary hypertension (PPH). There are many unknown causes of PPH.

[0004] When the cause of pulmonary hypertension is known, it is called secondary pulmonary hypertension (SPH). Common causes of SPH is the breathing disorders emphysema, bronchitis and chronic obstructive pulmonary disorder, among others. Other less frequent causes are the inflammatory or collagen vascular diseases such as scleroderma, CREST syndrome or systemic lupus erythematosus. Congenital heart diseases that cause shunting of extra blood through the lungs like ventricular and arterial septal defects, chronic pulmonary thromboembolism (old blood clots in the pulmonary artery), HIV infection, liver disease and diet drugs like fenfluramine and dexfenfluramine are also causes of pulmonary hypertension.

[0005] Angiotensin-converting enzyme inhibitors (ACEI) are drugs used to treat hypertension (high blood pressure) and congestive heart failure. These drugs are also used to alleviate the strain on hearts damaged from heart attacks. ACEIs block production of an enzyme that helps convert the protein angiotensin I into angiotensin II, a protein that makes blood vessels constrict and promotes retention of fluid in the body, thereby raising blood pressure. ACEIs also make blood vessels relax, which helps lower blood pressure and allows more oxygen-rich blood to reach the heart. Captorpirl

[0006] Angiotensin receptor blockers (ARBs) (also referred to as angiotensin II receptor agonists) such as losartan (Cozaar) and valsartan (Diovan) reduce hypertension by displacing angiotensin II from receptors on the surface of cells. ARBs are used as alternatives to the less expensive ACEI inhibitors because they have fewer side effects.

[0007] Beta-adrenergic blocking agents, or beta-blockers, are used in the treatment of high blood pressure. Beta-blockers are also used to relieve angina (chest pain) and in heart attack patients to help prevent additional heart attacks. Beta-blockers are also used to correct irregular heartbeat, prevent migraine headaches, and treat tremors. Beta-blockers are competitive inhibitors and interfere with the action of stimulating hormones on beta-adrenergic receptors in the nervous system. Beta-blockers can be subdivided into two distinct groups, known as beta-1 and beta-2. Beta-1 blockers mainly affect the heart, and beta-2 blockers mainly affect receptors in bronchial tissue. Most beta-blockers are non-specific, i.e., they have both beta-1 and beta-2 effects.

[0008] Calcium-channel blockers are presently used to control hypertension, chest pain and irregular heartbeats. Calcium-channel blockers slow the rate at which calcium passes into the heart muscle and into the vessel walls, thereby relaxing the vessels. The relaxed vessels let blood flow more easily through them, thereby lowering blood pressure.

[0009] Vasodilators are medicines that act directly on muscles in blood vessel walls to make blood vessels widen (dilate). Vasodilators are used to treat high blood pressure. By widening the arteries, these drugs allow blood to flow through more easily, reducing blood pressure. Controlling high blood pressure is important because the condition puts a burden on the heart and the arteries, which can lead to permanent damage over time. If untreated, high blood pressure increases the risk of heart attacks, heart failure, stroke, or kidney failure. Examples of vasodilators include prostacyclin and its analogs.

[0010] It has been shown that vasodilators such as prostacyclin and prostacyclin analogs as well as calcium channel blockers such as diltiazem (Cardizem) or nifedipine (Procardia) decrease pulmonary vascular resistance in some patients when administered systemically. For example, it has been found that continuous intravenous infusion of the vasodilator epoprostenol (Flolan), or prostacyclin, improves exercise capacity, quality of life, hemodynamics and long-term survival in patients with primary pulmonary hypertension. Epoprostenol is a potent, short-acting vasodilator and inhibitor of platelet aggregation by vascular endothelium.

[0011] Continuous intravenous prostacyclin is far from ideal as a treatment for pulmonary hypertension, however, because the agent is available only in limited supply, it is very costly, and optimal management requires that the intravenous therapy with prostacyclin be started in specialized centers familiar with the technique, equipment, and dose ranging. Moreover, continuous intravenous administration of prostacyclin results in significant side effects in patients, including jaw pain, nausea, and anorexia, plus the inconvenience and potential danger from prolonged catheterization and breakdowns in the delivery system. Further, because the agent is delivered systemically with only a small

[0012] Epoprostenol or the prostacyclin analog treprostinil sodium may be administered via injection to treat pulmonary hypertension. Delivery, however, is systemic and not localized to the lung. Thus, the drug must be administered in high doses, with only a small percentage actually reaching the lungs.

[0013] It has also been shown that calcium channel blockers may alleviate pulmonary vasoconstriction and prolong life in about 20 percent of patients with PPH. Rich S, Kaufmann E, Levy P S. *The effect of high doses of calcium-channel blockers on survival in primary pulmonary hypertension*. N Engl J Med 1992;327:76-81, which is incorporated herein by reference. In patients who show evidence of an acute hemodynamic response, long-term treatment with calcium channel blockers administered orally can produce a sustained hemodynamic response and increase survival. However, oral administration does not produce a localized effect on the lungs and therefore high doses must be administered producing a systemic effect, perhaps unnecessarily. Moreover, oral administration in high dosages over an extended period of time may produce unwanted side-effects in some patients.

[0014] There is, therefore, a need for an improved method of treating hypertension.

III. SUMMARY OF THE INVENTION

[0015] The formulations provided herein are used for treating, preventing and/or ameliorating one or more symptoms of a medical condition, disorder or disease. As used herein, treatment means any manner in which one or more of the symptoms of the condition, disorder or disease are ameliorated or otherwise beneficially altered. Treatment also encompasses any pharmaceutical or medicinal use of the formulations herein. As used herein, amelioration of the symptoms of a particular disorder by administration of a particular formulation refers to any lessening, whether permanent or temporary, lasting or transient that can be attributed to or associated with administration of the formulation. As used herein, a "therapeutic effective amount" means a sufficient amount of drug substance to treat, prevent and/or ameliorate one or more symptoms of a medical condition, disorder or disease. It also may include a safe and tolerable amount of drug substance, as based on industry and/or regulatory standards.

[0016] In one alternative embodiment, the formulations provided herein are used for treating, preventing and/or ameliorating one or more symptoms of a respiratory disorder in an individual. In another alternative embodiment, the present invention provides a formulation for the treatment, prophylaxis and/or amelioration of one or more symptoms of pulmonary hypertension or other related disorders.

[0017] In one preferred embodiment, the present invention provides a formulation for the treatment of pulmonary hypertension in a mammal (e.g., humans), wherein the formulation is suitable for administration via inhalation. Preferably, the formulation of the present invention is suitable for administration via nebulization. The formulations of the present invention comprise a therapeutically effective amount of a hypertension reducing agent. Hypertension reducing agents suitable for use in the present formulations [illegible] alternative embodiment, the formulation of the present invention comprises a combination of two or more hypertension reducing agents.

[0018] The formulations of the present inventions may be provided as a solution or as aqueous suspension, so long as the formulation is suitable for inhalation. Preferably, the present formulation is sterile. In another embodiment, the formulation of the present invention is stable. Further, buffering agents may be added to adjust the pH level of the formulation. Moreover, the formulations of the present invention may contain an anti-microbial preservative. Alternatively, the formulations herein may be preservative-free. In one embodiment, the formulations of the present invention are suitable for treating any diagnosis or level of pulmonary hypertension.

[0019] The present invention also relates to a method for treating pulmonary hypertension in a mammal, which includes animals or humans. In one embodiment, the method of the present invention comprises the step of administering the formulation of the present invention to a mammal in need thereof. In one embodiment, the method of the present invention further comprises the step of administering another therapy or pharmaceutical agent useful to or related to the treatment of pulmonary hypertension. Such therapies and/or pharmaceutical agents including, for example, anticoagulants and diuretics.

[0020] Additionally, the present invention is directed to a kit for treating pulmonary hypertension in a mammal. In one embodiment, the kit of the present invention comprises the formulation of the present invention. In another embodiment, the formulation of the kit is premeasured, premixed and prepackaged. In an alternative embodiment, the kit further comprises instructions for administering the formulation.

[0021] Other embodiments, features and advantages of the present invention will be apparent to those of ordinary skill in the art in view of the following detailed description of the invention.

IV. DETAILED DESCRIPTION OF THE INVENTION

[0022] As used herein, the terms "angiotensin converting enzyme inhibitor" or "ACEI" means any pharmaceutical agent that inhibits the enzymatic activity of angiotensin converting enzyme. ACEIs suitable for use herein include, but are not limited to, Benazepril, Captopril, Enalapril, Fosinopril, Lisinopril, Moexipril, Perindopril, Quinapril, Ramipril, Trandolapril, and prodrugs, salts and isomers thereof.

[0023] As used herein, the terms "angiotensin receptor blocker" or "ARB" or "angiotensin II receptor agonist" means any pharmaceutical agent that selectively blocks the binding of angiotensin II to receptors found in many tissues. ARBs suitable for use herein include, but are not limited to, Candesartan, Eprosartan, Irbesartan, Losartan, Olmesartan, Telmisartan, Valsartan, and prodrugs, salts and isomers thereof.

[0024] As used herein, the terms "beta adrenergic blocking agent" or "beta-blocker" means any pharmaceutical [illegible]

substance adrenaline (epinephrine), a key agent in the "sympathetic" portion of the autonomic (involuntary) nervous system and activation of heart muscle. Beta-blockers suitable for use herein include, but are not limited to, Acebutolol, Atenolol, Betaxolol, Bisoprolol, Carteolol, Carvedilol, Esmolol, Labetalol, Metoprolol, Nadolol, Oxprenolol, Penbutolol, Pindolol, Propranolol, Sotalol and Timolol and prodrugs, salts and isomers thereof.

[0025] As used herein, the term "calcium-channel blocker" means any pharmaceutical agent which slows or blocks the entry of calcium into the muscle cells of the heart and the arteries. Calcium channel blockers suitable for use herein include, but are not limited to, Amlodipine, Bepridil, Diltiazem, Felodipine, Flunarizine, Isradipine, Nicardipine, Nifedipine, Nimodipine, Verapamil and prodrugs, salts and isomers thereof.

[0026] As used herein, the term "vasodilator" means any pharmaceutical agent that causes dilation of blood vessels. Vasodilators suitable for use herein include, but are not limited to, Adenine, Arginine, Doxazosin, Hydralazine Hydrochloride, Isosorbide Initrate, Isosorbide Mononitrate Minoxidil, Nicotinates, Nitroglycerin, Phentolamine, Prazosin, Terazosin and prodrugs, salts and isomers thereof. Vasodilators for use herein also include prostaglandins (Eicosanoids), including prostacyclin (Epoprostenol) and prostacyclin analogs, including Iloprost and Treprostinil, and prodrugs, salts and isomers thereof. Also included herein are various prostaglandins, including, but not limited to PGE-1; PGE-2; PGF-2.alpha.; PGA-1; PGB-1; PGD-2; PGE-M; PGF-M; PGH-2; PGI-2; 19-hydroxy-PGA-1; 19-hydroxy-PGB-1; PGA-2; PGB-2; 19-hydroxy-PGA-2; 19-hydroxy-PGB-2; PGB-3; PGF-1.alpha.; 15-methyl-PGF-2.alpha.; 16,16-dimethyl-.DELTA.sup.2-PGE-1 methyl ester; 15-deoxy-16-hydroxy-16-methyl-PGE-1 methyl ester; 16,16-dimethyl-PGE-2; 11-deoxy-15-methyl-PGE-1; 16-methyl-18,18,19,19-tetrahydrocarbacyclin; (16RS)-15-deoxy-16-hydroxy-16-methyl-PGE-1 methyl ester; (+)-4,5-didehydro-16-phenoxy-.alpha.-tetranor-PGE-2 methyl ester; 11-deoxy-11a,16,16-trimethyl-PGE-2; (+)-11a, 16a,b-dihydroxy-1,9-dioxo-1-(hydroxymethyl)-16-methyl-trans-prostene; 9-chloro-16,16-dimethyl-PGE-2; arboprostil; iloprost; CL 15.347: and semisynthetic or synthetic derivatives of these natural prostaglandins, or any derivative or any prostaglandin analog capable of acting as a vasodilator, and prodrugs, salts and isomers thereof.

[0027] As used herein, the term "hypertension reducing pharmaceutical agent" means any ACEI, ARB, beta-blocker, calcium-channel blocker, vasodilator, or any other compound capable of treating pulmonary hypertension through oral inhalation, such as nebulization. It is understood that the above list of hypertension reducing agents include those not currently approved for use in clinical practice in the U.S., and those that will be approved in the future.

[0028] As used herein, the term "pulmonary hypertension" means any form, diagnosis, level or stage of pulmonary hypertension, including, but not limited to, primary or secondary pulmonary hypertension, pulmonary arterial hypertension, pulmonary venous hypertension, pulmonary hypertension associated with disorders of the respiratory system or hypothermia, pulmonary hypertension resulting from [illegible] pulmonary vasculature. The term "pulmonary hypertension" also includes other respiratory disorders characterized by acute pulmonary vasoconstriction such as those disorders resulting from pneumonia, traumatic injury, aspiration or inhalation injury, fat embolism in the lung, acidosis inflammation of the lung, adult respiratory distress syndrome, acute pulmonary edema, acute mountain sickness, post-cardiac surgery, acute pulmonary hypertension, persistent pulmonary hypertension of the newborn, perinatal aspiration syndrome, hyaline member disease, acute pulmonary thromboembolism, heparin-protomine reactions, sepsis, status asthamaticus or hypoxia (including iatrogenic hypoxia) and other forms of reversible pulmonary vasoconstriction. Such pulmonary disorders are also characterized by inflammation of the lung including those associated with the migration into the lung of non-resident cell types including the various leucocyte subclasses.

[0029] In one alternative embodiment, formulations of the present invention may include pharmaceutically acceptable derivates of a hypertension reducing agent. As used herein, pharmaceutically acceptable derivatives of such compounds include but are not limited to salts, esters, enol ethers, enol esters, acids, bases, solvates, hydrates or prodrugs thereof. Such derivatives may be readily prepared by those of skill in this art using known methods for such derivatization. Such derivatives produced may be administered to animals or humans without substantial toxic effects.

[0030] Suitable "pharmaceutically acceptable salts" include conventionally used non-toxic salts, for example a salt with an inorganic base such as an alkali metal salt (such as sodium salt and potassium salt), an alkaline earth metal salt (such as calcium salt and magnesium salt), an ammonium salt; or a salt with an organic base, for example, an amine salt (such as methylamine salt, dimethylamine salt, cyclohexylamine salt, benzylamine salt, piperidine salt, ethylenediamine salt, ethanolamine salt, diethanolamine salt, triethanolamine salt, tris(hydroxymethylamino) ethane salt, monomethyl-monoethanolamine salt, procaine salt and caffeine salt), a basic amino acid salt (such as arginine salt and lysine salt), tetraalkyl ammonium salt and the like, or other salt forms that enable the pulmonary hypertension reducing agent to remain soluble in a liquid medium, or to be prepared and/or effectively administered in a liquid medium, preferable an aqueous medium. The above salts may be prepared by a conventional process, for example from the corresponding acid and base or by salt interchange.

[0031] For example, one alternative embodiment, the hypertension reducing agent may be employed in a free base form or in a salt form (e.g., as pharmaceutically acceptable salts). Examples of suitable pharmaceutically acceptable salts include inorganic acid addition salts such as hydrochloride, hydrobromide, sulfate, phosphate, and nitrate; organic acid addition salts such as acetate, propionate, succinate, lactate, glycolate, malate, tartrate, citrate, maleate, fumarate, methansulfonate, p-toluenesulfonate, and ascorbate; salts with acidic amino acid such as aspartate and glutamate; alkali metal salts such as sodium salt and potassium salt; alkaline earth metal salts such as magnesium salt and calcium salt; ammonium salt; organic basic salts such as [illegible]

ylenediamine salt; and salts with basic amino acid such as lysine salt and arginine salt. The salts may be in some cases hydrates or ethanol solvates.

[0032] Examples of the ethers may include, but are not limited to, alkyl ethers, for example, lower alkyl ethers such as methyl ether, ethyl ether, propyl ether, isopropyl ether, butyl ether, isobutyl ether, t-butyl ether, pentyl ether and 1-cyclopropyl ethyl ether; and medium or higher alkyl ethers such as octyl ether, diethylhexyl ether, lauryl ether and cetyl ether; unsaturated ethers such as oleyl ether and linolenyl ether; lower alkenyl ethers such as vinyl ether, allyl ether; lower alkynyl ethers such as ethynyl ether and propynyl ether; hydroxy (lower) alkyl ethers such as hydroxyethyl ether and hydroxyisopropyl ether; lower alkoxy (lower) alkyl ethers such as methoxymethyl ether and 1-methoxyethyl ether; optionally substituted aryl ethers such as phenyl ether, tosyl ether, t-butylphenyl ether, salicyl ether, 3,4-dimethoxyphenyl ether and benzamidophenyl ether; and aryl (lower) alkyl ethers such as benzyl ether, trityl ether and benzhydryl ether, or other ether forms that enable the pulmonary hypertension reducing agent to remain soluble in a liquid medium, or to be prepared and/or effectively administered in a liquid medium, preferably an aqueous medium.

[0033] Examples of the esters may include, but are not limited to, aliphatic esters, for example, lower alkyl esters such as methyl ester, ethyl ester, propyl ester, isopropyl ester, butyl ester, isobutyl ester, t-butyl ester, pentyl ester and 1-cyclopropylethyl ester; lower alkenyl esters such as vinyl ester and allyl ester; lower alkynyl esters such as ethynyl ester and propynyl ester; hydroxy (lower) alkyl ester such as hydroxyethyl ester; lower alkoxy (lower) alkyl esters such as methoxymethyl ester and 1-methoxyethyl ester; and optionally substituted aryl esters such as, for example, phenyl ester, tosyl ester, t-butylphenyl ester, salicyl ester, 3,4-di-methoxyphenyl ester and benzamidophenyl ester; and aryl(lower-)alkyl ester such as benzyl ester, trityl ester and benzhydryl ester, or other ester forms that enable the pulmonary hypertension reducing agent to remain soluble in a liquid medium, or to be prepared and/or effectively administered in a liquid medium, preferably an aqueous medium.

[0034] Also, the hypertension reducing agent for use in the formulations and methods provided herein may contain chiral centers. Such chiral centers may be of either the (R) or (S) configuration, or may be a mixture thereof. Thus, the compounds for use in the formulations provided herein may be enantiomerically pure, or be stereoisomeric or diastereomeric mixtures. It is to be understood that the chiral centers of the compounds provided herein may undergo epimerization in vivo. Thus, one of skill in the art will recognize that administration of a compound in its (R) form is equivalent, for compounds that undergo epimerization in vivo, to administration of the compound in its (S) form.

[0035] The present invention provides an inhalable formulation for treating pulmonary hypertension, wherein the formulation comprises a therapeutically effective amount of a hypertension-reducing agent for the treatment of pulmonary hypertension, wherein the hypertension-reducing agent is an ACEI, ARB, beta-blocker, calcium-channel blocker or vasodilator, or any combination thereof.

[0036] The present invention is premised, in part, on the [illegible] lators to treat pulmonary hypertension. It is believed that the formulations of the present invention represent an improvement over conventional means for treating pulmonary hypertension, because the delivery of the hypertension-reducing agent would be localized to the user's pulmonary system, as opposed to systemic delivery. It is believed that localized therapy may increase bioavailability as well as increased efficacy and/or prolonged therapeutic effect. Due to increased bioavailability, the present formulations may contain lower dosages of the hypertension-reducing agents while effectively treating pulmonary hypertension. Additionally, it is believed that localized therapy may result in a decrease in side-effects due to lower dosages and a decrease in patient discomfort and inconvenience due to the less invasive or time-consuming systemic delivery method.

[0037] In one embodiment of the present invention, a therapeutically effective amount of a hypertension-reducing agent may include from about 0.001 mg/ml to about 20 mg/ml of an ACEI, ARB, beta-blocker, calcium-channel blocker, vasodilator, or any combination thereof. In an alternative embodiment, a therapeutically effective amount of a hypertension-reducing agent may include from about 0.008 mg/ml to about 15.0 mg/ml. It may also include the following intermediate ranges: about 0.001 mg/ml to about 0.50 mg/ml; about 0.51 mg/ml to about 1.00 mg/ml; about 1.01 mg/ml to about 1.50 mg/ml; about 1.51 mg/ml to about 2.00 mg/ml; about 2.51 mg/ml to about 3.00 mg/ml; about 3.01 mg/ml to about 3.50 mg/ml; about 3.51 mg/ml to about 4.00 mg/ml; about 4.01 mg/ml to about 4.50 mg/ml; about 4.51 mg/ml to about 5.00 mg/ml; about 5.01 mg/ml to about 5.50 mg/ml; about 5.51 mg/ml to about 6.00 mg/ml; about 6.01 mg/ml to about 6.50 mg/ml; about 6.51 mg/ml to about 7.00 mg/ml; about 7.01 mg/ml to about 7.50 mg/ml; about 7.51 mg/ml to about 8.00 mg/ml; about 8.01 mg/ml to about 8.50 mg/ml; about 8.51 mg/ml to about 9.00 mg/ml; about 9.01 mg/ml to about 9.50 mg/ml; about 9.51 mg/ml to about 10.00 mg/ml; about 10.01 mg/ml to about 10.50 mg/ml; about 10.51 mg/ml to about 11.00 mg/ml; about 11.01 mg/ml to about 11.50 mg/ml; about 11.50 mg/ml to about 12.00 mg/ml; about 12.00 mg/ml to about 12.51 mg/ml; about 12.51 mg/ml to about 13.00 mg/ml; about 13.01 mg/ml to about 13.50 mg/ml; about 13.51 mg/ml to about 14.00 mg/ml; about 14.01 mg/ml to about 14.50 mg/ml; about 14.51 mg/ml to about 15.00 mg/ml.

[0038] In one alternative embodiment of the present invention, a therapeutically effective amount of a hypertension-reducing agent may include the following intermediate ranges; about 0.001 mg/ml to about 1.0 mg/ml; about 0.005 mg/ml to about 1.0 mg/ml; about 0.01 mg/ml to about 1.0 mg/ml; about 0.05 mg/ml to about 0.1 mg/ml; about 0.05 mg/ml to about 0.5 mg/ml.

[0039] In another alternative embodiment of the present invention, a therapeutically effective amount of a hypertension-reducing agent may include from about 0.001 to about 10 mg/ml of a hypertension-reducing pharmaceutical agent, including the following intermediate amounts: about 0.001 mg/ml to about 1.25 mg/ml; about 1.25 mg/ml to about 1.50 mg/ml; about 1.50 mg/ml to about 1.75 mg/ml; about 1.75 mg/ml to about 2.00 mg/ml; about 2.0 mg/ml to about 2.25 mg/ml; about 2.25 mg/ml to about 2.50 mg/ml; about 2.50 mg/ml to about 2.75 mg/ml; about 2.75 mg/ml to about 3.00 [illegible]

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