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(54) **Title**: A PHARMACEUTICAL COMPOSITION OF VORAPAXAR AND METOPROLOL

(57) **Abstract**: The present invention relates to the combination of vorapaxar and metoprolol, pharmaceutical compositions containing them and their use in the treatment of cardiovascular diseases/disorders.

A PHARMACEUTICAL COMPOSITION OF VORAPAXAR AND METOPROLOL

Field of Invention

The present invention relates to the combination of vorapaxar and metoprolol, pharmaceutical compositions containing them and their use in the treatment of cardiovascular diseases/disorders.

Background of the invention

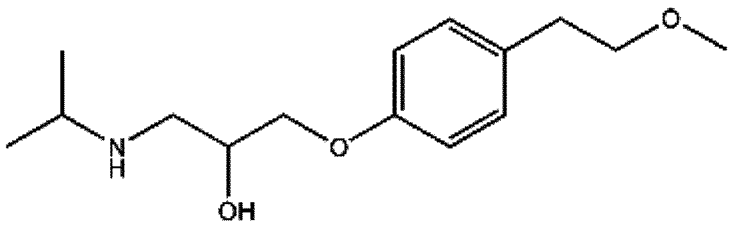
Cardiovascular disease/disorder is intended to mean any cardiovascular disease or disorder known in the art, including, but not limited to, congestive heart failure, complications associated with diabetes mellitus, hyperhomocysteinemia, hypercholesterolemia, atherosclerosis, inflammatory heart disease, valvular heart disease, restenosis, hypertension (e.g. pulmonary hypertension, labile hypertension, idiopathic hypertension, low-renin hypertension, salt-sensitive hypertension, low-renin, salt-sensitive hypertension, thromboembolic pulmonary hypertension; pregnancy-induced hypertension; renovascular hypertension; hypertension-dependent end-stage renal disease, hypertension associated with cardiovascular surgical procedures, hypertension with left ventricular hypertrophy, and the like), diastolic dysfunction, coronary artery disease, myocardial infarctions, cerebral infarctions, arteriosclerosis, atherogenesis, cerebrovascular disease, angina (including chronic, stable, unstable and variant (Prinzmetal) angina pectoris), aneurysm, ischemic heart disease, cerebral ischemia, myocardial ischemia, thrombosis, platelet aggregation, platelet adhesion, smooth muscle cell proliferation, vascular or nonvascular complications associated with the use of medical devices, vascular or non-vascular wall damage, peripheral vascular disease, neointimal hyperplasia following percutaneous transluminal coronary angiograph, vascular grafting, coronary artery bypass surgery, thromboembolic events, post-angioplasty restenosis, coronary plaque inflammation, embolism, stroke, shock, arrhythmia, atrial fibrillation or atrial flutter, thrombotic occlusion and reclusion cerebrovascular incidents, and the like.

Many individuals at an elevated risk of suffering serious to life-threatening cardiovascular events, such as myocardial infarction (heart attack), cardiac arrest, congestive heart failure, stroke, peripheral vascular disease and/or claudication. And the risk factors for

these are numerous and widespread throughout the world. They include cigarette smoking, diabetes, hypercholesterolemia (high serum cholesterol), hypertension, angina, systemic lupus erythematosus, prior heart attacks or strokes, hemodialysis, hyperhomocysteine levels, obesity, sedentary lifestyle, receiving an organ transplant, atherosclerosis, and others. There is a need for a safe and convenient pharmaceutical composition that would effectively reduce the risk of incurring a cardiovascular event in individuals who have these risk factors.

The treatments and drugs are known in the art for cardiovascular disease includes the beta-blockers like atenolol, metoprolol, nadolol, oxprenolol, pindolol, propranolol, timolol; alpha blockers like doxazosin, phentolamine, indoramin, phenoxybenzamine, prazosin, terazosin, tolazoline; mixed alpha and beta blockers, for example, bucindolol, carvedilol and labetalol, etc.

Metoprolol (Formula I) is a beta-selective (cardioselective) adrenoreceptor blocking agent. It is available in three salt forms; metoprolol tartrate, metoprolol succinate and metoprolol fumarate. Metoprolol is indicated in the treatment of hypertension, heart failure and angina pectoris. Metoprolol acts by blocking the adrenergic stimulation of the heart and thus reduces the oxygen demand of the cardiac tissue. Apparently, this explains their beneficial effects in angina pectoris and cardioprotective action in myocardial infarction. In addition, beta-blockers normalize blood pressure in a large proportion of patients with arterial hypertension, which probably is due to an additional action on the control of peripheral resistance to blood-flow.

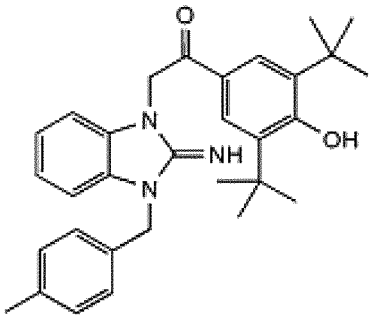


Formula I. Metoprolol

Another treatments and drugs are known in the art for cardiovascular disease includes thrombin receptor antagonists like vorapaxar. Thrombin is known to have a variety of activities in different cell types and thrombin receptors are known to be present in such cell types as human platelets, vascular smooth muscle cells, endothelial cells and fibroblasts. It is therefore possible that thrombin receptor antagonists, also known as

protease activated receptor (PAR) antagonists will be useful in the treatment of thrombotic, inflammatory, atherosclerotic and fibroproliferative disorders, as well as other disorders in which thrombin and its receptor play a pathological role. Thrombin receptor antagonist compounds can have anti-thrombotic, anti-platelet aggregation, antiatherosclerotic, antirestenotic and/or anti-coagulant activity. Thrombosis-related diseases treated by this compounds include thrombosis, atherosclerosis, restenosis, hypertension, angina pectoris, arrhythmia, heart failure, myocardial infarction, glomerulonephritis, thrombotic and thromboembolytic stroke, peripheral vascular diseases, other cardiovascular diseases, cerebral ischemia, inflammatory disorders and cancer, as well as other disorders in which thrombin and its receptor play a pathological role.

Vorapaxar (Formula II) is a tricyclic himbacine-derived selective inhibitor of platelet aggregation mediated by PAR-1. It is available in a salt form, vorapaxar sulfate. The vorapaxar has obtained registration from the FDA in 2014 for the indication "reduction of thrombotic events in patients with a history of myocardial infarction or peripheral arterial disease."



Formula II. Vorapaxar

This compound has undergone clinical trials and is disclosed in US 7,304,048. US 7,235,567 discloses the bisulfate salt of vorapaxar and indicates that this salt has at least two crystalline polymorphic forms. US 7,235,567 indicates that Form 2 was found to be unstable and reverted over time to the crystalline structure of Form 1. U.S. Patent Applications US 2008/0026050; US 2008/0031943; and US 2008/0152712 disclose capsule compositions, tablet compositions and lyophilized compositions (respectively) of vorapaxar or a pharmaceutically acceptable salt thereof as well methods of treating various conditions affected by antagonizing the PAR-1 receptor by administering same to

a patient. US 7,304,048 and US 7,235,567 describe inter alia pharmaceutical combinations of vorapaxar and aspirin.

However, there is no patent application comprising the combination of vorapaxar and metoprolol. There is a need to develop pharmaceutical compositions comprising a therapeutically effective amount of a combination of vorapaxar and metoprolol in a pharmaceutically acceptable carrier for cardiovascular diseases/disorders.

According to the composition of the present invention it is desired to provide a dosage form comprising in combination a therapeutically effective amount of vorapaxar and metoprolol which overcomes above described problems. The main challenges when combining those molecules in the same pharmaceutical form are:

(a) to guarantee the physico-chemical compatibility between those different active ingredients and/or between the active ingredients and the excipients used; and

(b) to insure the pharmaceutical compatibility between those active ingredients regarding their stability characteristics. When vorapaxar is combined with metoprolol, these two drug substances must be released, dissolved and absorbed harmoniously. For the efficiency of the composition, an easy dissolution of both drug substances at a desired time is an important factor.

Detailed description of the invention

The present invention relates to the combination of vorapaxar and metoprolol, pharmaceutical compositions containing them and their use in the treatment of cardiovascular diseases/disorders.

Drugs of different action mechanisms can be combined. It is possible, however, to state that a combination of drugs having different action mechanisms, but showing actions on similar targets, will have absolutely positive effects.

The term “combination” means that when drugs are administered together, a combined action is obtained which is higher than the individual actions of the respective drugs when they are used separately. On the other hand, using a lower dose of each drug to be combined according to the present invention will reduce the total dosage. Put

differently, the dosages have not to be relatively less in all cases, but the drugs can be dosed less frequently or this may be beneficial in reducing the recurrence rate of side effects. These are advantageous in terms of patients to be treated.

An aspect of the present invention is the use of vorapaxar and metoprolol for the manufacture of a medicament for the treatment, amelioration or prevention of one or more conditions associated with antagonizing the PAR-1 receptor.

The compounds of the present invention could be useful in the treatment, amelioration or prevention of one or more conditions associated with antagonizing the PAR-1 receptor by administering a therapeutically effective amount of vorapaxar and metoprolol to a mammal in need of such treatment. Conditions that could be treated or prevented by antagonizing the PAR-1 receptor include acute coronary syndromes (ACS), secondary prevention, peripheral arterial disease (PAD), thrombosis, atherosclerosis, restenosis, hypertension, angina pectoris, arrhythmia, heat failure, myocardial infarction (MI), glomerulonephritis, thrombotic stroke, thromboembolic stroke, deep vein thrombosis, venous embolism a cardiovascular disease associated with hormone replacement therapy, renal ischemia, cerebral stroke, cerebral ischemia, cerebral infarction, migraine, or renal vascular homeostasis. Other conditions that could be treated by antagonizing the PAR-1 receptor are the reduction of atherothrombotic events in patients with a history of MI and reducing the rate of a combined endpoint of cardiovascular death, MI, stroke and urgent coronary revascularization.

The pharmaceutical composition comprising vorapaxar or a pharmaceutically acceptable salt thereof and metoprolol or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable excipient.

The invention comprises two active components is administered by a single pharmaceutical composition comprising vorapaxar and metoprolol in a pharmaceutically acceptable carrier.

According to this embodiment, the pharmaceutical composition is administrated oral, parenteral, intranasal, sublingual, transdermal, transmucosal, ophthalmic, intravenous, pulmonary, intramuscular or rectal administration, and preferably for oral administration.

According to this embodiment of the invention, said pharmaceutical composition may be formulated with suitable pharmaceutical diluents, excipients or carriers, suitably selected with respect to a dosage form for oral administration.

Another embodiment of this invention, the pharmaceutical composition is in the form of solid, liquid or semisolid dosage form.

According to this embodiment of the invention, the pharmaceutical composition is formulated as tablets including compressed tablets including compressed tablets comprising compressed tablets, coated or uncoated tablets, multilayer tablets, mini tablets, buccal tablets, sublingual tablets, effervescent tablets, immediate release tablets, modified release tablets, film-coated tablets, orally disintegrating tablets, gastric disintegrating tablets, pellets, effervescent compositions, pills, capsules, hard or soft gelatin capsules, powders, mini tablets, pellets, coated bead systems, granules, microspheres, ion exchange resin systems, sterile solutions or suspensions, steril ocular solutions, aerosols, sprays, drops, ampoules, suppositories, ocular systems, parenteral systems, creams, gels, ointments, dragees, sachets, films, orally administrable films, solutions, solids, elixirs, tinctures, suspensions, syrups, colloidal dispersions, dispersions, emulsions and thereof.

The pharmaceutical composition of the invention is formulated preferably in the form of pellet or tablet or mini tablet or multilayer tablet or capsule.

The preferred dosages of active agents included to the pharmaceutical combination according to the present invention are therapeutically active dosages, and particularly correspond to the dosage of those which are commercially available. Therapeutically active amount not only includes therapeutic doses, but also preventive/prophylactic doses.

According to one embodiment, vorapaxar is present in an amount of between 0.01mg and 50mg, preferably between 0.1mg and 30mg and more preferably it is in an amount of between 1mg and 20mg.

The term "vorapaxar", as used herein, refers to a vorapaxar base, or any pharmaceutically acceptable salt thereof. For the purpose of present invention, the pharmaceutical acceptable salt of vorapaxar is preferably vorapaxar sulfate.

The daily dose of vorapaxar for treatment of a disease or condition cited above is about 0.001 to about 100 mg/kg of body weight per day, preferably about 0.001 to about 10 mg/kg. e.g., from about 1 mg to about 75 mg, from about 1 mg to about 50 mg, (e.g., 2.5 mg) according to the particular application. For an average body weight of 70 kg, the dosage level is therefore from about 0.1 to about 700 mg of drug per day, given in a single dose or 2 divided doses.

In further embodiment, the dosage form of the present invention comprises vorapaxar sulfate 2.5mg equivalent to 2.08mg vorapaxar base.

According to one embodiment, metoprolol is present in an amount of between 5mg and 500mg, preferably between 10mg and 250mg and more preferably it is in an amount of between 15mg and 220mg.

The term "metoprolol", as used herein, refers to a metoprolol base, or any pharmaceutically acceptable salt thereof. For the purpose of present invention, the pharmaceutical acceptable salt of metoprolol are preferably metoprolol tartrate, metoprolol succinate and metoprolol fumarate.

In further embodiment, the dosage form of the present invention comprises metoprolol succinate 23.75mg, 47.5mg, 95mg and 190mg equivalent to 25mg, 50mg, 100mg and 200 mg of metoprolol tartarate or 11.85mg, 23.68mg, 47.37mg and 94.74mg of metoprolol fumarate equivalent to 9.75mg, 19.5mg, 39mg and 78mg of metoprolol base respectively.

The pharmaceutical composition comprises vorapaxar in an amount of between 1mg and 20mg and metoprolol is in an amount of between 15mg and 220mg.

According to one embodiment, the ratio of metoprolol to vorapaxar is in the range of 1 to 220(w/w) and preferably 1 to 100 (w/w) and more preferably 2 to 80 (w/w).

According to one embodiment, the ratios used in this present invention ensure the required effective doses for the treatment and desired dissolution profile for both vorapaxar and metoprolol.

An embodiment of this present invention is to combine vorapaxar and metoprolol in a same and stable dosage form with desired dissolution profiles.

Another embodiment of this invention, the pharmaceutical composition comprising vorapaxar and metoprolol is administrated once a day (QD) or twice a day (BID).

The pharmaceutical composition is administrated to any subject in need of therapy including humans or animals.

According to the challenges mentioned above the selection of the excipients thus very important. According to this embodiment, one or more pharmaceutically acceptable excipient is selected from buffering agents, stabilizers, antioxidants, binders, diluents, dispersing agents, lubricants, glidants, disintegrants, plasticizers, preservatives, sweeteners, flavoring agents, coloring agents, inert agent, coating agents or mixtures thereof.

Suitable buffering agents may comprise but not limited to alkali metal citrate, citric acid/sodium citrate, tartaric acid, fumaric acid, sorbic acid, citric acid, succinic acid, adipic acid, ascorbic acid, glutaric acid, potassium hydrogen tartrate, sodium hydrogen tartrate, potassium hydrogen phthalate, sodium hydrogen phthalate, potassium dihydrogen phosphate, sodium dihydrogen phosphate, disodium hydrogen phosphate, hydrochloric acid/sodium hydroxide or mixtures thereof, and preferably citric acid, fumaric acid, ascorbic acid, sodium dihydrogen phosphate, glycin , glutamic acid or mixtures thereof.

Suitable stabilizers may comprise but not limited to citric acid, fumaric acid, tartaric acid, sodium citrate, sodium benzoate, sodium dihydrogen phosphate, calcium carbonate, magnesium carbonate, arginine, lysine, meglamine, ascorbic acid, gallic acid esters or the mixtures thereof, and preferably, citric acid, fumaric acid, arginine or mixtures thereof.

Suitable antioxidants may comprise but not limited to alpha tocopherol, ascorbic acid, ascorbyl palmitate, butylhydroxyanisole (BHA), butylhydroxytoluene (BHT), erythorbic acid, monothioglycerol, potassium metabisulfite, propyl gallate, sodium ascorbate, sodium metabisulfite, sodium sulfite, thymol or mixtures thereof.

Suitable binders may include but not limited to polyvinylpyrrolidone, polyethylene glycol, polyvinyl alcohol, starch, pregelatinized starch, glucose, glucose syrup, natural gums, sucrose, sodium alginate, cellulose derivatives such as hydroxypropyl methyl cellulose, hydroxypropyl cellulose, carboxy methyl cellulose, methyl cellulose, gelatin, carrageenan, guar gum, carbomer, polymethacrylates, methacrylate polymers, collagens, proteins like gelatin, agar, alginate, alginic acid, xanthan gum, hyaluronic acid, pectin, polysaccharides, carbomer, poloxamer, polyacrylamide, aluminium hydroxide, laponit, bentonit, polyoxyethylene-alkyl ether, polydextrose, polyethylene oxide or mixtures thereof.

Suitable diluents may comprise but not limited to microcrystalline cellulose, mannitol, spray-dried mannitol, lactose, lactose monohydrate, starch, dextrose, sucrose, fructose, maltose, sorbitol, xylitol, inositol, kaolin, inorganic salts, calcium salts, polysaccharides, dicalcium phosphate, sodium chloride, dextrates, lactitol, maltodextrin, sucrose-maltodextrin mixture, trehalose, sodium carbonate, sodium bicarbonate, calcium carbonate or mixtures thereof.

Suitable dispersing agents may comprise but not limited to calcium silicate, magnesium aluminum silicate or mixtures thereof.

Suitable lubricants may comprise but not limited to magnesium stearate, colloidal silicon dioxide, calcium stearate, zinc stearate, talc, waxes, boric acid, hydrogenated vegetable oil, sodium chlorate, magnesium lauryl sulfate, sodium oleate, sodium acetate, sodium benzoate, polyethylene glycol, stearic acid, fatty acid, fumaric acid, glyseryl palmito sulphate, sodium stearyl fumarate, sodium lauryl sulphate or mixtures thereof.

Suitable glidants may comprise but not limited to talc, aluminium silicate, colloidal silica, starch or mixtures thereof.

Suitable disintegrants may comprise but not limited to cross-linked polyvinil pyrrolidone (crospovidone), povidone, cross-linked carboxymethyl cellulose (croscarmellose sodium), low-substituted hydroxypropyl cellulose, pregelatinized starch, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, carboxymethyl cellulose, docusate sodium, guar gum, low substituted hydroxypropyl cellulose, polyacryline potassium, sodium alginate, corn starch, sodium starch glycolate, alginic acid, alginates,

ion-exchange resins, magnesium aluminium silica, sodium dodesyl sulphate, poloxamer, sodium glycine carbonate, sodium lauryl sulphate or mixtures thereof.

Suitable plasticizers may comprise but not limited to polyethylene glycols of different molecular weights, propylene glycol or mixtures thereof.

Suitable preservatives may comprise but not limited to methyl paraben, propyl paraben and their salts (such as sodium, potassium), sodium benzoate, citric acid, benzoic acid, butylated hydroxytoluene or butylated hydroxyanisole, m-cresol, phenol or mixtures thereof.

Suitable sweeteners may comprise but not limited to aspartame, potassium acesulfame, sodium saccharinate, neohesperidine dihydrochalcone, sucralose, saccharin, sugars such as sucrose, glucose, lactose, fructose or sugar alcohols such as mannitol, sorbitol, xylitol, erythritol or mixtures thereof.

Suitable flavoring agents may comprise but not limited to menthol, peppermint, cinnamon, chocolate, vanillin or fruit essences such as cherry, orange, strawberry, grape, black currant, raspberry, banana, red fruits, wild berries or mixtures thereof.

Suitable coloring agents may comprise but not limited to ferric oxide, titanium dioxide, Food, Drug & Cosmetic (FD&C) dyes (such as; FD&C blue, FD&C green, FD&C red, FD&C yellow, FD&C lakes), poncau, indigo Drug & Cosmetic (D&C) blue, indigotine FD&C blue, carmoisine indigotine (indigo Carmine); iron oxides (such as; iron oxide red, yellow, black), quinoline yellow, flaming red, carmine, carmoisine, sunset yellow or mixtures thereof.

Suitable inert agents between the two molecules wherein the inert agent is selected from starch, lactose, sugar alcohol like D-mannitol, erythritol; lowsubstituted hydroxypropyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, polyvinyl alcohol, methylcellulose, hydroxyethyl methylcellulose or mixtures thereof.

According to this embodiment, the pharmaceutical composition comprises inert agents in an amount of between 10-60%.

According to the pharmaceutical incompatibility problem between vorapaxar and metoprolol, the present invention provides a pharmaceutical composition comprising inert agents which is present in the middle in such a way that it separates vorapaxar and metoprolol layers or covers vorapaxar pellets and metoprolol pellets. By the virtue of the inert agents, interaction between the vorapaxar and metoprolol molecules is prevented and at the same time vorapaxar and metoprolol molecules are enabled to remain stable in the dosage form. Moreover, another important reason is that the compositions of the active substances with different release properties can be provided in the same form with inert agents. Thus, vorapaxar and metoprolol molecules are formulated in a way not to interact, and at the same time it is provided that these molecules remain stable in their own form.

Thus, according to the present invention comprising vorapaxar and metoprolol molecules separately and it is characterized in releasing these molecules together and rapidly.

In one embodiment of the invention, the pharmaceutical composition may comprise optionally a coating wherein the coating agent is selected from polyvinylalcohol based films, polyethylene glycol, ethyl acrylate and methyl methacrylate copolymer dispersion, iron oxide yellow, polyvinyl alcohol, polyvinyl alcohol-polyethylene glycol copolymers, hydroxypropyl methyl cellulose, ethyl cellulose, ethylcellulose dispersions, polyvinylprolidone, polyvinylprolidone-vinyl acetate copolymer (PVP-VA), pigments, dyes, titanium dioxide, iron oxide, talc, iron oxide, triacetin , polymethylmetacrylate copolymers or mixtures thereof.

According to the pharmaceutical compositions of the invention may be prepared by conventional technology well known to those skilled in the art such as direct compression, dry granulation, wet granulation. During direct compression, active agent and excipients are mixed, sieved and compressed into dosage forms. During wet granulation, the ingredients are mixed and granulated with a granulation liquid. The granulation process provides agglomerates with a desired homogeneity. The mixture is dried and sieved and optionally mixed with additional excipients. Finally, it is compressed into dosage forms. In addition, this novel pharmaceutical composition is produced by various technologies such as fluidized bed granulation technique or extrusion/spheronization or spray drying and lyofilization.

The pharmaceutical composition is for use in the treatment of cardiovascular diseases or disorders.

Examples:

Example–1: Vorapaxar+Metoprolol Tablet

Ingredients	**% amount**
Active Ingredients	
Vorapaxar	5-95%
Metoprolol	5-95%
Inactive Ingredients	
Microcrystalline cellulose (MCC)	20-90%
Croscarmellose Sodium	0.5-5%
Magnesium stearate	0.25-5%
Colloidal silicon dioxide	0.1-2%
Lactose monohydrate	10-90 %
Povidone	0.5-10 %
Film Coating	
HPMC	1-5%
Ethyl cellulose	1-3%
Talc	10-25%
Titanium dioxide	10-20%
Iron oxide	1-2%

The process for the preparation of film coated tablet of vorapaxar and metoprolol including the steps of:

a) blending vorapaxar with lactose monohydrate, microcrystalline cellulose (MCC), croscarmellose sodium, colloidal silicon dioxide, magnesium stearate.
b) Dry granulating the blend of step a);
c) sieved the blend of step b);

d) blending metoprolol with microcrystalline cellulose (MCC), povidone, croscarmellose sodium.
e) Wet granulating the blend of step d);

f) sieved the blend of step e);

g) blending the granules of step c) and f) with magnesium stearate and colloidal silicon dioxide

h) compressing the blend of step g) into a tablet;

i) optionally, film coating the tablet of step h).

Example–2: Vorapaxar+Metoprolol Pellets (Tablet or Capsule)

Ingredients	**% amount**
Vorapaxar Pellets	
Vorapaxar	5-95%
Microcrystalline cellulose (MCC)	20-90%
Pregelatinized starch	5- 75%
Metoprolol Pellets	
Metoprolol	5-95%
Polyvinylpyrrolidone K30 (PVP K30)	2-5%
Sugar pellets	20-60%
Inactive ingredients	
Silicon dioxide	0.1-0.2%
Magnesium stearate	0.25 – 2.0%

The process for the preparation of pellets of vorapaxar and metoprolol including the steps of:

Vorapaxar Pellets:

a) blending vorapaxar with microcrystalline cellulose (MCC) and pregelatinized starch

b) by spraying water a wet mass is formed from step a);

c) pellets produced from this wet mass of step b) by extrusion/spheronization pelletizing technique

Metoprolol Pellets:

a) blending metoprolol with PVP K30

b) by adding water a solution/dispersion is prepared from step a)

c) sugar pellets are coated with the solution/dispersion from step b);

The vorapaxar and metoprolol pellets first mixed with silicon dioxide and then with magnesium stearate. The pellets are:

i. pressed as tablets and coated

ii. or filled into the capsules

Example–3: Vorapaxar+Metoprolol Multilayer Tablet

Ingredients	**% amount**
Vorapaxar Layer	
Vorapaxar	5-95%
Microcrystalline cellulose (MCC)	20-90%
Croscarmellose sodium	0.5-5%
Lactose monohydrate	10-90%
Inert layer	
Microcrystalline cellulose (MCC)	20-90%
Hydroxypropyl cellulose	2-6%
Iron oxide	0.1-2%
Metoprolol Layer	
Metoprolol	5-95%
Croscarmellose sodium	0.5-5%
Microcrystalline cellulose (MCC)	20-90%
Starch	3-25%
Other Excipients	
Magnesium stearate	0.25 – 5.0%
Colloidal silicon dioxide	0.1 – 2%

The process for the preparation of multilayer tablet of vorapaxar and metoprolol including the steps of:

Vorapaxar Layer

a) blending vorapaxar with microcrystalline cellulose (MCC) and croscarmellose and lactose monohydrate
b) granulating the blend of step a);
c) sieved the blend of step b);
d) blending the granules of step c) with magnesium stearate and colloidal silicon dioxide)

Metoprolol Layer

a) blending Metoprolol with microcrystalline cellulose (MCC) and croscarmellose sodium and starch
b) granulating the blend of step a);
c) sieved the blend of step b);
d) blending the granules of step c) with magnesium stearate and colloidal silicon dioxide

Inert layer

There are two ways for the preparation of inert layer:

a) A solution/dispersion is prepared by adding microcrystalline cellulose (mcc), hydroxypropyl cellulose and iron oxide as inert layer and one of the layers of vorapaxar or metoprolol is coated by spraying this mixture in fluidized bed.
b) Microcrystalline cellulose (mcc), hydroxypropyl cellulose and iron oxide are blended. The mixture is sieved and magnesium stearate and colloidal silicon dioxide are added.

At last, these different mixtures obtained are pressed in the form of multilayer tablets so that the inert layer is formed in the middle, i.e. forms the intermediate layer. Optionally, this multilayer tablet can be coated.

CLAIMS

1. A pharmaceutical composition comprising vorapaxar or a pharmaceutically acceptable salt thereof and metoprolol or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable excipient.

2. The pharmaceutical composition according to claim 1, wherein the pharmaceutical composition is administrated oral, parenteral, intranasal, sublingual, transdermal, transmucosal, ophthalmic, intravenous, pulmonary, intramuscular or rectal administration, and preferably for oral administration.

3. The pharmaceutical composition according to claim 1, wherein the pharmaceutical composition is formulated as tablets including compressed tablets comprising compressed tablets, coated or uncoated tablets, multilayer tablets, mini tablets, buccal tablets, sublingual tablets, effervescent tablets, immediate release tablets, modified release tablets, film-coated tablets, orally disintegrating tablets, gastric disintegrating tablets, pellets, effervescent compositions, pills, capsules, hard or soft gelatin capsules, powders, mini tablets, pellets, coated bead systems, granules, microspheres, ion exchange resin systems, sterile solutions or suspensions, steril ocular solutions, aerosols, sprays, drops, ampoules, suppositories, ocular systems, parenteral systems, creams, gels, ointments, dragees, sachets, films, orally administrable films, solutions, solids, elixirs, tinctures, suspensions, syrups, colloidal dispersions, dispersions, emulsions and thereof.

4. The pharmaceutical composition according to claim 1, wherein vorapaxar is present in an amount of between 0.01mg and 50mg, preferably between 0.1mg and 30mg and more preferably it is in an amount of between 1mg and 20mg.

5. The pharmaceutical composition according to claim 1 or 4, wherein the pharmaceutical acceptable salt of vorapaxar is preferably vorapaxar sulfate.

6. The pharmaceutical composition according to claim 1, wherein metoprolol is present in an amount of between 5mg and 500mg, preferably between 10mg and 250mg and more preferably it is in an amount of between 15mg and 220mg.

7. The pharmaceutical composition according to claim 1 or 6, wherein the pharmaceutical acceptable salt of metoprolol are preferably metoprolol tartrate, metoprolol succinate and metoprolol fumarate.

8. The pharmaceutical composition according to claim 1, wherein the pharmaceutical composition comprising vorapaxar in an amount of between 1mg and 20mg and metoprolol is in an amount of between 15mg and 220mg.

9. The pharmaceutical composition according to claim 8, wherein the ratio of metoprolol to vorapaxar is in the range of 1 to 220 (w/w) and preferably 1 to 100 (w/w) and more preferably 2 to 80 (w/w).

10. The pharmaceutical composition to any preceding claims, wherein the pharmaceutical composition is administrated once a day or twice a day.

11. The pharmaceutical composition to any preceding claims, wherein the pharmaceutical composition is administrated to any subject in need of therapy including humans or animals.

12. The pharmaceutical composition according to claim 1, wherein pharmaceutically acceptable excipient is selected from buffering agents, stabilizers, antioxidants, binders, diluents, dispersing agents, lubricants, glidants, disintegrants, plasticizers, preservatives, sweeteners, flavoring agents, coloring agents, inert agent, coating agents or mixtures thereof.

13. The pharmaceutical composition according to claim 12, wherein the inert agent is selected from starch, lactose, sugar alcohol like D-mannitol, erythritol; lowsubstituted hydroxypropyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone, polyvinyl alcohol, methylcellulose, hydroxyethyl methylcellulose or mixtures thereof.

14. The pharmaceutical composition according to claim 13, wherein the inert agent in an amount of between 10-60%.

15. The pharmaceutical composition according to any preceding claims, wherein the pharmaceutical composition is for use in the treatment of cardiovascular diseases or disorders.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2017/052337

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K9/20 A61K9/24 A61K9/50 A61K31/138 A61K31/443
A61P9/00
ADD.
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, WPI Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 April 2017	12/04/2017

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2

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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A	DAN FINTEL: "Oral antiplatelet therapy for atherothrombotic disease: overview of current and emerging treatment options", VASCULAR HEALTH AND RISK MANAGEMENT, 1 February 2012 (2012-02-01), page 77, XP55140255, ISSN: 1176-6344, DOI: 10.2147/VHRM.S26030 page 86, column 1, line 18 - column 2	1-15
A	WO 03/089428 A1 (SCHERING CORP [US]) 30 October 2003 (2003-10-30) claims 1,21,26	1-15
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