US 20080275030A1

(19) **United States**

(12) **Patent Application Publication**

(10) **Pub. No.: US 2008/0275030 A1**

(43) **Pub. Date: Nov. 6, 2008**

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(54) **METHODS AND COMPOSITIONS FOR THE DELIVERY OF A THERAPEUTIC AGENT**

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(21) Appl. No.: **12/016,724**

(22) Filed: **Jan. 18, 2008**

(30) **Foreign Application Priority Data**

Jan. 19, 2007 (IS) 8593/2007

Publication Classification

(51) **Int. Cl.**

A61K 47/30	(2006.01)
A61K 31/5513	(2006.01)
A61K 31/5517	(2006.01)

(52) **U.S. Cl.** **514/220**; 514/772.3; 514/221

(57) **ABSTRACT**

The present invention provides a liquid pharmaceutical composition comprising a therapeutic agent and an alkoxy-polyethylene glycol, for example, methoxy-polyethylene glycol, for administration of the therapeutic agent to the mammal. The compositions can be applied to a membrane, for example, a nasal membrane during intranasal administration. The invention also provides methods of administering such compositions to a mammal.

METHODS AND COMPOSITIONS FOR THE DELIVERY OF A THERAPEUTIC AGENT

RELATED APPLICATIONS

[0001] This application claims the benefit of and priority to Icelandic Patent Application Serial No. 8593/2007, filed Jan. 19, 2007, the entire disclosure of which is incorporated by reference herein for all purposes.

FIELD OF THE INVENTION

[0002] This invention relates generally to compositions for the delivery of a therapeutic agent and to related methods, and more particularly relates to compositions containing one or more alkoxy-polyethylene glycols for the delivery of a therapeutic agent and to related methods.

BACKGROUND

[0003] The administration of a therapeutic agent by injection (e.g., intravenous, intramuscular or subcutaneous injection) typically is regarded as the most convenient way of administration when the purpose is to achieve a rapid and strong systemic effect, for example, within 3-10 minutes, when the agent is not absorbed by the gastrointestinal tract, or when the agent is inactivated in the gastrointestinal tract or by first-pass hepatic metabolism. However, administration by injection presents a range of disadvantages. For example, sterile syringes must be used and injections cannot be administered by untrained personnel. Furthermore, this mode of administration may cause pain and/or irritation, especially in the case of repeated injections at the same site.

[0004] Mucosal administration, such as, intranasal, buccal, sublingual, rectal and pulmonal administration, is receiving particular interest as it avoids many of the disadvantages of injecting a therapeutic agent while, at the same time, still providing a strong and rapid systemic effect. In order to be an attractive alternative to injection, mucosal administration, for example, intranasal administration, should neither cause significant pain, discomfort or irritation nor cause any irreversible damage to the mucosal surface. However, in the case of acute health threatening indications, a relatively high local irritation to the mucosa may be acceptable.

[0005] In mucosal administration, such as during nasal, buccal or rectal administration, the therapeutic agent should be applied to the mucosa in a vehicle that permits it to penetrate, or be absorbed through, the mucosa. In order to penetrate the mucus, the vehicle should be biocompatible with mucus and hence have a certain degree of hydrophilicity. However, the vehicle should preferably also possess lipophilic properties to dissolve a clinically relevant amount of the therapeutic agent of interest.

[0006] The extensive network of blood capillaries under the mucosal surface, especially in the nasal mucosa, is well suited to provide a rapid and effective systemic absorption of drugs, vaccines and biologicals. Moreover, the nasal epithelial membrane in effect contains a single layer of epithelial cells (*pseudostratified epithelium*) and, therefore, is more suited for drug administration than other mucosal surfaces having squamous epithelial layers, such as, the mouth and vagina.

[0007] It has been hypothesized that the usefulness of nasal administration can be limited if the therapeutic agent has limited solubility in water (Proctor, D. F. (1985) *Nasal Physiology in Intranasal Drug Administrations*, in Chien, Y. W. (Ed.) TRANSNASAL SYSTEMIC MEDICATIONS, FUNDAMEN-

105). As a result, this hypothesis, if correct, may limit the delivery of certain therapeutic agents that are sparingly soluble in water.

[0008] To facilitate delivery to the nasal cavity, an effective amount of the therapeutic agent should be dissolved in a small volume, for example, less than about 1000 μL, preferably less than 300 μL, and more preferably less than 150 μL. Larger volumes drain out anteriorly through the nostrils or posteriorly toward the pharynx where excess liquid is swallowed. As a result, if large volumes are administered, a portion of the therapeutic agent can be lost from the absorption site, and it can be difficult if not impossible to reproducibly administer the correct dose of the therapeutic agent.

[0009] A variety of delivery systems have been developed for the nasal administration of therapeutic agents. Lau and Slattery studied the absorption characteristics of diazepam and lorazepam following their intranasal administration for the treatment of epilepticus (Lau, S. W. J. & Slattery, J. T. (1989), *Absorption of Diazepam and Lorazepam Following Intranasal Administration*, INT. J. PHARM., 54, 171-174). In order to solubilize the therapeutic agent, a non-ionic surfactant—polyoxyethylated castor oil—was selected as the least irritating solvent of several solvents studied, including polyethylene glycol 400 (PEG 400). Diazepam absorption was 84% and 72%, respectively, in two adults measured over a period of 60 hours. However, the peak concentration was not observed until 1.4 hours after the nasal administration and was only about 27% with reference to intravenous administration, suggesting that most of the absorption had taken place after the test substance passed down to pharynx and swallowed. Similar results were obtained for lorazepam but with an even longer time to peak (2.3 hours). The authors concluded that the intranasal route of administration had limited potential for the acute treatment of epileptic seizures.

[0010] Wilton et al. attempted to administer midazolam to 45 children to achieve pre-anesthetic sedation (Wilton et al. (1988) *Preanaesthetic Sedation of Preschool Children Using Intranasal Midazolam*, ANESTHESIOLOGY, 69, 972-975). However, the volumes used were impractical and exceeded the maximal volume required for efficient administration. This resulted in coughing and sneezing with expulsion of at least part of the dose.

[0011] Morimoto et al. studied a gel preparation for nasal application in rats of nifedipine containing the gelling agent carbopol (polyacrylic acid) in PEG 400, for achieving prolonged action and high bioavailability of the therapeutic agent (Morimoto et al. (1987) *Nasal Absorption of Nifedipine from Gel Preparations in Rats*, CHEMICAL AND PHARMACEUTICAL BULLETINS, 35, No. 7, 3041-3044). A mixture of equal amounts of carbopol and PEG 400 was preferred. It was shown that nasal application provided higher bioavailability of nifedipine than after peroral administration, but the peak plasma concentration was not observed until 30 minutes after administration.

[0012] Danish Patent Application No. 2586/87 discloses a pharmaceutical composition comprising an anti-inflammatory steroid, water, 2 to 10% (v/v) propylene glycol, 10 to 25% (v/v) PEG 400, and 1 to 4% (v/v) Tween 20.

[0013] U.S. Pat. No. 4,153,689 discloses a stable aqueous solution of insulin intended for intranasal administration. The solutions had a pH not more than 4.7, and contained from 0.1 to 20% by weight of a stabilizing agent including (a) one or more non-ionic surface active agents whose hydrophile-lipophile balance value was in the range of 9 to 22, and/or (b) polyethylene glycol whose molecular weight was in the range

ethylene higher alcohol ether, a polyoxyethylene alkylphenyl ether, or a polyoxyethylene alkylphenyl ether, or a polyoxyethylene hydrogenated castor oil.

[0014] International Patent Publication No. DK-2075/90 discloses the nasal administration of therapeutic agents, for example, benzodiazepines, in compositions containing n-glycofurol, a derivative of polyethyleneglycol, for mucosal administration. The application discloses the nasal administration of therapeutic agents, for example, benzodiazepines, in formulations containing at least 30% n-ethyleneglycols ranging from 1-8 ethylene glycol, for example, polyethylene glycol 200 (PEG 200).

[0015] U.S. Pat. No. 5,693,608 discloses a method of administering a therapeutic agent via the nasal mucosa of a mammal, where the agent is dissolved or suspended in an n-ethyleneglycol containing vehicle where the n-ethyleneglycol is represented by the formula, $H(OCH_2CH_2)_pOH$, wherein p is a number from 1 to 8.

[0016] Notwithstanding, there is still a need for compositions deliverable through mucosal membranes that produce therapeutic plasma concentrations of the therapeutic agent as fast as or nearly as fast as by intravenous administration but without causing irritation and/or unacceptable damage to the mucosal membrane.

SUMMARY OF THE INVENTION

[0017] The invention is based, in part, upon the discovery that the inclusion of one or more alkoxy-polyethylene glycols in a formulation provides certain advantages when the resulting composition is to be applied, for example, to a mucosal surface. For example, it has been discovered that when alkoxy-polyethylene glycol is used in such formulations, the therapeutic agent can be still be solubilized (which is especially useful for poorly soluble therapeutic agents) but the resulting formulations are less viscous and cause less irritation to mucosal membranes because the amount of other potentially viscous and irritable excipients, for example, polyethylene glycol or propylene glucol, can be reduced or eliminated altogether. As a result, the lower viscosity formulations, when converted into droplets, for example, by a nasal sprayer during intranasal delivery, can produce a spray pattern optimized for delivering the therapeutic agent to the mucosal membrane. In addition, formulations containing alkoxy-polyethylene glycols create less irritation (burning sensation) when applied to a mucosal surface, for example, a nasal membrane following nasal administration. In addition, when administered intranasally, the compositions of the invention minimize undesirable after taste (for example, a petroleum-like after taste) that can be associated with certain other excipients.

[0018] In one aspect, the invention provides a liquid pharmaceutical composition comprising a therapeutic agent and an alkoxy-polyethylene glycol represented by Formula I:

$$R—O—(CH_2CH_2O)_n—H \quad (I)$$

wherein,

[0019] R is methyl, ethyl, n-propyl, isopropyl, or cyclopropyl; and

[0020] n, which is the average number of oxyethylene repeating units, is a number in the range of from about 1 to about 25.

[0021] In another aspect, the invention provides a liquid formulation for solubilizing a poorly soluble therapeutic agent and an alkoxy-polyethylene glycol represented by Formula I:

$$R—O—(CH_2CH_2O)_n—H \quad (I)$$

wherein,

[0022] R is $(C_1\text{-}C_6)$alkyl; and

[0023] n, which is the average number of oxyethylene repeating units, is a number in the range of from about 1 to about 25.

[0024] In another aspect, the invention provides methods of delivering a therapeutic agent of interest to a mammal, for example, a human, using an alkoxy-polyethylene glycol containing composition described herein. The composition is particularly useful when the composition is applied to a mucosal membrane, for example, a nasal membrane during intranasal drug delivery.

[0025] These and other aspects and advantages of the invention will become apparent upon consideration of the following detailed description and claims.

DETAILED DESCRIPTION OF THE INVENTION

[0026] The invention is based, in part, upon the discovery that the inclusion of one or more alkoxy-polyethylene glycols into formulations provides certain advantages over other excipients when the formulations are applied, for example, to a mucosal surface. For example, it has been discovered that when an alkoxy-polyethylene glycol is used in such a formulation, the therapeutic agent (for example, a poorly soluble therapeutic agent) can be solubilized more easily and in larger amounts than when other excipients, for example, polyethylene glycol (more particularly PEG 400), are used. However, the resulting formulations are less viscous and cause less irritation to mucosal membranes as the amount of other viscous and irritable excipients can be reduced or eliminated altogether. As a result, the lower viscosity formulations, when converted into droplets, for example, by a nasal sprayer during intranasal delivery, produce a spray pattern optimized for delivering the therapeutic agent to the mucosal membrane. In addition, formulations containing one or more alkoxy-polyethylene glycols cause less irritation (for example, a burning sensation) when applied to a mucosal surface, for example, a nasal membrane during intranasal administration. In addition, when administered intranasally, the compositions of the invention have less undesirable after taste (for example, a petroleum-like after taste) than when other excipients, for example, propylene glycol, are used.

[0027] Under certain circumstances, the alkoxy-group also increases the bioadhesion of the composition to the site of administration on the mucosal surface thereby prolonging the duration of the composition at the site of administration. This can increase the amount of therapeutic agent that is ultimately absorbed.

I Formulations

[0028] In one aspect, the invention provides a liquid pharmaceutical composition comprising a therapeutic agent and an alkoxy-polyethylene glycol represented by Formula I:

$$R—O—(CH_2CH_2O)_n—H \quad (I)$$

wherein,

[0029] R is methyl, ethyl, n-propyl, isopropyl, or cyclopropyl; and

[0030] n is the average number of oxyethylene repeating units and is a number in the range of from about 1 to about 25.

[0031] In another aspect, the invention provides a liquid

poorly soluble therapeutic agent, for example, a poorly soluble organic therapeutic agent, and an alkoxy-polyethylene glycol represented by Formula I:

$$R—O—(CH_2CH_2O)_n—H \quad (I)$$

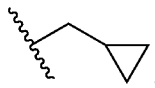
wherein,

[0032] R is (C_1-C_6)alkyl; and

[0033] n is the average number of oxyethylene repeating units and is a number in the range of from about 1 to about 25. The formulations typically are in liquid form at 20° C., 25° C., 30° C., 35° C., or 40° C. Certain formulations preferably are liquid formulations at 37° C.

[0034] The term "poorly soluble therapeutic agent" refers to a compound having biological activity and a solubility in water of less than about 1 mg/mL at pH 7 and 20° C. In certain embodiments, the poorly soluble therapeutic agent is an organic compound that has a molecular weight of less than 1500 g/mol, and preferably less than 500 g/mol. In certain embodiments, the poorly soluble therapeutic agent is a compound, for example, an organic compound, having an aqueous solubility of less than about 0.5 mg/mL, less than about 0.3 mg/mL, or less than about 0.1 mg/mL, at pH 7 and 20° C.

[0035] In addition, the term "alkyl" is art-recognized, and includes saturated aliphatic groups, including straight-chain alkyl groups, branched-chain alkyl groups, cycloalkyl (alicyclic) groups, alkyl substituted cycloalkyl groups, and cycloalkyl substituted alkyl groups. The term "(C_1-C_6)alkyl" refers to an alkyl group having between 1 and 6 carbon atoms. Representative alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopropylmethylene, cyclopentyl, cyclobutylmethylene, cyclobutylethylene, cyclohexyl, cyclopropylpropylene, cyclobutylethylene, and cyclopentylmethylene. The term cyclopropylmethylene, for example, is art-recognized and refers to a radical having the following formula:



[0036] In certain embodiments, the alkoxy-polyethylene glycol can comprise from about 0.1% (v/v) to about 80% (v/v), or from about 0.5% (v/v) to about 70% (v/v), of the composition. In certain other embodiments, the alkoxy-polyethylene glycol can comprise from about 5% (v/v) to about 80% (v/v), or from about 30% (v/v) to about 75% (v/v) or from about 40% (v/v) to about 70% (v/v), of the composition. For certain hydrophilic drugs, the alkoxy-polyethylene glycol can comprise from about 0.1% (v/v) to about 80% (v/v), or from about 0.5% (v/v) to about 70% (v/v), or from about 1% (v/v) to about 60% of the composition. For certain lipophilic drugs, the alkoxy-polyethylene glycol can comprise from about 1% (v/v) to about 80% (v/v), or from about 2% (v/v) to about 65% (v/v), or from about 5% (v/v) to about 50% of the composition. Furthermore, the therapeutic agent can comprise from about 0.001% (w/v) to about 20% (w/v) of the composition, or from about 0.1% (w/v) to about 10% (w/v) of the composition.

[0037] The pharmaceutical composition can have a pH in the range of from about 4.5 to about 8.5, or from about 4.5 to about 7.5, or from about 4.5 to about 6.5, or from about 5.5 to about 8.5, or from about 6.5 to about 8.5, or from about 5.5 to about 7.5.

can be used to reduce the amount of other excipients, for example, certain polyethylene glycols and propylrnr glycol, so as to reduce the viscosity of the resulting formulation. By reducing the viscosity of the resulting formation it is possible to create sprays that have more uniform spray characteristics (for example, more uniform droplet sizes and/or plume geometries) for the intranasal administration of therapeutic agent. The resulting pharmaceutical composition at a temperature of 20° C. has a viscosity in the range of about 1.5 cP to about 60 cP, or from about 2 cP to about 50 cP, or from about 3 cP to about 40 cP, or from about 4 cP to about 30 cP, or from about 5 cP to about 25 cP.

[0039] Exemplary alkoxy-polyethylene glycols, therapeutic agents, and other excipients useful in creating compositions of the invention are described in the following sections.

[0040] A. Alkoxy-polyethylene Glycol

[0041] Useful alkoxy-polyethylene glycol excipients useful in the practice of the invention are represented by Formula (I):

$$R—O—(CH_2CH_2O)_n—H \quad (I)$$

wherein, n, as the average number of oxyethylene repeating units, is a number in the range of from about 1 to about 25. Accordingly, n can be a number about 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, or 25. In certain embodiments, n is an number in the range of from about 2 to about 15, or from about 2 to about 14, or from about 2 to about 13, or from about 2 to about 12, or from about 2 to about 11, or from about 2 to about 10, or from about 3 to about 15, or from about 3 to about 14, or from about 3 to about 13, or from about 3 to about 12, or from about 3 to about 11, or from about 3 to about 10.

[0042] In certain embodiments, R is (C_1-C_6)alkyl. For example, as discussed above, R can be methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, pentyl, hexyl, cyclopropyl, cyclobutyl, cyclopropylmethylene, cyclopentyl, cyclobutylmethylene, cyclobutylethylene, cyclohexyl, cyclopropylpropylene, cyclobutylethylene, or cyclopentylmethylene. In certain embodiments, R is selected from the group consisting of methyl, ethyl, n-propyl, isopropyl, and cyclopropyl.

[0043] In a preferred embodiment, the alkoxy-polyethylene glycol is methoxy-polyethylene glycol where R is methyl and n is an number from about 1 to about 25, or from about 2 to about 12, or from about 3 to about 10.

[0044] Useful methoxy-polyethylene glycols include, for example, methoxy-diethyleneglyol (m2EG), methoxy-triethylene glycol (m3EG), methoxy-tetraethylene glycol (m4EG), methoxy-pentaethylene glycol (m5EG), methoxy-hexaethylene glycol (m6EG), methoxy-heptaethylene glycol (m7EG), methoxy-octaethylene glycol (m8EG), methoxy-nonaethylene glycol (m9EG), methoxy-decaethylene glycol (m10EG), methoxy-undecaethylene glycol (m11EG), methoxy-dodecaethylene glycol (m12EG), methoxy-tridecaethylene glycol (m13EG) and methoxy-tetradecaethylene glycol (m14EG). The ethylene glycols may be used in the form of the single compounds or as a mixture of two or more methoxy-n-ethylene glycols.

[0045] In certain embodiments, the alkoxy-polyethylene glycol is methoxy-polyethylene glycol 350 (mPEG 350) or is methoxy-polyethylene glycol 550 (mPEG 550) or is methoxy-polyethylene glycol 750 (mPEG 750). The term "mPEG 350" is understood to mean methoxy polyethylene glycol having an average molecular weight of about 350, and in certain embodiments "n," as denoted in Formula I, is 7.2. The term "mPEG550" is understood to mean methoxy polyethyl-

11.8. The term "mPEG750" is understood to mean methoxy polyethylene glycol having an average molecular weight of about 750, and in certain embodiments "n," as denoted in Formula I, is 16.3.

[0046] Certain, preferred alkoxy-polyethylene glycols include Carbowax™ mPEG 350, Carbowax™ mPEG 550 or Carbowax™ mPEG 750, which are available commercially from Dow Chemical Company. Both mPEG350 and mPEG550 are colorless liquids that are miscible with water, alcohols, such as methanol, ethanol, n-propanol, glycerol and various oils in all proportions, and have a boiling point about 155° C. It is understood that alkoxy-polyethylene glycols are known by other names, where, for example, methoxy-polyethylene glycol is also known as mono-methyl polyethylene glycol and poly(ethylene glycol) methyl ether.

[0047] By using one or more of the alkoxy-polyethylene glycols described herein, the resulting pharmaceutical compositions can be optimized, for example, with respect to bioadhesion, viscosity and sprayability. For example, mPEG 350, at an equivalent concentration as PEG 200, can still solubilize a therapeutic agent but the resulting composition has a lower viscosity. As a result, this substitution has a surprisingly positive effect on the sprayability compared with lower molecular weight PEG 200, which is important where the formulation is to be sprayed.

[0048] B. Therapeutic Agent

[0049] The pharmaceutical composition of the invention may comprise one or more therapeutic agents (also referred to as biologically active substances) selected from the group consisting of hydrophobic therapeutic agents, hydrophilic therapeutic agents, and combinations thereof.

[0050] The alkoxy-polyethylene glycol excipients are surprisingly capable of solubilizing and delivering a wide variety of hydrophilic and hydrophobic therapeutic agents. The hydrophobic drugs have little or no water solubility. It is understood that the excipients described herein can be used to solubilize therapeutic agents that have a solubility in water of less than about 1.0 mg/mL, less than about 0.5 mg/mL, less than about 0.3 mg/mL, or less than about 0.1 mg/mL, or less than about 0.01 mg/mL, at pH 7 and 20° C. Such therapeutic agents can be any agents having therapeutic or other value when administered to a mammal, for example, a human, and can include organic molecules (for example, small molecule drugs having a molecular weight of less than 1,500 g/mol., or less than 500 g/mol.), proteins, peptides, immungens (e.g. vaccines, cytokines, etc.), nutrients, and cosmetics (cosmeceuticals).

[0051] In certain embodiments, the therapeutic agent is an analgesic agent, an anti-inflammatory agent, an anti-arrhythmic agent, an anti-asthma agent, an anti-bacterial agent, an anti-viral agent, an anti-coagulant, an anti-depressant, an anti-diabetic, an anti-epileptic, an anti-fungal agent, an anti-hypertensive agent, an anti-malarial, an anti-migraine agent, an anti-muscarinic agent, an anti-neoplastic agent, an immunosuppressant, an anti-protozoal agent, an anti-thyroid agent, an anxiolytic agent, a sedative, a hypnotic agent, a neuroleptic agent, a beta-Blocker, a cardiac inotropic agent, a corticosteroid, a diuretic agent, an anti-Parkinsonian agent, a gastrointestinal agent, an anti-histamine, a histamine-receptor antagonist, a lipid regulating agent, a muscle relaxant, nitrate and other anti-anginal agent, a nutritional agent, an opioid analgesic, sex hormone, stimulant, cytokine, peptidomimetic, peptide, protein, toxoid, sera, antibody, vaccine, nucleoside, nucleotide, nucleic acid and peptidyl-nucleic acid.

[0052] Specific examples of the therapeutic agents suitable for compositions of the present invention include the following representative compounds, as well as their pharmaceutically acceptable salts, isomers, esters, ethers and other derivatives including, for example: (1) analgesics and anti-inflammatory agents, such as, aloxiprin, auranofin, azapropazone, benorylate, capsaicin, celecoxib, diclofenac, diflunisal, etodolac, fenbufen, fenoprofen calcium, flurbiprofen, ibuprofen, indomethacin, ketoprofen, ketorolac, leflunomide, meclofenamic acid, mefenamic acid, nabumetone, naproxen, oxaprozin, oxyphenbutazone, phenylbutazone, piroxicam, refocoxib, sulindac, tetrahydrocannabinol, tramadol and tromethamine; (2) anti-arrhythmic agents, such as, amiodarone HCl, disopyramide, flecainide acetate and quinidine sulfate; (3) anti-asthma agents, such as, zileuton, zafirlukast, montelukast, and albuterol; (4) anti-bacterial agents, such as, baclofen, benzathine penicillin, cinoxacin, clarithromycin, clofazimine, cloxacillin, demeclocycline, dirithromycin, doxycycline, erythromycin, ethionamide, furazolidone, grepafloxacin, imipenem, levofloxacin, lorefloxacin, moxifloxacin HCl, nalidixic acid, nitrofurantoin, norfloxacin, ofloxacin, rifampicin, rifabutine, rifapentine, sparfloxacin, spiramycin, sulphabenzamide, sulphadoxine, sulphamerazine, sulphacetamide, sulphadiazine, sulphafurazole, sulphamethoxazole, sulphapyridine, tetracycline, trimethoprim and trovafloxacin; (5) anti-viral agents, such as, abacavir, amprenavir, delavirdine, efavirenz, indinavir, lamivudine, nelfinavir, nevirapine, ritonavir, saquinavir, and stavudine; (6) anti-coagulants, such as, cilostazol, clopidogrel, dicumarol, dipyridamole, nicoumalone, oprelvekin, phenindione, ticlopidine, and tirofiban; (7) anti-depressants, such as amoxapine, bupropion, citalopram, clomipramine, maprotiline HCl, mianserin HCl, nortriptyline HCl, paroxetine HCl, sertraline HCl, trazodone HCl, trimipramine maleate, and venlafaxine HCl; (8) anti-diabetics, such as, acetohexamide, chlorpropamide, glibenclamide, gliclazide, glipizide, glimepiride, miglitol, pioglitazone, repaglinide, rosiglitazone, tolazamide, tolbutamide and troglitazone; (9) anti-epileptics, such as, beclamide, carbamazepine, clonazepam, ethotoin, felbamate, fosphenytoin sodium, lamotrigine, methoin, methsuximide, methylphenobarbitone, oxcarbazepine, paramethadione, phenacemide, phenobarbitone, phenyloin, phensuximide, primidone, sulthiame, tiagabine HCl, topiramate, valproic acid, and vigabatrin; (10) anti-fungal agents, such as, amphotericin, butenafine HCl, butoconazole nitrate, clotrimazole, econazole nitrate, fluconazole, flucytosine, griseofulvin, itraconazole, ketoconazole, miconazole, natamycin, nystatin, sulconazole nitrate, oxiconazole, terbinafine HCl, terconazole, tioconazole and undecenoic acid; (11) anti-hypertensive agents, such as, amlodipine, benidipine, benezepril, candesartan, captopril, darodipine, dilitazem HCl, diazoxide, doxazosin HCl, elanapril, eposartan, losartan mesylate, felodipine, fenoldopam, fosenopril, guanabenz acetate, irbesartan, isradipine, lisinopril, minoxidil, nicardipine HCl, nifedipine, nimodipine, nisoldipine, phenoxybenzamine HCl, prazosin HCl, quinapril, reserpine, terazosin HCl, telmisartan, and valsartan; (12) anti-malarials, such as, amodiaquine, chloroquine, chlorproguanil HCl, halofantrine HCl, mefloquine HCl, proguanil HCl, pyrimethamine and quinine sulfate; (13) anti-migraine agents, such as, dihydroergotamine mesylate, ergotamine tartrate, frovatriptan, methysergide maleate, naratriptan HCl, pizotyline malate, rizatriptan benzoate, sumatriptan succinate, and zolmitriptan; (14) anti-muscarinic agents, such as, atropine, benzhexol HCl, biperiden, ethopropazine HCl, hyoscyamine, oxyphencyclimine HCl and tropicamide; (15) anti-neoplastic agents

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Sync your system to PACER to automate legal marketing.