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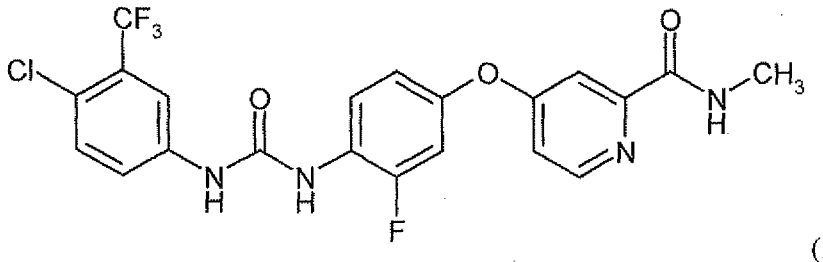
(54) Title: COATED PHARMACEUTICAL COMPOSITION CONTAINING REGORAFENIB

(57) Abstract: Abstract The present invention relates to a coated pharmaceutical composition containing regorafenib, a hydrate, solvate, metabolite or pharmaceutically acceptable salt thereof or a polymorph thereof and its process of preparation and its use for treating disorders.

Coated Pharmaceutical Composition containing Regorafenib

The present invention relates to a coated pharmaceutical composition containing regorafenib, a hydrate, solvate, metabolite or pharmaceutically acceptable salt thereof or a polymorph thereof and its process of preparation and its use for treating disorders.

Regorafenib which is 4{4-[3-(4-chloro-3-trifluoromethylphenyl)-ureido]-3-fluorophenoxy}-pyridine-2-carboxylic acid methylamide, a compound of formula (I)



(I)

is a potent anti-cancer and anti-angiogenic agent that possesses various activities including inhibitory activity on the VEGFR, PDGFR, raf, p38, and/or flt-3 kinase signalling molecules and it can be used in treating various diseases and conditions like hyper-proliferative disorders such as cancers, tumors, lymphomas, sarcomas and leukemias as described in WO 2005/009961. Furthermore salts of the compound of formula (I) such as its hydrochloride, mesylate and phenylsulfonate are mentioned in WO 2005/009961. The monohydrate of the compound of formula (I) is mentioned in WO 2008/043446. An improved process for the manufacturing of regorafenib in high purity is described in WO 2011/128261. Due to the limited solubility of regorafenib monohydrate (see table 1) an applicable pharmaceutical composition containing regorafenib is in form of a solid dispersion as described in WO 2006/026500.

Table 1: thermodynamic solubility of regorafenib monohydrate in different solvents

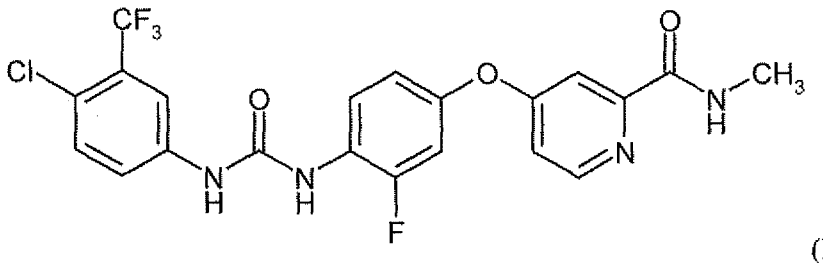
Solvent	**Solubility (mg/ml)**
Water	< 0.1
Ligth liquid paraffin	< 0.1
Ethanol	6.4
Polyethylenglycol (PEG) 400	67.3
HPß-Cyclodextrin/water (10:90)	< 0.1
PEG 400/water (30:70)	0.27
Oleoylpolyethylenglycol glycerides	3.6

The preferred route of drug administration is through the oral cavity. This route provides the greatest comfort and convenience of dosing. Tablets are preferred forms of pharmaceutical compositions for oral administration. In order to administrate solid formulations conveniently a coating is often needed. Objective of a coating can be to provide a homogeneous appearance, to mask discoloration during storage, to add color for product identification, to mask a bad taste, to prevent dusting during handling, to prevent abrasion or friction of a tablet, to increase mechanical stability, to facilitate and give a more convenient feeling when swallowing the tablet, in particular when the dimensions are large, to provide light protection for the drug or to protect the drug against humidity. Typical tablet coating agents are hydroxyethyl cellulose, hydroxypropyl cellulose, methyl cellulose, hydroxypropyl methyl cellulose, sucrose, liquid glucose, ethyl cellulose, cellulose acetate phthalate and shellac. The coating agents can be mixed with further applicable coating excipients or commercially available ready-to-use coating mixtures can be used like Opadry™ II 85G35294 pink, Opadry™ II 85G25457 red, Opadry™ II 85G23665 orange. The coating temperature usually depends on the type of coating agent and solvent used. Polyvinyl alcohol based coatings are typically processed at bed temperatures of 45-48°C (inlet air temperature 60-65°C). Often even higher temperatures are used for other coating materials. When using aqueous solvents in the coating procedure (e.g. the outlet air temperature) coating is usually conducted at higher temperatures.

The problem to be solved by the present invention is to provide a coated pharmaceutical composition containing regorafenib in high purity, in particular directly after the coating and/or after storage.

Surprisingly the pharmaceutical composition according to the invention shows a reduced degradation of the active agent.

The present invention pertains to a pharmaceutical composition comprising regorafenib which is the compound of the formula (I)



(I),

a hydrate, solvate, metabolite or pharmaceutically acceptable salt of regorafenib, or a polymorph thereof and at least one pharmaceutically acceptable excipient wherein the pharmaceutical composition is coated by a coating comprising a polyvinyl alcohol based polymer and optionally one or more further pharmaceutically acceptable excipients.

The pharmaceutical compositions according to the present invention can be utilized to achieve the desired pharmacological effect by administration to a patient in need thereof. A patient, for the purpose of this invention, is a mammal, including a human, in need of treatment for the particular condition or disease. Therefore, the present invention includes pharmaceutical compositions which are comprised of a pharmaceutically acceptable excipient and a pharmaceutically effective amount of a compound of the invention. A pharmaceutically acceptable excipient is any excipient which is relatively non-toxic and innocuous to a patient at concentrations consistent with effective activity of the active ingredient so that any side effects ascribable to the carrier do not vitiate the beneficial effects of the active ingredient. A pharmaceutically effective amount of compound is that amount which produces a result or exerts an influence on the particular condition being treated.

The term "the compound of formula (I)" or "regorafenib" refer to 4-{4-[({[4-chloro-3-(trifluoromethyl)phenyl]amino}carbonyl)amino]-3-fluorophenoxy}-*N*-methylpyridine-2-carboxamide as depicted in formula (I).

The term "compound of the invention" or "active agent" or "active ingredient" refer to regorafenib, a hydrate, solvate, metabolite or pharmaceutically acceptable salt of regorafenib, or a polymorph thereof.

Solvates for the purposes of the invention are those forms of the compounds or their salts where solvent molecules form a stoichiometric complex in the solid state and include, but are not limited to for example water, ethanol and methanol.

Hydrates are a specific form of solvates, where the solvent molecule is water. Hydrates of the compounds of the invention or their salts are stoichiometric compositions of the compounds or salts with water, such as, for example, hemi-, mono- or dihydrates. Preference is given to the monohydrate of regorafenib.

Salts for the purposes of the present invention are preferably pharmaceutically acceptable salts of the compounds according to the invention. Suitable pharmaceutically acceptable salts are well known to those skilled in the art and include salts of inorganic and organic acids, such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulphonic acid, trifluoromethanesulfonic acid, benzenesulfonic acid, *p*-toluenesulfonic acid (tosylate salt), 1-

naphthalenesulfonic acid, 2-naphthalenesulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, and mandelic acid. In addition, pharmaceutically acceptable salts include salts of inorganic bases, such as salts containing alkaline cations (e.g., Li^{+} Na^{+} or K^{+}), alkaline earth cations (e.g., Mg^{+2} , Ca^{+2} or Ba^{+2}), the ammonium cation, as well as acid salts of organic bases, including aliphatic and aromatic substituted ammonium, and quaternary ammonium cations, such as those arising from protonation or peralkylation of triethylamine, *N,N*-diethylamine, *N,N*-dicyclohexylamine, lysine, pyridine, *N,N*-dimethylaminopyridine (DMAP), 1,4-diazabiclo[2.2.2]octane (DABCO), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). Preference is given to the hydrochloride, mesylate or phenylsulfonate salt of regorafenib.

Metabolites of regorafenib for the purpose of the present invention include 4-[4-({[4-chloro-3-(trifluoromethyl)phenyl]carbamoyl}amino)-3-fluorophenoxy]-N-methylpyridine-2-carboxamide 1-oxide, 4-[4-({[4-chloro-3-(trifluoromethyl)phenyl]carbamoyl}amino)-3-fluorophenoxy]-N-(hydroxymethyl)pyridine-2-carboxamide, 4-[4-({[4-chloro-3-(trifluoromethyl)phenyl]carbamoyl}amino)-3-fluorophenoxy]pyridine-2-carboxamide and 4-[4-({[4-chloro-3-(trifluoromethyl)phenyl]carbamoyl}amino)-3-fluorophenoxy]pyridine-2-carboxamide 1-oxide.

Preferred are regorafenib and the monohydrate of regorafenib as a compound of the present invention.

The total amount of the active ingredient (compound of the invention) to be administered preferably via the oral route using the pharmaceutical composition of the present invention will generally range from about 0.1 mg/kg to about 50 mg/kg body weight per day. Based upon standard laboratory techniques known to evaluate compounds useful for the treatment of hyper-proliferative disorders, by standard toxicity tests and by standard pharmacological assays for the determination of treatment of the conditions identified above in mammals, and by comparison of these results with the results of known medicaments that are used to treat these conditions, the effective dosage of the pharmaceutical compositions of this invention can readily be determined by those skilled in the art. The amount of the administered active ingredient can vary widely according to such considerations as the particular compound and dosage unit employed, the mode and time of administration, the period of treatment, the age, sex, and general condition of the patient treated, the nature and extent of the condition treated, the rate of drug metabolism and excretion, the potential drug combinations and drug-drug interactions, and the like.

Preference is given to an amount of the compound of the invention in the pharmaceutical composition from 4 to 400 mg, preferably from 10 to 200 mg, more preferably from 10 to 100 mg.

An aspect of the invention of particular interest is a pharmaceutical composition comprising regorafenib in an amount of 4 to 400 mg, preferably from 10 to 200 mg, more preferably from 10 to 100 mg.

The daily dose of the compound of the present invention, in particular regorafenib, is from 10 to 1000 mg, preferably 40 to 500 mg, more preferably 80 to 320 mg, e.g. 160 mg.

The pharmaceutical composition according to the invention is administered one or more, preferably up to three, more preferably up to two times per day. Preference is given to an administration via the oral route.

Nevertheless, it may in some cases be advantageous to deviate from the amounts specified, depending on body weight, individual behavior toward the active ingredient, type of preparation and time or interval over which the administration is affected. For instance, less than the aforementioned minimum amounts may be sufficient in some cases, while the upper limit specified has to be exceeded in other cases. In the case of administration of relatively large amounts, it may be advisable to divide these into several individual doses over the day.

This pharmaceutical composition will be utilized to achieve the desired pharmacological effect by preferably oral administration to a patient in need thereof, and will have advantageous properties in terms of drug release, bioavailability, and/or compliance in mammals. A patient, for the purpose of this invention, is a mammal, including a human, in need of treatment for the particular condition or disease.

Preference is given to a pharmaceutical composition which is a an immediate release tablet.

The pharmaceutical composition according to the invention is preferably a solid pharmaceutical compositions and is administered orally or rectally, preferably orally.

The pharmaceutical composition of the present invention includes any solid formulation which is applicable to be coated.

Pharmaceutical compositions according to the invention include but are not limited to granules, pellets, tablets, dragées, pills, melts or solid dispersions and may be prepared according to methods known to the art for the manufacture of pharmaceutical compositions. Preference is given to tablets, solid dispersions, pellets and granules. Most preferably the pharmaceutically compositions according to the invention is a tablet.

An aspect of the invention of particular interest is a pharmaceutical composition in the form of a solid dispersion or a pharmaceutical composition comprising a solid dispersion. The solid dispersion may be a solid solution, glass solution, glass suspension, amorphous precipitation in a crystalline carrier, eutectic or monotectic, compound or complex formation or combinations thereof.

A solid dispersion according to the present invention comprises at least a compound of the invention and a pharmaceutically acceptable matrix.

The term "matrix" or "matrix agents" as used herein refers to both polymeric excipients, non-polymeric excipients and combinations thereof, capable of dissolving or dispersing the compound of the invention.

An aspect of the invention of particular interest is a pharmaceutical composition comprising a solid dispersion, wherein the matrix comprises a pharmaceutically acceptable polymer, such as polyvinylpyrrolidone, vinylpyrrolidone/vinylacetate copolymer, polyalkylene glycol (i.e. polyethylene glycol), hydroxyalkyl cellulose (i.e. hydroxypropyl cellulose), hydroxyalkyl methyl cellulose (i.e. hydroxypropyl methyl cellulose), carboxymethyl cellulose, sodium carboxymethyl cellulose, ethyl cellulose, polymethacrylates, polyvinyl alcohol, polyvinyl acetate, vinyl alcohol/vinyl acetate copolymer, polyglycolized glycerides, xanthan gum, carrageenan, chitosan, chitin, polydextrin, dextrin, starch, proteins or a mixture thereof.

Another aspect of the invention is a pharmaceutical composition comprising a solid dispersion, wherein the matrix comprises a sugar and/or sugar alcohol and/or cyclodextrin, for example sucrose, lactose, fructose, maltose, raffinose, sorbitol, lactitol, mannitol, maltitol, erythritol, inositol, trehalose, isomalt, inulin, maltodextrin, ß-cyclodextrin, hydroxypropyl-ß-cyclodextrin or sulfobutyl ether cyclodextrin or a mixture thereof.

In a preferred embodiment at least one from the group of polyvinylpyrrolidone, copovidone, hydroxypropyl cellulose, hydroxypropyl methyl cellulose, polyethylene glycol and polyethylene oxide is used as matrix agent in the solid dispersion. More preferably polyvinylpyrrolidone and/or hydroxypropyl cellulose are used as matrix agents. Most preferably polyvinylpyrrolidone is used as matrix agent.

An embodiment of particular interest the solid dispersion comprises the compound of the invention (calculated as solvent-free regorafenib base which is the compound of formula (I)) and the matrix agent in a weight ratio of 1:0.5 to 1:20, preferably 1:1 to 1:10, most preferably 1:1 to 1:5.

Additional suitable excipients that are useful in the formation of the matrix of the solid dispersion include, but are not limited to alcohols, organic acids, organic bases, amino acids, phospholipids, waxes, salts, fatty acid esters, polyoxyethylene sorbitan fatty acid esters, and urea.

The solid dispersion may contain certain additional pharmaceutical acceptable ingredients, such as surfactants, fillers, disintegrants, recrystallization inhibitors, plasticizers, defoamers, antioxidants, detackifier, pH-modifiers, glidants and lubricants.

Another aspect of the invention of particular interest are solid dispersions containing croscarmellose sodium, sodium starch glycolate, crospovidone, low substituted hydroxypropyl cellulose (L-HPC), starch, microcrystalline cellulose or a combination thereof as carrier or disintegrant. Preferably the solid dispersion comprises microcrystalline cellulose and/or croscarmellose sodium.

In another preferred embodiment, the solid dispersion comprises polyvinylpyrrolidone, croscarmellose sodium and optionally microcrystalline cellulose.

An embodiment of particular interest the solid dispersion comprises the compound of the invention (calculated as solvent-free regorafenib base which is the compound of formula (I)) and the sum of carrier and disintegrant in a weight ratio of 1:0.5 to 1:20, preferably 1:1 to 1:10, most preferably 1:1 to 1:6.

The solid dispersion of the invention can be prepared according to methods known to the art for the manufacture of solid dispersions, such as fusion/melt technology, hot melt extrusion, solvent evaporation (i.e. freeze drying, spray drying or layering of powders of granules), coprecipitation, supercritical fluid technology and electrostatic spinning method which are for example described in WO 2006/026500.

Hot melt extrusion or solvent evaporation techniques are preferred processes for preparation of solid dispersion formulations of this invention.

A solvent suitable for manufacture of solid dispersions by solvent evaporation processes such as spray-drying, layering or fluid-bed granulation can be any compound, wherein the compound of the invention can be dissolved. Preferred solvents include alcohols (e.g. methanol, ethanol, n-propanol, isopropanol, and butanol), ketones (e.g. acetone, methyl ethyl ketone and methyl isobutyl ketone), esters (e.g. ethyl acetate and propyl acetate) and various other solvents such as acetonitrile, methylene chloride, chloroform, hexane, toluene, tetrahydrofurane, cyclic ethers, and 1,1,1-trichloroethane. Lower volatility solvents, such as dimethyl acetamide or dimethyl sulfoxide can also be used. Mixtures of solvents, such as 20% ethanol and 80% acetone, can also be used, as

can mixtures with water as long as the drug and if necessary the matrix agent are sufficiently soluble to make the process practicable.

In a preferred embodiment the solvent used for manufacture of the solid dispersion is methanol, ethanol, n-propanol, isopropanol, acetone or a mixture thereof. More preferably a mixture of ethanol and acetone is used as solvent.

An aspect of the invention of particular interest is a composition, wherein the solid dispersion is substantially homogeneous.

An aspect of the invention of particular interest is a pharmaceutical composition, in which the compound of the invention is substantially amorphous.

The coating of the pharmaceutical composition of the present invention comprises a polyvinyl alcohol based polymer as film-forming agent. The polyvinyl alcohol based polymer according to the present invention includes but is not limited to fully hydrolysed polyvinyl alcohol polymer, partially hydrolysed polyvinyl alcohol polymer (contains free alcohol groups and esterified alcohol groups i.e. as acetate) esterified polyvinyl alcohol polymer for example polyvinyl acetate polymer, a co-polymer of the aforementioned with polyethylene glycol for example a polyvinyl alcohol-polyethylene glycol co-polymer or a mixture of the aforementioned. Preference is given to a partially hydrolysed polyvinyl alcohol polymer.

The polyvinyl alcohol based polymer in the coating is present in an amount of 30 to 70%, preferably 35 to 60%, more preferably 35 to 50% by weight of the total coating.

Furthermore the coating of the pharmaceutical composition of the present invention comprises optionally one or more further pharmaceutically acceptable excipients such as plasticizers, colorants, opacifiers, anti-tacking agents, dispersing agents and suspending agents.

Plasticizers which may be used in the coating include but are not limited to polyethylene glycol, propylene glycol, sorbitol, glycerol, maltitol, xylitol, mannitol, erythritol, glycerol trioleate, tributyl citrate, triethyl citrate acetyl triethyl citrate, glyceryl triacetate, stearic acid, medium chain triglycerides or a mixture thereof. Preference is given to polyethylene glycol, medium chain triglycerides and/or stearic acid.

The plasticizer in the coating may be present in an amount of 5 to 30%, preferably 8 to 25%, more preferably 10 to 20% by weight of the total coating.

Colorants which may be used in the coating include but are not limited to ferric oxide red, ferric oxide yellow, ferric oxide black, titanium dioxide, indigotine, sunset yellow FCF, tartrazin,

erythrosine, quinoline yellow, carbon black, anthocyanin, riboflavin, carmine, curcumin, chlorophyll, carotene or a mixture thereof. Preference is given to ferric oxides and titanium dioxide.

The colorants in sum in the coating are present in an amount of 5 to 40%, preferably 8 to 30%, more preferably 10 to 20% by weight of the total coating.

Anti-tacking agents which may be used in the coating include but are not limited to talc, magnesium stearate, stearic acid, lecithin, soy lecithin, mineral oil, carnauba wax, acetylated monoglycerides, polysorbate or a mixture thereof. Preference is given to talc, lecithin, soy lecithin, and polysorbate.

Anti-tacking agents in sum in the coating are present in an amount of 3 to 30%, preferably 5 to 25%, more preferably 10 to 20% by weight of the total coating.

Opacifiers which may be used in the coating include by are not limited to talc and titanium dioxide. Opacifiers in sum in the coating are present in an amount of 10 to 45%, preferably 15 to 35%, more preferably 15 to 25% by weight of the total coating.

The coating material can be prepared from the individual components as mentioned before. Alternatively ready-to-use mixtures can be used which include but are not limited to for example Opadry™ II 85G35294 pink, Opadry™ II 85G25457 red, Opadry™ II 85G23665 orange (provided by Colorcon), Kollicoat™ IR white (provided by BASF), Sepifilm™ IR (provided by SEPPIC). Preference is given to Opadry™ II 85G35294 pink, Opadry™ II 85G25457 red, Opadry™ II 85G23665 orange.

An aspect of the invention of particular interest is a pharmaceutical composition which is a tablet comprising regorafenib, a hydrate, solvate, metabolite or pharmaceutically acceptable salt of regorafenib, or a polymorph thereof, preferably regorafenib, and at least one pharmaceutically acceptable excipient wherein the pharmaceutical composition is coated by a coating comprising a polyvinyl alcohol based polymer and optionally one or more further pharmaceutically acceptable excipients.

An aspect of the invention of particular interest is a pharmaceutical composition comprising a solid dispersion comprising regorafenib and at least one pharmaceutically acceptable excipient wherein the pharmaceutical composition is coated by a coating comprising a polyvinyl alcohol based polymer and optionally one or more further pharmaceutically acceptable excipients.

Preference is given to a pharmaceutical composition which is a tablet comprising a solid dispersion comprising regorafenib and at least one pharmaceutically acceptable excipient wherein the pharmaceutical composition is coated by a coating comprising a polyvinyl alcohol based polymer and optionally one or more further pharmaceutically acceptable excipients.

More preferably the pharmaceutical composition according to the present invention is a tablet comprising a solid dispersion comprising regorafenib and at least a pharmaceutically acceptable matrix agent selected from the group consisting of polyvinylpyrrolidone, vinylpyrrolidone/vinylacetate copolymer, polyalkylene glycol like polyethylene glycol, hydroxyalkyl cellulose like hydroxypropyl cellulose, hydroxyalkyl methyl cellulose like hydroxypropyl methyl cellulose, carboxymethyl cellulose, sodium carboxymethyl cellulose, ethyl cellulose, polymethacrylates, polyvinyl alcohol, polyvinyl acetate, vinyl alcohol/vinyl acetate copolymer, polyglycolized glycerides, xanthan gum, carrageenan, chitosan, chitin, polydextrin, dextrin, starch, proteins or a mixture thereof, preferably polyvinylpyrrolidone, wherein the pharmaceutical composition is coated by a coating comprising a polyvinyl alcohol based polymer and optionally one or more further pharmaceutically acceptable excipients.

Most preferably the pharmaceutical composition according to the present invention is a tablet comprising a solid dispersion comprising regorafenib, polyvinylpyrrolidone as pharmaceutically acceptable matrix agent and microcrystalline cellulose and/or croscarmellose sodium as further pharmaceutically acceptable excipients wherein the pharmaceutical composition is coated by a coating comprising a polyvinyl alcohol based polymer in particular a partially hydrolysed polyvinyl alcohol polymer and optionally one or more further pharmaceutically acceptable excipients.

In this connection the pharmaceutical composition according to the invention – when investigated for release testing – contains 4-(4-amino-3-fluorophenoxy)pyridine-2-carboxylic acid methylamide (IUPAC: 4-(4-amino-3-fluorophenoxy)-N-methylpyridine-2-carboxamide) (AFP-PMA) in an amount of equal or less than 0.050%, that means from 0.001% to a maximum of 0.050%, preferably in an amount of equal or less than 0.025%, that means from 0.001% to a maximum of 0.025%, most preferably in an amount of equal or less than 0.015%, that means from 0.001% to a maximum of 0.015% by weight based on the amount of the compound of the formula (I). It is commonly understood that release testing is performed without undue delay after the manufacturing of a batch of the product has been completed. Release testing is also formally required before the respective product batch can be marketed.

Furthermore, the pharmaceutical composition according to the invention – when investigated at the end of the product shelf life – contains 4-(4-amino-3-fluorophenoxy)pyridine-2-carboxylic acid methylamide (IUPAC: 4-(4-amino-3-fluorophenoxy)-N-methylpyridine-2-carboxamide) (AFP-PMA) in an amount of equal or less than 0.10%, that means from 0.001% to a maximum of 0.10%, preferably in an amount of equal or less than 0.08%, that means from 0.001% to a maximum of 0.08%, most preferably in an amount of equal or less than 0.05%, that means from 0.001% to a maximum of 0.05% by weight based on the amount of the compound of the formula (I).

Another aspect of the present invention is a film-coated pharmaceutical composition, preferably a tablet, comprising regorafenib and – when investigated for release testing – 4-(4-amino-3-fluorophenoxy)pyridine-2-carboxylic acid methylamide (IUPAC: 4-(4-amino-3-fluorophenoxy)-N-methylpyridine-2-carboxamide) (AFP-PMA) in an amount of equal or less than 0.050%, that means from 0.001% to a maximum of 0.050%, preferably in an amount of equal or less than 0.025%, that means from 0.001% to a maximum of 0.025%, most preferably in an amount of equal or less than 0.015%, that means from 0.001% to a maximum of 0.015% by weight based on the amount of regorafenib and at least one pharmaceutically acceptable excipient.

Preference is given to a tablet comprising regorafenib and – when investigated for release testing – 4-(4-amino-3-fluorophenoxy)pyridine-2-carboxylic acid methylamide (IUPAC: 4-(4-amino-3-fluorophenoxy)-N-methylpyridine-2-carboxamide) (AFP-PMA) in an amount of equal or less than 0.050%, that means from 0.001% to a maximum of 0.050%, preferably in an amount of equal or less than 0.025%, that means from 0.001% to a maximum of 0.025%, most preferably in an amount of equal or less than 0.015%, that means from 0.001% to a maximum of 0.015% by weight based on the amount of regorafenib and at least one pharmaceutically acceptable excipient wherein the tablet is coated by a coating comprising a polyvinyl alcohol based polymer in particular a partially hydrolysed polyvinyl alcohol polymer and optionally one or more further pharmaceutically acceptable excipients.

Still another aspect of the present invention is a film-coated pharmaceutical composition, preferably a tablet, comprising regorafenib and – when investigated at the end of the product shelf life – 4-(4-amino-3-fluorophenoxy)pyridine-2-carboxylic acid methylamide (IUPAC: 4-(4-amino-3-fluorophenoxy)-N-methylpyridine-2-carboxamide) (AFP-PMA) in an amount of equal or less than 0.10%, that means from 0.001% to a maximum of 0.10%, preferably in an amount of equal or less than 0.08%, that means from 0.001% to a maximum of 0.08%, most preferably in an amount of equal or less than 0.05%, that means from 0.001% to a maximum of 0.05% by weight based on the amount of regorafenib and at least one pharmaceutically acceptable excipient.

Preference is given to a tablet comprising regorafenib and – when investigated at the end of the product shelf life – 4-(4-amino-3-fluorophenoxy)pyridine-2-carboxylic acid methylamide (IUPAC: 4-(4-amino-3-fluorophenoxy)-N-methylpyridine-2-carboxamide) (AFP-PMA) in an amount of equal or less than 0.10%, that means from 0.001% to a maximum of 0.10%, preferably in an amount of equal or less than 0.08%, that means from 0.001% to a maximum of 0.08%, most preferably in an amount of equal or less than 0.05%, that means from 0.001% to a maximum of 0.05% by weight based on the amount of regorafenib and at least one pharmaceutically acceptable excipient wherein the tablet is coated by a coating comprising a polyvinyl alcohol based polymer in

particular a partially hydrolysed polyvinyl alcohol polymer and optionally one or more further pharmaceutically acceptable excipients.

The pharmaceutical composition according to the invention can be packed into packaging systems like bottles or containers together with a desiccant like molecular sieve. Preferably the pharmaceutical composition according to the invention is packed in a bottle together with molecular sieve. More preferably the pharmaceutical composition which is a tablet comprising regorafenib optionally coated with a coating comprising polyvinyl alcohol is packed in a bottle together with molecular sieve. Most preferably the pharmaceutical composition which is a tablet comprising a solid dispersion comprising regorafenib coated with a coating comprising a polyvinyl alcohol based polymer is packed in a bottle together with molecular sieve.

In general, a molecular sieve is a material containing tiny pores of a precise and uniform size. The maximum size of the molecular or ionic species that can enter the pores of a molecular sieve material is controlled by the dimensions of the channels, e.g. 0.4 nm (= 4 Å, Angstroem). Small molecules can enter the pores and are adsorbed while larger molecules are not. For instance, a water molecule is small enough and forced into the pores which act as a trap for the penetrating water molecules, which are retained within the pores.

A widely used molecular sieve material are aluminosilicate minerals, e.g. zeolites.

For the drug product a molecular sieve with a pore size of 0.3 nm (= 3 Å, Angstroem) or 0.4 nm (= 4 Å, Angstroem) is used because water molecules with a size of approximately 0.28 nm (= 2.8 Å, Angstroem) are effectively trapped while larger molecules are not. Preference is given to molecular sieve with a pore size of or 0.4 nm (= 4 Å, Angstroem). The used molecular sieve is highly effective with an adsorption capacity of at least 16% (w/w) at 25 °C even at high relative humidity of 80%.

Molecular sieves are commercially available like CAN TRI-SORB™ 4A from Süd-Chemie.

The pharmaceutical composition according to the invention is chemically stable for more than 18 months, preferably more than 24 months, most preferably more than 36 months during storage e.g. in climatic zones 1 to 2 , preferably in climatic zones 1 to 4b.

The pharmaceutical composition according to the invention is chemically stable and comprises 4-(4-amino-3-fluorophenoxy)pyridine-2-carboxylic acid methylamide (AFP-PMA) in an amount of or less than 0.100%, that means from 0.001% to a maximum of 0.100%, preferably in an amount of equal or less than 0.08%, that means from 0.001% to a maximum of 0.08%, most preferably in an amount of equal or less than 0.050%, that means from 0.001% to a maximum of 0.050% by

weight based on the amount of regorafenib in the composition for at least 18 months, preferably at least 24 months, most preferably at least 36 months during storage e.g. in climatic zones 1 to 2, preferably in climatic zones 1 to 4b. Climatic zones are a well-known concept to define the storage conditions for long-term stability studies in order to determine the shelf-life of pharmaceutical products . For example, data obtained from storage at 25 °C and 60 % relative humidity are used to justify a shelf-life for climatic zones 1 to 2, whereas data obtained from storage at 40 °C and 75 % relative humidity are used to justify a shelf-life for climatic zones 1 to 4b.

The monthly increase rate of the amount of AFP-PMA in the pharmaceutical composition according to the invention during storage at 25°C / 60 % relative humidity is equal or less than 0.0015%, that means from 0.0001% to a maximum of 0.0015%, preferably equal or less than 0.001%, that means from 0.0001% to a maximum of 0.001% by weight based on the amount of regorafenib in the composition per month.

The monthly increase rate of the amount of AFP-PMA in the pharmaceutical composition according to the invention during storage at 30°C / 75 % relative humidity is equal or less than 0.0030%, that means from 0.0001% to a maximum of 0.0030%, preferably equal or less than 0.0025%, that means from 0.0001% to a maximum of 0.0025% by weight based on the amount of regorafenib in the composition per month.

Surprisingly the generation of side products preferably of 4-(4-amino-3-fluorophenoxy)pyridine-2-carboxylic acid methylamide during storage of the pharmaceutical composition according to the invention is less when the pharmaceutical composition according to the invention is co-packed with molecular sieve than co-packed with other desiccants like silica gel.

Process for manufacturing (coating)

Pharmaceutical compositions according to the invention include but are not limited to granules, pellets, tablets, dragées, pills, melts or solid dispersions, preferably tablets, solid dispersions, pellets and granules, most preferably tablets, and may be prepared according to methods known to the art for the manufacture of pharmaceutical compositions which are for example described in WO 2006/026500.

The pharmaceutical compositions according to the invention, preferably a tablet comprising regorafenib, is coated according to methods known to the art like spraying the coating liquid in a pan or perforated drum coater onto the pharmaceutical composition provided that the outlet air temperature is equal to or below 42 °C, for example 20°C to 42°C, preferably equal to or below 40 °C, for example 30°C to 40°C, most preferably equal to or below 38 °C, for example 32°C to 38°C.

The solvent/vehicle used in the coating step for dissolving or dispersing the coating material is an aqueous solvent/vehicle, preferably water.

Another topic of the present invention is a pharmaceutical composition comprising regorafenib, a hydrate, solvate, metabolite or pharmaceutically acceptable salt of regorafenib, or a polymorph thereof, preferably regorafenib, wherein the pharmaceutical composition is coated by a coating wherein the coating is obtainable or obtained by a coating process wherein the outlet air temperature in the coating process is equal to or below 42 °C, for example 20°C to 42°C, preferably equal to or below 40 °C, for example 30°C to 40°C, most preferably equal to or below 38 °C, for example 32°C to 38°C. and the solvent/vehicle used in the coating step is an aqueous solvent/vehicle, preferably water.

The coating step with a coating material comprising a polyvinyl alcohol based polymer can be conducted by homogeneously dissolving or dispersing the coating material, for example Opadry™ II 85G35294 pink, Opadry™ II 85G25457 red, Opadry™ II 85G23665 orange, in the solvent/vehicle, for example water. Alternatively the coating material can be prepared from the individual components. The coating liquid then is sprayed on the pharmaceutical composition according to the invention, for example a tablet, in a perforated drum coater.

Surprisingly good coating results can be obtained at low coating temperatures, i.e. at outlet air temperatures equal to or below 42 °C, for example 20°C to 42°C, preferably equal to or below 40 °C, for example 30°C to 40°C, most preferably equal to or below 38 °C, for example 32°C to 38°C.

Surprisingly the amount of the 4-(4-amino-3-fluorophenoxy)pyridine-2-carboxylic acid methylamide (IUPAC: 4-(4-amino-3-fluorophenoxy)-N-methylpyridine-2-carboxamide) (AFP-PMA) from the uncoated to the final coated pharmaceutical composition according to the invention increases only by 0.0005 to 0.0030%, preferably by 0.0005 to 0.0020% by weight based on the amount of regorafenib.

Therefore another aspect of the present invention is a process for the manufacturing of a coated pharmaceutical composition, preferably a tablet, comprising regorafenib wherein the amount of the 4-(4-amino-3-fluorophenoxy)pyridine-2-carboxylic acid methylamide (IUPAC: 4-(4-amino-3-fluorophenoxy)-N-methylpyridine-2-carboxamide) (AFP-PMA) in the uncoated pharmaceutical composition to the final coated pharmaceutical composition increases only by 0.0005 to 0.0030%, preferably by 0.0005 to 0.0020% by weight based on the amount of regorafenib.

Method for treatment:

The present invention also relates to a method for using the compound of the invention and compositions thereof, to treat mammalian hyper-proliferative disorders. This method comprises administering to a mammal in need thereof, including a human, an amount of a compound of the invention or composition thereof, which is effective to treat the disorder. Hyper-proliferative disorders include but are not limited to solid tumors, such as cancers of the breast, respiratory tract, brain, reproductive organs, digestive tract, urinary tract, eye, liver, skin, head and neck, thyroid, parathyroid and their distant metastases. Those disorders also include lymphomas, sarcomas, and leukemias.

Examples of breast cancer include, but are not limited to invasive ductal carcinoma, invasive lobular carcinoma, ductal carcinoma in situ, and lobular carcinoma in situ.

Examples of cancers of the respiratory tract include, but are not limited to small-cell and non-small-cell lung carcinoma, as well as bronchial adenoma and pleuropulmonary blastoma.

Examples of brain cancers include, but are not limited to brain stem and hypophtalmic glioma, cerebellar and cerebral astrocytoma, medulloblastoma, ependymoma, as well as neuroectodermal and pineal tumor.

Tumors of the male reproductive organs include, but are not limited to prostate and testicular cancer. Tumors of the female reproductive organs include, but are not limited to endometrial, cervical, ovarian, vaginal, and vulvar cancer, as well as sarcoma of the uterus.

Tumors of the digestive tract include, but are not limited to anal, colon, colorectal, esophageal, gallbladder, gastric, pancreatic, rectal, small intestine, and salivary gland cancers.

Preference is given to colorectal cancer.

Preference is also given to gastrointestinal stromal tumors (GIST).

Tumors of the urinary tract include, but are not limited to bladder, penile, kidney, renal pelvis, ureter, and urethral cancers.

Eye cancers include, but are not limited to intraocular melanoma and retinoblastoma.

Examples of liver cancers include, but are not limited to hepatocellular carcinoma (liver cell carcinomas with or without fibrolamellar variant), cholangiocarcinoma (intrahepatic bile duct carcinoma), and mixed hepatocellular cholangiocarcinoma.

Preference is given to hepatic cell cancer.

Skin cancers include, but are not limited to squamous cell carcinoma, Kaposi's sarcoma, malignant melanoma, Merkel cell skin cancer, and non-melanoma skin cancer.

Head-and-neck cancers include, but are not limited to laryngeal / hypopharyngeal / nasopharyngeal / oropharyngeal cancer, and lip and oral cavity cancer.

Lymphomas include, but are not limited to AIDS-related lymphoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, Hodgkin's disease, and lymphoma of the central nervous system.

Sarcomas include, but are not limited to sarcoma of the soft tissue, osteosarcoma, malignant fibrous histiocytoma, lymphosarcoma, and rhabdomyosarcoma.

Leukemias include, but are not limited to acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, and hairy cell leukemia.

These disorders have been well characterized in humans, but also exist with a similar etiology in other mammals, and can be treated by administering pharmaceutical compositions of the present invention.

Based upon standard laboratory techniques known to evaluate compounds useful for the treatment of hyper-proliferative disorders, by standard toxicity tests and by standard pharmacological assays for the determination of treatment of the conditions identified above in mammals, and by comparison of these results with the results of known medicaments that are used to treat these conditions, the effective dosage of the compounds of this invention can readily be determined for treatment of each desired indication. The amount of the active ingredient to be administered in the treatment of one of these conditions can vary widely according to such considerations as the particular compound and dosage unit employed, the mode of administration, the period of treatment, the age and sex of the patient treated, and the nature and extent of the condition treated.

The present invention further provides the use of the compound of the invention for the preparation of a pharmaceutical compositions for the treatment of the aforesaid disorders.

Combination with other pharmaceutical agents:

The compound of the invention can be administered as the sole pharmaceutical agent or in combination with one or more other pharmaceutical agents where the combination causes no unacceptable adverse effects. For example, the compound of the invention can be combined with known anti-hyper-proliferative or other indication agents, and the like, as well as with admixtures and combinations thereof.

Optional anti-hyper-proliferative agents which can be added to the compositions include but are not limited to compounds listed on the cancer chemotherapy drug regimens in the 11th Edition of the *Merck Index*, (1996), which is hereby incorporated by reference, such as asparaginase, bleomycin, carboplatin, carmustine, chlorambucil, cisplatin, colaspase, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, doxorubicin (adriamycine), epirubicin, etoposide, 5-fluorouracil, hexamethylmelamine, hydroxyurea, ifosfamide, irinotecan, leucovorin, lomustine, mechlorethamine, 6-mercaptopurine, mesna, methotrexate, mitomycin C, mitoxantrone, prednisolone, prednisone, procarbazine, raloxifen, streptozocin, tamoxifen, thioguanine, topotecan, vinblastine, vincristine, and vindesine.

Other anti-hyper-proliferative agents suitable for use with the compositions of the invention include but are not limited to those compounds acknowledged to be used in the treatment of neoplastic diseases in *Goodman and Gilman's The Pharmacological Basis of Therapeutics* (Ninth Edition), editor Molinoff et al., publ. by McGraw-Hill, pages 1225-1287, (1996), which is hereby incorporated by reference, such as aminoglutethimide, L-asparaginase, azathioprine, 5-azacytidine cladribine, busulfan, diethylstilbestrol, 2', 2'-difluorodeoxycytidine, docetaxel, erythrohydroxynonyladenine, ethinyl estradiol, 5-fluorodeoxyuridine, 5-fluorodeoxyuridine monophosphate, fludarabine phosphate, fluoxymesterone, flutamide, hydroxyprogesterone caproate, idarubicin, interferon, medroxyprogesterone acetate, megestrol acetate, melphalan, mitotane, paclitaxel, pentostatin, N-phosphonoacetyl-L-aspartate (PALA), plicamycin, semustine, teniposide, testosterone propionate, thiotepa, trimethylmelamine, uridine, and vinorelbine.

Other anti-hyper-proliferative agents suitable for use with the compositions of the invention include but are not limited to other anti-cancer agents such as epothilone and its derivatives, irinotecan, raloxifen and topotecan.

Generally, the use of the combinations of the present invention mentioned before will serve to:

(1) yield better efficacy in reducing the growth of a tumor or even eliminate the tumor as compared to administration of either agent alone,

(2) provide for the administration of lesser amounts of the administered chemotherapeutic agents,

(3) provide for a chemotherapeutic treatment that is well tolerated in the patient with fewer deleterious pharmacological complications than observed with single agent chemotherapies and certain other combined therapies,

(4) provide for treating a broader spectrum of different cancer types in mammals, especially humans,

(5) provide for a higher response rate among treated patients,

(6) provide for a longer survival time among treated patients compared to standard chemotherapy treatments,

(7) provide a longer time for tumor progression, and/or

(8) yield efficacy and tolerability results at least as good as those of the agents used alone, compared to known instances where other cancer agent combinations produce antagonistic effects.

"Combination" means for the purposes of the invention not only a dosage form which contains all the components (so-called fixed combinations), and combination packs containing the components separate from one another, but also components which are administered simultaneously or sequentially, as long as they are employed for the prophylaxis or treatment of the same disease.

It should be apparent to one of ordinary skill in the art that changes and modifications can be made to this invention without departing from the spirit or scope of the invention as it is set forth herein.

All publications, applications and patents cited above and below are incorporated herein by reference.

The weight data are, unless stated otherwise, percentages by weight and parts are parts by weight.

Examples:

Example 1: Coated tablet comprising regorafenib

a) Solid dispersion

A solution of 0.415 kg of regorafenib monohydrate (corresponding to 0.40 kg regorafenib) and 1.60 kg of polyvinyl pyrrolidone (PVP 25) in a mixture of 4.80 kg acetone and 1.20 kg ethanol was prepared. Using a fluidized bed vacuum granulator this solution was sprayed onto a powder bed of 1.00 kg croscarmellose sodium and 1.00 kg microcrystalline cellulose at a temperature of 60 - 70°C.

b) Tableting

The granulate of step a) was roller compacted and screened 3.15 mm and 1.0 mm. Subsequently the compacted granulate was blended with 0.54 kg croscarmellose sodium, 0.0240 kg colloidal anhydrous silica and 0.0360 kg magnesium stearate. This ready-to-press blend was compressed on a rotary tablet press into tablets containing 20 mg and 40 mg of regorafenib.

c) Film coating

For coating of the 20 mg tablets 0.160 kg of Opadry™ II 85G35294 pink was homogeneously dispersed in 0.640 kg water. For coating of the 40 mg tablets 0.120 kg of Opadry™ II 85G35294 pink was homogeneously dispersed in 0.480 kg water. These coating suspensions were sprayed onto the 20 mg respectively 40 mg tablets of step b) in a perforated drum coater at an outlet air temperature of 35°C. The coating process resulted in evenly coated tablets with a smooth surface. Coating defects could not be observed.

Commercially available Opadry™ II 85G35294 pink contains polyvinyl alcohol (partially hydrolyzed) [44% by weight of the total mixture], polyethylenglycol (PEG 3350) [12.4% by weight of the total mixture], lecithin (soya), ferric oxides, titanium dioxide and talc.

Table 2: Composition of tablets containing regorafenib

	Tablet A (20 mg)	Tablet B (40 mg)
	[mg/tablet]	[mg/tablet]
Regorafenib	20.00	40.00
Polyvinylpyrrolidone (PVP 25)	80.00	160.00
Croscarmellose sodium	77.00	154.00
Microcrystalline cellulose	50.00	100.00
Magnesium stearate	1.80	3.60
Silica colloidal anhydrous	1.20	2.40
Opadry II 85G35294 pink	8.00	12.00
Sum	238.00	472.00
Tablet format	round	oval
Dimensions of the tablet	diameter: 9 mm	Length: 16 mm, width: 7 mm

The formulation of Example 1 has also been manufactured in different, i.e. larger scales. The ratio of ingredients and the operating principle of the equipment was the same.

Example A: HPMC based coated tablet comprising regorafenib for comparison

Tablet cores equivalent to the uncoated tablets manufactured as described in Example 1 (a-b) were coated with a hydroxypropylmethyl cellulose (HMPC) based coating suspension (HPMC 15 cP 720 g, PEG 3350 24.0 g, Titanium dioxide 23.3 g, Ferric oxide red 0.72 g, water 1480 g) at an outlet air temperature of 60°C.

Test results:

Comparison between Example 1 and Example A

The degradation product 4-(4-amino-3-fluorophenoxy)pyridine-2-carboxylic acid methylamide (IUPAC: 4-(4-amino-3-fluorophenoxy)-N-methylpyridine-2-carboxamide) (AFP-PMA) was detected in the uncoated tablets in Example 1 after step b) in an amount of 0.0042% by weight based on the amount of regorafenib. After the final step c) in Example 1 AFP-PMA was detected in the coated tablet according to Example 1 in an amount of 0.0050% by weight based on the amount of regorafenib. The amount of AFP-PMA increased only by 0.0008%.

Analogous increase rate were observed when investigating tablets and coated tablets according to Example 1 manufactured in larger scale.

AFP-PMA was detected in the uncoated tablets used in comparative Example A in an amount of 0.0024% by weight based on the amount of regorafenib. After the coating (HPMC based coating) AFP-PMA was detected in the coated tablet according to Example A in an amount of 0.0078% by weight based on the amount of regorafenib. The amount of AFP-PMA increased by 0.0054%.

Storage Stability of Example 1

Coated tablets according to Example 1 were packed in HDPE (high density polyethylene) bottles together with molecular sieve (CAN TRI-SORB™ 4A, 3g, Süd-Chemie) at a) 25°C and 60% relative humidity, and b) 30°C and 75% relative humidity.

Similarly, coated tablets according to Example 1 were packed in HDPE bottles together with silica gel (CAN SORB-IT™ 3g, Süd-Chemie) at a) 25°C and 60% relative humidity, and b) 30°C and 75% relative humidity.

The results of both stability studies are displayed in Table 3. A nearly linear increase in the amount of AFP-PMA was found in all studies. Therefore, the stability results are expressed as mean monthly increase rates determined on several batches over a period of up to 30 months.

The actual amount of AFP-PMA present in coated tablets containing regorafenib at the end of the shelf-life of the respective batch can be estimated by adding the respective monthly increments to the initial amount present in the coated tablets at the time of release testing. Likewise, the shelf-life of the product packed in bottles together with a desiccant in a climatic zone can be deduced.

Table 3: Stability results of tablets containing regorafenib

	HDPE bottles containing tablets according to Example 1 with molecular sieve	HDPE bottles containing tablets according to Example 1 with silica
	Monthly increase rate [% / month]	Monthly increase rate [% / month]
Storage at 25 °C, 60% r.h.	0.0008	0.0019
Storage at 30 °C, 75% r.h.	0.0020	0.0034

What is claimed is:

1. A pharmaceutical composition comprising regorafenib, a hydrate, solvate, metabolite or pharmaceutically acceptable salt of regorafenib, or a polymorph thereof and at least one pharmaceutically acceptable excipient wherein the pharmaceutical composition is coated by a coating comprising a polyvinyl alcohol based polymer and optionally one or more further pharmaceutically acceptable excipients.

2. The composition of any of claim 1 which is a tablet.

3. The composition of any of claims 1 to 2 is an immediate release tablet.

4. The composition of any of claims 1 to 3 wherein the polyvinyl alcohol based polymer is a hydrolysed polyvinyl alcohol polymer, a partially hydrolysed polyvinyl alcohol polymer, an esterified polyvinyl alcohol polymer, a co-polymer thereof with polyethylene glycol or a mixture of the thereof.

5. The composition of claim 4 wherein the polyvinyl alcohol based polymer is a partially hydrolysed polyvinyl alcohol polymer.

6. The composition of any of claims 1 to 5 wherein the polyvinyl alcohol based polymer is present in an amount of 30 to 70% by weight of the total coating.

7. The composition of any of claims 1 to 6 wherein the coating comprises polyethylene glycol, propylene glycol, sorbitol, glycerol, maltitol, xylitol, mannitol, erythritol, glycerol trioleate, tributyl citrate, triethyl citrate acetyl triethyl citrate, glyceryl triacetate, stearic acid, medium chain triglycerides or a mixture thereof as plasticizer.

8. The composition of claim 7 wherein the plasticizer is polyethylene glycol.

9. The composition of any of claims 7 or 8 wherein the plasticizer is in an amount of 5 to 30% by weight of the total coating.

10. The composition of any of claims 1 to 9 comprising a solid dispersion comprising regorafenib.

11. The composition of claim 10 comprising regorafenib in an amorphous state and a pharmaceutically acceptable matrix wherein the matrix comprises polyvinylpyrrolidone, vinylpyrrolidone/vinylacetate copolymer, polyalkylene glycol, hydroxyalkyl, hydroxyalkyl methyl cellulose, carboxymethyl cellulose, sodium carboxymethyl cellulose, ethyl cellulose, polymethacrylates, polyvinyl alcohol, polyvinyl acetate, vinyl alcohol/vinyl acetate

copolymer, polyglycolized glycerides, xanthan gum, carrageenan, chitosan, chitin, polydextrin, dextrin, starch, proteins, sucrose, lactose, fructose, maltose, raffinose, sorbitol, lactitol, mannitol, maltitol, erythritol, inositol, trehalose, isomalt, inulin, maltodextrin, ß-cyclodextrin, hydroxypropyl-ß-cyclodextrin or sulfobutyl ether cyclodextrin or a mixture thereof.

12. The composition of any of claims 10 to 11 comprising regorafenib and the matrix agent in a weight ratio of 1:0.5 to 1:20.

13. The composition of any of claims 10 to 12 comprising regorafenib and polyvinylpyrrolidone, croscarmellose sodium and/or microcrystalline cellulose.

14. The composition of claim 13 comprising regorafenib and the sum of croscarmellose sodium and/or microcrystalline cellulose in a weight ratio of 1:0.5 to 1:20.

15. Film-coated pharmaceutical composition comprising regorafenib wherein the amount of 4-(4-amino-3-fluorophenoxy)pyridine-2-carboxylic acid methylamide is equal or less than 0.100 % by weight based on the amount of regorafenib.

16. Container containing molecular sieve and a pharmaceutical composition comprising regorafenib.

17. Pharmaceutical composition comprising regorafenib, a hydrate, solvate, metabolite or pharmaceutically acceptable salt of regorafenib, or a polymorph thereof, preferably regorafenib, wherein the pharmaceutical composition is coated by a coating wherein the coating is obtainable by a coating process wherein the outlet air temperature in the coating process is equal to or below 42 °C.

18. Process for the manufacture of a film-coated pharmaceutical composition comprising regorafenib wherein the coating liquid is sprayed onto the pharmaceutical composition in a pan or perforated drum coater and the outlet air temperature during the coating is equal to or below 42 °C.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER
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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, MEDLINE, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2006/026500 A1 (BAYER PHARMACEUTICAL CORP [US]; DUMAS JACQUES [US]; EHRLICH PAUL [DE];) 9 March 2006 (2006-03-09) cited in the application page 22 - page 23; examples 15-17 -----	15-18
X	WO 2007/068381 A1 (BAYER HEALTHCARE AG [DE]; WEBER OLAF [DE]; RIEDL BERND [DE]) 21 June 2007 (2007-06-21) page 24 - page 27; example 1 -----	15-18

☐ 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

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INTERNATIONAL SEARCH REPORT

Information on patent family members

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(54)发明名称

含有瑞戈非尼的包衣的药物组合物

(57)摘要

本发明涉及一种包衣药物组合物,包含:瑞戈非尼,其水合物、溶剂合物、代谢物或其药学上可接受的盐,或其晶型物;以及它的制备方法和其用于治疗疾病的用途。

CN 104902878 A

1. 一种药物组合物，其包含：瑞戈非尼，瑞戈非尼的水合物、溶剂合物、代谢物或药学上可接受的盐，或其多晶型物，和至少一种药学上可接受的赋形剂，其中所述药物组合物被含有基于聚乙烯醇的聚合物和任选地一种以上其他的药学上可接受的赋形剂的包衣包覆。

2. 权利要求 1 的组合物，其为片剂。

3. 权利要求 1 至 2 中任一项的组合物，其为速释片剂。

4. 权利要求 1 至 3 中任一项的组合物，其中基于聚乙烯醇的聚合物为水解的聚乙烯醇聚合物、部分水解的聚乙烯醇聚合物、酯化的聚乙烯醇聚合物、其与聚乙二醇的共聚物，或其混合物。

5. 权利要求 4 的组合物，其中基于聚乙烯醇的聚合物为部分水解的聚乙烯醇聚合物。

6. 权利要求 1 至 5 中任一项的组合物，其中基于聚乙烯醇的聚合物的存在量为全部包衣的 30 至 70 重量%。

7. 权利要求 1 至 6 中任一项的组合物，其中所述包衣包含作为增塑剂的聚乙二醇、丙二醇、山梨醇、丙三醇、麦芽糖醇、木糖醇、甘露醇、赤藓糖醇、三油酸甘油酯、柠檬酸三丁酯、柠檬酸三乙酯、乙酰柠檬酸三乙酯、三乙酸甘油酯、硬脂酸、中链甘油三酯或其混合物。

8. 权利要求 7 的组合物，其中增塑剂为聚乙二醇。

9. 权利要求 7 至 8 中任一项的组合物，其中增塑剂的量为全部包衣的 5 至 30 重量%。

10. 权利要求 1 至 9 中任一项的组合物，其包含固体分散剂，所述固体分散剂包含瑞戈非尼。

11. 权利要求 10 的组合物，其包含无定形态的瑞戈非尼和药学上可接受的基质，其中所述基质包括聚乙烯基吡咯烷酮、乙烯基吡咯烷酮 / 乙酸乙烯酯共聚物、聚烷二醇、羟烷基纤维素、羟烷基甲基纤维素、羧甲基纤维素、羧甲基纤维素钠、乙基纤维素、聚甲基丙烯酸酯、聚乙烯醇、聚乙酸乙烯酯、乙烯醇 / 乙酸乙烯酯共聚物、聚乙二醇化的甘油酯、黄原胶、角叉菜胶、壳聚糖、甲壳质、聚糊精、糊精、淀粉、蛋白质、蔗糖、乳糖、果糖、麦芽糖、棉子糖、山梨醇、乳糖醇、甘露醇、麦芽糖醇、赤藓糖醇、肌醇、海藻糖、益寿糖、菊糖、麦芽糖糊精、β - 环糊精、羟丙基 - β - 环糊精或磺丁基醚环糊精或其混合物。

12. 权利要求 10 至 11 中任一项的组合物，其包含的瑞戈非尼和基质剂的重量比为 1:0.5 至 1:20。

13. 权利要求 10 至 12 中任一项的组合物，其包含瑞戈非尼和聚乙烯基吡咯烷酮、交联羧甲基纤维素钠和 / 或微晶纤维素。

14. 权利要求 13 的组合物，其包含的瑞戈非尼与交联羧甲基纤维素钠和 / 或微晶纤维素的总和的重量比为 1:0.5 至 1:20。

15. 薄膜包衣的药物组合物，其含有瑞戈非尼，其中 4-(4- 氨基 -3- 氟苯氧基）吡啶 -2- 羧酸甲酰胺的量为等于或小于 0.100 重量%，基于瑞戈非尼的量计。

16. 容器，其装有分子筛和含有瑞戈非尼的药物组合物。

17. 药物组合物，其包含：瑞戈非尼，瑞戈非尼的水合物、溶剂合物、代谢物或药学上可接受的盐，或其多晶型物，优选瑞戈非尼，其中所述药物组合物被包衣包覆，其中所述包衣通过包衣过程得到，其中在包衣过程中排风温度等于或低于 42℃。

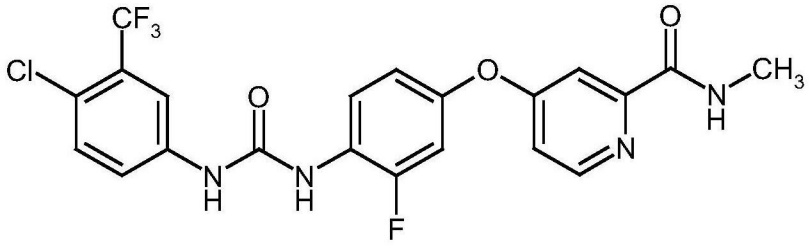
18. 用于制备含有瑞戈非尼的薄膜包衣的药物组合物的方法，其中在包衣锅或有孔滚筒包衣机中将包衣液体喷洒至药物组合物上，且在包衣过程中排风温度等于或低于 42℃。

含有瑞戈非尼的包衣的药物组合物

[0001] 本发明涉及一种包衣的药物组合物、其制备方法及其用于治疗疾病的用途，所述包衣的药物组合物包含：瑞戈非尼 (regorafenib)，其水合物、溶剂合物、代谢物或药学上可接受的盐或其多晶型物。

[0002] 瑞戈非尼为4{4-[3-(4-氯-3-三氟甲基苯基)-脲基]-3-氟苯氧基}-吡啶-2-羧酸甲酰胺，即式 (I) 的化合物，

[0003]



(I)

[0004] 瑞戈非尼是一种有效的抗癌和抗血管生成剂，其具有各种活性，包括对 VEGFR、PDGFR、raf、p38 和 / 或 flt-3 激酶信号分子的抑制活性，并且其可用于治疗各种疾病和病症，如过度增殖疾病，例如癌症、肿瘤、淋巴癌、肉瘤和白血病，如 WO 2005/009961 中所描述。此外，WO 2005/009961 中提及了式 (I) 的化合物的盐，如其盐酸盐、甲磺酸盐和苯磺酸盐。WO 2008/043446 中提到了式 (1) 的化合物的一水合物。WO 2011/128261 中描述了一种制备高纯度瑞戈非尼的改进的方法。由于瑞戈非尼一水合物的有限的溶解度 (参见表 1)，含有瑞戈非尼的可应用的药物组合物以固体分散剂的形式存在，如 WO 2006/026500 所描述。

[0005] 表 1 :瑞戈非尼一水合物在不同溶剂中的热力学溶解度

[0006]

溶剂	溶解度 (mg/ml)
水	< 0.1
轻质液体石蜡	< 0.1
乙醇	6.4
聚乙二醇(PEG) 400	67.3
HPß-环糊精/水(10:90)	< 0.1
PEG 400/水(30:70)	0.27

[0007]

油酰基聚乙二醇甘油酯	3.6

[0008] 优选的给药途径是通过口腔。该途径提供了给药的最大舒适性和便利性。对于口服给药而言，片剂是药物组合物的优选形式。为了方便地给予固体制剂，通常需要包衣。

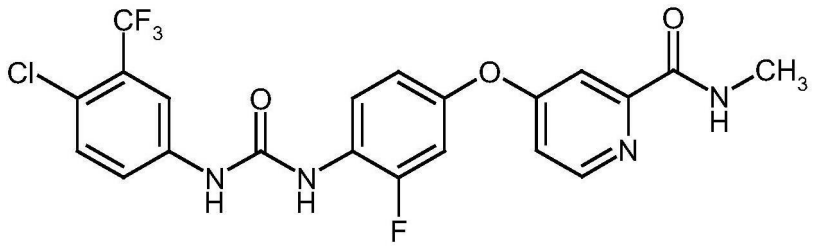
包衣的目的可以是提供均匀的外表、掩盖储存期间的变色、添加颜色以识别产品、掩盖不良味道、防止处理时沾灰、阻止片剂的磨损或摩擦、增加机械稳定性、吞下片剂时（特别是当片剂尺寸较大时）促进并给予更方便的感觉、为药物提供光保护或保护药物免于潮湿。常用片剂包衣剂为羟乙基纤维素、羟丙基纤维素、甲基纤维素、羟丙基甲基纤维素、蔗糖、液体葡萄糖、乙基纤维素、乙酸邻苯二甲酸纤维素和虫胶。包衣剂可与其他适用的包衣赋形剂混合或可使用市售可得的即用型包衣混合物，如 Opadry™ II 85G35294 粉、Opadry™ II 85G25457 红、Opadry™ II 85G23665 橙。包衣的温度通常取决于所使用的包衣剂和溶剂的类型。基于聚乙烯醇的包衣通常是在 45-48℃的床温（进风温度 60-65℃）下进行处理。对于其他包衣材料常使用甚至更高的温度。在包衣过程（例如排风温度）中使用水性溶剂时，包衣通常在更高温度下进行。

[0009] 本发明解决的问题是提供特别是直接包衣后和 / 或储存后含有高纯度的瑞戈非尼的包衣的药物组合物。

[0010] 令人惊讶地，本发明的药物组合物表现出降低的活性剂降解。

[0011] 本发明涉及一种药物组合物，其包含：瑞戈非尼（其为式 (I) 的化合物），瑞戈非尼的水合物、溶剂合物、代谢物或药学上可接受的盐，或其多晶型物，和至少一种药学上可接受的赋形剂，其中药物组合物被含有基于聚乙烯醇的聚合物和任选地一种以上其他的药学上可接受的赋形剂的包衣包覆，

[0012]



（I）。

[0013] 本发明的药物组合物能够通过向需要它的患者给药而得以利用，从而达到所需的药理作用。为了本发明的目的，患者为需要治疗具体的病症或疾病的哺乳动物，包括人。因此，本发明包括由药学上可接受的赋形剂和药学有效量的本发明化合物组成的药物组合物。药学上可接受的赋形剂为任何赋形剂，其在与活性成分的有效活性一致时的浓度下对患者相对无毒且无害，从而使得归因于载体的任何副作用不会削弱活性成分的有益效果。化合物的药学有效量是指对正在治疗的特殊病症产生效果或施加影响的量。

[0014] 术语“式 (I) 的化合物”或“瑞戈非尼”指的是如式 (I) 所描述的 4{4-[({[4-氯-3-(三氟甲基)苯基]氨基}羰基)氨基]-3-氟苯氧基}-N-甲基吡啶-2-甲酰胺。

[0015] 术语“本发明的化合物”或“活性剂”或“活性成分”指的是瑞戈非尼，瑞戈非尼的水合物、溶剂合物、代谢物或药学上可接受的盐，或其多晶型物。

[0016] 为了本发明的目的，溶剂合物为化合物或其盐的下述形式：其中溶剂分子形成化学计量的固态复合物，所述溶剂分子包括但不限于例如水、乙醇和甲醇。

[0017] 水合物为溶剂合物的特殊形式，其中溶剂分子为水。本发明化合物或其盐的水合物为该化合物或盐与水的化学计量的组合物，例如，半水合物、一水合物或二水合物。优选

瑞戈非尼的一水合物。

[0018] 为了本发明的目的，盐优选为本发明化合物的药学上可接受的盐。合适的药学上可接受的盐为本领域技术人员公知的并且包括无机酸和有机酸的盐，所述无机酸和有机酸包括如盐酸、氢溴酸、硫酸、磷酸、甲基磺酸、三氟甲基磺酸、苯磺酸、对甲苯磺酸（甲苯磺酸盐）、1- 萘磺酸、2- 萘磺酸、乙酸、三氟乙酸、苹果酸、酒石酸、柠檬酸、乳酸、乙二酸、琥珀酸、富马酸、马来酸、苯甲酸、水杨酸、苯乙酸和扁桃酸。另外，药学上可接受的盐包括无机碱的盐，如含有碱阳离子（例如，Li^+、Na^+或 K^+）、碱土阳离子（例如，Mg^{2+}、Ca^{2+}或 Ba^{2+}）、铵阳离子的盐；以及有机碱的酸式盐，包括脂族和芳族取代的铵，以及季铵阳离子，如由三乙胺、N,N- 二乙胺、N,N- 二环己胺、赖氨酸、吡啶、N,N- 二甲氨基吡啶 (DMPA)、1,4- 二氮杂二环 [2.2.2] 辛烷 (DABCO)、1,5- 二氮杂二环 [4.3.0] 壬 -5- 烯 (DBN) 和 1,8- 二氮杂二环 [5.4.0] 十一碳 -7- 烯 (DBU) 的质子化或过烷基化 (peralkylation) 产生的季铵阳离子。优选瑞戈非尼的盐酸盐、甲磺酸盐或苯磺酸盐。

[0019] 为了本发明的目的，瑞戈非尼的代谢物包括 4-[4-({[4- 氯 -3-（三氟甲基）苯基］氨基甲酰基｝氨基）-3- 氟苯氧基]-N- 甲基吡啶 -2- 甲酰胺 1- 氧化物、4-[4-({[4- 氯 -3-（三氟甲基）苯基］氨基甲酰基｝氨基）-3- 氟苯氧基]-N-（羟甲基）吡啶 -2- 甲酰胺、4-[4-({[4- 氯 -3-（三氟甲基）苯基］氨基甲酰基｝氨基）-3- 氟苯氧基］吡啶 -2- 甲酰胺和 4-[4-({[4- 氯 -3-（三氟甲基）苯基］氨基甲酰基｝氨基）-3- 氟苯氧基］吡啶 -2- 甲酰胺 1- 氧化物。

[0020] 优选瑞戈非尼和瑞戈非尼的一水合物作为本发明的化合物。

[0021] 利用本发明的药物组合物优选通过口服途径给药的活性成分（本发明的化合物）的总量通常为每天约 0.1mg/kg 体重至约 50mg/kg 体重。基于已知用于评估对治疗过度增殖疾病有效的化合物的标准实验室技术，通过用于在哺乳动物中确定上述病症的治疗方法的标准毒性实验和标准药理实验，以及通过比较这些结果与用于治疗这些病症的已知药物的结果，本领域技术人员可容易地确定本发明的药物组合物的有效剂量。给予的活性成分的量可根据如下考虑因素广泛变化：所使用的具体的化合物和剂量单位，给药方式和时间，治疗期，治疗的患者的年龄、性别和总体病情，治疗的病症的性质和程度，药物代谢和排泄的速度，潜在的药物结合和药物 - 药物相互作用等。

[0022] 优选药物组合物中本发明化合物的量为 4 至 400mg，优选 10 至 200mg，更优选 10 至 100mg。

[0023] 本发明令人特别感兴趣的一方面是药物组合物中含有的瑞戈非尼的量为 4 至 400mg，优选 10 至 200mg，更优选 10 至 100mg。

[0024] 本发明化合物（具体而言瑞戈非尼）的日剂量为 10 至 1000mg，优选 40 至 500mg，更优选 80 至 320mg，例如 160mg。

[0025] 每天给予本发明的药物组合物一次以上，优选最高达 3 次，更优选最高达 2 次。优选通过口服途径给药。

[0026] 然而，在某些情况下，根据体重、对于有效成分的个体行为、制剂类型和影响给药的时间或间隔，偏离规定的量是有利的。例如，在某些情况下，小于上述的最低量的给药量可能是足够的，然而，在其他情况下，给药量不得不超过规定的上限。在给药量较大的情况下，建议在一天内将这些药物分成若干单独的剂量。

[0027] 本发明的药物组合物优选通过向需要它的患者口服给药而实现所需的药理作用，并且在药物释放、生物利用度和 / 或哺乳动物依从性方面具有有利的特性。为了本发明的目的，患者为需要治疗具体的病症或疾病的哺乳动物，包括人。

[0028] 优选的药物组合物为速释片剂。

[0029] 本发明的药物组合物优选为固体药物组合物且为口服或直肠给药，优选口服给药。

[0030] 本发明的药物组合物包括任何适于包衣的固体制剂。

[0031] 本发明的药物组合物包括但不限于颗粒剂、丸粒 (pellet)、片剂、糖衣药丸、丸剂 (pill)、熔化剂 (melts) 或固体分散剂，且可根据本领域已知的用于制备药物组合物的方法制备。优选片剂、固体分散剂、丸粒和颗粒剂。本发明的药物组合物最优选为片剂。

[0032] 本发明令人特别感兴趣的一方面是固体分散剂形式的药物组合物或含有固体分散剂的药物组合物。所述固体分散剂可为固态溶液、玻璃溶液 (glass solution)、玻璃混悬液 (glass suspension)、透明载体中的无定形沉淀、共晶或偏晶的、复合的或络合的形成物或其结合。

[0033] 本发明的固体分散剂包括至少一种本发明的化合物和药学上可接受的基质。

[0034] 本文中所用的术语“基质”或“基质剂”指的是能够溶解或分散本发明化合物的聚合的赋形剂、非聚合的赋形剂及其结合。

[0035] 本发明令人特别感兴趣的一方面是含有固体分散剂的药物组合物，其中基质包括药学上可接受的聚合物，如聚乙烯基吡咯烷酮、乙烯基吡咯烷酮 / 乙酸乙烯酯共聚物、聚烷二醇（即聚乙二醇）、羟烷基纤维素（即羟丙基纤维素）、羟烷基甲基纤维素（即羟丙基甲基纤维素）、羧甲基纤维素、羧甲基纤维素钠、乙基纤维素、聚甲基丙烯酸酯、聚乙烯醇、聚乙酸乙烯酯、乙烯醇 / 乙酸乙烯酯共聚物、聚乙二醇化的甘油酯 (polyglycolized glycerides)、黄原胶、角叉菜胶、壳聚糖、甲壳质、聚糊精、糊精、淀粉、蛋白质或其混合物。

[0036] 本发明的另一方面是包括固体分散剂的药物组合物，其中基质包括糖和 / 或糖醇和 / 或环糊精，例如，蔗糖、乳糖、果糖、麦芽糖、棉子糖、山梨醇、乳糖醇、甘露醇、麦芽糖醇、赤藓糖醇、肌醇、海藻糖、益寿糖 (isomalt)、菊糖、麦芽糖糊精、β－环糊精、羟丙基－β－环糊精或磺丁基醚环糊精或其混合物。

[0037] 在一个优选的实施方案中，固体分散剂中使用选自聚乙烯基吡咯烷酮、共聚维酮、羟丙基纤维素、羟丙基甲基纤维素、聚乙二醇和聚环氧乙烷中的至少一种作为基质剂。更优选使用聚乙烯基吡咯烷酮和 / 或羟丙基纤维素作为基质剂。最优选使用聚乙烯基吡咯烷酮作为基质剂。

[0038] 在令人特别感兴趣的一个实施方案中，固体分散剂包括本发明的组合物（以无溶剂的式 (I) 的化合物的瑞戈非尼基体计算）和基质剂，重量比为 1:0.5 至 1:20，优选 1:1 至 1:10，最优选 1:1 至 1:5。

[0039] 在固体分散剂的基质的形成中可用的其他合适的赋形剂包括但不限于醇、有机酸、有机碱、氨基酸、磷脂、蜡、盐、脂肪酸酯、聚氧乙烯山梨聚糖脂肪酸酯和脲。

[0040] 固体分散剂可包括某些其他药学上可接受的成分，如表面活性剂、填料、崩解剂、再结晶抑制剂、增塑剂、消泡剂、抗氧化剂、防黏剂、pH 调节剂、助流剂和润滑剂。

[0041] 本发明令人特别感兴趣的另一方面是含有作为载体或崩解剂的交联羧甲基纤维

素钠、羟乙酸淀粉钠、交聚维酮、低取代的羟丙基纤维素 (L-HPC)、淀粉、微晶纤维素或其结合的固体分散剂。优选固体分散剂包括微晶纤维素和 / 或交联羧甲基纤维素钠。

[0042] 在另一优选的实施方案中，固体分散剂包括聚乙烯基吡咯烷酮、交联羧甲基纤维素钠和任选的微晶纤维素。

[0043] 在令人特别感兴趣的一个实施方案中，固体分散剂包括本发明组合物（以无溶剂的式 (I) 的化合物的瑞戈非尼基体计算）和载体与崩解剂的总量的重量比为 1:0.5 至 1:20，优选 1:1 至 1:10，最优选 1:1 至 1:6。

[0044] 本发明的固体分散剂可根据本领域已知的用于制备固体分散剂的方法制备，例如 WO 2006/026500 中记载的如融合 / 熔化技术、热熔挤出、溶剂蒸发（如冷冻干燥、喷雾干燥或颗粒剂的粉状物质的分层 (layering of powders of granules))、共沉淀、超临界流体技术和静电纺丝法 (electrostatic spinning method)。

[0045] 用于制备本发明的固体分散制剂的优选方法为热熔挤出和溶剂蒸发技术。

[0046] 适于通过溶剂蒸发法（如喷雾干燥、分层或流化床造粒）制备固体分散剂的溶剂可为任何化合物，本发明的化合物可溶解于其中。优选的溶剂包括醇，例如，甲醇、乙醇、正丙醇、异丙醇和丁醇；酮，例如，丙酮、甲基乙基酮和甲基异丁基酮；酯，例如，乙酸乙酯和乙酸丙酯；和各种其他溶剂，如乙腈、二氯甲烷、氯仿、己烷、甲苯、四氢呋喃、环醚和 1,1,1- 三氯乙烷。也可使用挥发性较低的溶剂，如二甲基乙酰胺或二甲亚砜。还可以使用溶剂混合物，如 20％乙醇和 80％丙酮，也可使用与水的混合物，只要药物和（如果需要）基质剂可充分溶解以使工艺可行即可。

[0047] 在一个优选的实施方案中，用于制备固体分散剂的溶剂为甲醇、乙醇、正丙醇、异丙醇、丙酮或其混合物。更优选使用乙醇和丙酮的混合物作为溶剂。

[0048] 本发明令人特别感兴趣的一方面是组合物，其中固体分散剂基本上均匀。

[0049] 本发明令人特别感兴趣的一方面是药物组合物，其中本发明的化合物基本上是无定形的。

[0050] 本发明的药物组合物的包衣包含作为成膜剂的基于聚乙烯醇的聚合物。本发明的基于聚乙烯醇的聚合物包括但不限于完全水解的聚乙烯醇聚合物、部分水解的聚乙烯醇聚合物（包括游离醇基团和酯化醇基团即如乙酸酯）、酯化的聚乙烯醇聚合物（例如，聚乙酸乙烯酯聚合物）、前述物质与聚乙二醇的共聚物（例如，聚乙烯醇 - 聚乙二醇共聚物）或前述物质的混合物。优选部分水解的聚乙烯醇聚合物。

[0051] 包衣中存在的基于聚乙烯醇的聚合物的量为全部包衣的 30 至 70 重量％，优选 35 至 60 重量％，更优选 35 至 50 重量％。

[0052] 此外，本发明的药物组合物的包衣任选地包含一种以上其他的药学上可接受的赋形剂，如增塑剂、着色剂、遮光剂 (opacifier)、防粘剂 (anti-tacking agent)、分散剂和悬浮剂。

[0053] 可在包衣中使用的增塑剂包括但不限于聚乙二醇、丙二醇、山梨醇、丙三醇、麦芽糖醇、木糖醇、甘露醇、赤藓糖醇、三油酸甘油酯、柠檬酸三丁酯、柠檬酸三乙酯、乙酰柠檬酸三乙酯、三乙酸甘油酯、硬脂酸、中链甘油三酯或其混合物。优选聚乙二醇、中链甘油三酯和 / 或硬脂酸。

[0054] 可存在于包衣中的增塑剂的量为全部包衣的 5 至 30 重量％，优选 8 至 25 重量％，

更优选 10 至 20 重量%。

[0055] 包衣中可使用的着色剂包括但不限于氧化铁红、氧化铁黄、氧化铁黑、二氧化钛、靛蓝、日落黄 FCF、柠檬黄、赤藓红、喹啉黄、炭黑、花色苷、核黄素、胭脂红、姜黄素、叶绿素、胡萝卜素或其混合物。优选氧化铁类和二氧化钛。

[0056] 包衣中存在的着色剂的总量为全部包衣的 5 至 40 重量%，优选 8 至 30 重量%，更优选 10 至 20 重量%。

[0057] 包衣中可使用的防粘剂包括但不限于滑石、硬脂酸镁、硬脂酸、卵磷脂、大豆卵磷脂、矿物油、巴西棕榈蜡、乙酰化的单酸甘油酯、聚山梨醇酯或其混合物。优选滑石、卵磷脂、大豆卵磷脂和聚山梨醇酯。

[0058] 包衣中的防粘剂的总量为全部包衣的 3 至 30 重量%，优选 5 至 25 重量%，更优选 10 至 20 重量%。

[0059] 包衣中可使用的遮光剂包括但不限于滑石和二氧化钛。包衣中存在的遮光剂的总量为全部包衣的 10 至 45 重量%，优选 15 至 35 重量%，更优选 15 至 25 重量%。

[0060] 包衣材料可由前面提及的各成分制备。或者，可使用即用型混合物，其包括但不限于例如 Opadry™ II 85G35294 粉、Opadry™ II 85G25457 红、Opadry™ II 85G23665 橙（由 Colorcon 提供）、Kollicoat™ IR 白（由 BASF 提供）、Sepifilm™ IR（由 SEPPIC 提供）。优选 Opadry™ II 85G35294 粉、Opadry™ II 85G25457 红、Opadry™ II 85G23665 橙。

[0061] 本发明令人特别感兴趣的一方面是一种药物组合物，其为片剂，包含：瑞戈非尼，瑞戈非尼的水合物、溶剂合物、代谢物或药学上可接受的盐，或其多晶形物，优选瑞戈非尼，和至少一种药学上可接受的赋形剂，其中所述药物组合物被包含基于聚乙烯醇的聚合物和任选地一种以上其他的药学上可接受的赋形剂的包衣包覆。

[0062] 本发明令人特别感兴趣的一方面是一种包含固体分散剂的药物组合物，所述固体分散剂包含瑞戈非尼和至少一种药学上可接受的赋形剂，其中药物组合物被包含基于聚乙烯醇的聚合物和任选地一种以上其他的药学上可接受的赋形剂的包衣包覆。

[0063] 优选如下的药物组合物，其为包含固体分散剂的片剂，所述固体分散剂包含瑞戈非尼和至少一种药学上可接受的赋形剂，其中药物组合物被包含基于聚乙烯醇的聚合物和任选地一种以上其他的药学上可接受的赋形剂的包衣包覆。

[0064] 更优选本发明的药物组合物为包含固体分散剂的片剂，所述固体分散剂包含瑞戈非尼和至少一种药学上可接受的基质剂，所述基质剂选自聚乙烯基吡咯烷酮、乙烯基吡咯烷酮 / 乙酸乙烯酯共聚物、聚烷二醇（如聚乙二醇）、羟烷基纤维素（如羟丙基纤维素）、羟烷基甲基纤维素（如羟丙基甲基纤维素）、羧甲基纤维素、羧甲基纤维素钠、乙基纤维素、聚甲基丙烯酸酯、聚乙烯醇、聚乙酸乙烯酯、乙烯醇 / 乙酸乙烯酯共聚物、聚乙二醇化的甘油酯、黄原胶、角叉菜胶、壳聚糖、甲壳质、聚糊精、糊精、淀粉、蛋白质或其混合物，优选聚乙烯基吡咯烷酮，其中所述药物组合物被含有基于聚乙烯醇的聚合物和任选地一种以上其他的药学上可接受的赋形剂的包衣包覆。

[0065] 最优选本发明的药物组合物为如下的包含固体分散剂的片剂，所述固体分散剂包含瑞戈非尼、作为药学上可接受的基质剂的聚乙烯基吡咯烷酮和作为其他药学上可接受的赋形剂的微晶纤维素和 / 或交联羧甲基纤维素钠，其中所述药物组合物被含有基于聚乙烯醇的聚合物（特别是部分水解的聚乙烯醇聚合物）和任选地一种以上其他的药学上可接受

的赋形剂的包衣包覆。

[0066] 在这一点上，本发明的药物组合物－当进行释放测试研究时－包含 4-(4- 氨基 -3- 氟苯氧基）吡啶 -2- 羧酸甲酰胺 (IUPAC:4-(4- 氨基 -3- 氟苯氧基)-N- 甲基吡啶 -2- 甲酰胺)(AFP-PMA) 的量基于式 (I) 的化合物的量计为等于或小于 0.050 重量％，意指 0.001 重量％至最大为 0.050 重量％；优选为等于或小于 0.025 重量％，意指 0.001 重量％至最大为 0.025 重量％；最优选为等于或小于 0.015 重量％，意指 0.001 重量％至最大为 0.015 重量％。应理解，释放测试在已完成一批产品的制备后无不当延误地进行。在各产品批次在上市前也会对释放测试做出正式要求。

[0067] 此外，本发明的药物组合物—在产品保质期的末期进行研究时—含有 4-(4- 氨基 -3- 氟苯氧基）吡啶 -2- 羧酸甲酰胺 (IUPAC:4-(4- 氨基 -3- 氟苯氧基)-N- 甲基吡啶 -2- 甲酰胺)(AFP-PMA) 的量基于式 (I) 的化合物的量计为等于或小于 0.10 重量％，意指 0.001 重量％至最大为 0.10 重量％；优选为等于或小于 0.08 重量％，意指 0.001 重量％至最大为 0.08 重量％；最优选为等于或小于 0.05％，意指 0.001 重量％至最大为 0.05 重量％。

[0068] 本发明的另一方面是薄膜包衣的药物组合物，优选片剂，其包含瑞戈非尼和—当进行释放测试研究时—4-(4- 氨基 -3- 氟苯氧基）吡啶 -2- 羧酸甲酰胺 (IUPAC:4-(4- 氨基 -3- 氟苯氧基)-N- 甲基吡啶 -2- 甲酰胺)(AFP-PMA) 的量基于瑞戈非尼和至少一种药学上可接受的赋形剂的量计为等于或小于 0.050 重量％，意指 0.001 重量％至最大为 0.050 重量％；优选为等于或小于 0.025 重量％，意指 0.001 重量％至最大为 0.025 重量％；最优选为等于或小于 0.015 重量％，意指 0.001 重量％至最大为 0.015 重量％。

[0069] 优选一种片剂，其包含瑞戈非尼和—当进行释放测试研究时—4-(4- 氨基 -3- 氟苯氧基）吡啶 -2- 羧酸甲酰胺 (IUPAC:4-(4- 氨基 -3- 氟苯氧基)-N- 甲基吡啶 -2- 甲酰胺)(AFP-PMA) 的量基于瑞戈非尼和至少一种药学上可接受的赋形剂的量计为等于或小于 0.050 重量％，意指 0.001 重量％至最大为 0.050 重量％；优选为等于或小于 0.025 重量％，意指 0.001 重量％至最大为 0.025 重量％；最优选为等于或小于 0.015 重量％，意指 0.001 重量％至最大为 0.015 重量％，其中所述片剂被含有基于聚乙烯醇的聚合物（特别是部分水解的聚乙烯醇聚合物）和任选地一种以上其他的药学上可接受的赋形剂的包衣包覆。

[0070] 本发明的另一方面是薄膜包衣的药物组合物，优选一种片剂，其包含瑞戈非尼和—在产品保质期的末期进行研究时—4-(4- 氨基 -3- 氟苯氧基）吡啶 -2- 羧酸甲酰胺 (IUPAC:4-(4- 氨基 -3- 氟苯氧基)-N- 甲基吡啶 -2- 甲酰胺)(AFP-PMA) 的量基于瑞戈非尼和至少一种药学上可接受的赋形剂的量计为等于或小于 0.10 重量％，意指 0.001 重量％至最大为 0.10 重量％；优选为等于或小于 0.08 重量％，意指 0.001 重量％至最大为 0.08 重量％；最优选为等于或小于 0.05 重量％，意指 0.001 重量％至最大为 0.05 重量％。。

[0071] 优选一种片剂，其包含瑞戈非尼和—在产品保质期的末期进行研究时—4-(4- 氨基 -3- 氟苯氧基）吡啶 -2- 羧酸甲酰胺 (IUPAC:4-(4- 氨基 -3- 氟苯氧基)-N- 甲基吡啶 -2- 甲酰胺)(AFP-PMA) 的量基于瑞戈非尼和至少一种药学上可接受的赋形剂的量计为等于或小于 0.10 重量％，意指 0.001 重量％至最大为 0.10 重量％；优选为等于小于 0.08 重量％，意指 0.001 重量％至最大为 0.08 重量％；最优选为等于或小于 0.05 重量％，意指 0.001 重量％至最大为 0.05 重量％，其中所述片剂被含有基于聚乙烯醇的聚合物（特别是

部分水解的聚乙烯醇聚合物）和任选地一种以上其他的药学上可接受的赋形剂的包衣包覆。

[0072] 可将本发明的药物组合物和干燥剂如分子筛一起包装于包装系统（像瓶或容器）。优选将本发明的药物组合物和分子筛一起包装于瓶中。更优选地，将任选地被包含聚乙烯醇的包衣包覆且为含有瑞戈非尼的片剂的药物组合物和分子筛一起包装于瓶中。最优选地，将任选地被包含基于聚乙烯醇的聚合物的包衣包覆且为含有瑞戈非尼的固体分散剂的片剂的药物组合物和分子筛一起包装于瓶中。

[0073] 通常，分子筛为含有精确和均一尺寸的微孔的材料。可进入分子筛材料的孔中的分子或离子的最大尺寸由通道的尺寸的控制，例如 0.4nm（ =4 Å，埃）。小分子可进入孔中并被吸附，而大分子却不能。例如，水分子足够小且强行进入孔中，该孔可对渗透的水分子起截留作用，从而使水分子保留在孔中。

[0074] 广泛使用的分子筛材料为铝硅酸盐矿物，例如沸石。

[0075] 对于药品，使用孔径为 0.3nm（ =3 Å，埃）或 0.4nm（ =4 Å，埃）的分子筛，因为尺寸为约 0.28nm（ =2.8Å，埃）的水分子被有效截留，而较大的分子却不能。优选孔径为 0.4nm（ =4 Å，埃）的分子筛。所使用的分子筛非常有效，其在 25℃下甚至在 80％的高相对湿度下具有至少 16％（重量 / 重量）的吸附容量。

[0076] 分子筛为市售可得的，如购于 Süd-Chemie 的 CAN TRI-SORB™4A。

[0077] 例如在气候带 1 至 2、优选在气候带 1 至 4b 中储存的过程中，本发明的药物组合物在大于 18 个月、优选大于 24 个月、最优选大于 36 个月的时间内是化学稳定的。

[0078] 例如在气候带 1 至 2、优选在气候带 1 至 4b 中储存的过程中，本发明的药物组合物在至少 18 个月、优选至少 24 个月、最优选至少 36 个月的时间内是化学稳定的，且本发明的药物组合物包含 4-(4- 氨基 -3- 氟苯氧基）吡啶 -2- 羧酸甲酰胺 (AFP-PMA) 的量为小于 0.100 重量％，意指 0.001 重量％至最大为 0.100 重量％；优选为等于或小于 0.08 重量％，意指 0.001 重量％至最大为 0.08 重量％；最优选为等于或小于 0.050 重量％，意指 0.001 重量％至最大为 0.050 重量％，基于组合物中的瑞戈非尼的量计。为了确定药品的保质期，气候带为公知概念，其限定了用于长期稳定性研究的储存条件，从而确定药品的保质期。例如，由在 25℃和 60％相对湿度下储存得到的数据用于证实气候带 1 至 2 的保质期，而由在 40℃和 75％相对湿度下储存得到的数据用于证实气候带 1 至 4b 的保质期。

[0079] 在 25℃ /60％相对湿度下储存的过程中，本发明药物组合物中 AFP-PMA 的量的月增长率为每月等于或小于 0.0015 重量％，意指 0.0001 重量％至最大为 0.0015 重量％；优选为等于或小于 0.001 重量％，意指 0.0001％至最大为 0.001 重量％，基于组合物中瑞戈非尼的量计。

[0080] 在 30℃ /75％相对湿度下储存的过程中，本发明药物组合物中 AFP-PMA 的量的月增长率为每月等于或小于 0.0030 重量％，意指 0.0001 重量％至最大为 0.0030 重量％；优选为等于或小于 0.0025 重量％，意指 0.0001 重量％至最大为 0.0025 重量％，基于组合物中瑞戈非尼的量计。

[0081] 令人惊讶地，在本发明的药物组合物的储存过程中，本发明药物组合物与分子筛一起包装时比与其他干燥剂如硅胶一起包装时产生更少的副产物，所述副产物优选为

4-(4- 氨基 -3- 氟苯氧基) 吡啶 -2- 羧酸甲酰胺。

[0082] 制备方法 (包衣)

[0083] 本发明的药物组合物包括但不限于颗粒剂、丸粒、片剂、糖衣药丸、丸剂、熔化剂或固体分散剂,优选片剂、固体分散剂、丸粒和颗粒剂,最优选片剂,且可根据本领域用于制备药物组合物的已知方法制备,其例如记载于 WO 2006/026500 中。

[0084] 本发明的药物组合物——优选含有瑞戈非尼的片剂——根据本领域已知方法包衣,所述方法如在包衣锅或有孔滚筒包衣机 (perforated drum coater) 中喷洒包衣液体至药物组合物上,条件是排风温度为等于或低于 42℃,例如 20℃至 42℃ ;优选等于或低于 40℃,例如 30℃至 40℃ ;最优选等于或低于 38℃,例如 32℃至 38℃。在包衣步骤中所使用的用于溶解或分散包衣材料的溶剂 / 媒介物为水性溶剂 / 媒介物,优选为水。

[0085] 本发明的另一主题是一种药物组合物,其包含 :瑞戈非尼,瑞戈非尼的水合物、溶剂合物、代谢物或药学上可接受的盐,或其多晶型物,优选瑞戈非尼,其中药物组合物被包衣包覆,其中包衣可通过包衣过程获得或通过包衣过程获得,其中所述包衣过程中排风温度为等于或低于 42℃,例如 20℃至 42℃ ;优选等于或低于 40℃,例如 30℃至 40℃ ;最优选等于或低于 38℃,例如 32℃至 38℃,且在包衣步骤中所使用的溶剂 / 媒介物为水性溶剂 / 媒介物,优选为水。

[0086] 使用含有基于聚乙烯醇的聚合物的包衣材料的包衣步骤可通过将包衣材料均匀地溶解或分散在溶剂 / 媒介物 (例如水) 中而进行,所述包衣材料例如 Opadry™ II 85G35294 粉、Opadry™ II 85G25457 红、Opadry™ II 85G23665 橙。或者,包衣材料可由单独的组分制备。然后在有孔滚筒包衣机中将包衣液体喷洒至本发明的药物组合物 (如片剂) 上。

[0087] 令人惊讶地,可在低包衣温度下得到良好的包衣结果,即,排风温度等于或低于 42℃,例如 20℃至 42℃;优选等于或低于 40℃,例如 30℃至 40℃;最优选等于或低于 38℃,例如 32℃至 38℃。

[0088] 令人惊讶地,4-(4- 氨基 -3- 氟苯氧基) 吡啶 -2- 羧酸甲酰胺 (IUPAC:4-(4- 氨基 -3- 氟苯氧基)-N- 甲基吡啶 -2- 甲酰胺)(AFP-PMA) 的量在由未包衣到最终包衣的本发明的药物组合物中仅增加 0.0005 重量%至 0.0030 重量%,优选增加 0.0005 重量%至 0.0020 重量%,基于瑞戈非尼的量计。

[0089] 因此,本发明的另一方面是制备包含瑞戈非尼的包衣的药物组合物的方法,所述药物组合物优选为片剂,其中 4-(4- 氨基 -3- 氟苯氧基) 吡啶 -2- 羧酸甲酰胺 (IUPAC:4-(4- 氨基 -3- 氟苯氧基)-N- 甲基吡啶 -2- 甲酰胺)(AFP-PMA) 的量在由未包衣的药物组合物到最终包衣的药物组合物中仅增加 0.0005 重量%至 0.0030 重量%,优选 0.0005 重量%至 0.0020 重量%,基于瑞戈非尼的量计。

[0090] 治疗方法

[0091] 本发明还涉及一种使用本发明的化合物及其组合物治疗哺乳动物过度增殖疾病的方法。该方法包括向有需要的哺乳动物包括人给予治疗所述疾病有效量的本发明的化合物或其组合物。过度增殖疾病包括但不限于实体瘤,如乳腺癌、呼吸道癌、脑癌、生殖器癌、消化道癌、尿道癌、眼癌、肝癌、皮肤癌、头颈癌、甲状腺癌、甲状旁腺癌及其远端转移。那些疾病还包括淋巴癌、肉瘤和白血病。

[0092] 乳腺癌的实例包括但不限于浸润性导管癌、浸润性小叶癌、原位导管癌、原位小叶癌。

[0093] 呼吸道癌的实例包括但不限于小细胞和非小细胞肺癌，以及支气管腺瘤和胸膜肺母细胞瘤。

[0094] 脑癌的实例包括但不限于脑干和下丘脑胶质瘤、小脑和大脑星形细胞瘤、髓母细胞瘤、室管膜瘤、以及神经外胚层肿瘤和松果体瘤。

[0095] 男性生殖器的肿瘤包括但不限于前列腺癌和睾丸癌。女性生殖器的肿瘤包括但不限于子宫内膜癌、子宫颈癌、卵巢癌、阴道癌和外阴癌以及子宫肉瘤。

[0096] 消化道肿瘤包括但不限于肛门癌、结肠癌、大肠癌、食管癌、胆囊癌、胃癌、胰腺癌、直肠癌、小肠癌和唾液腺癌。

[0097] 优选大肠癌。

[0098] 还优选胃肠道间质瘤 (GIST)。

[0099] 尿道肿瘤包括但不限于膀胱癌、阴茎癌、肾癌、肾盂癌、尿管癌和尿道癌。

[0100] 眼癌包括但不限于眼内黑色素瘤和视网膜母细胞瘤。

[0101] 肝癌包括但不限于肝细胞癌（有或无纤维板层变体的肝细胞癌）、胆管细胞型肝癌（肝内胆管癌）和混合型肝细胞 - 胆管细胞型肝癌。

[0102] 优选肝细胞癌。

[0103] 皮肤癌包括但不限于鳞状细胞癌、卡波西肉瘤、恶性黑色素瘤、梅克尔细胞皮肤癌和非黑色素皮肤癌。

[0104] 头颈癌包括但不限于喉癌 / 下咽癌 / 鼻咽癌 / 口咽癌以及嘴唇和口腔癌。

[0105] 淋巴瘤包括但不限于艾滋病相关淋巴瘤、非霍奇金淋巴瘤、皮肤 T 细胞淋巴瘤、霍奇金病和中枢神经系统淋巴瘤。

[0106] 肉瘤包括但不限于软组织肉瘤、骨肉瘤、恶性纤维组织细胞瘤、淋巴肉瘤和横纹肌肉瘤。

[0107] 白血病包括但不限于急性髓性白血病、急性淋巴母细胞白血病、慢性淋巴细胞白血病、慢性髓性白血病和多毛细胞白血病。

[0108] 这些疾病在人类中已得到充分表征，而且在其他哺乳动物中也具有类似的病原学，且可通过给予本发明的药物组合物治疗。

[0109] 基于已知用于评估对治疗过度增殖疾病有效的化合物的标准实验室技术，通过用于在哺乳动物中确定上述病症的治疗方法的标准毒性实验和标准药理实验，以及通过比较这些结果与用于治疗这些病症的已知药物的结果，可容易地确定用于治疗各个目标适应症的本发明化合物的有效剂量。在这些病症之一的治疗中给予的活性成分的量可根据如下考虑因素广泛变化 :所使用的具体化合物和剂量单位、给药方式、治疗期、治疗的患者的年龄和性别、治疗的病情的性质和程度。

[0110] 本发明还提供本发明的化合物在制备用于治疗上述疾病的药物组合物中的用途。

[0111] 与其他药剂结合

[0112] 本发明的化合物可作为单一药剂给药或与一种以上其他药剂结合给药，其中所述结合不会引起不可接受的副作用。例如，本发明的化合物可与已知的抗过度增殖的药剂或其他适应症药剂等结合，以及与所述抗过度增殖的药剂或其他适应症药剂的混合物或结合

物结合。

[0113] 可添加到该组合物中的任选的抗过度增殖的药剂包括但不限于 Merck Index 的第 11 版 (1996) 中的癌症化疗用药法中所列出的化合物，其以引用的方式纳入本说明书，如天冬酰胺酶、博来霉素、卡铂、卡莫司汀、苯丁酸氮芥、顺铂、门冬酰胺酶 (colaspase)、环磷酰胺、阿糖胞苷、达卡巴嗪、更生霉素、柔红霉素、多柔比星（阿霉素）、表柔比星、依托泊苷、5- 氟尿嘧啶、六甲嘧胺、羟基脲、异环磷酰胺、伊立替康、甲酰四氢叶酸、环己亚硝脲、氮芥、6- 巯基嘌呤、美司钠、甲氨蝶呤、丝裂霉素 C、米托蒽醌、泼尼松龙、强的松、丙卡巴肼、雷洛昔芬、链脲菌素、三苯氧胺、硫鸟嘌呤、托泊替康、长春碱、长春新碱和长春地辛。

[0114] 适合于与本发明组合物结合使用的其他抗过度增殖的药剂包括但不限于在 Goodman and Gilman's The Pharmacological Basis of Therapeutics（第九版），主编 Molinoff 等，由 McGraw-Hill 出版，第 1225-1287 页，(1996) 中公知的在肿瘤性疾病的治疗中使用的那些化合物，其以引用的方式纳入本说明书，如氨鲁米特、L- 天冬酰胺酶、硫唑嘌呤、5- 氮杂胞苷克拉屈滨、白消安、己烯雌酚、2',2'- 二氟脱氧胞苷、多西紫杉醇、赤式羟基壬基腺嘌呤 (erythrohydroxynonyladenine)、炔雌醇、5- 氟脱氧尿苷、5- 氟脱氧尿苷一磷酸盐、氟达拉滨磷酸酯、氟甲睾酮、氟他胺、己酸羟孕酮、伊达比星、干扰素、醋酸甲羟孕酮、醋酸甲地孕酮、美法仑、米托坦、紫杉醇、喷司他丁、N- 膦酰基乙酰基 - 天冬氨酸盐 (PALA)、普卡霉素、司莫司汀、替尼泊苷、丙酸睾酮、噻替哌、三甲基三聚氰胺、尿苷和长春瑞滨。

[0115] 适于与本发明组合物结合使用的其他抗过度增殖的药剂包括但不限于其他抗癌药剂，如埃博霉素类及其衍生物、伊立替康、雷洛昔芬和托泊替康。

[0116] 通常，使用上述的本发明的结合将有助于：

[0117] (1) 与单独给予任一药剂相比在减少肿瘤的生长或甚至消除肿瘤方面产生更好的功效，

[0118] (2) 提供所给予的化疗药剂的更少量的给药，

[0119] (3) 提供在患者中具有良好耐受的化疗治疗，与单一药剂化疗和某些其他结合治疗所观察到的相比，其不良药理学并发症更少，

[0120] (4) 提供治疗哺乳动物尤其是人中更广范围的不同癌症类型，

[0121] (5) 提供在所治疗患者之中的更高响应速率，

[0122] (6) 提供相比于标准的化疗治疗而言所治疗患者的更长的存活时间，

[0123] (7) 提供更长时间的肿瘤进展，和 / 或

[0124] (8) 与其他癌症药剂结合产生拮抗作用的已知情况相比较，产生与单独使用的那些药剂至少一样好的功效和耐受性。

[0125] 为了本发明的目的，“结合”不仅指包含所有组分的剂型（所谓的固定结合）以及含有彼此分开的组分的结合包装，还指同时或依次给药的组分，只要它们被用于相同疾病的预防或治疗即可。

[0126] 本领域普通技术人员应理解，在不脱离本文所述的本发明的精神或范围的情况下，可对本发明进行变化和修改。

[0127] 上文和下文所引用的所有出版物、申请和专利以引用的方式纳入本说明书。

[0128] 除非另有说明，否则重量数据为重量百分数且份数为重量份。

实施例

[0129] 实施例 1 :含有瑞戈非尼的包衣片剂

[0130] a) 固体分散剂

[0131] 制备 0.415kg 的瑞戈非尼一水合物 (对应于 0.40kg 瑞戈非尼) 和 1.60kg 的聚乙烯基吡咯烷酮 (PVP 25) 于 4.8kg 丙酮和 1.20kg 乙醇的混合物中的溶液。使用流化床真空制粒机在 60 至 70℃的温度下将该溶液喷洒在 1.00kg 交联羧甲基纤维素钠和 1.00kg 微晶纤维素的粉末层上。

[0132] b) 制片

[0133] 步骤 a) 的颗粒被滚筒压紧并筛出 3.15mm 和 1.0mm 的颗粒。随后压紧的颗粒与 0.54kg 交联羧甲基纤维素钠、0.0240kg 胶态无水二氧化硅和 0.0360kg 硬脂酸镁混合。在旋转压片机中将该预压混合物压制成含有 20mg 和 40mg 的瑞戈非尼的片剂。

[0134] c) 薄膜包衣

[0135] 对于 20mg 片剂的包衣,将 0.160kg 的 Opadry™ II 85G35294 粉均匀地分散于 0.640kg 水中。对于 40mg 片剂的包衣,将 0.120kg 的 Opadry™ II 85G35294 粉均匀地分散于 0.480kg 水中。在 35℃的排风温度下,在有孔滚筒包衣机中将这些包衣混悬液喷洒在分别为 20mg 和 40mg 的步骤 b) 的片剂上。包衣过程产生具有光滑表面的均匀包衣片。不能观察到包衣缺陷。

[0136] 市售可得的 Opadry™ II 85G35294 粉包含聚乙烯醇 (部分水解)[全部混合物的 44 重量%]、聚乙二醇 (PEG 3350)[全部混合物的 12.4 重量%]、卵磷脂 (大豆)、氧化铁、二氧化钛和滑石。

[0137] 表 2 :含有瑞戈非尼的片剂的组成

[0138]

	片剂 A (20 mg)	片剂 B (40 mg)
	[mg/片剂]	[mg/片剂]
瑞戈非尼	20.00	40.00
聚乙烯基吡咯烷酮 (PVP 25)	80.00	160.00
交联羧甲基纤维素钠	77.00	154.00
微晶纤维素	50.00	100.00

[0139]

硬脂酸镁	1.80	3.60
胶态无水二氧化硅	1.20	2.40
OpadryII 85G35294 粉	8.00	12.00
总和	238.00	472.00
片剂形状	圆形	椭圆形
片剂尺寸	直径: 9 mm	长度: 16 mm, 宽度: 7 mm

[0140] 实施例 1 的制剂也以不同（即更大）规模制备。配料比和设备的操作原理相同。

[0141] 实施例 A :基于 HPMC 包衣的含有瑞戈非尼的片剂用于对比

[0142] 在 60℃的排风温度下，将与如实施例 1(a-b) 所述制备的未包衣片剂相同的片剂芯用基于羟丙基甲基纤维素 (HMPC) 的包衣混悬液 (HMPC 15cp 720g,PEG 335024.0g,二氧化钛 23.3g,氧化铁红 0.72g,水 1480g) 包衣。

[0143] 实验结果 :

[0144] 实施例 1 与实施例 A 之间的比较

[0145] 在步骤 b) 之后在实施例 1 的未包衣片剂中检测到的降解产物 4-(4- 氨基 -3- 氟苯氧基）吡啶 -2- 羧酸甲酰胺 (IUPAC:4-(4- 氨基 -3- 氟苯氧基)-N- 甲基吡啶 -2- 甲酰胺)(AFP-PMA) 的量为 0.0042 重量％，基于瑞戈非尼的量计。在实施例 1 的最后的步骤 c) 之后，在实施例 1 的包衣片剂中检测到 AFP-PMA 的量为 0.0050 重量％，基于瑞戈非尼的量计。AFP-PMA 的量仅增加 0.0008％。

[0146] 在研究以更大规模制备的实施例 1 的片剂和包衣片剂时，观察到类似的增长率。

[0147] 在对比实施 A 中使用的未包衣片剂中检测到 AFP-PMA 的量为 0.0024 重量％，基于瑞戈非尼的量计。在包衣（基于 HMPC 的包衣）之后，在实施例 A 的包衣片中检测到 AFP-PMA 的量为 0.0078 重量％，基于瑞戈非尼计。AFP-PMA 的量增加 0.0054％。

[0148] 实施例 1 的储存稳定性

[0149] 在 a)25℃和 60％相对湿度，以及 b)30℃和 75％相对湿度下，将实施例 1 的包衣片剂连同分子筛 (CAN TRI-SORB™ 4A,3g, Süd-Chemie) 一起包装于 HDPC（高密度聚乙烯）瓶中。

[0150] 类似地，在 a)25℃和 60％相对湿度，以及 b)30℃和 75％相对湿度下，将实施例 1 的包衣片剂连同硅胶 (CAN SORB-IT™3g, Süd-Chemie) 一起包装于 HDPC 瓶中。

[0151] 两个稳定性研究的结果如表 3 所示。在所有的研究中发现 AFP-PMA 的量近似线性增加。因此，稳定性结果以在最高达 30 个月的时间内在若干批次上测定的平均月增长率表示。

[0152] 在各批次的保质期的末期存在于含有瑞戈非尼的包衣片剂中的 AFP-PMA 的实际量可通过在释放测试时向存在于包衣片剂中的起始量加上各月增量来估算。同样地，可推

算与干燥剂一起包装于瓶中的产品在气候带的保质期。

[0153] 表 3 :含有瑞戈非尼的片剂的稳定性结果

[0154]

	含有实施例 1 的片剂和分子筛的 HDPE 瓶	含有实施例 1 的片剂和二氧化硅的 HDPE 瓶
	月增长率[% /月]	月增长率[% / 月]
在 25 °C，60% 相对湿度下储存	0.0008	0.0019
在 30 °C，75%相对湿度下储存	0.0020	0.0034