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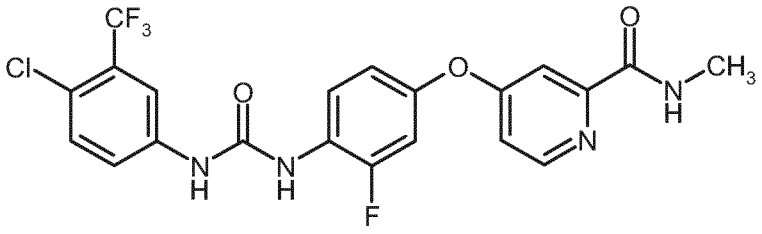
(54) **Title**: COMBINATION OF REGORAFENIB AND ACETYLSALICYLIC ACID FOR TREATING CANCER

(57) **Abstract**: The present invention relates to pharmaceutical compositions and combinations comprising regorafenib and acetylsalicylic acid, or a hydrate, solvate, metabolite or pharmaceutically acceptable salt thereof or a polymorph thereof for treating, preventing or managing diseases and conditions including hyperproliverative disorders such as cancer in humans and other mammals.

**Combination of Regorafenib and Acetylsalicylic Acid for Treating Cancer**

The present invention relates to pharmaceutical compositions and combinations comprising regorafenib and acetylsalicylic acid, or a hydrate, solvate, metabolite or pharmaceutically acceptable salt thereof or a polymorph thereof for treating, preventing or managing diseases and conditions including hyperproliverative disorders such as cancer in humans and other mammals.

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. It is currently developed for the treatment of colorectal cancer and gastrointestinal stromal tumors. 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.

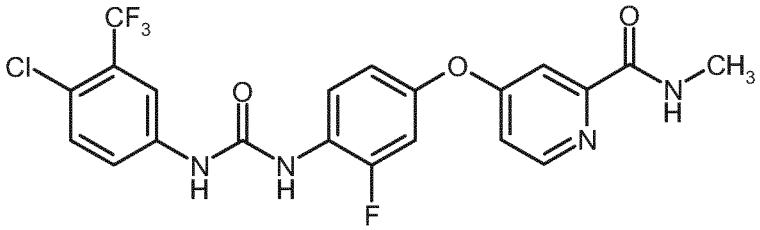
Acetylsalicylic acid is a well-known drug which cannot only be used for treating pain or reducing the risk to develop a cardiovascular event or disease but there are also hints for reducing the risk of developing cancer diseases (Rothwell PM et al (2012) Short-term effects of daily acetylsalicylic acid on cancer incidence, mortality and non-vascular death: analysis of the time course of risks and benefits in 51 randomized controlled trials. Lancet. 379: 1602-1612).

Furthermore acetylsalicylic acid can reduce metastasis of tumors effecting a reduction of mortality in particular in patients with colorectal cancer (Rothwell PM et al (2012) Effect of daily acetylsalicylic acid on risk of cancer metastasis: a study of incident cancers during randomised controlled trials. Lancet. 379: 1591-1601).

Object of the present invention is the improvement of the cancer therapy by the administration of regorafenib and acetylsalicylic acid in combination.

Surprisingly the combination of regorafenib and acetylsalicylic acid shows a significant efficacy improvement over the sum of the monotherapies. Furthermore the profile of the side effects (e.g. hand-foot syndrome, elevated blood pressure, fatigue, diarrhea and mucosal inflammation) can be improved.

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



(I),

and acetylsalicylic acid, or a hydrate, solvate, metabolite or pharmaceutically acceptable salt of thereof, or a polymorph thereof.

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).

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 compounds of the invention may be prepared by use of known chemical reactions and procedures.

Method for treatment:

The present invention also relates to a method for using the combination 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 the combination, 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.

Administration

Combinations of the present invention can be administered in any form by any effective route, including, e.g., oral, parenteral, enteral, intravenous, intraperitoneal, topical, transdermal (e.g., using any standard patch), ophthalmic, nasally, local, non-oral, such as aerosal, inhalation, subcutaneous, intramuscular, buccal, sublingual, rectal, vaginal, intra-arterial, and intrathecal, etc. They can be administered alone, or in combination with any ingredient(s), active or inactive.

Preference is given to an oral administration.

Alternatively acetylsalicylic acid can be administered intravenously.

Combinations of the present invention can be converted in a known manner into the usual formulations, which may be liquid or solid formulations e.g. without limitation normal and enteric coated tablets, capsules, pills, powders, granules, elixirs, tinctures, solution, suspensions, syrups, solid and liquid aerosols and emulsions.

Examples of solid formulations for oral administration are described in US provisional application No. 60/605,752.

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.

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.

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

A further aspect of the invention of particular interest is a combination comprising acetylsalicylic acid in an amount of 50 to 100 mg, preferably from 60 to 500 mg, more preferably from 70 to 350 mg. Typical doses of acetylsalicylic acid are 78 mg, 81 mg, 100 mg, 325 mg, 500 mg and 1000 mg.

The daily dose of regorafenib is from 10 to 1000 mg, preferably 40 to 500 mg, more preferably 80 to 320 mg, e.g. 160 mg.

The daily dose of acetylsalicylic acid is from 50 to 1000 mg, preferably from 60 to 500 mg, more preferably from 70 to 350 mg. Typical daily doses of acetylsalicylic acid are 78 mg, 81 mg, 100 mg, 325 mg, 500 mg and 1000 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. With each administration the number of tablets or capsules taken in at the same time should not exceed two.

Nevertheless, it may in some cases be advantageous to deviate from the amounts specified, depending on body weight, individual behaviour 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.

Examples of an administration scheme are as follows: In the first cycle daily doses of 160 mg regorafenib and 81 mg acetylsalicylic acid are administered for 3 weeks. In week four only 81 mg acetylsalicylic acid are administered. Then the cycle can be repeated. Alternatively the daily dose of acetylsalicylic acid can be equal or less than 325 mg (e.g. 100 mg) or it can be more than 325 mg (e.g. 500 mg).

The combination can comprise effective amounts of the compound of Formula I and acetylsalicylic acid, which achieves a greater therapeutic efficacy than when either compound is used alone.

The relative ratios of each compound in the combination can also be selected based on their respective mechanisms of action and the disease biology. The relative ratios of each compound can vary widely.

The release of one or more agents of the combination can also be controlled, where appropriate, to provide the desired therapeutic activity when in a single dosage form, combination pack, kit or when in separate independent dosage forms.

The present invention includes pharmaceutical compositions which are comprised of a pharmaceutically acceptable carrier and a pharmaceutically effective amount of the compounds of the present invention. A pharmaceutically acceptable carrier is any carrier 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.

For oral administration, the compounds can be formulated into solid or liquid preparations such as solid dispersion, capsules, pills, tablets, troches, lozenges, melts, powders, solutions, suspensions, or emulsions, and may be prepared according to methods known to the art for the manufacture of pharmaceutical compositions. The solid unit dosage forms can be a capsule which can be of the ordinary hard- or soft-shelled gelatin type containing, for example, surfactants, lubricants, and inert fillers such as lactose, sucrose, calcium phosphate, and corn starch.

In another embodiment, the compounds of this invention may be tableted with conventional tablet bases such as lactose, sucrose and cornstarch in combination with binders such as acacia, corn starch or gelatin, disintegrating agents intended to assist the break-up and dissolution of the tablet following administration such as potato starch, alginic acid, corn starch, and guar gum, gum tragacanth, acacia, lubricants intended to improve the flow of tablet granulation and to prevent the adhesion of tablet material to the surfaces of the tablet dies and punches, for example talc, stearic acid, or magnesium, calcium or zinc stearate, dyes, coloring agents, and flavoring agents such as peppermint, oil of wintergreen, or cherry flavoring, intended to enhance the aesthetic qualities of the tablets and make them more acceptable to the patient. Suitable excipients for use in oral liquid dosage forms include dicalcium phosphate and diluents such as water and alcohols, for example, ethanol, benzyl alcohol, and polyethylene alcohols, either with or without the addition of a pharmaceutically acceptable surfactant, suspending agent or emulsifying agent. Various other materials may be present as coatings or to otherwise modify the physical form of the dosage unit. For instance tablets, pills or capsules may be coated with shellac, sugar or both.

Dispersible powders and granules are suitable for the preparation of an aqueous suspension. They provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example those sweetening, flavoring and coloring agents described above, may also be present.

The pharmaceutical compositions of this invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil such as liquid paraffin or a mixture of vegetable oils. Suitable emulsifying agents may be (1) naturally occurring gums such as gum acacia and gum tragacanth, (2) naturally occurring phosphatides such as soy bean and lecithin, (3) esters or partial esters derived form fatty acids and hexitol anhydrides, for example, sorbitan monooleate, (4) condensation products of said partial esters with ethylene oxide, for example, polyoxyethylene

sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil such as, for example, arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent such as, for example, beeswax, hard paraffin, or cetyl alcohol. The suspensions may also contain one or more preservatives, for example, ethyl or *n*-propyl p-hydroxybenzoate; one or more coloring agents; one or more flavoring agents; and one or more sweetening agents such as sucrose or saccharin.

Syrups and elixirs may be formulated with sweetening agents such as, for example, glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, and preservative, such as methyl and propyl parabens and flavoring and coloring agents.

The compounds of this invention may also be administered parenterally, that is, subcutaneously, intravenously, intraocularly, intrasynovially, intramuscularly, or interperitoneally, as injectable dosages of the compound in a physiologically acceptable diluent with a pharmaceutical carrier which can be a sterile liquid or mixture of liquids such as water, saline, aqueous dextrose and related sugar solutions, an alcohol such as ethanol, isopropanol, or hexadecyl alcohol, glycols such as propylene glycol or polyethylene glycol, glycerol ketals such as 2,2-dimethyl-1,1-dioxolane-4-methanol, ethers such as poly(ethylene glycol) 400, an oil, a fatty acid, a fatty acid ester or, a fatty acid glyceride, or an acetylated fatty acid glyceride, with or without the addition of a pharmaceutically acceptable surfactant such as a soap or a detergent, suspending agent such as pectin, carbomers, methycellulose, hydroxypropylmethylcellulose, or carboxymethylcellulose, or emulsifying agent and other pharmaceutical adjuvants.

Illustrative of oils which can be used in the parenteral formulations of this invention are those of petroleum, animal, vegetable, or synthetic origin, for example, peanut oil, soybean oil, sesame oil, cottonseed oil, corn oil, olive oil, petrolatum and mineral oil. Suitable fatty acids include oleic acid, stearic acid, isostearic acid and myristic acid. Suitable fatty acid esters are, for example, ethyl oleate and isopropyl myristate. Suitable soaps include fatty acid alkali metal, ammonium, and triethanolamine salts and suitable detergents include cationic detergents, for example dimethyl dialkyl ammonium halides, alkyl pyridinium halides, and alkylamine acetates; anionic detergents, for example, alkyl, aryl, and olefin sulfonates, alkyl, olefin, ether, and monoglyceride sulfates, and sulfosuccinates; non-ionic detergents, for example, fatty amine oxides, fatty acid alkanolamides, and poly(oxyethylene-oxypropylene)s or ethylene oxide or propylene oxide copolymers; and amphoteric detergents, for example, alkyl-beta-aminopropionates, and 2-alkylimidazoline quarternary ammonium salts, as well as mixtures.

The parenteral compositions of this invention will typically contain from about 0.5% to about 25% by weight of the active ingredient in solution. Preservatives and buffers may also be used advantageously. In order to minimize or eliminate irritation at the site of injection, such compositions may contain a non-ionic surfactant having a hydrophile-lipophile balance (HLB) of from about 12 to about 17. The quantity of surfactant in such formulation ranges from about 5% to about 15% by weight. The surfactant can be a single component having the above HLB or can be a mixture of two or more components having the desired HLB.

Illustrative of surfactants used in parenteral formulations are the class of polyethylene sorbitan fatty acid esters, for example, sorbitan monooleate and the high molecular weight adducts of ethylene oxide with a hydrophobic base, formed by the condensation of propylene oxide with propylene glycol.

The pharmaceutical compositions may be in the form of sterile injectable aqueous suspensions. Such suspensions may be formulated according to known methods using suitable dispersing or wetting agents and suspending agents such as, for example, sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethyl-cellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents which may be a naturally occurring phosphatide such as lecithin, a condensation product of an alkylene oxide with a fatty acid, for example, polyoxyethylene stearate, a condensation product of ethylene oxide with a long chain aliphatic alcohol, for example, heptadeca-ethyleneoxycetanol, a condensation product of ethylene oxide with a partial ester derived form a fatty acid and a hexitol such as polyoxyethylene sorbitol monooleate, or a condensation product of an ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride, for example polyoxyethylene sorbitan monooleate.

The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent. Diluents and solvents that may be employed are, for example, water, Ringer's solution, isotonic sodium chloride solutions and isotonic glucose solutions. In addition, sterile fixed oils are conventionally employed as solvents or suspending media. For this purpose, any bland, fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid can be used in the preparation of injectables.

A compositions of the invention may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritation excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug. Such material is, for example, cocoa butter and polyethylene glycol.

Controlled release formulations for parenteral administration include liposomal, polymeric microsphere and polymeric gel formulations which are known in the art.

The pharmaceutical compositions of this invention may also be in the form of a solid dispersion. The solid dispersion may be a solid solution, glass solution, glass suspension, amorphous precipitation in a crystalline carrier, eutectic or monotecic, compound or complex formation and combinations thereof.

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, poyldextrin, dextrin, starch and proteins.

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, β-cyclodextrin, hydroxypropyl-β-cyclodextrin or sulfobutyl ether cyclodextrin.

Additional suitable carriers 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 of regorafenib in the matrix may contain certain additional pharmaceutical acceptable ingredients, such as surfactants, fillers, disintegrants, recrystallization inhibitors, plasticizers, defoamers, antioxidants, detackifier, pH-modifiers, glidants and lubricants.

The solid dispersion of the invention is 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.

The compositions of the invention can also contain other conventional pharmaceutically acceptable compounding ingredients, generally referred to as carriers or diluents, as necessary or desired.

Conventional procedures for preparing such compositions in appropriate dosage forms can be utilized.

Commonly used pharmaceutical ingredients which can be used as appropriate to formulate the composition for its intended route of administration include:

**acidifying agents** (examples include but are not limited to acetic acid, citric acid, fumaric acid, hydrochloric acid, nitric acid);

**alkalinizing agents** (examples include but are not limited to ammonia solution, ammonium carbonate, diethanolamine, monoethanolamine, potassium hydroxide, sodium borate, sodium carbonate, sodium hydroxide, triethanolamine, trolamine);

**adsorbents** (examples include but are not limited to powdered cellulose and activated charcoal);

**aerosol propellants** (examples include but are not limited to carbon dioxide, $CCl_2F_2$, $F_2ClC\text{-}CClF_2$ and $CClF_3$)

**air displacement agents** (examples include but are not limited to nitrogen and argon);

**antifungal preservatives** (examples include but are not limited to benzoic acid, butylparaben, ethylparaben, methylparaben, propylparaben, sodium benzoate);

**antimicrobial preservatives** (examples include but are not limited to benzalkonium chloride, benzethonium chloride, benzyl alcohol, cetylpyridinium chloride, chlorobutanol, phenol, phenylethyl alcohol, phenylmercuric nitrate and thimerosal);

**antioxidants** (examples include but are not limited to ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorus acid, monothioglycerol, propyl gallate, sodium ascorbate, sodium bisulfite, sodium formaldehyde sulfoxylate, sodium metabisulfite);

**binding materials** (examples include but are not limited to block polymers, natural and synthetic rubber, polyacrylates, polyurethanes, silicones, polysiloxanes and styrene-butadiene copolymers);

**buffering agents** (examples include but are not limited to potassium metaphosphate, dipotassium phosphate, sodium acetate, sodium citrate anhydrous and sodium citrate dihydrate)

**carrying agents** (examples include but are not limited to acacia syrup, aromatic syrup, aromatic elixir, cherry syrup, cocoa syrup, orange syrup, syrup, corn oil, mineral oil, peanut oil, sesame oil, bacteriostatic sodium chloride injection and bacteriostatic water for injection)

**chelating agents** (examples include but are not limited to edetate disodium and edetic acid)

**colorants** (examples include but are not limited to FD&C Red No. 3, FD&C Red No. 20, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, D&C Red No. 8, caramel and ferric oxide red);

**clarifying agents** (examples include but are not limited to bentonite);

**emulsifying agents** (examples include but are not limited to acacia, **cetomacrogol**, cetyl alcohol, glyceryl monostearate, lecithin, sorbitan monooleate, polyoxyethylene 50 monostearate);

**encapsulating agents** (examples include but are not limited to gelatin and cellulose acetate phthalate)

**flavorants** (examples include but are not limited to anise oil, cinnamon oil, cocoa, menthol, orange oil, peppermint oil and vanillin);

**humectants** (examples include but are not limited to glycerol, propylene glycol and sorbitol);

**levigating agents** (examples include but are not limited to mineral oil and glycerin);

**oils** (examples include but are not limited to arachis oil, mineral oil, olive oil, peanut oil, sesame oil and vegetable oil);

**ointment bases** (examples include but are not limited to lanolin, hydrophilic ointment, polyethylene glycol ointment, petrolatum, hydrophilic petrolatum, white ointment, yellow ointment, and rose water ointment);

**penetration enhancers (transdermal delivery)** (examples include but are not limited to monohydroxy or polyhydroxy alcohols, mono-or polyvalent alcohols, saturated or unsaturated fatty alcohols, saturated or unsaturated fatty esters, saturated or unsaturated dicarboxylic acids, essential oils, phosphatidyl derivatives, cephalin, terpenes, amides, ethers, ketones and ureas)

**plasticizers** (examples include but are not limited to diethyl phthalate and glycerol);

**solvents** (examples include but are not limited to ethanol, corn oil, cottonseed oil, glycerol, isopropanol, mineral oil, oleic acid, peanut oil, purified water, water for injection, sterile water for injection and sterile water for irrigation);

**stiffening agents** (examples include but are not limited to cetyl alcohol, cetyl esters wax, microcrystalline wax, paraffin, stearyl alcohol, white wax and yellow wax);

**suppository bases** (examples include but are not limited to cocoa butter and polyethylene glycols (mixtures));

**surfactants** (examples include but are not limited to benzalkonium chloride, nonoxynol 10, oxtoxynol 9, polysorbate 80, sodium lauryl sulfate and sorbitan mono-palmitate);

**suspending agents** (examples include but are not limited to agar, bentonite, carbomers, carboxymethylcellulose sodium, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, kaolin, methylcellulose, tragacanth and veegum);

**sweetening agents** (examples include but are not limited to aspartame, dextrose, glycerol, mannitol, propylene glycol, saccharin sodium, sorbitol and sucrose);

**tablet anti-adherents** (examples include but are not limited to magnesium stearate and talc);

**tablet binders** (examples include but are not limited to acacia, alginic acid, carboxymethylcellulose sodium, compressible sugar, ethylcellulose, gelatin, liquid glucose, methylcellulose, non-crosslinked polyvinyl pyrrolidone, and pregelatinized starch);

**tablet and capsule diluents** (examples include but are not limited to dibasic calcium phosphate, kaolin, lactose, mannitol, microcrystalline cellulose, powdered cellulose, precipitated calcium carbonate, sodium carbonate, sodium phosphate, sorbitol and starch);

**tablet coating agents** (examples include but are not limited to liquid glucose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, ethylcellulose, cellulose acetate phthalate and shellac);

**tablet direct compression excipients** (examples include but are not limited to dibasic calcium phosphate);

**tablet disintegrants** (examples include but are not limited to alginic acid, carboxymethylcellulose calcium, microcrystalline cellulose, polacrillin potassium, cross-linked polyvinylpyrrolidone, sodium alginate, sodium starch glycollate and starch);

**tablet glidants** (examples include but are not limited to colloidal silica, corn starch and talc);

**tablet lubricants** (examples include but are not limited to calcium stearate, magnesium stearate, mineral oil, stearic acid and zinc stearate);

**tablet/capsule opaquants** (examples include but are not limited to titanium dioxide);

**tablet polishing agents** (examples include but are not limited to carnauba wax and white wax);

**thickening agents** (examples include but are not limited to beeswax, cetyl alcohol and paraffin);

**tonicity agents** (examples include but are not limited to dextrose and sodium chloride);

**viscosity increasing agents** (examples include but are not limited to alginic acid, bentonite, carbomers, carboxymethylcellulose sodium, methylcellulose, polyvinyl pyrrolidone, sodium alginate and tragacanth); and

**wetting agents** (examples include but are not limited to heptadecaethylene oxycetanol, lecithin, sorbitol monooleate, polyoxyethylene sorbitol monooleate, and polyoxyethylene stearate).

It is believed that one skilled in the art, utilizing the preceding information, can utilize the present invention to its fullest extent.

**What is claimed is:**

1. A pharmaceutical combination comprising regorafenib and acetylsalicylic acid, or a hydrate, solvate, metabolite or pharmaceutically acceptable salt thereof, or a polymorph thereof.

2. The combination of claim 1 which is a pharmaceutical composition comprising regorafenib and acetylsalicylic acid, or a hydrate, solvate, metabolite or pharmaceutically acceptable salt thereof, or a polymorph thereof in one dosage form.

3. The combination of claim 1 which is a combination pack containing the components separate from one another.

4. The combination of claim 1 wherein the components are administered in separate dosage forms simultaneously or sequentially for the treatment of the same disease.

5. The combination of any of claims 1 to 4 for the use as medicament for treating hyper-proliferative disorders.

6. The combination of claim 5 wherein the hyper-proliferative disorders are selected from the group consisting of 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.

7. The combination of any of claims 5 to 6 wherein the hyper-proliferative disorders are selected from the group consisting of colorectal cancer and gastrointestinal stromal tumors (GIST).

8. The combination of any of claims 1 to 7 administered in a way wherein regorafenib and acetylsalicylic acid are administered daily for the first three weeks and in the fourth week only regorafenib is administered daily.

9. The combination of any of claims 1 to 8 containing regorafenib in an amount of 10 to 1000 mg and acetylsalicylic acid in an amount of 50 to 1000 mg.

10. 10. A method of treating hyper-proliferative disorders in a subject in need thereof comprising administering effective amounts of regorafenib and acetylsalicylic acid, or a hydrate, solvate, metabolite or pharmaceutically acceptable salt thereof, or a polymorph thereof.

# INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2013/069735

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K45/06 A61K31/4412 A61K31/616 A61P35/00 A61P35/04
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 A61P

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, BIOSIS, EMBASE, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO 2007/054303 A2 (BAYER HEALTHCARE AG [DE]; WEBER OLAF [DE]; RIEDL BERND [DE]) 18 May 2007 (2007-05-18) | 1-4,9 |
| Y | paragraphs [0055] - [0056]; claims 1,4, ----- -/-- | 5-8,10 |

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

[X] 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 | Date of mailing of the international search report |
|---|---|
| 29 October 2013 | 05/11/2013 |

| Name and mailing address of the ISA/ | Authorized officer |
|---|---|
| European Patent Office, P.B. 5818 Patentlaan 2<br>NL - 2280 HV Rijswijk<br>Tel. (+31-70) 340-2040,<br>Fax: (+31-70) 340-3016 | Ansaldo, M |

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# INTERNATIONAL SEARCH REPORT

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| Y | J Burn ET AL: "Long-term eff ect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial", , vol. 378, no. 9809 17 December 2011 (2011-12-17), pages 2081-2087, XP055085755, DOI: 10.1016/S0140-6736(11)61049-0 Retrieved from the Internet: URL:http://www.sciencedirect.com/science/article/pii/S0140673611610490/pdfft?md5=19ba873b6a5e35d3b91007d03cd8334a&pid=1-s2.0-S0140673611610490-main.pdf [retrieved on 2013-10-29] the whole document | 1-10 |
| X,P | Axel Grothey ET AL: "Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial for the CORRECT Study Group", , vol. 381, no. 9863 26 January 2013 (2013-01-26), pages 303-312, XP055085767, England ISSN: 1474-547X, DOI: 10.1016/S0140-6736(12)61900-X Retrieved from the Internet: URL:http://www.sciencedirect.com/science/article/pii/S014067361261900X/pdfft?md5=e17489b174c639b82e7af7ee8d13a5a6&pid=1-s2.0-S014067361261900X-main.pdf [retrieved on 2013-10-29] the whole document | 1-10 |
| Y | US 2004/121004 A1 (TANEJA RAJNEESH [US]) 24 June 2004 (2004-06-24) the whole document | 1-10 |
| Y | US 2005/038080 A1 (BOYER STEPHEN [DE] ET AL) 17 February 2005 (2005-02-17) claims 1,9,21,22,26 | 1-10 |

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
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| Patent document cited in search report | Publication date | Patent family member(s) | Publication date |
|---|---|---|---|
| WO 2007054303 A2 | 18-05-2007 | CA 2628881 A1 | 18-05-2007 |
| | | JP 2009514921 A | 09-04-2009 |
| | | KR 20080074974 A | 13-08-2008 |
| | | WO 2007054303 A2 | 18-05-2007 |
| US 2004121004 A1 | 24-06-2004 | AT 427747 T | 15-04-2009 |
| | | CA 2506930 A1 | 22-07-2004 |
| | | EP 1594499 A1 | 16-11-2005 |
| | | ES 2325502 T3 | 07-09-2009 |
| | | JP 2006514049 A | 27-04-2006 |
| | | JP 2012107021 A | 07-06-2012 |
| | | MX PA05006629 A | 30-09-2005 |
| | | PL 213637 B1 | 30-04-2013 |
| | | US 2004121004 A1 | 24-06-2004 |
| | | US 2009074863 A1 | 19-03-2009 |
| | | WO 2004060372 A1 | 22-07-2004 |
| US 2005038080 A1 | 17-02-2005 | AR 048741 A1 | 24-05-2006 |
| | | AR 079933 A2 | 29-02-2012 |
| | | AU 2004259760 A1 | 03-02-2005 |
| | | AU 2011201337 A1 | 14-04-2011 |
| | | BR PI0412219 A | 22-08-2006 |
| | | CA 2532865 A1 | 03-02-2005 |
| | | CL 18342004 A1 | 03-06-2005 |
| | | CN 1856469 A | 01-11-2006 |
| | | CN 102816113 A | 12-12-2012 |
| | | CR 10193 A | 30-09-2008 |
| | | CY 1107094 T1 | 24-10-2012 |
| | | DE 602004010407 T2 | 16-10-2008 |
| | | DK 1663978 T3 | 07-04-2008 |
| | | EC SP066302 A | 28-07-2006 |
| | | EP 1663978 A2 | 07-06-2006 |
| | | ES 2297490 T3 | 01-05-2008 |
| | | HR P20060073 A2 | 30-06-2006 |
| | | IL 173256 A | 31-03-2011 |
| | | JP 4777887 B2 | 21-09-2011 |
| | | JP 2006528196 A | 14-12-2006 |
| | | JP 2011168599 A | 01-09-2011 |
| | | KR 20060052866 A | 19-05-2006 |
| | | MA 27946 A1 | 01-06-2006 |
| | | ME P38308 A | 10-02-2011 |
| | | MY 142799 A | 31-12-2010 |
| | | NZ 544920 A | 27-11-2009 |
| | | NZ 580384 A | 31-03-2011 |
| | | PT 1663978 E | 15-02-2008 |
| | | RS 20060037 A | 05-06-2008 |
| | | SI 1663978 T1 | 29-02-2008 |
| | | US 2005038080 A1 | 17-02-2005 |
| | | US 2009192127 A1 | 30-07-2009 |
| | | US 2013131122 A1 | 23-05-2013 |
| | | WO 2005009961 A2 | 03-02-2005 |

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权利要求书1页 说明书9页

(54)发明名称

用于治疗癌症的瑞戈非尼和乙酰水杨酸的组合

(57)摘要

本发明涉及包含瑞戈非尼和乙酰水杨酸、或其水合物、溶剂化物、代谢物或可药用盐、或其多晶型物的药物组合物和组合，其用于治疗、预防或控制人类和其他哺乳动物中的疾病和疾病状态，包括过度增殖性病症如癌症。

CN 104994876 A

1.药物组合产品，包含瑞戈非尼和乙酰水杨酸、或其水合物、溶剂化物、代谢物或可药用盐、或其多晶型物。

2.权利要求 1 的组合产品，其为包含在一个剂型中的瑞戈非尼和乙酰水杨酸、或其水合物、溶剂化物、代谢物或可药用盐、或其多晶型物的药物组合物。

3.权利要求 1 的组合产品，其为含有彼此分开的组分的组合包装。

4.权利要求 1 的组合产品，其中组分以单独剂型同时或顺序给予以用于治疗相同疾病。

5.权利要求 1 至 4 中任一项的组合产品，用作治疗过度增殖性病症的药物。

6.权利要求 5 的组合产品，其中所述过度增殖性病症选自：乳腺癌、呼吸道癌、脑癌、生殖器官癌、消化道癌、泌尿道癌、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。

7.权利要求 5 至 6 中任一项的组合产品，其中所述过度增殖性病症选自结直肠癌和胃肠道间质瘤 (GIST)。

8.权利要求 1 至 7 中任一项的组合产品，其以如下方式给予：其中在第一个三周内每日给予瑞戈非尼和乙酰水杨酸，并且在第四周内每日仅给予瑞戈非尼。

9.权利要求 1 至 8 中任一项的组合产品，其含有 10 至 1000mg 的量的瑞戈非尼和 50 至 1000mg 的量的乙酰水杨酸。

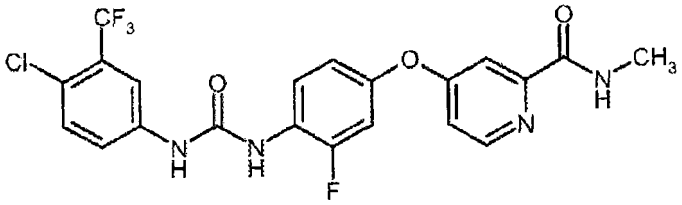
10.一种治疗需要其的主体中过度增殖性病症的方法，包括给予有效量的瑞戈非尼和乙酰水杨酸、或其水合物、溶剂化物、代谢物或可药用盐、或其多晶型物。

# 用于治疗癌症的瑞戈非尼和乙酰水杨酸的组合

[0001] 本发明涉及包含瑞戈非尼 (regorafenib) 和乙酰水杨酸、或其水合物、溶剂化物、代谢物或可药用盐、或其多晶型物的药物组合物和组合，其用于治疗、预防或控制人类和其他哺乳动物中的疾病和疾病状态，包括过度增殖性病症，例如癌症。

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

[0003]



(I)

[0004] 是一种有效的抗癌和抗血管生成试剂，其具有多种活性，包括对 VEGFR、PDGFR、raf、p38 和 / 或 flt-3 激酶信号传导分子的抑制活性，并且其可以用于治疗多种疾病和疾病状态，如过度增殖性病症，例如癌症、肿瘤、淋巴瘤、肉瘤和白血病，如在 WO 2005/009961 中所述。目前其被开发用于治疗结直肠癌和胃肠道间质瘤。而且，WO 2005/009961 中提及式 (I) 的化合物的盐如其盐酸盐、甲磺酸盐和苯磺酸盐。WO 2008/043446 中提及式 (I) 的化合物的一水合物。WO 2011/128261 中描述了一种用于制备高纯度的瑞戈非尼的改进的方法。

[0005] 乙酰水杨酸是一种熟知的药物，其不仅可用于治疗疼痛或减少发展为心血管事件或疾病的风险，而且还存在用于减少发展为癌症疾病的风险的暗示 (Rothwell PM et al(2012)Short-term effects of daily acetylsalicylic acid on cancer incidence, mortality and non-vascular death :analysis of the time course of risks and benefits in 51 randomized controlled trials.Lancet.379 :1602-1612)。

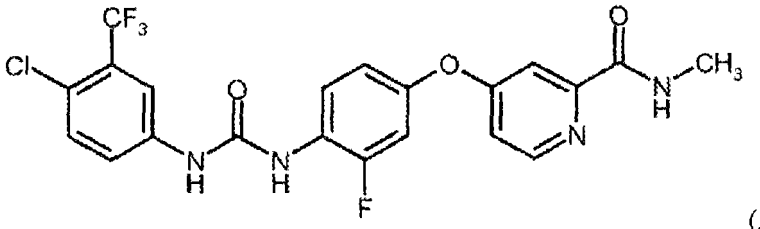
[0006] 而且，乙酰水杨酸可以减少肿瘤转移，导致死亡率降低，特别是在患有结直肠癌的患者中 (Rothwell PM et al(2012)Effect of daily acetylsalicylic acid on risk of cancer metastasis :a study of incident cancers during randomised controlled trials.Lancet.379 :1591-1601)。

[0007] 本发明的目的是通过给予瑞戈非尼和乙酰水杨酸的组合改善癌症的治疗。

[0008] 令人惊奇地，瑞戈非尼和乙酰水杨酸的组合相对于单一疗法的加合显示显著的功效改善。而且，可以改善副作用 ( 例如，手足综合征、血压升高、疲劳、腹泻和粘膜炎症 ) 的特性。

[0009] 本发明涉及一种组合，包含瑞戈非尼，其为式 (I) 的化合物

[0010]



(I),

[0011] 和乙酰水杨酸、或其水合物、溶剂化物、代谢物或可药用盐、或其多晶型物。

[0012] 术语“式 (I) 的化合物”或“瑞戈非尼”指 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,如式 (I) 描述的。

[0013] 为了本发明的目的,溶剂化物为其中溶剂分子形成固态的化学计量复合物且包括但不限于例如水、乙醇和甲醇的化合物或其盐的那些形式。

[0014] 水合物为溶剂化物的特定形式,其中溶剂分子为水。本发明的化合物或其盐的水合物为化合物或盐与水的化学计量组合物,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。

[0015] 为了本发明的目的,盐优选地为根据本发明的化合物的可药用盐。合适的可药用盐是本领域技术人员熟知的,并且包括无机酸和有机酸的盐,所述无机酸和有机酸例如盐酸、氢溴酸、硫酸、磷酸、甲磺酸、三氟甲磺酸、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、草酸、琥珀酸、富马酸、马来酸、苯甲酸、水杨酸、苯乙酸和扁桃酸。另外,可药用盐包括无机碱的盐,例如含有碱阳离子 ( 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,以及有机碱的酸盐,包括脂族和芳族取代的铵和季铵阳离子,例如来自三乙胺、N,N- 二乙胺、N,N- 二环己胺、赖氨酸、吡啶、N,N- 二甲基氨基吡啶 (DMAP)、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) 的质子化或全烷基化 (peralkylation) 的那些。优选瑞戈非尼的盐酸盐、甲磺酸盐或苯磺酸盐。

[0016] 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- 羟基甲基 ) 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。

[0017] 作为本发明的化合物,优选瑞戈非尼和瑞戈非尼一水合物。

[0018] 本发明的化合物可以通过使用已知的化学反应和程序制备。

[0019] 治疗方法 :

[0020] 本发明还涉及一种使用所述组合及其组合物治疗哺乳动物过度增殖性病症的方法。该方法包括向需要其的哺乳动物 ( 包括人类 ) 给予有效地治疗所述病症的量的所述组合。过度增殖性病症包括,但不限于 :实体瘤,例如乳腺癌、呼吸道癌、脑癌、生殖器官癌、消化道癌、泌尿道癌、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。那些病症还包括淋巴瘤、肉瘤和白血病。

[0021] 乳腺癌的实例包括,但不限于浸润性导管癌、浸润性小叶癌、原位导管癌和原位小

叶癌。

[0022] 呼吸道癌的实例包括，但不限于小细胞和非小细胞肺癌，及支气管腺瘤和胸膜肺母细胞瘤。

[0023] 脑癌的实例包括，但不限于脑干和下丘脑 (hypophtalmic) 胶质瘤、小脑和大脑星形细胞瘤、成神经管细胞瘤、室管膜瘤及神经外胚层瘤和松果体瘤。

[0024] 雄性生殖器官肿瘤包括，但不限于前列腺癌和睾丸癌。雌性生殖器官肿瘤包括，但不限于子宫内膜癌、宫颈癌、卵巢癌、阴道癌和外阴癌，以及子宫肉瘤。

[0025] 消化道肿瘤包括，但不限于肛门癌、结肠癌、结直肠癌、食道癌、胆囊癌、胃癌、胰腺癌、直肠癌、小肠癌和唾液腺癌。

[0026] 优选结直肠癌。

[0027] 还优选胃肠道间质瘤 (GIST)。

[0028] 泌尿道肿瘤包括，但不限于膀胱癌、阴茎癌、肾癌、肾盂癌、输尿管癌和尿道癌。

[0029] 眼癌包括，但不限于眼内黑素瘤和视网膜母细胞瘤。

[0030] 肝癌的实例包括，但不限于肝细胞癌（具有或不具有羽层状变体 (fibrolamellar variant) 的肝细胞癌）、胆管癌（肝内胆管癌）和混合型肝细胞胆管癌。

[0031] 优选肝细胞癌。

[0032] 皮肤癌包括，但不限于鳞状细胞癌、卡波济氏肉瘤、恶性黑素瘤、Merkel 细胞皮肤癌和非黑素瘤皮肤癌。

[0033] 头颈癌包括，但不限于喉 / 下咽部 / 鼻咽部 / 口咽部癌症，及唇和口腔癌。

[0034] 淋巴瘤包括，但不限于 AIDS 相关淋巴瘤、非霍奇金淋巴瘤、皮肤 T- 细胞淋巴瘤、霍奇金病、和中枢神经系统的淋巴瘤。

[0035] 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。

[0036] 白血病包括，但不限于急性髓性白血病、急性淋巴母细胞性白血病、慢性淋巴细胞性白血病、慢性粒细胞白血病和毛细胞白血病。

[0037] 这些病症在人类中已很好地表征，而且也以类似的病因存在于其它哺乳动物中，并且可通过给予本发明的药物组合物治疗。

[0038] 基于已知用于评价治疗过度增殖性病症的化合物的标准实验室技术，通过标准毒性检验和通过标准药理学试验，其用于确定对哺乳动物中上述疾病状态的治疗，并且通过将这些结果与用于治疗这些疾病状态的已知药物的结果进行比较，可以容易地确定用于治疗每种期望适应症的本发明的化合物的有效剂量。在这些疾病状态之一的治疗中所给予的活性成分的量可以根据如下考量而在很大程度上变化 :使用的具体化合物和剂量单位、给药方式、疗程、治疗患者的年龄和性别、治疗疾病状态的性质和程度。

[0039] 本发明进一步提供本发明的化合物在制备用于治疗前述病症的药物组合物中的用途。

[0040] 给药

[0041] 本发明的组合可以通过任何有效的途径以任何形式给药，包括例如口服、肠胃外、肠、静脉内、腹膜内、局部 (topical)、透皮（例如，使用任何标准贴剂）、眼用、鼻、局部 (local)、非口服例如气雾剂、吸入、皮下、肌内、颊、舌下、直肠、阴道、动脉内和鞘内等。它们

可以单独或与任何成分（活性或非活性）组合给予。

[0042] 优选口服给药。

[0043] 可选地，乙酰水杨酸可以静脉内给药。

[0044] 本发明的组合可以以已知的方式转化成常用制剂，其可以是液体或固体制剂，例如不限于普通和肠溶包衣片剂、胶囊剂、丸剂、粉剂、颗粒剂、酏剂、酊剂、溶液剂、悬浮剂、糖浆剂、固体和液体气雾剂和乳剂。

[0045] 用于口服给药的固体制剂的实例描述在美国临时申请号 No. 60/605,752 中。

[0046] 通常，使用之前提及的本发明的组合将起如下作用：

[0047] (1) 与单独给予任一种药剂相比，其在减少肿瘤生长或者甚至消除肿瘤中获得了更好的功效，

[0048] (2) 提供给予更少量的所给予的化疗剂，

[0049] (3) 提供化疗性治疗，其在患者中是良好耐受的并且具有的有害药理学并发症比单一药剂化疗和某些其它联合疗法中观察到的少，

[0050] (4) 在哺乳动物，尤其人类中提供治疗更广谱的不同癌症类型，

[0051] (5) 在治疗的患者中提供更高反应速率，

[0052] (6) 与标准化疗治疗相比，在治疗的患者中提供更长存活时间，

[0053] (7) 提供更长的肿瘤进展时间，和 / 或

[0054] (8) 与其中其它癌症药剂组合产生拮抗作用的已知情况相比，得到与单独使用那些药剂至少一样好的功效和耐受性结果。

[0055] 为了本发明的目的，“组合”不仅指剂型，其包含所有组分（所谓的固定组合）及包含彼此分开的组分的组合包装，而且还指同时或顺序给予的组分，只要其用于预防或治疗相同疾病。

[0056] 给予活性成分的量可以根据如下考量在很大程度上变化：使用的具体化合物和剂量单位、给药方式和时间、疗程、治疗患者的年龄、性别和一般状况、治疗疾病状态的性质和程度、药物代谢和排泄的速率、可能的药物组合和药物 - 药物相互作用等。

[0057] 特别感兴趣的本发明的一个方面是包含 4 至 400mg、优选 10 至 200mg、更优选 10 至 100mg 的量的瑞戈非尼的组合。

[0058] 特别感兴趣的本发明的一个进一步的方面是包含 50 至 100mg、优选 60 至 500mg、更优选 70 至 350mg 的量的乙酰水杨酸的组合。乙酰水杨酸的典型剂量为 78mg、81mg、100mg、325mg、500mg 和 1000mg。

[0059] 瑞戈非尼的每日剂量为 10 至 1000mg、优选 40 至 500mg、更优选 80 至 320mg，例如 160mg。

[0060] 乙酰水杨酸的每日剂量为 50 至 1000mg、优选 60 至 500mg、更优选 70 至 350mg。乙酰水杨酸的典型的每日剂量为 78mg、81mg、100mg、325mg、500mg 和 1000mg。

[0061] 根据本发明的药物组合物是每天给予一次或多次、优选地至多三次、更优选地至多两次。优选地经由口服途径给予。对于每次给药，同时服用片剂或胶囊剂的数量不应超过 2。

[0062] 尽管如此，在某些情况下，根据体重、对于活性成分的个体行为、制剂种类和影响给药的时间或间隔，偏离所指定量可能是有利的。例如，在某些情况下低于前述最低量可能

是足够的，而在其它情况下必须超过所指定上限。在给予相对大量的情况下，可将这些量分成一天内几个单独剂量是适当的。

[0063] 给药方案的实例如下：在第一周期，给予每日剂量为 160mg 的瑞戈非尼和 81mg 的乙酰水杨酸 3 周。在第 4 周，仅给予 81mg 的乙酰水杨酸。然后，重复该周期。可选地，乙酰水杨酸的每日剂量可以等于或低于 325mg（例如 100mg），或者其可以超过 325mg（例如 500mg）。

[0064] 所述组合可以包括有效量的式 I 的化合物和乙酰水杨酸，其获得比单独使用任一种化合物更大的治疗效果。

[0065] 所述组合中每种化合物的相对比例也可以基于他们相应的作用机制和疾病生物学选择。每种化合物的相对比例可以在很大程度上变化。

[0066] 当在单一剂型、组合包装、试剂盒中时或当在分离的独立剂型中时，当合适时，也可以控制所述组合的一种或多种药剂的释放，以提供期望的治疗活性。

[0067] 本发明包括药物组合物，其包含或由下列组成（comprised of）：可药用载体和药学上有效量的本发明的化合物。可药用载体是在符合活性成分的有效活性的浓度下对患者相对无毒和无害以使与载体有关的任何副作用不损害活性成分的有益作用的任何载体。化合物的药学上有效量是对所治疗的具体疾病状态产生结果或施加影响的量。

[0068] 对于口服给药，可将所述化合物配制为固体或液体制剂，例如固体分散体、胶囊剂、丸剂、片剂、糖锭剂、锭剂、熔体（melt）、粉剂、溶液剂、悬浮剂或乳剂，可以根据本领域中已知制备药物组合物的方法制备。固体单位剂量形式可以是可为普通硬壳或软壳明胶类型的胶囊剂，含有例如表面活性剂、润滑剂和惰性填充剂例如乳糖、蔗糖、磷酸钙和玉米淀粉。

[0069] 在另一个实施方案中，本发明的化合物可以用常规片剂基质例如乳糖、蔗糖和玉米淀粉与如下组分的组合压片：粘合剂例如阿拉伯胶、玉米淀粉或明胶，给予后预期帮助片剂崩解和溶解的崩解剂例如马铃薯淀粉、藻酸、玉米淀粉和瓜尔胶、黄蓍胶、阿拉伯胶，预期改善片剂颗粒流动和防止片剂材料与片剂模具和冲床表面粘附的润滑剂例如滑石、硬脂酸或硬脂酸镁、硬脂酸钙或硬脂酸锌，预期增强片剂的美学品质和使它们更容易被患者接受的染料、着色剂和矫味剂例如薄荷油、冬青油或樱桃香精。用于口服液体剂型的合适的赋形剂包括磷酸二钙和稀释剂例如水和醇，例如乙醇、苯甲醇和聚乙二醇，加入或不加入可药用表面活性剂、助悬剂或乳化剂。各种其它材料可以作为包衣剂存在或以其他方式修饰剂量单位的物理形式。例如，可以用虫胶、糖或二者将片剂、丸剂或胶囊剂包衣。

[0070] 可分散粉末和颗粒适于制备含水悬浮剂。它们提供活性成分和分散剂或湿润剂、助悬剂和一种或多种防腐剂的混合物。合适的分散剂或湿润剂和助悬剂为通过上面已经提及的那些举例说明的。也可存在另外的赋形剂，例如上述那些甜味剂、矫味剂和着色剂。

[0071] 本发明的药物组合物也可以是水包油乳液形式。油相可以是植物油，例如液体石蜡或植物油的混合物。合适的乳化剂可以是 (1) 天然存在的树胶，例如阿拉伯胶和黄蓍胶，(2) 天然存在的磷脂，例如大豆和卵磷脂，(3) 由脂肪酸和己糖醇酐衍生的酯或偏酯，例如失水山梨糖醇单油酸酯，(4) 所述偏酯与环氧乙烷的缩合产物，例如聚氧乙烯失水山梨糖醇单油酸酯。乳液也可以含有甜味剂和矫味剂。

[0072] 可以通过将活性成分悬浮于植物油例如落花生油、橄榄油、芝麻油或椰子油或矿物油例如液体石蜡中配制油性悬浮剂。油性悬浮剂可含有增稠剂，例如蜂蜡、硬石蜡或鲸蜡

醇。悬浮剂也可含有一种或多种防腐剂，例如对羟基苯甲酸乙酯或对羟基苯甲酸正丙酯；一种或多种着色剂；一种或多种矫味剂；和一种或多种甜味剂例如蔗糖或糖精。

[0073] 可以用甜味剂，例如甘油、丙二醇、山梨醇或蔗糖配制糖浆剂和酏剂。这样的制剂也可含有缓和剂和防腐剂，例如尼泊金甲酯和尼泊金丙酯和矫味剂和着色剂。

[0074] 本发明的化合物也可以肠胃外给予，即皮下、静脉内、眼内、滑膜内、肌内或腹膜间，作为在生理上可接受的稀释剂和药物载体中的化合物的可注射剂量给予，药物载体可以是无菌液体或液体的混合物，例如水、盐水、右旋糖水溶液和相关糖溶液，醇例如乙醇、异丙醇或十六醇，二醇例如丙二醇或聚乙二醇，甘油缩酮例如 2,2- 二甲基 -1,1- 二氧戊环 -4- 甲醇，醚例如聚（乙二醇）400、油、脂肪酸、脂肪酸酯或脂肪酸甘油酯或乙酰化脂肪酸甘油酯，加入或不加入可药用表面活性剂例如皂或洗涤剂，助悬剂例如果胶、卡波姆、甲基纤维素、羟丙基甲基纤维素或羧甲基纤维素，或乳化剂及其它药物助剂。

[0075] 可用于本发明的肠胃外制剂的示例性油为石油、动物、植物或合成来源的那些油，例如花生油、大豆油、芝麻油、棉籽油、玉米油、橄榄油、矿脂和矿物油。合适的脂肪酸包括油酸、硬脂酸、异硬脂酸和肉豆蔻酸。合适的脂肪酸酯为例如油酸乙酯和肉豆蔻酸异丙酯。合适的皂包括脂肪酸的碱金属、铵和三乙醇胺盐，合适的洗涤剂包括阳离子洗涤剂，例如二甲基二烷基卤化铵、烷基卤化吡啶鎓和烷基胺乙酸盐；阴离子洗涤剂，例如磺酸的烷基酯、芳基酯和烯烃酯，硫酸的烷基酯、烯烃酯、醚和甘油单酯，和磺基琥珀酸酯；非离子洗涤剂，例如脂肪胺氧化物、脂肪酸烷醇酰胺，和聚（氧乙烯 - 氧丙烯）或环氧乙烷或环氧丙烷共聚物；和两性洗涤剂，例如 β - 氨基丙酸烷基酯，和 2- 烷基咪唑啉季铵盐及其混合物。

[0076] 本发明的肠胃外组合物的溶液通常含有约 0.5 重量％至约 25 重量％的活性成分。也可以有利地使用防腐剂和缓冲剂。为使注射部位刺激最小化或将其消除，这样的组合物可含有具有约 12 至约 17 的亲水 - 亲油平衡值 (HLB) 的非离子表面活性剂。这样的制剂中的表面活性剂的量为约 5 重量％至约 15 重量％。表面活性剂可以是具有以上 HLB 的单一组分，或可以是具有需要的 HLB 的两种或多种组分的混合物。

[0077] 用于肠胃外制剂的示例性表面活性剂是聚乙烯失水山梨糖醇脂肪酸酯类表面活性剂，例如失水山梨糖醇单油酸酯，和环氧乙烷与疏水性基质的高分子量加合物，由环氧丙烷和丙二醇缩合形成。

[0078] 药物组合物可以是无菌可注射含水悬浮液形式。可以根据已知方法，使用合适的分散剂或湿润剂和助悬剂例如羧甲基纤维素钠、甲基纤维素、羟丙基甲基 - 纤维素、藻酸钠、聚乙烯吡咯烷酮、黄蓍胶和阿拉伯胶；分散剂或湿润剂，其可以为天然存在的磷脂例如卵磷脂、环氧烷与脂肪酸的缩合产物例如聚氧乙烯硬脂酸酯、环氧乙烷与长链脂肪醇的缩合产物例如十七乙烯氧基鲸蜡醇 (heptadeca-ethyleneoxycetanol)、环氧乙烷与由脂肪酸和己糖醇衍生的偏酯的缩合产物例如聚氧乙烯山梨糖醇单油酸酯、或环氧乙烷与由脂肪酸和己糖醇酐衍生的偏酯的缩合产物例如聚氧乙烯失水山梨糖醇单油酸酯，配制这样的悬浮液。

[0079] 无菌可注射制剂也可以是在无毒肠胃外可接受的稀释剂或溶剂中的无菌可注射溶液或悬浮液。可以使用的稀释剂和溶剂是例如水、林格氏液、等渗氯化钠溶液和等渗葡萄糖溶液。另外，可方便地使用无菌非挥发油作为溶剂或悬浮介质。为此目的，可以使用包括合成甘油单酯或甘油二酯的任何非刺激性非挥发油。另外，脂肪酸例如油酸可用于制备注

射剂。

[0080] 本发明的组合物也可以栓剂形式给予以用于药物的直肠给药。这些组合物可以通过将药物与在常温下为固体但在直肠温度下为液体因而在直肠中熔化释放药物的合适的非刺激性赋形剂混合来制备。这样的材料为例如可可脂和聚乙二醇。

[0081] 用于肠胃外给予的控释制剂包括本领域中已知的脂质体、聚合物微球和聚合物凝胶制剂。

[0082] 本发明的药物组合物也可以是固体分散体形式。固体分散体可以为固体溶液、玻璃溶液、玻璃悬浮液、在结晶载体中的无定形沉淀、低共熔或偏晶化合物或复合物形成及其组合。

[0083] 特别感兴趣的本发明的一个方面是包含固体分散体的药用组合物，其中基质包含可药用聚合物，例如聚乙烯吡咯烷酮、乙烯基吡咯烷酮 / 乙酸乙烯酯共聚物、聚亚烷基二醇（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、聚乙二醇化甘油酯 (polyglycolized glyceride)、黄原胶、角叉菜胶、壳聚糖、壳多糖、聚葡萄糖、糊精、淀粉和蛋白质。

[0084] 本发明的另一个方面是包含固体分散体的药物组合物，其中基质包含糖和 / 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、异麦芽酮糖醇、菊糖、麦芽糖糊精、β - 环糊精、羟丙基 - β - 环糊精或磺基丁基醚环糊精。

[0085] 用于形成固体分散体的基质的其他合适的载体包括，但不限于醇、有机酸、有机碱、氨基酸、磷脂、蜡、盐、脂肪酸酯、聚氧乙烯失水山梨糖醇脂肪酸酯和脲。

[0086] 瑞戈非尼在基质中的固体分散体可以含有某些其它可药用成分，例如表面活性剂、填充剂、崩解剂、重结晶抑制剂、增塑剂、消泡剂、抗氧化剂、防粘剂、pH- 调节剂、助流剂和润滑剂。

[0087] 本发明的固体分散体可以根据本领域制备固体分散体的已知方法制备，例如熔融 / 熔化技术、热熔挤出、溶剂蒸发（即，冷冻干燥、喷雾干燥或分层颗粒粉末）、共沉淀、超临界流体技术和静电旋涂方法。

[0088] 根据需要或期望，本发明的组合物也可以含有通常称为载体或稀释剂的其它常规可药用混合成分。可以使用制备这样的合适剂型的组合物的常规程序。

[0089] 根据需要，可以用于配制组合物以用于其预定给药途径的常用药物成分包括：

[0090] 酸化剂（实例包括但不限于乙酸、柠檬酸、富马酸、盐酸、硝酸）；

[0091] 碱化剂（实例包括但不限于氨水溶液、碳酸铵、二乙醇胺、一乙醇胺、氢氧化钾、硼酸钠、碳酸钠、氢氧化钠、三乙醇胺 (triethanolamine)、三乙醇胺 (trolamine)）；

[0092] 吸附剂（实例包括但不限于粉状纤维素和活性碳）；

[0093] 气雾剂抛射剂（实例包括但不限于二氧化碳、$CCl_2F_2$、$F_2ClC\text{-}CClF_2$和 $CClF_3$）；

[0094] 空气置换剂（实例包括但不限于氮气和氩气）；

[0095] 抗真菌防腐剂（实例包括但不限于苯甲酸、尼泊金丁酯、尼泊金乙酯、尼泊金甲酯、尼泊金丙酯、苯甲酸钠）；

[0096] 抗菌防腐剂（实例包括但不限于苯扎氯铵、苄索氯铵、苯甲醇、西吡氯铵、氯丁醇、

苯酚、苯乙醇、硝酸苯汞和硫柳汞）；

[0097] 抗氧化剂（实例包括但不限于抗坏血酸、抗坏血酸棕榈酸酯、丁羟茴醚、丁羟甲苯、次磷酸、硫代甘油、没食子酸丙酯、抗坏血酸钠、亚硫酸氢钠、甲醛合次硫酸氢钠、焦亚硫酸钠）；

[0098] 粘合物质（实例包括但不限于嵌段聚合物、天然和合成橡胶、聚丙烯酸酯、聚氨酯、硅酮、聚硅氧烷和苯乙烯－丁二烯共聚物）；

[0099] 缓冲剂（实例包括但不限于偏磷酸钾、磷酸二钾、乙酸钠、无水柠檬酸钠和柠檬酸钠二水合物）；

[0100] 载体（实例包括，但不限于阿拉伯胶糖浆、芳香糖浆、芳香酏剂、樱桃糖浆、可可糖浆、柑桔糖浆、糖浆、玉米油、矿物油、花生油、芝麻油、抑菌的氯化钠注射液和抑菌的注射用水）

[0101] 螯合剂（实例包括但不限于依地酸二钠和依地酸）

[0102] 着色剂（实例包括但不限于FD&C Red No.3、FD&C Red No.20、FD&C Yellow No.6、FD&C Blue No.2、D&C Green No.5、D&C Orange No.5、D&C Red No.8、焦糖和氧化铁红）；

[0103] 澄清剂（实例包括但不限于皂土）；

[0104] 乳化剂（实例包括但不限于阿拉伯胶、聚西托醇（cetomacrogol）、鲸蜡醇、单硬脂酸甘油酯、卵磷脂、失水山梨糖醇单油酸酯、聚氧乙烯 50 单硬脂酸酯）；

[0105] 包囊剂（实例包括但不限于明胶和邻苯二甲酸乙酸纤维素）

[0106] 香料（实例包括但不限于茴芹油、肉桂油、可可、薄荷醇、橙油、薄荷油和香草醛）；

[0107] 保湿剂（实例包括但不限于甘油、丙二醇和山梨醇）；

[0108] 研磨剂（实例包括但不限于矿物油和甘油）；

[0109] 油（实例包括但不限于落花生油、矿物油、橄榄油、花生油、芝麻油和植物油）；

[0110] 软膏基质（实例包括但不限于羊毛脂、亲水性软膏、聚乙二醇软膏、矿脂、亲水性矿脂、白色软膏、黄色软膏和玫瑰水软膏）；

[0111] 渗透促进剂（透皮递送）（实例包括但不限于单羟基或多羟基醇、一价或多价醇、饱和或不饱和脂肪醇、饱和或不饱和脂肪酸酯、饱和或不饱和二羧酸、精油、磷脂酰衍生物、脑磷脂、萜烯、酰胺、醚、酮和脲）

[0112] 增塑剂（实例包括但不限于邻苯二甲酸二乙酯和甘油）；

[0113] 溶剂（实例包括但不限于乙醇、玉米油、棉籽油、甘油、异丙醇、矿物油、油酸、花生油、纯净水、注射用水、无菌注射用水和无菌冲洗用水）；

[0114] 硬化剂（实例包括但不限于鲸蜡醇、十六烷基酯蜡、微晶蜡、石蜡、硬脂醇、白蜡和黄蜡）；

[0115] 栓剂基质（实例包括但不限于可可脂和聚乙二醇（混合物））；

[0116] 表面活性剂（实例包括但不限于苯扎氯铵、壬苯醇醚10、辛苯昔醇9、聚山梨酯80、十二烷基硫酸钠和失水山梨糖醇单棕榈酸酯）；

[0117] 助悬剂（实例包括但不限于琼脂、皂土、卡波姆、羧甲基纤维素钠、羟乙基纤维素、羟丙基纤维素、羟丙基甲基纤维素、高岭土、甲基纤维素、黄蓍胶和硅酸镁铝（veegum））；

[0118] 甜味剂（实例包括但不限于阿司帕坦、右旋糖、甘油、甘露醇、丙二醇、糖精钠、山梨醇和蔗糖）；

[0119] 片剂抗粘附剂（实例包括但不限于硬脂酸镁和滑石）；

[0120] 片剂粘合剂（实例包括但不限于阿拉伯胶、藻酸、羧甲基纤维素钠、可压缩糖、乙基纤维素、明胶、液体葡萄糖、甲基纤维素、非交联聚乙烯吡咯烷酮和预胶化淀粉）；

[0121] 片剂和胶囊剂稀释剂（实例包括但不限于磷酸氢钙、高岭土、乳糖、甘露醇、微晶纤维素、粉状纤维素、沉淀碳酸钙、碳酸钠、磷酸钠、山梨醇和淀粉）；

[0122] 片剂包衣剂（实例包括但不限于液体葡萄糖、羟乙基纤维素、羟丙基纤维素、羟丙基甲基纤维素、甲基纤维素、乙基纤维素、邻苯二甲酸乙酸纤维素和虫胶）；

[0123] 直接压片赋形剂（实例包括但不限于磷酸氢钙）；

[0124] 片剂崩解剂（实例包括但不限于藻酸、羧甲基纤维素钙、微晶纤维素、聚克立林钾、交联聚乙烯吡咯烷酮、藻酸钠、淀粉羟乙酸钠和淀粉）；

[0125] 片剂助流剂（实例包括但不限于胶体二氧化硅、玉米淀粉和滑石）；

[0126] 片剂润滑剂（实例包括但不限于硬脂酸钙、硬脂酸镁、矿物油、硬脂酸和硬脂酸锌）；

[0127] 片剂／胶囊剂遮光剂（实例包括但不限于二氧化钛）；

[0128] 片剂抛光剂（实例包括但不限于巴西棕榈蜡和白蜡）；

[0129] 增稠剂（实例包括但不限于蜂蜡、鲸蜡醇和石蜡）；

[0130] 张度剂（实例包括但不限于右旋糖和氯化钠）；

[0131] 增粘剂（实例包括但不限于藻酸、皂土、卡波姆、羧甲基纤维素钠、甲基纤维素、聚乙烯吡咯烷酮、藻酸钠和黄蓍胶）；和

[0132] 湿润剂（实例包括但不限于十七乙烯氧基鲸蜡醇、卵磷脂、山梨醇单油酸酯、聚氧乙烯山梨醇单油酸酯和聚氧乙烯硬脂酸酯）。

[0133] 据信，本领域技术人员使用前述信息，可在其最完全的程度上利用本发明。