



(43) International Publication Date
10 August 2017 (10.08.2017)

(10) International Publication Number
WO 2017/134200 A1

(51) International Patent Classification:

A61K 9/20 (2006.01) A61K 31/138 (2006.01)
A61K 9/24 (2006.01) A61K 31/443 (2006.01)
A61K 9/50 (2006.01) A61P 9/00 (2006.01)

(21) International Application Number:

PCT/EP2017/052339

(22) International Filing Date:

3 February 2017 (03.02.2017)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

TR 2016/01548 5 February 2016 (05.02.2016) TR
TR 2016/02035 17 February 2016 (17.02.2016) TR

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(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— with international search report (Art. 21(3))

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

(57) Abstract: The present invention relates to a pharmaceutical composition comprising vorapaxar and metoprolol as active agents with at least one pharmaceutically acceptable excipient, wherein at least one of the active agents is in the form of controlled release and their use in the treatment of cardiovascular diseases/disorders.



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A NOVEL PHARMACEUTICAL COMPOSITION OF VORAPAXAR AND METOPROLOL

5 **Field of Invention**

The present invention relates to a pharmaceutical composition comprising vorapaxar and metoprolol as active agents with at least one pharmaceutically acceptable excipient, wherein at least one of the active agents is in the form of controlled release and their use
10 in the treatment of cardiovascular diseases/disorders.

Background of the invention

Cardiovascular disease/disorder is intended to mean any cardiovascular disease or
15 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,
20 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,
25 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
30 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.

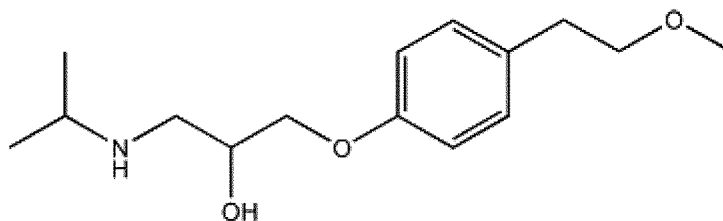
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Many individuals at an elevated risk of suffering serious to life-threatening cardiovascular

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.

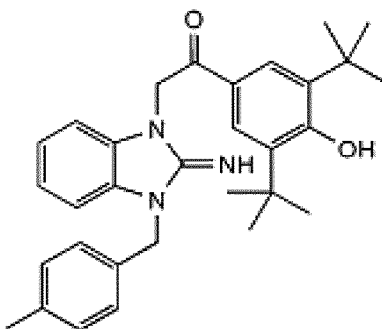


Formula I. Metoprolol

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.

5 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.

10 It is well known that drugs used in the same therapeutic area or even for treating the same indication cannot always be combined a priori with the expectation of at least additive therapeutic effects. The scientific literature is full of examples wherein compounds of different classes, which are used to treat the same indications, cannot be combined into safe and efficacious dosage forms thereby resulting in incompatible drug
15 combinations. No pharmaceutical composition has been produced until today, which contains a combination of vorapaxar and metoprolol. Even if some medicaments comprising either of these active agents have been administered concomitantly in practice, this fact requires the patients to carry more than one drug and causes application-related difficulties. Additionally, administering and formulating a combination,
20 in place of the individual use of each active agent, may provide improved treatment features. Especially, controlled release compositions represent an alternative for such patients and provide for a better patient compliance.

According to the composition of the present invention it is desired to provide a dosage
25 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
30 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
35 efficiency of the composition, an easy dissolution of both drug substances at a desired time is an important factor.

Controlled-release dosage forms are designed to release a drug at a predetermined rate by maintaining a constant drug level for a specific period of time with minimum side effects. Compared to immediate release formulations, a controlled release formulation containing a physiologically active drug allows blood concentrations of the drug to be maintained for a long time or above the therapeutic concentration. By providing a controlled-release formulation of vorapaxar and metoprolol, it may be possible to reduce the frequency of administration, while providing the same or better therapeutic effects, potentially improving compliance. The controlled-release formulation may avoid a rapid increase in blood plasma concentration levels immediately after administration of the drug, thus potentially reducing or eliminating adverse side effects.

Various formulations and methods are already known for the preparation of oral formulations of vorapaxar and metoprolol. However, no controlled release pharmaceutical composition has been produced until today, which contains a combination of vorapaxar and metoprolol. On the other hand, controlled release formulations are becoming an increasingly important issue in the area of better patient compliance comparative to the conventional solid dosage forms for oral administration such as capsules and tablets, which are the most commonly used. In particular, pediatric and geriatric patients and patients with mental problems. Thus, controlled release compositions represent an alternative for such patients and provide for a better patient compliance with long-term pharmaceutical therapies such as the treatment of cardiovascular diseases.

Thus, more need rises for oral controlled release formulations of vorapaxar and metoprolol and a process for preparing such formulation which overcomes the above described problems in prior art and having additive advantages over them. According to these embodiments, there is provided a controlled-release formulation comprising vorapaxar and metoprolol and at least one pharmaceutically acceptable excipient.

As a result, based on said drawbacks, a novelty is required in the art of pharmaceutical compositions having therapeutic effects against cardiovascular diseases/disorders.

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.

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.

A further object of the present invention is to obtain a combination composition having a desired level of compatibility.

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

The present invention provides 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 wherein at least one of the active agents is in the form of controlled release.

The term “controlled release” means that prolonged release or sustained release or modified release or extended release or delayed release or retarded release or gradual release or programmed release. The phase has a rate controlling agent that allows it to dissolve slowly either in the stomach or small intestine. The active ingredient is then slowly dissolved, therefore slowly absorbed into the bloodstream. So the rate controlling agents affect dissolution rate or dissolution profile of the active ingredient.

Another object of the present invention is to provide a pharmaceutical formulation making the plasma concentration level stable by maintaining release of vorapaxar and metoprolol in the blood stream for a longer time period sufficient to justify once daily or twice daily dosing and thus increases patient compliance.

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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.

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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 0.5mg and 20mg.

15

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.

20 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
25 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.

30 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
35 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.

5 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.

10 The pharmaceutical composition comprises vorapaxar in an amount of between 0.5mg 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).

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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.

20 Another object of the present invention is to provide the pharmaceutical formulation of vorapaxar or a pharmaceutically acceptable salt thereof and metoprolol or a pharmaceutically acceptable salt thereof comprising immediate release phase and controlled release phase comprising at least one rate controlling agent, for the treatment of cardiovascular diseases/disorders by eliminating all the aforementioned drawbacks and providing additional advantages to the respective technical field.

25 **The term "immediate release" means that** the phase dissolves within our stomachs and is taken up into the bloodstream. There is no excipient that affects dissolution rate or dissolution profile of the active ingredient.

30 In one embodiment, the pharmaceutical composition comprising an immediate release phase of vorapaxar and a controlled release phase of metoprolol and at least one pharmaceutically acceptable excipient which is a rate controlling agent.

35 In one embodiment, the pharmaceutical composition comprising a controlled release phase of vorapaxar and an immediate release phase of metoprolol and at least one pharmaceutically acceptable excipient which is a rate controlling agent.

In one embodiment, the pharmaceutical composition comprising a controlled release phase of vorapaxar and a controlled release phase of metoprolol and at least one pharmaceutically acceptable excipient which is a rate controlling agent.

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

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In this novel invention, the active agents in different phases, allows to obtain a desired release profile in the formulation which comprises vorapaxar and metoprolol. The treatment onset can be realized at a desired level depending particularly on the dissolution rate. This composition provides to ensure convenient release profiles for vorapaxar and metoprolol both.

15

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

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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.

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

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

35

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 present invention relates to a pharmaceutical combination comprising immediate release phase of vorapaxar and controlled release phase of metoprolol comprising a rate controlling agent that provides such therapeutic relief that dose dumping is prevented and requisite blood levels are maintained for an extended time period sufficient to justify once daily or twice daily dosing and thus increase patient compliance.

According to the embodiment of the present invention, vorapaxar and/or metoprolol is in the form of controlled release, which, on average, and in a single dose per day in vitro release profile, the controlled release phase of the formulation dissolves about 25 % within 1 hour, between 20-40 % within 4 hours, between 40-60% within 8 hours and is released by 80% at least in 20 hours.

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

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, rate controlling agents, lubricants, glidants, disintegrants, plasticizers, preservatives, sweeteners, flavoring agents, coloring agents, inert agent, coating agents or mixtures thereof.

Suitable buffering agents are selected from 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, glycine, glutamic acid or mixtures thereof.

Suitable stabilizers are selected from 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.

5

Suitable antioxidants are selected from 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.

10

Suitable binders are selected from 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.

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Suitable diluents are selected from 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.

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Suitable dispersing agents are selected from calcium silicate, magnesium aluminum silicate or mixtures thereof.

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Suitable rate controlling agents are selected from ethyl acrylate, ethyl methacrylate copolymer, ethylcellulose, methylcellulose, hypromellose phthalate, polydextrose, polyvinylacetate phthalate, zein, polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose E4M, hydroxypropyl methylcellulose K100MCR, hydroxyethyl cellulose, hydroxymethyl cellulose, gelatin, polyethylene oxide, acacia, dextrin, starch,

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polyhydroxyethylmethacrylate, sodium carboxymethylcellulose, carboxymethyl cellulose, sodium alginate, alginic acid, pectin, polyglucuronic acid, polygalacturonic acid, chondroitin sulfate, carrageenan, lambda carrageenan, iota carrageenan, furcellaran, xanthan gum, a polymer of acrylic acid, carbopol, agar, gellan gum, psyllium seed gum, 5 gellan gum, locust bean gum, tara gum, tamarind gum, gum arabic, curdlan, galactomannan, glucomannan, nitrocellulose, methylcellulose, proteoglycan, glycoprotein, actin, tubulin, hemoglobin, insulin, fibrin, albumin, myosin, collagen, casein, pullulan, chitosan, glycerol, propylene glycol, macrogols, phthalate esters, dibutyl sebacate, citrate esters, triacetin, castor oil, acetylated monoglycerides, fractionated 10 coconut oil, hydrogenated vegetable oil, hydrogenated castor oil, carnauba wax, candellia wax, beeswax, paraffin wax, stearic acid, glyceryl behenate, cetyl alcohol, cetostearyl alcohol, or a mixture thereof.

According to this embodiment, the pharmaceutical composition comprises rate 15 controlling agents in an amount of between 5-85% (w/w).

Suitable lubricants are selected from 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 20 benzoate, polyethylene glycol, stearic acid, fatty acid, fumaric acid, glyceryl palmito sulphate, sodium stearyl fumarate, sodium lauryl sulphate or mixtures thereof.

Suitable glidants are selected from talc, aluminium silicate, colloidal silica, starch or 25 mixtures thereof.

Suitable disintegrants are selected from cross-linked polyvinyl pyrrolidone (croscopolone), povidone, cross-linked carboxymethyl cellulose (crosscarmellose sodium), low-substituted hydroxypropyl cellulose, pregelatinized starch, sodium carboxymethyl cellulose, calcium 30 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 dodecyl sulphate, poloxamer, sodium glycine carbonate, sodium lauryl sulphate or mixtures thereof.

Suitable plasticizers are selected from polyethylene glycols of different molecular 35 weights, propylene glycol or mixtures thereof.

Suitable preservatives are selected from 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.

5

Suitable sweeteners are selected from 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.

10

Suitable flavoring agents are selected from 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.

15 Suitable coloring agents are selected from 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.

20

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.

25

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

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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
5 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,
10 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, polymethylmethacrylate copolymers or mixtures thereof.

15 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
20 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
25 extrusion/spheronization or spray drying and lyophilization.

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

30 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.

That provides once daily dosing for effective management of associated with
35 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, heart 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.

Examples:

Example–1: Vorapaxar IR phase + Metoprolol CR phase

Immediate release phase (Vorapaxar)	% amount (w/w)
Vorapaxar	5.00-95.00%
Lactose monohydrate	10.00-90.00%
Corn starch	3.00-25.00 %
Polyvinylpyrrolidone (PVP)	0.50-5.00%
Microcrystalline cellulose (MCC)	20.00-90.00%
Colloidal silicon dioxide	0.10-2.00%
Magnesium stearate	0.25-5.00%
Controlled release phase (Metoprolol)	% amount (w/w)
Metoprolol	5.00-95.00%
Hydroxypropyl methylcellulose E4M (HPMC E4M)	2.00-25.00%
Hydroxypropyl methylcellulose K100MCR (HPMC K100MCR)	2.00-25.00%
Microcrystalline cellulose (MCC)	20.00-90.00%
Colloidal silicon dioxide	0.10-2.00%
Magnesium stearate	0.25-5.00%

Immediate release phase (Vorapaxar)

The process for the preparation of the immediate release phase of the pharmaceutical formulation, including the steps of:

a) Blending vorapaxar, lactose monohydrate, corn starch, MCC;

b) granulating the blend of step a); with PVP;

- c) sieved the blend of step b);
- d) blending the granules of step c) with colloidal silicon dioxide and magnesium stearate.

5 **Controlled release phase (Metoprolol)**

The process for the preparation of the controlled release phase of the pharmaceutical formulation, including the steps of:

- a) Blending metoprolol, HPMC E4M and microcrystalline cellulose;
- b) granulating the blend of step a); with water or without water (wet or dry granulation);
- c) sieved the blend of step b);
- d) blending the granules of step c) with HPMC K100MCR, colloidal silicon dioxide and mg stearate.

These different mixtures obtained are;

- i. Pressed in the form of multilayer tablets or mini tablets or pellets. Optionally, this multilayer tablet or mini tablets or pellets can be coated.
- ii. or filled into the capsules.

20 **Example–2: Vorapaxar IR Phase Coated on Metaprolol CR Phase**

Immediate release phase (Vorapaxar)	% amount (w/w)
Vorapaxar	5.00-95.00%
Hydroxypropyl methyl cellulose (HPMC)	5.00-50.00%
Polyethylene glycol	5.00-30.00%
Controlled release phase (Metoprolol)	% amount (w/w)
Metoprolol	5.00-95.00%
Polyethylene oxide	5.00-85.00%
Lactose monohydrate	5.00-75.00%
Colloidal silicon dioxide	0.10-2.00%
Magnesium stearate	0.25-5.00%

Immediate release phase (Vorapaxar)

The process for the preparation of the immediate release phase of the pharmaceutical formulation, including the steps of:

- a) Blending vorapaxar, HPMC and polyethylene;
- 5 b) Add water to the blend of step a);
- c) Homogenized the blend of step b);

Controlled release phase (Metoprolol)

The process for the preparation of the controlled release phase of the pharmaceutical formulation, including the steps of:

- 10 a) blending metoprolol, lactose monohydrate, polyethylene oxide;
- b) granulating the blend of step a); with water or without water (wet or dry granulation);
- c) sieved the blend of step b);
- d) blending the granules of step c) with colloidal silicon dioxide and magnesium
- 15 stearate
- e) CR phase pressed in the form of tablets

These CR core tablets obtained are finally coated with IR phase Vorapaxar.

Example 3: Vorapaxar IR phase + Metoprolol CR phase
(tablet in tablet technology)

Immediate release phase (Vorapaxar)	% amount (w/w)
Vorapaxar	5.00-95.00%
Microcrystalline cellulose (MCC)	5.00-50.00%
Corn starch	5.00-25.00%
Crospovidone	2.00-5.00%
Polyvinylpyrrolidone (PVP)	0.50-5.00%
Talc	5.00-30.00%
Magnesium stearate	0.25-5.00%
Controlled release phase (Metoprolol)	% amount (w/w)
Metoprolol	5.00-95.00%

Polyethylene oxide	5.00-85.00%
Lactose monohydrate	5.00 – 75.00%
Colloidal silicon dioxide	0.10-2.00%
Magnesium stearate	0.25-5.00%

Immediate release phase (Vorapaxar)

The process for the preparation of the immediate release phase of the pharmaceutical formulation, including the steps of:

- a) Blending vorapaxar, MCC, corn starch, croscopovidone;
- 5 b) granulating the blend of step a); with polyvinylpyrrolidone (PVP);
- c) sieved the blend of step b);
- d) blending the granules of step c) with talc and magnesium stearate.

Controlled release phase (Metoprolol)

10 The process for the preparation of the controlled release phase of the pharmaceutical formulation, including the steps of:

- a) blending metoprolol, lactose monohydrate and polyethylene oxide;
- b) granulating the blend of step a); with water or without water (wet or dry granulation);
- c) sieved the blend of step b);
- 15 d) blending the granules of step c) with colloidal silicon dioxide and magnesium stearate

These different mixtures obtained are;

- i. Used tablet in tablet technology. Optionally, this tablet can be coated.

20

Example—4: Vorapaxar CR phase + Metoprolol CR phase

Controlled release phase (Vorapaxar)	% amount (w/w)
Vorapaxar	5.00-95.00%
Polyethylene oxide	0.50-25.00%
Sodium Alginate	2.00-20.00%

Crospovidone	1.00-5.00%
Polyethylene glycol	1.00-10.00%
Aluminium silicate	0.10-1.00%
Calcium stearate	0.10-2.00%
Controlled release phase (Metoprolol)	% amount (w/w)
Metoprolol	5.00-95.00%
Hydroxypropyl cellulose	5.00-40.00%
Ethyl cellulose	1.00-20.00%
Alginic acid	1.00-5.00%
Stearic acid	0.50-5.00%
Colloidal silicon dioxide	0.10-2.00%

Controlled release phase (Vorapaxar)

The process for the preparation of the controlled release phase of the pharmaceutical formulation, including the steps of:

- a) blending vorapaxar, polyethylene oxide and sodium alginate;
- 5 b) granulating the blend of step a); with polyethylene glycol;
- c) sieved the blend of step b);
- d) blending the granules of step c) with crospovidone, aluminium silicate and calcium stearate.

10 **Controlled release phase (Metoprolol)**

The process for the preparation of the controlled release phase of the pharmaceutical formulation, including the steps of:

- a) Blending Metoprolol, hydroxypropyl cellulose, ethyl cellulose;
- b) granulating the blend of step a); with alginic acid;
- 15 c) sieved the blend of step b);
- d) blending the granules of step c) with stearic acid and colloidal silicon dioxide.

These different mixtures obtained are;

- i. Pressed in the form of multilayer tablets. Optionally, this multilayer tablet can be coated.
- ii. Or filled into the capsules.

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 wherein at least one of the active agents is in the form of controlled release.
2. 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 0.5mg and 20mg.
3. The pharmaceutical composition according to claim 2, wherein the pharmaceutical acceptable salt of vorapaxar is preferably vorapaxar sulfate.
4. 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.
5. The pharmaceutical composition according to claim 4, wherein the pharmaceutical acceptable salt of metoprolol are preferably metoprolol tartrate, metoprolol succinate and metoprolol fumarate.
6. The pharmaceutical composition according to claim 1, wherein the pharmaceutical composition comprising vorapaxar in an amount of between 0.5mg and 20mg and metoprolol is in an amount of between 15mg and 220mg.
7. The pharmaceutical composition according to claim 6, 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).
8. The pharmaceutical composition according to claim 1, wherein the pharmaceutical composition comprising an immediate release phase of vorapaxar and a controlled release phase of metoprolol and at least one pharmaceutically acceptable excipient which is a rate controlling agent.

- 5
9. The pharmaceutical composition to any preceding claims, wherein the pharmaceutical composition is administrated oral, parenteral, intranasal, sublingual, transdermal, transmucosal, ophthalmic, intravenous, pulmonary, intramuscular or rectal administration, and preferably for oral administration.
- 10
10. The pharmaceutical composition to any preceding claims, wherein the pharmaceutical composition is formulated as tablets, compressed tablets, coated or uncoated tablets, multilayer tablets, mini tablets, buccal tablets, sublingual tablets, modified release tablets, film-coated tablets, gastric disintegrating tablets, pellets, effervescent compositions, pills, capsules, hard gelatin capsules, powders, mini tablets, pellets, coated bead systems, granules, microspheres, ion exchange resin systems, sterile solutions or suspensions, ampoules, parenteral systems, creams, gels, dragees, films, orally administrable films, solutions, solids, suspensions, colloidal dispersions, dispersions, emulsions and thereof.
- 15
11. The pharmaceutical composition to any preceding claims, wherein the pharmaceutical composition is administrated once a day or twice a day and preferably once a day.
- 20
12. The pharmaceutical composition to any preceding claims, wherein the pharmaceutical composition is administrated to any subject in need of therapy including humans or animals.
- 25
13. The pharmaceutical composition according to claim 1, wherein pharmaceutically acceptable excipient is selected from buffering agents, stabilizers, antioxidants, binders, diluents, dispersing agents, rate controlling agents, lubricants, glidants, disintegrants, plasticizers, preservatives, sweeteners, flavoring agents, coloring agents, inert agent, coating agents or mixtures thereof.
- 30
14. The pharmaceutical composition according to claim 13, wherein the rate controlling agents are selected from ethyl acrylate, ethyl methacrylate copolymer, ethylcellulose, methylcellulose, hypromellose phthalate, polydextrose, polyvinylacetate phthalate, zein, polyvinylpyrrolidone, polyvinyl alcohol, polyvinyl acetate, hydroxypropyl cellulose, hydroxypropyl methylcellulose, hydroxypropyl methylcellulose E4M, hydroxypropyl methylcellulose K100MCR, hydroxyethyl cellulose, hydroxymethyl cellulose, gelatin, polyethylene oxide, acacia, dextrin,
- 35

5 starch, polyhydroxyethylmethacrylate, sodium carboxymethylcellulose, carboxymethyl cellulose, sodium alginate, alginic acid, pectin, polyglucuronic acid, polygalacturonic acid, chondroitin sulfate, carrageenan, lambda carageenan, iota carageenan, furcellaran, xanthan gum, a polymer of acrylic
10 acid, carbopol, agar, gua gum, psyllium seed gum, gellan gum, locust bean gum, tara gum, tamarind gum, gum arabic, curdlan, galactomannan, glucomannan, nitrocellulose, methylcellulose, proteoglycan, glycoprotein, actin, tubulin, hemoglobin, insulin, fibrin, albumin, myosin, collagen, casein, pullulan, chitosan, glycerol, propylene glycol, macrogols, phfcholate esters, dibutyl sebacetate, citrate esters, triacetin, castor oil, acetylated monoglycerides, fractionated
15 coconut oil, hydrogenated vegetable oil, hydrogenated castor oil, carnauba wax, candellia wax, beeswax, paraffin wax, stearic acid, glyceryl behenate, cetyl alcohol, cetostearyl alcohol, or a mixtures thereof.

- 15 **15.** The pharmaceutical composition according to claim 14, wherein the rate controlling agents in an amount of between 5-85 % (w/w).
- 16.** The pharmaceutical composition according to any preceding claims, wherein the
20 pharmaceutical composition is for use in the treatment of cardiovascular diseases or disorders.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2017/052339

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 <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 10%;">Category*</th> <th style="width: 70%;">Citation of document, with indication, where appropriate, of the relevant passages</th> <th style="width: 20%;">Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td style="text-align: center; vertical-align: top;">Y</td> <td>WO 2013/084089 A1 (WOCKHARDT LTD [IN]) 13 June 2013 (2013-06-13) claims 1,2,6,11-14 -----</td> <td style="text-align: center; vertical-align: top;">1-16</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">Y</td> <td>WO 2008/155335 A1 (PF MEDICAMENT [FR]; PEREZ MICHEL [FR]; LE GRAND BRUNO [FR]; LETIENNE R) 24 December 2008 (2008-12-24) page 4, line 28 - page 5, line 2 claims 1,4,7 -----</td> <td style="text-align: center; vertical-align: top;">1-16</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">Y</td> <td>WO 2013/177473 A1 (UNIV VERMONT [US]) 28 November 2013 (2013-11-28) page 2, lines 16-17 page 6, lines 9-16 page 18, lines 23-24 page 25, lines 3-7 claims 21,40,41 ----- -/-</td> <td style="text-align: center; vertical-align: top;">1-16</td> </tr> </tbody> </table>			Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.	Y	WO 2013/084089 A1 (WOCKHARDT LTD [IN]) 13 June 2013 (2013-06-13) claims 1,2,6,11-14 -----	1-16	Y	WO 2008/155335 A1 (PF MEDICAMENT [FR]; PEREZ MICHEL [FR]; LE GRAND BRUNO [FR]; LETIENNE R) 24 December 2008 (2008-12-24) page 4, line 28 - page 5, line 2 claims 1,4,7 -----	1-16	Y	WO 2013/177473 A1 (UNIV VERMONT [US]) 28 November 2013 (2013-11-28) page 2, lines 16-17 page 6, lines 9-16 page 18, lines 23-24 page 25, lines 3-7 claims 21,40,41 ----- -/-	1-16
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☒ Further documents are listed in the continuation of Box C. ☒ See patent family annex.														
* Special categories of cited documents : "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family														
Date of the actual completion of the international search 4 April 2017		Date of mailing of the international search report 19/04/2017												
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016		Authorized officer Hedegaard, Anette												

INTERNATIONAL SEARCH REPORT

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