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(54) Title: COMBINATION THERAPY TO TREAT DIARRHEA INDUCED BY CANCER TREATMENT

(57) Abstract: This invention relates to a method of treating drug side effects in cancer treatment. More particularly, the present invention relates to preventing, reducing, alleviating, or reversing diarrhea caused by the administration of the isothiazole 3-(4-Bromo-2,6-difluoro-benzoyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido]-isothiazole-4-carboxylic acid amide in the treatment of cancer comprising the step of administering to a patient in need of such treatment, prior to, simultaneously, or sequentially, a therapeutically effective amount of 3-(4-Bromo-2,6-difluoro benzoyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido]-isothiazole-4-carboxylic acid amide or a pharmaceutically acceptable salt thereof, and a therapeutically effective amount of an antidiarrheal agent, a bulking agent, or an anti-estrogen. The combinations of the present invention may optionally include an anti-hypertensive agent.



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COMBINATION THERAPY TO TREAT
DIARRHEA INDUCED BY CANCER TREATMENT

BACKGROUND OF THE INVENTION

5 This invention relates to a combination therapy to treat, prevent, reduce, or decrease diarrhea induced by cancer treatment comprising administering to a patient prior to, simultaneously or sequentially with a therapeutically effective amount of the isothiazole derivative 3-(4-Bromo-2,6-difluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido]-isothiazole-4-carboxylic acid amide and a therapeutically effective amount of an anti-diarrheal agent. The
10 methods of the present invention may optionally include an anti-hypertensive agent.

 Cancer continues to be one of the leading causes of death in the United States and other developed countries. A side effect of cancer therapy is diarrhea, which often develops during clinical treatment with chemotherapeutic agents. Diarrhea is characterized by the frequent defecation of liquid or liquid-like stools. This adverse effect is most commonly
15 associated with chemotherapeutic agents such as 5-fluorouracil, cisplatin or irinotecan hydrochloride. In particular, late diarrhea due to the administration of chemotherapeutic agents can be prolonged, may lead to dehydration and electrolyte imbalance and can be, in some cases, sufficiently serious that chemotherapeutic agent administration must be modified, interrupted or discontinued.

20 Diarrhea is a problematic symptom for patients, and because it may provoke reductions in chemotherapeutic agent doses or the frequency of administration, diarrhea may compromise the therapeutic efficacy of chemotherapeutic agents. Late-onset diarrhea, a severe delayed chronic grade 3-4 diarrhea, is a major dose-limiting toxicity in cancer patients. The loss of fluids and electrolytes associated with late diarrhea can result in life-threatening
25 dehydration, renal insufficiency, and electrolyte imbalances. The life-threatening aspects of persistent or severe diarrhea can require aggressive treatment and may lead to hospitalization. Persistent and severe diarrhea can also have a negative effect on the patient's quality of life, interferes with roles and responsibilities, affects interpersonal relationships and promotes feelings of social isolation.

30 While there is a substantial need for development of an agent for treating cancer therapy induced diarrhea, particularly late diarrhea caused by chemotherapeutic agents, no definite and efficacious method has been identified. The present invention provides a method for treating diarrhea observed after the administration of the isothiazole derivative 3-(4-Bromo-2,6-difluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido]-isothiazole-4-carboxylic acid
35 amide. In preventing diarrheal symptoms in patients receiving 3-(4-Bromo-2,6-difluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido]-isothiazole-4-carboxylic acid amide, the anti-diarrheal agents of the present invention have the potential to reduce the incidence, severity,

and/or duration of diarrhea; improve patient quality of life; avoid hospitalization; and/or prevent dose reduction, interruption, or discontinuation of cancer therapy.

It is therefore the object of the present invention to provide an anti-diarrheal agent for preventing or decreasing diarrhea, in particular late diarrhea, induced by the administration of the isothiazole derivative 3-(4-Bromo-2,6-difluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido]-isothiazole-4-carboxylic acid amide. The compound 3-(4-Bromo-2,6-difluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido]-isothiazole-4-carboxylic acid amide described in U.S. Patent No. 6,235,764 is hereby incorporated by reference in its entirety.

SUMMARY OF THE INVENTION

The present invention relates to a method of treating a cancer treatment side effect. More particularly, this invention relates to a combination therapy to treat the drug side effect in cancer treatment of diarrhea comprising administering to a patient prior to, simultaneously or sequentially with a therapeutically effective amount of the isothiazole derivative 3-(4-Bromo-2,6-difluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido]-isothiazole-4-carboxylic acid amide or a pharmaceutically acceptable salt, and a therapeutically effective amount of an anti-diarrheal agent selected from the group consisting of Octreotide, Loperamide, bulking agents, Tamoxifen, or an anti-estrogen selected from the group consisting of droloxifene, TAT-59, and raloxifene. The methods of the present invention may optionally include an anti-hypertensive agent.

In one embodiment of the present invention a therapeutically effective amount of 3-(4-Bromo-2,6-difluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido]-isothiazole-4-carboxylic acid amide, an analog, a pharmaceutically acceptable salt or a metabolite thereof is administered to a patient being treated prior to, simultaneously, or sequentially with a therapeutically effective amount of an anti-diarrheal agent selected from the list consisting of Octreotide, Loperamide, Tamoxifen, a bulking agent, or an anti-estrogen selected from the group consisting of droloxifene, TAT-59, and raloxifene.

In a preferred embodiment of the invention, the diarrhea is late diarrhea.

In a preferred embodiment, the 3-(4-Bromo-2,6-difluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido]-isothiazole-4-carboxylic acid amide is the hydrochloride salt form.

In a preferred embodiment, the 3-(4-Bromo-2,6-difluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido]-isothiazole-4-carboxylic acid amide is the acetate salt form.

In a preferred embodiment, the 3-(4-Bromo-2,6-difluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido]-isothiazole-4-carboxylic acid amide is formulated in a long-acting release dosage form.

In a preferred embodiment, the Octreotide is Octreotide Acetate.

In a preferred embodiment, Octreotide Acetate is formulated in a long-acting release formulation.

In a preferred embodiment, the anti-diarrheal agents are selected from the group consisting of Loperamide, bulking agents, and Tamoxifen.

In a preferred embodiment, the anti-diarrheal agents are selected from the group consisting of droloxifene, TAT-59, and raloxifene and administered prior to administration of the 3-(4-Bromo-2,6-difluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido]-isothiazole-4-carboxylic acid amide.

In a preferred embodiment, the anti-estrogen is administered about 48 hours prior to 3-(4-Bromo-2,6-difluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido]-isothiazole-4-carboxylic acid amide administration.

In a preferred embodiment, the anti-estrogen is administered at a time effective to impede intestinal epithelial cell replication in the G₀/G₁ phase of the cell cycle.

In a preferred embodiment, the anti-estrogen is administered to a prior to administration of the 3-(4-Bromo-2,6-difluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido]-isothiazole-4-carboxylic acid amide.

In a preferred embodiment, the anti-estrogen is administered to said patient about at least 48 hours prior to administration of the 3-(4-Bromo-2,6-difluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido]-isothiazole-4-carboxylic acid amide.

In a preferred embodiment, the amount of anti-estrogen administered to a patient is in the range of about 0.4-0.8 mg/kg/day.

In a preferred embodiment, the anti-diarrheal agent, Tamoxifen, is administered prior to administration of the 3-(4-Bromo-2,6-difluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido]-isothiazole-4-carboxylic acid amide.

In a preferred embodiment, Tamoxifen is administered about 48 hours prior to the administration of 3-(4-Bromo-2,6-difluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido]-isothiazole-4-carboxylic acid amide.

In a preferred embodiment, the administration of Tamoxifen is at a time effective to impede intestinal epithelial cell replication in the G₀/G₁ phase of the cell cycle.

In a preferred embodiment, the Tamoxifen is administered to a patient about at least 48 hours prior to administration of the 3-(4-Bromo-2,6-difluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido]-isothiazole-4-carboxylic acid amide.

In a preferred embodiment, the Tamoxifen is administered to a patient in the range of about 0.4-0.8 mg/kg/day.

In one embodiment of the method of the present invention the cancer is selected from the group consisting of brain, squamous cell, bladder, gastric, pancreatic, breast, head, neck, esophageal, prostate, colorectal, lung, renal, kidney, ovarian, gynecological and thyroid cancer.

In one preferred embodiment the cancer is selected from the group consisting of prostate, breast, lung, colon or ovarian cancer.

In a more preferred embodiment the cancer is selected from the group consisting of prostate, breast, and lung cancer.

5 In one preferred embodiment the breast cancer is metastatic breast cancer.

In another preferred embodiment the lung cancer is non-small cell lung cancer (NSCL).

In one embodiment of the present invention the anti-hypertensive agent is selected from the group consisting of calcium channel blockers, angiotensin converting enzyme inhibitors (ACE inhibitors), angiotensin II receptor antagonists (A-II antagonists), diuretics, 10 beta-adrenergic receptor blockers (β -blockers), vasodilators and α -adrenergic receptor blockers (α -blockers).

In a preferred embodiment of the present invention the anti-hypertensive agent is an angiotensin converting enzyme inhibitor (ACE inhibitor).

In one embodiment the ACE inhibitor is accupril (quinapril) or accuretic (quinapril and 15 hydrochlorothiazide).

In another preferred embodiment of the present invention the anti-hypertensive agent is an α -adrenergic receptor blocker (α -blocker).

In one embodiment of the present invention the α -adrenergic receptor blocker (α -blocker) is selected from the group consisting of cardura (doxazosin) or cardura XL 20 (doxazosin GITS).

In another preferred embodiment of the present invention the anti-hypertensive agent is a calcium channel blocker.

In one embodiment the calcium channel blocker is selected from the group consisting of Norvasc (amlodipine), procardia (nifedipine), and procardia XL (nifedipine GITS).

25 The present invention also relates to a pharmaceutical composition for the treatment of cancer in a patient which comprises a therapeutically effective amount of Octreotide, Loperamide, Tamoxifen, a bulking agent, an anti-estrogen selected from the group consisting of droloxifene, TAT-59, or raloxifene and a therapeutically effective amount of 3-(4-Bromo-2,6-difluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido]-isothiazole-4-carboxylic acid amide, in 30 combination with one or more pharmaceutically acceptable carriers or vehicles.

The present invention also relates to a pharmaceutical composition for the treatment of cancer in a patient which comprises a therapeutically effective amount of Octreotide, Loperamide, Tamoxifen, a bulking agent, an anti-estrogen selected from the group consisting of droloxifene, TAT-59, or raloxifene and a therapeutically effective amount of 3-(4-Bromo-2,6- 35 difluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido]-isothiazole-4-carboxylic acid amide and a therapeutically effective amount of an anti-hypertensive agent, in combination with one or more pharmaceutically acceptable carriers or vehicles.

In one preferred embodiment the pharmaceutical composition is for the treatment of cancer selected from brain, squamous cell, bladder, gastric, pancreatic, breast, head, neck, esophageal, prostate, colorectal, lung, renal, kidney, ovarian, gynecological and thyroid cancer. In a more preferred embodiment the pharmaceutical composition is for the treatment of prostate, breast, lung, colon and ovarian cancer. In an even more preferred embodiment the pharmaceutical composition is for the treatment of prostate, breast, and lung cancer. In a most preferred embodiment the pharmaceutical composition is for the treatment of metastatic breast cancer or NSCL.

The present invention also relates to a kit comprising in a first compartment a therapeutically effective amount of 3-(4-Bromo-2,6-difluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido]-isothiazole-4-carboxylic acid amide and in a second compartment a therapeutically effective amount of Octreotide, Loperamide, Tamoxifen, a bulking agent, droloxifene, TAT-59, or raloxifene.

The present invention also relates to a kit comprising a first compartment containing a therapeutically effective amount of 3-(4-Bromo-2,6-difluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido]-isothiazole-4-carboxylic acid amide a second compartment containing a therapeutically effective amount of Octreotide, Loperamide, Tamoxifen, a bulking agent, droloxifene, TAT-59, or raloxifene, and a third compartment containing an anti-hypertensive agent.

In one embodiment of the kit of the present invention the compound in the second compartment is Octreotide.

In another embodiment of the kit of the present invention the second compartment is Loperamide.

In another preferred embodiment of the kit of the present invention the compound in the second compartment is Tamoxifen.

In one preferred embodiment of the kit of the present invention the compound in the second compartment is an anti-estrogen selected from the group consisting of droloxifene, TAT-59, or raloxifene.

In another preferred embodiment of the kit of the present invention the second compartment is droloxifene.

In another preferred embodiment of the kit of the present invention the second compartment is TAT-59.

In another preferred embodiment of the kit of the present invention the second compartment is raloxifene.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a method of treating diarrhea in a patient which comprises administering to said patient in need of such treatment, prior to, simultaneously, or

sequentially with a therapeutically effective amount of the isothiazole derivative 3-(4-Bromo-2,6-difluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido]-isothiazole-4-carboxylic acid amide and a therapeutically effective amount of Octreotide, Loperamide, Tamoxifen, a bulking agent, or an anti-estrogen selected from the group consisting of droloxifene, TAT-59, and raloxifene.

- 5 The methods of the present invention may optionally include an anti-hypertensive agent.

The isothiazole compound of the present invention and its pharmaceutically acceptable salts and solvates may be prepared as described in U.S. Patent No. 6,235,764, the contents of which are incorporated by reference.

- One embodiment of the combination therapy of the present invention includes
- 10 Octreotide. Octreotide is the acetate salt of a cyclic octapeptide. It is a long-acting octapeptide with pharmacologic properties mimicking those of the natural hormone somatostatin. Octreotide has been used in co-therapy for ameliorating delayed diarrhea (Cascinu S. Management of diarrhea induced by tumors or cancer therapy. Curr. Opin. Oncol. 1995;7:325-329). In 1990, Kennedy et al. reported encouraging results of treatment with Octreotide in
- 15 patients with colorectal cancer suffering from diarrhea after chemotherapy with 5-fluorouracil (Proc. Am. Soc. Clin. Oncol., 1990 9:324). These data were confirmed in other pilot trials (Cascinu S. et al., Eur. J. Cancer, 1992 28-482-483; and Petrelli N. et al., Cancer 1993, 75-1543-1546) and in a randomized trial comparing Octreotide with Loperamide in the therapy of
- 20 5-fluorouracil-induced diarrhea, in which Octreotide was shown to be more effective than Loperamide and probably more cost-effective (Cascinu S. et al., J. Clin. Oncol., 1993, 11:148-151). Octreotide has been found to be active in preventing diarrhea associated with the administration of cisplatin in patients who experienced this side-effect during a previous course of chemotherapy (Cascinu S., Fedeli A., Luzi Fedeli S. and Catalano G., Oncology, 1994;51:70-73).

- 25 Alternatively, the combination therapy of the present invention can include Loperamide. In humans, intensive, immediate application of Loperamide (an agent that slows intestinal motility and affects water and electrolyte movement through the bowel) has been used to reduce or control diarrhea once diarrhea has started (Rougier P, Bugat R. CPT-11 in the treatment of colorectal cancer: Clinical efficacy and safety profile. Semin Oncol
- 30 1996;23(Suppl 3): 34-41.

- Another embodiment of the combination therapy of the present invention includes Tamoxifen. Tamoxifen (Nolvadex®) interferes with the activity of the hormone, estrogen. Estrogen promotes the growth of breast cancer cells. Tamoxifen works against the effects of estrogen on these cells. It is often called an "anti-estrogen. Tamoxifen, a marketed
- 35 antiestrogen chemotherapeutic agent, is known to induce a block in the G0/G1 phase of the cell cycle. Unlike most chemotherapeutics, which act in the S, G2 and M phases of the cell cycle, Tamoxifen clearly blocks cell cycle progression in G0/G1 (Otto A M, Paddenberg R,

Schubert S, Mannherz H G. Cell cycle arrest, micronucleus formation, and cell death in growth inhibition of MCF-7 breast cancer cells by tamoxifen and cisplatin. J Canc Res & Clin Oncol 1996;122:603-612). This is thought to be through repression of G1-specific protein kinase activity. PCT application WO/96/01127 (published Jan. 18, 1996) discloses a wide variety of agents to be co-administered with Irinotecan, including Tamoxifen. However, it does not disclose prior administration of tamoxifen. The use of Tamoxifen as a therapy to reduce Irinotecan Hydrochloride-induced diarrhea is claimed in U.S. Patent 6,087,377. One embodiment of the combination therapy of the present invention includes bulking agents. Bulking agents, such as Metamucil and Citrucel contain high amounts of fiber and help to slow down diarrhea.

Another embodiment of the combination therapy of the present invention includes an anti-estrogen selected from the group consisting of droloxifene, TAT-59, and raloxifene (Evista). Raloxifene is a selective estrogen receptor modulator that produces both estrogen-agonistic effects on bone and lipid metabolism and estrogen-antagonistic effects on uterine endometrium and breast tissue. Because of its tissue selectivity, raloxifene may have fewer side effects than are typically observed with estrogen therapy. Raloxifene (Evista) has the ability to bind to and activate the estrogen receptor while exhibiting tissue-specific effects distinct from estradiol. As a result, raloxifene is the first of a benzothiophene series of anti-estrogens to be labeled a SERM.

The present invention also relates to a method of treating diarrhea in a patient which comprises administering to said patient in need of such treatment, prior to, simultaneously, or sequentially, a therapeutically effective amount of 3-(4-Bromo-2,6-difluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido]-isothiazole-4-carboxylic acid amide and a therapeutically effective amount of Octreotide, Loperamide, Tamoxifen, a bulking agent, an anti-estrogen selected from the group consisting of droloxifene, TAT-59, and a therapeutically effective amount of an anti-hypertensive agent. When combinations of the present invention are administered sequentially each agent may be administered, first, second or third. In one preferred embodiment, the agents of the combination are administered as (i), the 3-(4-Bromo-2,6-difluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido]-isothiazole-4-carboxylic acid amide followed by a therapeutically effective amount of Octreotide, Loperamide, Tamoxifen, a bulking agent, an anti-estrogen selected from the group consisting of droloxifene, TAT-59, and raloxifene and followed by the anti-hypertensive agent.

Combinations of the invention may be administered sequentially or may be administered simultaneously.

The term "anti-hypertensive" means any agent, which lowers blood pressure. There are many different categories of anti-hypertensive agents including calcium channel blockers, angiotensin converting enzyme inhibitors (ACE inhibitors), angiotensin II receptor antagonists

(A-II antagonists), diuretics, beta-adrenergic receptor blockers (β -blockers), vasodilators and alpha-adrenergic receptor blockers (α -blockers). Any anti-hypertensive agent may be used in accordance with this invention and examples from each class are given hereinafter.

Calcium channel blockers, which are within the scope of this invention include, but are not limited to: Norvasc (amlodipine) (U.S. Patent No. 4,572,909); procardia (nifedipine), procardia XL (nifedipine GITS); bepridil (U.S. Patent No. 3,962,238 or U.S. Reissue No. 30,577); clentiazem (U.S. Patent No. 4,567,175); diltiazem (U.S. Patent No. 3,562,257); fendiline (U.S. Patent No. 3,262,977); gallopamil (U.S. Patent No. 3,261,859); mibefradil (U.S. Patent No. 4,808,605); prenylamine (U.S. Patent No. 3,152,173); semotiadil (U.S. Patent No. 4,786,635); terodiline (U.S. Patent No. 3,371,014); verapamil (U.S. Patent No. 3,261,859); aranidipine (U.S. Patent No. 4,446,325); bamidipine (U.S. Patent No. 4,220,649); benidipine (European Patent Application Publication No. 106,275); cilnidipine (U.S. Patent No. 4,672,068); efonidipine (U.S. Patent No. 4,885,284); elgodipine (U.S. Patent No. 4,952,592); felodipine (U.S. Patent No. 4,264,611); isradipine (U.S. Patent No. 4,466,972); lacidipine (U.S. Patent No. 4,801,599); lercanidipine (U.S. Patent No. 4,705,797); manidipine (U.S. Patent No. 4,892,875); nicardipine (U.S. Patent No. 3,985,758); nifedipine (U.S. Patent No. 3,485,847); nilvadipine (U.S. Patent No. 4,338,322); nimodipine (U.S. Patent No. 3,799,934); nisoldipine (U.S. Patent No. 4,154,839); nitrendipine (U.S. Patent No. 3,799,934); cinnarizine (U.S. Patent No. 2,882,271); flunarizine (U.S. Patent No. 3,773,939); lidoflazine (U.S. Patent No. 3,267,104); lomerizine (U.S. Patent No. 4,663,325); bencyclane (Hungarian Patent No. 151,865); etafenone (German Patent No. 1,265,758); and perhexiline (British Patent No. 1,025,578). The disclosures of all such patents and patent applications are incorporated herein by reference.

Angiotensin Converting Enzyme Inhibitors (ACE-Inhibitors) which are within the scope of this invention include, but are not limited to: accupril (quinapril); accuretic (quinapril and hydrochlorothiazide); alacepril (U.S. Patent No. 4,248,883); benazepril (U.S. Patent No. 4,410,520); captopril (U.S. Patents Nos. 4,046,889 and 4,105,776); ceronapril (U.S. Patent No. 4,452,790); delapril (U.S. Patent No. 4,385,051); enalapril (U.S. Patent No. 4,374,829); fosinopril (U.S. Patent No. 4,37,201); imidapril (U.S. Patent No. 4,508,727); lisinopril (U.S. Patent No. 4,555,502); moveltipril (Belgium Patent No. 893,553); perindopril (U.S. Patent No. 4,508,729); quinapril (U.S. Patent No. 4,344,949); ramipril (U.S. Patent No. 4,587,258); spirapril (U.S. Patent No. 4,470,972); temocapril (U.S. Patent No. 4,699,905); andtrandolapril (U.S. Patent No. 4,933,361). The disclosures of all such patents are incorporated herein by reference.

Angiotensin-II receptor antagonists (A-II antagonists) which are within the scope of this invention include, but are not limited to: candesartan (U.S. Patent No. 5,196,444); eprosartan (U.S. Patent No. 5,185,351); irbesartan (U.S. Patent No. 5,270,317); losartan (U.S.

Patent No. 5,138,069); and valsartan (U.S. Patent No. 5,399,578). The disclosures of all such U.S. patents are incorporated herein by reference.

β -Blockers which are within the scope of this invention include, but are not limited to: acebutolol (U.S. Patent No. 3,857,952); alprenolol (Netherlands Patent Application No. 6,605,692); amosulalol (US. Patent No. 4,217,305); arotinolol (U.S. Patent No. 3,932,400); atenolol (U.S. Patents Nos. 3,663,607 and 3,836,671); befunolol (U.S. Patent No. 3,853,923); betaxolol (U.S. Patent No. 4,252,984); bevantolol (U.S. Patent No. 3,857,891); bisoprolol (U.S. Patent No. 4,258,062); bopindolol (U.S. Patent No. 4,340,541); bucumolol (U.S. Patent No. 3,663,570); bufetolol (U.S. Patent No. 3,723,476); bufuralol (U.S. Patent No. 3,929,836); bunitrolol (U.S. Patent No. 3,541,130); bupranolol (U.S. Patent No. 3,309,406); butidrine hydrochloride (French Patent No. 1,390,056); butofilolol (U.S. Patent No. 4,302,601); carazolol (German Patent No. 2,240,599); carteolol (U.S. Patent No. 3,910,924); carvedilol (U.S. Patent No. 4,503,067); celiprolol (U.S. Patent No. 4,034,009); cetamolol (U.S. Patent No. 4,059,622); cloranolol (German Patent No. 2, 213,044); dilevalol (Clifton et al., Journal of Medicinal Chemistry, 1982, 25, 670); epanolol (U.S. Patent No. 4,167,581); indenolol (U.S. Patent No. 4,045,482); labetalol (U.S. Patent No. 4,012,444); levobunolol (U.S. Patent No. 4,463,176); mepindolol (Seeman et al, Helv. Chim. Acta, 1971, 54, 2411); metipranolol (Czechoslovakian Patent Application No. 128,471); metoprolol (U.S. Patent No. 3,873,600); moprolol (U.S. Patent No. 3,501,769); nadolol (U.S. Patent No. 3,935,267); nadoxolol (U.S. Patent No. 3,819,702); nebivolol (U.S. Patent No. 4,654,362); nipradilol (U.S. Patent No. 4,394,382); oxprenolol (British Patent No. 1,077,603); penbutolol (U.S. Patent No. 3,551,493); pindolol (Swiss Patents Nos. 469,002 and 472,404); practolol (U.S. Patent No. 3,408,387); pronethalol (British Patent No. 909,357); propranolol (U.S. Patents Nos. 3,337,628 and 3,520,919); sotalol (Uloth et al., Journal of Medicinal Chemistry, 1966, 9, 88); sulfinalol (German Patent No. 2,728,641); talinolol (U.S. Patents Nos. 3,935,259 and 4,038,313); tertatolol (U.S. Patent No. 3,960,891); tilisolol (U.S. Patent No. 4,129,565); timolol (U.S. Patent No. 3,655,663); toliprolol (U.S. Patent No. 3,432,545); and xibenolol (U.S. Patent No. 4,018,824). The disclosures of all such patents, patent applications and references are incorporated herein by reference.

α -Blockers which are within the scope of this invention include, but are not limited to: cardura (doxazosin); cardura XL (doxazosin GITS); amosulalol (U.S. Patent No. 4,217,305); arotinolol; dapiprazole (U.S. Patent No. 4,252,721); doxazosin (U.S. Patent No. 4,188,390); fenspiride (U.S. Patent No. 3,399,192); indoramin (U.S. Patent No. 3,527,761); labetalol, naftopidil (U.S. Patent No. 3,997,666); nicergoline (U.S. Patent No. 3,228,943); prazosin (U.S. Patent No. 3,511,836); tainsulosin (U.S. Patent No. 4,703,063); tolazoline (U.S. Patent No. 2,161,938); trimazosin (U.S. Patent No. 3,669,968); and yohimbine, which may be isolated from natural sources according to methods well known to those skilled in the art. The disclosures of all such U.S. patents are incorporated herein by reference.

Preferred anti-hypertensive agents of the invention include calcium channel blockers, alpha-adrenergic blockers, and ACE inhibitors.

The anti-hypertensives described herein are generally commercially available, or they may be made by standard techniques including those described in the references cited herein.

5 The term "treating", as used herein, refers to reversing, decreasing, alleviating, inhibiting the progress of, or preventing the disorder or condition to which such term applies, or one or more symptoms of such disorder or condition. The term "treatment", as used herein, refers to the act of treating, as "treating" is defined immediately above.

10 The phrase "pharmaceutically acceptable salt(s)", as used herein, unless otherwise indicated, includes salts of acidic or basic groups of 3-(4-Bromo-2,6-difluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido]-isothiazole-4-carboxylic acid amide. This compound which is basic in nature is capable of forming a wide variety of salts with various inorganic and organic acids. The acids that may be used to prepare pharmaceutically acceptable acid addition salts of this compound are those that form non-toxic acid addition salts, i.e., salts containing
15 pharmacologically acceptable anions, such as the hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, isonicotinate, acetate, lactate, salicylate, citrate, acid citrate, tartrate, pantothenate, bitartrate, ascorbate, succinate, maleate, gentisinate, fumarate, gluconate, glucaronate, saccharate, formate, benzoate, glutamate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [i.e.,
20 1,1'-methylene-bis-(2-hydroxy-3-naphthoate)] salts.

The terms "concurrently" and "simultaneously" are used interchangeably and mean the compounds of the combination therapy of the present invention are administered (1) simultaneously in time, or (2) at different times during the course of a common treatment schedule.

25 The term "sequentially" as used herein means administration of 3-(4-Bromo-2,6-difluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido]-isothiazole-4-carboxylic acid amide or of Octreotide, Loperamide, Tamoxifen, droloxifene, TAT-59, or raloxifene followed by administration of the other component; after administration of one component, the second component can be administered substantially immediately after the first component, or the
30 second component can be administered after an effective time period after the first component; the effective time period is the amount of time given for realization of maximum benefit from the administration of the first component.

Administration of the compounds of the present invention can be effected by any method that enables delivery of the compounds to the site of action. These methods include oral
35 routes, intraduodenal routes, parenteral injection (including intravenous, subcutaneous, intramuscular, intravascular or infusion), intraocular, intraperitoneal, intravesicular, intravaginal, topical, and rectal administration.

The amount of the active compounds administered will depend on the subject being treated, the severity of the diarrhea, or the rate of administration and the judgement of the prescribing physician.

5 The products of which the combination are composed may be administered simultaneously, separately or spaced out over a period of time so as to obtain the maximum efficacy of the combination; it being possible for each administration to vary in its duration from a rapid administration to a continuous perfusion. As a result, for the purposes of the present invention, the combinations are not exclusively limited to those which are obtained by physical association of the constituents, but also to those which permit a separate administration, which
10 can be simultaneous or spaced out over a period of time. The compositions according to the invention are preferably compositions which can be administered parentally. However, these compositions may be administered orally or intraperitoneally in the case of localized regional therapies.

The compositions for parental administration are generally pharmaceutically acceptable,
15 sterile solutions or suspensions which may optionally be prepared as required at the time of use. For the preparation of non-aqueous solutions or suspensions, natural vegetable oils such as olive oil, sesame oil or liquid petroleum or injectable organic esters such as ethyl oleate may be used. The sterile aqueous solutions can consist of a solution of the product in water. The aqueous solutions are suitable for intravenous administration provided the pH is appropriately
20 adjusted and the solution is made isotonic, for example with a sufficient amount of sodium chloride or glucose. The sterilization may be carried out by heating or by any other means which does not adversely affect the composition.

The combinations may also take the form of liposomes or the form of an association with carriers as cyclodextrins or polyethylene glycols. The compositions for oral or intraperitoneal
25 administration are preferably aqueous suspensions or solutions.

The combinations of the present invention are formulated alone, however they may also be formulated together if desired. This facilitates the easy of use (i.e., less tablets for a patient to swallow) and patient compliance since one tablet is a desired dosage form.

The pharmaceutical composition may, for example, be in a form suitable for oral
30 administration as a tablet, capsule, pill, powder, sustained release formulations, solution, suspension, for parenteral injection as a sterile solution, suspension or emulsion, for topical administration as an ointment or cream or for rectal administration as a suppository. The pharmaceutical composition may be in unit dosage forms suitable for single administration of precise dosages. The pharmaceutical composition will include a conventional pharmaceutical
35 carrier or excipient and a compound according to the invention as an active ingredient. In addition, it may include other medicinal or pharmaceutical agents, carriers, adjuvants, etc.

Exemplary parenteral administration forms include solutions or suspensions of active compounds in sterile aqueous solutions, for example, aqueous propylene glycol or dextrose solutions. Such dosage forms can be suitably buffered, if desired.

Suitable pharmaceutical carriers include inert diluents or fillers, water and various organic solvents. The pharmaceutical compositions may, if desired, contain additional ingredients such as flavorings, binders, excipients and the like. Thus for oral administration, tablets containing various excipients, such as citric acid may be employed together with various disintegrants such as starch, alginic acid and certain complex silicates and with binding agents such as sucrose, gelatin and acacia. Additionally, lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc are often useful for tableting purposes. Solid compositions of a similar type may also be employed in soft and hard filled gelatin capsules. Preferred materials, therefore, include lactose or milk sugar and high molecular weight polyethylene glycols. When aqueous suspensions or elixirs are desired for oral administration the active compound therein may be combined with various sweetening or flavoring agents, coloring matters or dyes and, if desired, emulsifying agents or suspending agents, together with diluents such as water, ethanol, propylene glycol, glycerin, or combinations thereof.

Methods of preparing various pharmaceutical compositions with a specific amount of active compound are known, or will be apparent, to those skilled in this art. For examples, see Remington's Pharmaceutical Sciences, Mack Publishing Company, Easter, Pa., 15th Edition (1975).

The example provided below illustrates and exemplifies a method of administration of the combination therapy of the present invention. It is to be understood that the scope of the present invention is not limited in any way by the scope of the following prophetic example.

Example 1

In a Phase 1 trial with 3-(4-Bromo-2,6-difluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido]-isothiazole-4-carboxylic acid amide HCl almost all subjects treated with doses greater than 160 mg/day may develop Grade 1 or 2 diarrhea within the first few days. Susceptible subjects are encouraged to adhere to a daily schedule of prophylactic anti-diarrheal agents, such as Loperamide, Octreotide, Loperamide, Tamoxifen, a bulking agent, or an anti-estrogen. To treat the diarrhea in these patients, a therapeutically effective amount of 3-(4-Bromo-2,6-difluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido]-isothiazole-4-carboxylic acid amide HCl is administered to a patient in need of such therapy, prior to, simultaneously or sequentially with a therapeutically effective amount of Loperamide, Octreotide, Loperamide, Tamoxifen, a bulking agent, or an anti-estrogen.

The following table shows a recommended treatment for various stages of diarrhea induced by 3-(4-Bromo-2,6-difluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido]-isothiazole-4-carboxylic acid amide HCl cancer therapy.

Table 1. Intervention for Diarrhea

Severity of Diarrhea	CTC Grade	Intervention
<4 stools/day over baseline	1	Use anti-diarrheal agent at subject's own discretion according to their comfort level
Increase of 4-6 stools/day or nocturnal stools	2	Recommend prophylactic anti-diarrheal agent on a daily basis in combination with cancer therapy

CLAIMS

1. A method of treating diarrhea in a patient with cancer which comprises administering to said patient, prior to, simultaneously or sequentially a therapeutically effective amount of 3-(4-Bromo-2,6-difluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido]-isothiazole-4-carboxylic acid amide or a pharmaceutically acceptable salt thereof, and a therapeutically effective amount of an anti-diarrheal agent.
2. The method according to claim 1 wherein the anti-diarrheal agent is selected from the group consisting of Octreotide, Loperamide, Tamoxifen, a bulking agent, and an anti-estrogen.
3. The method according to claim 2, wherein the anti-estrogen is selected from the group consisting of droloxifene, TAT-59, and raloxifene.
4. The method of claim 1 wherein said cancer is selected from the group consisting of brain, squamous cell, bladder, gastric, pancreatic, breast, head, neck, esophageal, prostate, colorectal, lung, renal, kidney, ovarian, gynecological and thyroid cancer.
5. A pharmaceutical composition for the treatment of diarrhea in a patient with cancer which comprises a therapeutically effective amount of 3-(4-Bromo-2,6-difluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido]-isothiazole-4-carboxylic acid amide and a therapeutically effective amount of an anti-diarrhea agent selected from the group consisting of Octreotide, Loperamide, Tamoxifen, a bulking agent, or an anti-estrogen in combination with one or more pharmaceutically acceptable carriers or vehicles.
6. A kit comprising in a first compartment 3-(4-Bromo-2,6-difluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido]-isothiazole-4-carboxylic acid amide and in a second compartment a therapeutically effective amount of Octreotide, Loperamide, Tamoxifen, a bulking agent, or an anti-estrogen selected from the group consisting of droloxifene, TAT-59, and raloxifene.
7. A method according to claim 1 of treating diarrhea in a patient with cancer which comprises administering to said patient in need of such treatment, prior to, simultaneously or sequentially a therapeutically effective amount of 3-(4-Bromo-2,6-difluoro-benzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido]-isothiazole-4-carboxylic acid amide or a pharmaceutically acceptable salt thereof, and a therapeutically effective amount of Octreotide, Loperamide, Tamoxifen, a bulking agent, or an anti-estrogen selected from the group consisting of droloxifene, TAT-59, and raloxifene; and further comprising a therapeutically effective amount of an anti-hypertensive agent.
8. The method according to claim 7, wherein the anti-hypertensive agent is selected from the group consisting of calcium channel blockers, angiotensin converting enzyme inhibitors (ACE inhibitors), angiotensin II receptor antagonists (A-II antagonists),

diuretics, beta-adrenergic receptor blockers (β -blockers), vasodilators and alpha-adrenergic receptor blockers (α -blockers).

9. The method according to claim 1, wherein the 3-(4-Bromo-2,6-difluorobenzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido]-isothiazole-4-carboxylic acid amide is the
5 hydrochloride salt form.

10. The method according to claim 1, wherein the 3-(4-Bromo-2,6-difluorobenzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido]-isothiazole-4-carboxylic acid amide is the acetate salt form.

11. The method according to claim 1 wherein the 3-(4-Bromo-2,6-difluorobenzyloxy)-5-[3-(4-pyrrolidin-1-yl-butyl)-ureido]-isothiazole-4-carboxylic acid amide is
10 formulated in a long-acting release dosage form.

INTERNATIONAL SEARCH REPORT

PCT/IB2005/001066

A. CLASSIFICATION OF SUBJECT MATTER
 IPC 7 A61K31/425 A61P1/12 A61P35/00

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)

IPC 7 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 practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BEEBE JEAN S ET AL: "Pharmacological characterization of CP-547,632, a novel vascular endothelial growth factor receptor-2 tyrosine kinase inhibitor for cancer therapy." CANCER RESEARCH, vol. 63, no. 21, 1 November 2003 (2003-11-01), pages 7301-7309, XP002337231 ISSN: 0008-5472 the whole document ----- -/--	1-11

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in 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 document 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.
- *Z* document member of the same patent family

Date of the actual completion of the international search

21 July 2005

Date of mailing of the international search report

04/08/2005

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INTERNATIONAL SEARCH REPORT

PCT/IB2005/001066

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CASCINU STEFANO ET AL: "Octreotide versus loperamide in the treatment of fluorouracil-induced diarrhea: A randomized trial" JOURNAL OF CLINICAL ONCOLOGY, vol. 11, no. 1, 1993, pages 148-151, XP002337221 ISSN: 0732-183X cited in the application abstract -----	1-11
Y	US 6 087 377 A (ULRICH ET AL) 11 July 2000 (2000-07-11) cited in the application claim 3 -----	1-11
P,X	TOLCHER, A.: "A phase I study of an oral vascular endothelial growth factor receptor-2 (VEGFR-2) tyrosine kinase inhibitor, CP-547,632, in patients with advanced solid tumors" EJC SUPPLEMENTS, vol. 2, no. 137, 29 September 2004 (2004-09-29), pages 44-44, XP009051052 abstract -----	1-11

INTERNATIONAL SEARCH REPORT

PCT/IB2005/001066

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: —
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1-4 and 7-11 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

PCT/IB2005/001066

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 6087377	A	11-07-2000	US - 5955466 A	21-09-1999
			AU 746875 B2	02-05-2002
			AU 6435298 A	18-09-1998
			BR 9807271 A	23-05-2000
			CA 2280855 A1	03-09-1998
			EP 1011675 A1	28-06-2000
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			WO 9837892 A1	03-09-1998
