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(54) Title: METHODS AND COMPOSITIONS FOR THE TREATMENT OF GASTROINTESTINAL DISORDERS

(57) Abstract: The present invention features compositions and related methods for treating IBS and other gastrointestinal disorders and conditions (e.g., gastrointestinal motility disorders, functional gastrointestinal disorders, gastroesophageal reflux disease (GERD), duodenogastric reflux, Crohn's disease, ulcerative colitis, Inflammatory bowel disease, functional heartburn, dyspepsia (including functional dyspepsia or nonulcer dyspepsia), gastroparesis employing. The methods and compositions employ guanosine 3', 5'-cyclic monophosphate pharmaceutically acceptable salt thereof.

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Methods and Compositions for the Treatment of Gastrointestinal Disorders

TECHNICAL FIELD

This invention relates to methods and compositions for treating various disorders, including diarrhea, irritable bowl syndrome, particularly diarrhea-predominant irritable bowel syndrome, and gastrointestinal motility disorders.

BACKGROUND

Irritable bowel syndrome (IBS) is a common chronic disorder of the intestine that affects 20 to 60 million individuals in the US alone (Lehman Brothers, Global Healthcare-Irritable bowel syndrome industry update, September 1999). IBS is the most common disorder diagnosed by gastroenterologists (28% of patients examined) and accounts for 12% of visits to primary care physicians (Camilleri 2001, Gastroenterology 120:652-668). In the US, the economic impact of IBS is estimated at $25 billion annually, through direct costs of health care use and indirect costs of absenteeism from work (Talley 1995, Gastroenterology 109:1736-1741). Patients with IBS have three times more absenteeism from work and report a reduced quality of life. Sufferers may be unable or unwilling to attend social events, maintain employment, or travel even short distances (Drossman 1993, Dig Dis Sci 38:1569-1580). There is a tremendous unmet medical need in this population since few prescription options exist to treat IBS.

Patients with IBS suffer from abdominal pain and a disturbed bowel pattern. Three subgroups of IBS patients have been defined based on the predominant bowel habit: constipation-predominant (c-IBS), diarrhea-predominant (d-IBS) or alternating between the two (a-IBS). Estimates of individuals who suffer from c-IBS range from 20-50% of the IBS patients with 30% frequently cited. In contrast to the other

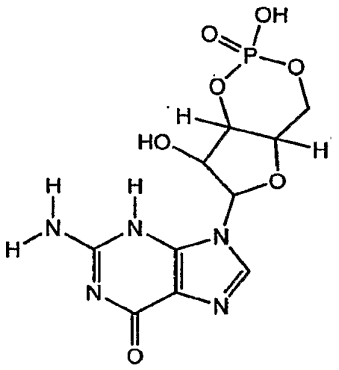
two subgroups that have a similar gender ratio, c-IBS is more common in women (ratio of 3:1) (Talley et al. 1995, Am J Epidemiol 142:76-83).

The definition and diagnostic criteria for IBS have been formalized in the "Rome Criteria" (Drossman et al. 1999, Gut 45:Suppl II: 1-81), which are well accepted in clinical practice. Briefly, the criteria specify that for at least 12 weeks (consecutive or non-consecutive) in the preceding 12 months, the subject experiences abdominal discomfort or pain in which least two of the following three features must occur: (1) relieved with defecation, (2) onset associated with a change in frequency of stool, and (3) onset associated with a change in form (appearance) of stool. The Rome II criteria also state that the symptoms that cumulatively support the diagnosis of irritable bowel syndrome include: abnormal stool frequency ("abnormal" may be defined as greater than 3 bowel movements per day or less than 3 bowel movements per week), abnormal stool form (lumpy/hard or loose/watery stool), abnormal stool passage (straining, urgency, or feeling of incomplete evacuation), passage of mucus in the stool, and bloating or feeling of abdominal distension. However, the complexity of symptoms has not been explained by anatomical abnormalities or metabolic changes. This has led to the classification of IBS as a functional GI disorder, which is diagnosed on the basis of the Rome criteria and limited evaluation to exclude organic disease (Ringel et al. 2001, Annu Rev Med 52: 319-338). IBS is considered to be a "biopsychosocial" disorder resulting from a combination of three interacting mechanisms: altered bowel motility, an increased sensitivity of the intestine or colon to pain stimuli (visceral sensitivity) and psychosocial factors (Camilleri 2001, Gastroenterology 120:652-668). Recently, there has been increasing evidence for a role of inflammation in etiology of IBS. Reports indicate that subsets of IBS patients have small but significant increases in colonic inflammatory and mast cells, increased inducible nitric oxide (NO) and synthase (iNOS) and altered expression of inflammatory cytokines (reviewed by Talley 2000, Medscape Coverage of DDW week).

SUMMARY

The present invention features compositions and related methods for treating IBS and other disorders and conditions (e.g., certain gastrointestinal motility disorders, inflammatory bowel disorder (IBD), Crohn's disease, duodenogastric reflux, dyspepsia, functional dyspepsia, nonulcer dyspepsia, a functional gastrointestinal disorder, functional heartburn, gastroesophageal reflux disease (GERD), gastroparesis, ulcerative colitis, chronic diarrhea, and disorders and conditions associated with diarrhea (e.g. scours, diarrhea associated with a functional digestive disorder, exudative diarrhea, non-exudative diarrhea, decreased absorption diarrhea, non-decreased absorption diarrhea, inflammatory diarrhea, non-inflammatory diarrhea, secretory diarrhea, non-secretory diarrhea, early chemotherapy related diarrhea, late chemotherapy related diarrhea, drug-induced diarrhea, bacteria-induced diarrhea, viral-induced diarrhea, protozoa-induced diarrhea, HIV associated diarrhea, Highly Active Anti-Retroviral Therapy-associated diarrhea, antibiotic-associated diarrhea, nasogastric tube feeding associated diarrhea, diarrhea associated with rapid narcotic detoxification, and diarrhea associated with a neuroendocrine tumor) as well as other conditions and disorders are described herein.

The methods described herein entail administration of guanosine 3', 5'-cyclic monophosphate (cGMP; CAS Registry No. 7665-99-8), which is known by a variety of other names, including, for example : 3', 5'-GMP; 3', 5'-cyclic GMP; cyclic GMP; cyclic guanosine 3', 5'-cyclic monophosphate; guanosine 3', 5'-(hydrogen phosphate); guanosine 3', 5'-cyclic phosphate; guanosine 3', 5'-monophosphate; and guanosine cyclic-monophosphate. The structure of cGMP is shown below in Formula I.



Formula I

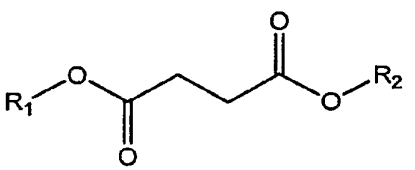
cGMP as discussed herein also includes, for example, a product created by exposure of cGMP to one or more enzymes present in the digestive tract, e.g., the dephosphorylated cGMP (e.g., riboguanosine or guanosine or deoxyriboguanosine or deoxyguanosine), phosphorylated forms of GMP and GMP derivatives (e.g., guanylate monophosphate or riboguanylate monophosphate or ribodeoxyguanylate monophosphate or deoxyriboguanylate monophosphate whether as the 5'-monophosphate, the 2'-monophosphate, the 3'-monophosphate or the 2', 3'-monophosphate intermediate form); the hydroxylated or deoxy forms of the ribose sugar of the nucleotide (e.g., ribose, deoxyribose, ribose monophosphate, or deoxyribose monophosphate); guanine; and methylated guanine and cGMP such N2-methylguanine, N7-methylguanine, cGMP methylated at N2 or cGMP methylated at N7. Thus analogues of cGMP include, but are not limited to, those that have modifications to the purine ring system, to the ribose, or to the phosphate group. In some cases the metabolic end products of cGMP such as xanthine and uric acid might be useful in the methods and compositions described herein. The analogue of cGMP may be cell membrane permeable.

cGMP and analogs thereof useful in the methods and compositions described herein include, but are not limited to: 8-(4-chlorophenylthio)guanosine 3',5'-cyclic monophosphate (Menshikov et al. 1993 Eur J Pharmacol. 245:281-4), dibutyryl guanosine 3',5'-cyclic monophosphate (db cGMP), 8-bromo-guanosine 3',5'-cyclic

monophosphate (8-bromo cGMP), 8-(4-chlorophenylthio)-guanosine 3',5'-cyclic monophosphate (8-(4, chlorophenylthio) cGMP, Rp-guanosine 3',5'-cyclic monophosphate (Rp-cGMP) and Sp-guanosine 3',5'-cyclic monophosphate (Sp-cGMPS) (the S isomer of cGMP), cyclic guanosine-3',5'-triphosphate, cyclic guanosine-3',5'-diphosphate, cyclic guanosine-3',5'-triphosphate, cyclic deoxyguanosine-3',5'-monophosphate, cyclic deoxyguanosine-3',5'diphosphate, cyclic deoxyguanosine-3',5'-triphosphate, cyclic guanosine-2',3'-monophosphate, cyclic guanosine-2,3'-diphosphate, cyclic guanosine-2',3'-triphosphate, cyclic 2-(N-methyl)-guanosine-3',5'-monophosphate, cyclic 2-(N-methyl)-guanosine-3',5'-diphosphate, cyclic 2-(N-methyl)-guanosine-3',5'-triphosphate, cyclic 2-(N-methyl)-deoxyguanosine-3',5'-monophosphate, cyclic 2-(N-methyl)-doxyguanosine-3',5'-diphosphate, cyclic 2-(N-methyl)-deoxyguanosine-3',5'-triphosphate, cyclic 2-(N-methyl)-guanosine-2',3'-monophosphate, cyclic 2-(N-methyl)-guanosine-2',3'-diphosphate, cyclic 2-(N-methyl)-guanosine-2',3'-triphosphate, cyclic 7-(N-methyl)-guanosine-3',5'-monophosphate, cyclic 7-(N-methyl)-guanosine-3',5'-diphosphate, cyclic 7-(N-methyl)-guanosine-3',5'-triphosphate, cyclic 7-(N-methyl)-deoxyguanosine-3',5'-monophosphate, cyclic 7-(N-methyl)-deoxyguanosine-3',5'-diphosphate, cyclic 7-(N-methyl)-deoxyguanosine-3',5'-triphosphate, cyclic 7-(N-methyl)-guanosine-2',3'-monophosphate, cyclic 7-(N-methyl)-guanosine-2',3'-diphosphate, cyclic 7-(N-methyl)-guanosine-2',3'-triphosphate, cyclic 2,7-(N,N'-dimethyl)-guanosine-3',5'-monophosphate, cyclic 2,7-(N,N'-dimethyl)-guanosine-3',5'-diphosphate, cyclic 2,7-(N,N'-dimethyl)-guanosine-3',5'-triphosphate, cyclic 2,7-(N,N'-dimethyl)-deoxyguanosine-3',5'-monophosphate, cyclic 2,7-(N,N'-dimethyl)-deoxyguanosine-3',5'-diphosphate, cyclic 2,7-(N,N'-dimethyl)-deoxyguanosine-3',5'-triphosphate, cyclic 2,7-(N,N'-dimethyl)-guanosine-2',3'-monophosphate, cyclic 2,7-(N,N'-dimethyl)-guanosine-2',3'-diphosphate, and cyclic 2,7-(N,N'-dimethyl)-guanosine-2',3'-triphosphate; cGMP analogs available from TWC Biosearch International (Hong Kong, China) including but not limited to: Rp-8-pCPT-cGMPS (CN-206), Sp-8-pCPT-cGMPS (CN-207), 8-Bromoguanosine-3',5'-cyclic monophosphate, sodium salt (CN-205), Rp-8-Bromoguanosine-3',5'-cyclic monophosphorothioate, sodium salt (CN-216), Sp-8-Bromoguanosine-3',5'-cyclic

monophosphorothioate, sodium salt (CN-217), and N2,2'-O-Dibutyrylguanosine-3',5'-cyclic monophosphate, sodium salt (CN-215); cGMP analogs disclosed in Corbin et al. 1986 Journ. Biol. Chem. 261:1208 including but not limited to: 5'-NH-cGMP, 3'-NH-cGMP, cGMPS(R_p), cGMPS(S_p), cGMP-$N(CH_3)_2(S_p)$, cGMP-$N(CH_3)_2(R_p)$, 8-BR-cGMP, β-H_5C_6-1-N^2-etheno-cGMP, 8-S(4-Cl)-C_6H_4-cGMP, 7-Deaza-cGMP, 8-$H_5C_6H_2CS$-cGMP, 6-HS-cGMP, 1-H_3C-cGMP, 8-HS-cGMP, N^2-$nH_{13}C_6$-cGMP, 8-$H_5C_6(O)C$-$_c$GMP, 8-HO-$_c$GMP, N^2-$_nH_7C_3(O)C$-$_c$GMP, 8-H(2-HO-$iH_7C_3)_c$GMP, 8-$H_3C(O)C$-$_c$GMP, 8-$(H_5C_2)_2N$-$_c$GMP, N^2-[2,4-$(O_2N)_2$-H_3C_6]$_C$GMP, 8-H_2N-$_c$IMP, and 2`-Deoxy-$_c$GMP; cGMP analogs available from Biolog Life Science Institute (Hayward, CA) including but not limited to : N^2-MB-cGMP (cIMP), 3-deaza cGMP, 2- Aminopurine riboside- 3', 5'- cyclic monophosphate (2-NH2-cPuMP), 2'- Deoxyguanosine- 3', 5'- cyclic monophosphate (2'-cdGMP), 2'- O-(N- Methylanthraniloyl)guanosine- 3', 5'- cyclic monophosphate (MANT-cGMP), 2'-O-Me-cGMP, and cGMP-AM; 8-bromoadenosine-cGMP, N2,2'-O-Dibutyrylguanosine-3',5'-cyclic monophosphate, sodium salt (available from Biomol; Plymouth, PA), and cGMP analogs available from other commercial supplier including Sigma Aldrich and Boehringer Mannheim).

In certain cases the composition administered to a patient includes succinic acid (also referred to as succinate or butaneoic acid) or a succinic acid derivative, e.g., pharmaceutically acceptable salts and esters of succinic acid such as monosodium succinate, disodium succinate, monopotassium succinate, dipotassium succinate, and mono- and di- mono- C_{1-6} alkyl succinates. Thus, the composition can include a compound having Formula II, below, wherein R_1 and R_2 are independently selected from H and a $C_1 - C_6$ alkyl. In various embodiments R_1 ans R_2 are both H, both methyl and both ethyl.



Formula II

The present invention also features compositions and related methods for treating cachexia, e.g., cachexia associated with AIDS or cancer.

The present invention also features compositions and related methods for treating obesity.

Without being bound by any particular theory, in the case of IBS (e.g. d-IBS), IBD, gastrointestinal-associated ulcers and other gastrointestinal disorders the compositions are useful because they may alter gastrointestinal motility, eg., by reducing gastrointestinal motility.

Without being bound by any particular theory, in the case of IBS and certain other gastrointestinal disorders the compositions are also useful because they may decrease gastrointestinal pain, visceral pain, chronic visceral hypersensitivity, dyspepsia or hypersensitivity to colorectal distension.

Methods for treating various disorders by administering (e.g., orally administering) pharmaceutical compositions comprising cGMP and analogs thereof are described herein with or without succinic acid or a derivative thereof. Also described are pharmaceutical compositions comprising cGMP or an analog thereof and one or more additional therapeutic agents including, without limitation, the agents described herein. Also described are methods comprising administering cGMP and one or more additional therapeutic agents including, without limitation, the agents described herein. The other agents can be administered with the cGMP or cGMP analog (simultaneously or sequentially).

Also described are methods and compositions for altering intestinal motility in all or a portion of the digestive tract. Intestinal motility involves spontaneous coordinated

dissentions and contractions of the stomach, intestines, colon and rectum to move food through the gastrointestinal tract during the digestive process.

In certain embodiments the patient has been diagnosed as suffering from IBS according to the Rome criteria. In certain embodiments, the IBS is d-IBS. In certain embodiments the IBS is alternating IBS. In certain embodiments the patient is female.

Also described is a method for treating a patient suffering from diarrhea. In general, diarrhea is a disorder resulting in a secretory imbalance. Diarrhea is characterized by the frequent defecation of liquid or liquid-like stools. Diarrhea may be accompanied by cramps, flatulence, stomach pain, and weakness. The major medical consequences of diarrhea include dehydration, renal insufficiency, electrolyte imbalance, acidosis, impaired growth, malnutrition, and death. 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, interfere with roles and responsibilities, affect interpersonal relationships and promote feelings of social isolation. In certain embodiments the patient is a human, the patient is an adolescent, the patient is under the age of eighteen years of age, the patient is an infant, the patient is female, the patient is male. In one embodiment, the diarrhea is caused by increased chloride ion and water secretion.

Besides being useful for human treatment, the present invention is also useful for veterinary treatment of companion mammals, exotic animals and domesticated animals, including mammals, rodents, and the like. In one embodiment, the mammals include cows, pigs and horses, sheep, goats, cats and dogs. Diarrhea in animals and pets such as cows, pigs and horses, sheep, goats, cats and dogs, also known as scours, is a major cause of death in these animals. Diarrhea can result from any major transition, such as weaning or physical movement. One form of diarrhea is characterized by diarrhea in response to a bacterial or viral infection and generally

occurs within the first few hours of the animal's life. Infections with rotavirus and coronavirus are common in newborn calves and pigs. Rotavirus infection often occurs within 12 hours of birth. Symptoms of rotaviral infection include excretion of watery feces, dehydration and weakness. Coronavirus which causes a more severe illness in the newborn animals, has a higher mortality rate than rotaviral infection. Often, however, a young animal may be infected with more than one virus or with a combination of viral and bacterial microorganisms at one time. This dramatically increases the severity of the disease.

Diarrhea can be classified as exudative diarrhea, non-exudative diarrhea, decreased absorption diarrhea, non-decreased absorption diarrhea, inflammatory diarrhea, non-inflammatory diarrhea, secretory diarrhea, and non-secretory diarrhea.

Exudative diarrheas result from loss of functional intestinal mucosa due to damage by disease. Inflammatory processes leading to impaired colonic absorption, and outpouring of cells and colloid caused by disorders including but not limited to ulcerative colitis, shigellosis, and amebiasis can result in exudative diarrhea.

Disorders related to decreased absorption diarrhea include osmotic, anatomic derangement, and motility disorders. Osmotic diarrhea results from the ingestion of poorly absorbed substances that retard fluid absorption. Thus, osmotic diarrhea can occur as a result of digestive abnormalities such as lactose intolerance. Anatomic derangement (also called postresection) associated diarrhea results from a decreased absorption surface related to surgical removal of some amount of functional mucosa associated with procedures such as subtotal colectomy and gastrocolic fistula. Motility/motor diarrhea can result from abnormally rapid transit time (causing reduced exposure of luminal contents to the intestinal wall). Thus, diseases such as hyperthyroidism and irritable bowel syndrome which result in decreased contact time can lead to motility diarrhea.

Secretory diarrhea can result from either inhibition of mucosal absorption or hypersecretion of fluid and electrolytes from the cells of the intestinal wall. Within the intestine, immature crypt cells secrete fluid into the lumen, and villi cells absorb fluid from the lumen. Secretory diarrhea can occur when either of these processes is disrupted and there is a net flow of fluid into the lumen. Movement of fluid across the crypt and villi cells is controlled chiefly by membrane-associated proteins involved in epithelial ion transport and smooth muscle contraction. These proteins, in turn, are regulated by secondary messengers, including cyclic nucleotides, elements of the phosphoinositide-diacylglycerol pathway, and free intracellular calcium. In classical form, hypersecretion related secretory diarrhea is due to changes which are independent of the permeability, absorptive capacity and exogenously generated osmotic gradients within the intestine. However, all forms of diarrhea can manifest a secretory component.

Secretory diarrhea can accompany gastrointestinal disorders such as inflammatory bowel disease. Secretory diarrheas are a dangerous condition in unhealthy subjects especially in patients with acquired immunodeficiency syndrome (AIDS) and chronic inflammatory bowel disease. Diarrhea in AIDS patients can cause wasting and can be an important factor in the decline of these patients. AIDS patients often develop diarrhea due to enteric infections which their immune system is not capable of fighting off, but AIDS patients may also develop diarrhea by AIDS enteropathy. AIDS enteropathy is a disorder characterized by diarrhea without the involvement of secondary infections. It is caused by the human immunodeficiency virus (HIV) infection of the small bowel mucosal cells and colonic mucosal cells.

Diarrhea can result from a variety of pathophysiological disorders including gastroenteritis, bacterial, viral and parasitic infections, damage to the intestinal mucosa (including damage due to severe chronic ulcers, colitis, or radiation), and disease or debilitation of organs such as liver, adrenal and others. It can also occur as a result of other therapy or diet. In all cases, diarrhea is generally a symptom of organic gastrointestinal disorders and not itself a disorder. Chronic diarrhea is

generally due to: (1) hypersecretion of fluid and electrolytes of the stomach, small intestine and colon; (2) inability to absorb certain nutrients (malabsorption); and (3) intestinal hypermotility and rapid transport. These may occur separately or in combination. Certain disorders may have diarrhea as a prominent feature of the disease/syndrome, but the specific etiology is unclear. In this latter group, emotional tension and psychological factors may adversely influence the frequency of the symptoms

Diarrhea may be drug-induced, for example, diarrhea may be a side effect of cancer (e.g. brain, squamous cell, bladder, gastric, pancreatic, breast, head, neck, esophageal, prostate, colorectal, lung, renal, kidney, ovarian, gynecological or thyroid cancer) therapy, which often develops during clinical treatment with chemotherapeutic agent. Chemotherapy can be associated with early and/or late diarrhea. Early diarrhea is often mild and may occur at the time of administration with a chemotherapeutic agent or up to 24 hours later. Late diarrhea occurs more than 24 hours after chemotherapy and is often more severe and can be life threatening. Chemotherapeutic agents associated with diarrhea include but are not limited to methroxate, methotrexate, fluoropyrimidines (e.g. 5-fluorouracil), platinum derivatives (e.g. cisplatin, oxaliplatin), thymidylate synthase inhibitors (e.g. raltitrexed), and camptothecin derivatives (e.g. irinotecan (e.g. Camptostar™, Campto™), irinotecan hydrochloride, SN-38 (10-ethyl 7-hydroxy camptothecin), rubitecan and topotecan).

Drug-induced diarrhea also includes diarrhea observed in individuals infected with human immunodeficiency virus (HIV) who are receiving carefully-planned combinations of anti-retroviral agents known as HAART, or Highly Active Anti-Retroviral Therapy. HAART therapy may include protease inhibitors, nucleoside reverse transcriptase inhibitors, and non-nucleoside reverse transcriptase inhibitors such as Indinavir sulfate, Amprenavir, Ritonavir, Saquinavir, Nelfinavir mesylate, Saquinavir mesylate, Elfavirenz, Nevirapine, Abacavir sulfate, Delavirdine

mesylate, Zalcitabine, Stavudine, Zidovudine, Lamivudine, Lamivudine/Zidovudine combo and Didanosine.

Diarrhea in AIDS patients is a very serious condition which causes wasting and may be an important factor in the decline of these patients. Although AIDS patients often develop diarrhea due to enteric infections which their immune system is not capable of fighting off, AIDS patients may also develop diarrhea by AIDS enteropathy. AIDS enteropathy is a disorder characterized by diarrhea without the involvement of secondary infections. It is caused by the human immunodeficiency virus (HIV) infection of the small bowel mucosal cells and colonic mucosal cells. The most common infective agent causing diarrhea due to enteric infection in AIDS patients in cryptosporidium. The methods for treating diarrhea in AIDS patients include administration of antibiotics and administration of immunoglobulins or an immunoglobulin enriched fraction of bovine colostrum.

Drug-induced diarrhea has also been associated with administration of adrenergic neuron blocking agents, such as reserpine and guanethidine; antimicrobials, such as sulfonamides, tetracyclines and most broad-spectrum agents; bile acids; carcinoid tumor secretions (e.g., 5-hydroxytryptamine and vasoactive intestinal peptide); cholinergic agonists and cholinesterase inhibitors; fatty acids; osmotic laxatives, such as sorbitol and saline cathartics; prokinetic agents, such as metoclopramide and domperidone; prostaglandins; quinidine; and stimulant laxatives.

Diarrhea can be induced by various microorganisms including viruses (e.g. rotavirus, cytomegalovirus, enteric adenovirus, Norwalk virus, picornavirus, adenovirucoronavirus, Calicivirus (family Caliciviridae), and bovine viral diarrhea virus); bacteria (e.g. enterotoxigenic and invasive Escherichia coli (e.g. enterotoxogenic E-coli having the K99 pilus antigen), shigella, salmonella, Vibrio bacteria (e.g. Vibrio cholerae), Clostridium difficile, and Campylobacter jejuni; protozoa (e.g. Microsporridia spp., Cryptospordia spp. (e.g. Cryptosporidium parvum), Isospora belli, Blastocystis hominis, Dientamoeba fragilis, Balantinium

coli, Isopora belli, Cylclospora cayetanensis, Enterocytozoon bieneusi, *E*ntamoeba histolytica, Giardia lamblia (also called Lamblia intestinalis) and Encephalitozoon intestitnalis); and helminthes (e.g. Strongyloides stercoralis). In addition, other microorganisms responsible for diarrhea include those that cause infectious colitis and bacteremia.

Diarrhea can also be classified as Antibiotic-associated diarrhea (AAD). AAD is the most common cause of diarrhea in hospitalized patients, representing an important source of morbidity, mortality, and cost. Although no infectious agent is found in most cases of AAD, *Clostridium difficile* is frequently identified in patients with signs and symptoms of colitis. All types of antimicrobial agents have been implicated, leading to a wide range of clinical manifestations, from asymptomatic carrier state to severe pseudomembranous colitis. Most cases of AAD respond to supportive measures and withdrawal of antibiotics. In patients with severe and persistent symptoms effective antibiotic therapy is available, but relapses are common.

Diarrhea is experienced by approximately 10 to 40% of patients who receive nasogastric tube fed enteral nutritional products. Diarrhea is cited as the most common cause of interrupted tube feeding and the most frequent complaint of tube-fed patients. It is also known, to a lesser extent, that tube-fed patients experience nausea and abdominal distension.

Acute and/or severe diarrhea may also accompany rapid narcotic detoxification.

Diarrhea is also associated with certain neuroendocrine tumors. For example, pancreatic endocrine tumors including VIPomas, Gastrinomas, Somatostatinomas may result in diarrhea. VIPomas are associated with secretory diarrhea.

The details of one or more embodiments of the invention are set forth in the accompanying description. All of the publications, patents and patent applications are hereby incorporated by reference.

DETAILED DESCRIPTION

Intestinal transit assays

In order to determine whether a composition decreases or increases the rate of gastrointestinal transit, the composition can be test using a murine gastrointestinal transit (GIT) assay (Moon et al. *Infection and Immunity* 25:127, 1979). In this assay, charcoal, which can be readily visualized in the gastrointestinal tract is administered to mice after the administration of a test compound. The distance traveled by the charcoal is measured and expressed as a percentage of the total length of the colon.

Mice are fasted with free access to water for 12 to 16 hours before the treatment with a test composition or control buffer. The composition is orally administered at 1μg/kg – 1mg/kg in buffer (20mM Tris pH 7.5) 7 minutes before being given an oral dose of 5% Activated Carbon (Aldrich 242276-250G). Control mice are administered buffer only before being given a dose of Activated Carbon. After 15 minutes, the mice are sacrificed and their intestines from the stomach to the cecum are dissected. The total length of the intestine as well as the distance traveled from the stomach to the charcoal front is measured for each animal and the results are expressed as the percent of the total length of the intestine traveled by the charcoal front.

Similar testing can be carried out to determine if a composition is effective in a chronic dosing treatment regimen. Briefly, 8 week old CD1 female mice are dosed orally once a day for 5 days with the test compound and vehicle alone (20mM Tris pH 7.5). On the 5th day, a GIT assay is performed identical to that above except 200μl of a 10% charcoal solution is administered.

Suckling mouse model of intestinal secretion (SuMi assay)

The agents of the invention can be tested for their ability to increase intestinal secretion using a suckling mouse model of intestinal secretion. In this model a test compound is administered to suckling mice that are between seven and nine days old. After the mice are sacrificed, the gastrointestinal tract from the stomach to the cecum is dissected ("guts"). The remains ("carcass") as well as the guts are weighed and the ratio of guts to carcass weight is calculated. If the ratio is above 0.09, one can conclude that the test compound increases intestinal secretion. Controls for this assay may include bacterial ST peptide and Zelnorm®.

Stool formation and consistency assays

The agents of the invention can be tested for their ability to alter stool consistency and/or volume. Stool consistency and/or volume are measured in the presence and absence of test compound administration to mice or rats. In certain cases, diarrhea is induced by administration of bacterial ST peptide prior to test compound dosing. Water content in the stool can be measured as well as stool weight/volume/number of pellets.

Colonic hyperalgesia animal models

Hypersensitivity to colorectal distension is common in patients with IBS and may be responsible for the major symptom of pain. Both inflammatory and non-inflammatory animal models of visceral hyperalgesia to distension have been developed to investigate the effect of compounds on visceral pain in IBS.

I. Trinitrobenzenesulphonic acid (TNBS)-induced rectal allodynia model

Male Wistar rats (220-250 g) are premedicated with 0.5 mg/kg of acepromazine injected intraperitoneally (IP) and anesthetized by intramuscular administration of 100 mg/kg of ketamine. Pairs of nichrome wire electrodes (60 cm in length and 80 μm in diameter) are implanted in the striated muscle of the abdomen, 2 cm laterally

from the white line. The free ends of electrodes are exteriorized on the back of the neck and protected by a plastic tube attached to the skin. Electromyographic (EMG) recordings are started 5 days after surgery. Electrical activity of abdominal striated muscle is recorded with an electroencephalograph machine (Mini VIII, Alvar, Paris, France) using a short time constant (0.03 sec.) to remove low-frequency signals (<3 Hz).

Ten days post surgical implantation, trinitrobenzenesulphonic acid (TNBS) is administered to induce rectal inflammation. TNBS (80 mg kg^{-1} in 0.3 ml 50 % ethanol) is administered intrarectally through a silicone rubber catheter introduced at 3 cm from the anus under light diethyl-ether anesthesia, as described (Morteau et al. 1994 Dig Dis Sci 39:1239). Following TNBS administration, rats are placed in plastic tunnels where they are severely limited in mobility for several days before colorectal distension (CRD). Experimental compound is administered one hour before CRD which is performed by insertion into the rectum, at 1 cm of the anus, a 4 cm long balloon made from a latex condom (Gue et al, 1997 *Neurogastroenterol. Motil.* 9:271). The balloon is fixed on a rigid catheter taken from an embolectomy probe (Fogarty). The catheter attached balloon is fixed at the base of the tail. The balloon, connected to a barostat, is inflated progressively by step of 15 mmHg, from 0 to 60 mmHg, each step of inflation lasting 5 min. Evaluation of rectal sensitivity, as measured by EMG, is performed before (1-2 days) and 3 days following rectal instillation of TNBS.

The number of spike bursts that corresponds to abdominal contractions is determined per 5 min periods. Statistical analysis of the number of abdominal contractions and evaluation of the dose-effects relationships can be performed by a one way analysis of variance (ANOVA) followed by a post-hoc (Student or Dunnett tests) and regression analysis for ED_{50} if appropriate.

II. Stress-induced hyperalgesia model

The effect of a composition containg cGMP or an analog thereof on colorectal sensitivity can be tested in a stress induced hyperglasia model (Morteau et al. 1994 Dig Dis Sci 39:1239-48). Partial restraint stress (PRS), a relatively mild stress, is induced as previously described (Morteau et al. 1994 Dig Dis Sci 39:1239-48). Female rats are lightly anesthetized with diethyl ether and their shoulders, upper forelimbs and thoracic trunk are wrapped in a confining harness of paper tape to restrict, but not prevent body movements. Control sham-stress animals are anesthitized but not wrapped. Animals receive isobaric colorectal distensions (CRD) directly prior to (control CRD) and 15 minutes after two hours of partial restraint induced stress. Rats are treated orally with a test composition or vehicle only (distilled water 1 mL) one hour before the CRD procedure. For the CRD procedure, rats are acclimatized to restraint in polypropylene tunnels (diameter: 7 cm; length: 20 cm) periodically for several days before CRD in order to minimize recording artifacts. The balloon used for distension is 4 cm long and made from a latex condom. It is fixed on a rigid catheter taken from an embolectomy probe (Fogarty). CRD is performed by insertion of the balloon in the rectum at 1 cm from the anus. The tube is fixed at the base of the tail. Isobaric distensions are performed from 0 to 60 mmHg, with each distension step lasting 5 minutes. The first distension is performed at a pressure of 15 mmHg and an increment of 15 mmHg is added at each following step, until a maximal pressure of 60 mmHg is attained. Electromyographic recordings are begun 5 days after surgery. Electrical activity is recorded with an electroencephalograph (e.g., Mini VIII, Alvar, Paris, France) using a short time constant (0.03 sec.) to remove low-frequency signals (<3 Hz). Isobaric distensions of the colon re performed by connecting the balloon to a computerized barostat. Colonic pressure and balloon volume are continuously monitored on a potentiometric recorder (e.g., L6514, Linseis, Selb, Germany). The number of spike bursts, corresponding to abdominal contractions, are evaluated per 5-minute period. Colorectal volumes are determined as the maximal volume obtained for each stage

of distension using the potentiometric recorder. Statistical analysis of these two parameters can be performed using a one way analysis of variance (ANOVA) followed by an unpaired two-tailed Student's *t* test using GraphPad Prism 4.0.

Phenylbenzoquinone-induced writhing model

The PBQ-induced writhing model can be used to assess pain control activity of compositions containing cGMP or an analog thereof. This model is described by Siegmund et al. (1957 Proc. Soc. Exp. Bio. Med. 95:729-731). Briefly, one hour after oral dosing with a test compound, e.g., cGMP, morphine or vehicle, 0.02% phenylbenzoquinone (PBQ) solution (12.5 mL/kg) is injected by intraperitoneal route into the mouse. The number of stretches and writhings are recorded from the 5^{th} to the 10^{th} minute after PBQ injection, and can also be counted between the 35^{th} and 40^{th} minute and between the 60^{th} and 65^{th} minute to provide a kinetic assessment. The results are expressed as the number of stretches and writhings (mean ± SEM) and the percentage of variation of the nociceptive threshold calculated from the mean value of the vehicle-treated group. The statistical significance of any differences between the treated groups and the control group is determined by a Dunnett's test using the residual variance after a one-way analysis of variance ($P < 0.05$) using SigmaStat Software.

The effects of cGMP and analogs thereof can be assessed in standard animal models of diarrhea. For example, the rodent prostaglandin E2 induced diarrhea model (for example, see Riviere et al. J Pharmacol. 1991 256:547-52) and the castor oil induced diarrhea model.

Bowel movement related assays

The effect of a test compound on bowel movements can be assessed by administering the test compound to patients (e.g. human or non-human) after at least a 10-hour fast. Bowel habits (including Bristol Stool Form Scale score, stool frequency, and stool weight) are evaluated for each collected bowel movement 48 hours prior to dose and up to approximately 48 hours postdose.

Seven daily doses of a test compound can be administered to patients in order to assess the effect of a test compound on frequency of bowel movements. Briefly, daily doses are initiated after at least a 10-hour fast. Mean stool frequency and mean ease of passage are calculated.

Urgency of bowel movement can also be determined as decribed in US20040197321. For example, urgency of bowel movement can be quantified as a percentage in the improvement (reduction) that the patient experiences and as a "reduction in the "Severity" of the "Rate of Urgency". Data is collected both in the absence and presence of cGMP therapy. Bowel movement urgency can be rated as, for example, no urgency, mild urgency, severe urgency, maximum severity. To determine the reduction in "Severity" of the "Rate of Urgency" of bowel movements before and after a given time period of cGMP therapy a weighted average of the difference between patients before and after is conducted.

Duration of diarrhea episodes can also be quantified in the absence and presence of cGMP administration. The duration of diarrhea is determined by the number of days between first and last reported watery or loose stool.

Administration of cGMP and analogs thereof

For treatment of gastrointestinal disorders, cGMP or an analog thereof is preferably administered orally. Orally administered compositions can include binders, lubricants, inert diluents, lubricating, surface active or dispersing agents, flavoring agents, humectants or other excipients, for example, as described herein. Orally administered formulations such as tablets may optionally be coated or scored and may be formulated so as to provide sustained, delayed or controlled release of the active ingredient therein. The cGMP or analog thereof can be co-administered with other agents used to treat gastrointestinal disorders including but not limited to the agents described herein. The cGMP or analog thereof can also be administered by rectal suppository.

cGMP or an analog thereof can be administered alone or in combination with other agents. For example, they can be administered together with an analgesic peptide or compound.

Combination therapy can be achieved by administering two or more agents, e.g., cGMP and an analgesic peptide or compound, each of which is formulated and administered separately, or by administering two or more agents in a single formulation. Other combinations are also encompassed by combination therapy. For example, two agents can be formulated together and administered in conjunction with a separate formulation containing a third agent. While the two or more agents in the combination therapy can be administered simultaneously, they need not be. For example, administration of a first agent (or combination of agents) can precede administration of a second agent (or combination of agents) by minutes, hours, days, or weeks. Thus, the two or more agents can be administered within minutes of each other or within 1, 2, 3, 6, 9, 12, 15, 18, or 24 hours of each other or within 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14 days of each other or within 2, 3, 4, 5, 6, 7, 8, 9, or 10 weeks of each other. In some cases even longer intervals are possible. While in many cases it is desirable that the two or more agents used in a combination therapy be present in within the patient's body at the same time, this need not be so.

Combination therapy can also include two or more administrations of one or more of the agents used in the combination. For example, if agent X and agent Y are used in a combination, one could administer them sequentially in any combination one or more times, e.g., in the order X-Y-X, X-X-Y, Y-X-Y, Y-Y-X, X-X-Y-Y, etc.

Combination therapy can also include the administration of two or more agents via different routes or locations. For example, (a) one agent is administered orally and another agents is administered intravenously or (b) one agent is administered orally and another is administered locally. In each case, the agents can either simultaneously or sequentially. Approximated dosages for some of the combination therapy agents described herein are found in the "BNF Recommended Dose" column of tables on pages 11-17 of WO01/76632 (the data in the tables being attributed to the March 2000 British National Formulary) and can also be found in other standard formularies and other drug prescribing directories. For some drugs, the customary presecribed dose for an indication will vary somewhat from country to country.

The agents, alone or in combination, can be combined with any pharmaceutically acceptable carrier or medium. Thus, they can be combined with materials that do not produce an adverse, allergic or otherwise unwanted reaction when administered to a patient. The carriers or mediums used can include solvents, dispersants, coatings, absorption promoting agents, controlled release agents, and one or more inert excipients (which include starches, polyols, granulating agents, microcrystalline cellulose (e.g. Celphere beads®), diluents, lubricants, binders, disintegrating agents, and the like), etc. If desired, tablet dosages of the disclosed compositions may be coated by standard aqueous or nonaqueous techniques.

Pharmaceutical compositions may also optionally include other therapeutic ingredients, anti-caking agents, preservatives, sweetening agents, colorants, flavors, desiccants, plasticizers, dyes, glidants, anti-adherents, anti-static agents, surfactants (wetting agents), anti-oxidants, film-coating agents, and the like. Any such optional

ingredient must be compatible with the other componments to insure the stability of the formulation.

The composition may contain other additives as needed, including for example lactose, glucose, fructose, galactose, trehalose, sucrose, maltose, raffinose, maltitol, melezitose, stachyose, lactitol, palatinite, starch, xylitol, mannitol, myoinositol, and the like, and hydrates thereof, and amino acids, for example alanine, glycine and betaine, and peptides and proteins, for example albumen.

Examples of excipients for use as the pharmaceutically acceptable carriers and the pharmaceutically acceptable inert carriers and the aforementioned additional ingredients include, but are not limited to binders, fillers, disintegrants, lubricants, anti-microbial agents, and coating agents such as:

BINDERS: corn starch, potato starch, other starches, gelatin, natural and synthetic gums such as acacia, xanthan, sodium alginate, alginic acid, other alginates, powdered tragacanth, guar gum, cellulose and its derivatives (*e.g.*, ethyl cellulose, cellulose acetate, carboxymethyl cellulose calcium, sodium carboxymethyl cellulose), polyvinyl pyrrolidone (*e.g.*, povidone, crospovidone, copovidone, etc), methyl cellulose, pre-gelatinized starch (*e.g.*, STARCH 1500® and STARCH 1500 LM®, sold by Colorcon, Ltd.), hydroxypropyl methyl cellulose, microcrystalline cellulose (*e.g.* AVICEL™, such as, AVICEL-PH-101™, -103™ and -105™, sold by FMC Corporation, Marcus Hook, PA, USA), or mixtures thereof,

FILLERS: talc, calcium carbonate (*e.g.*, granules or powder), dibasic calcium phosphate, tribasic calcium phosphate, calcium sulfate (*e.g.*, granules or powder), microcrystalline cellulose, powdered cellulose, dextrates, kaolin, mannitol, silicic acid, sorbitol, starch, pre-gelatinized starch, dextrose, fructose, honey, lactose anhydrate, lactose monohydrate, lactose and aspartame, lactose and cellulose, lactose and microcrystalline cellulose, maltodextrin, maltose, mannitol, microcrystalline cellulose & guar gum, molasses, sucrose, or mixtures thereof,

DISINTEGRANTS: agar-agar, alginic acid, calcium carbonate, microcrystalline cellulose, croscarmellose sodium, crospovidone, polacrilin potassium, sodium starch glycolate, potato or tapioca starch, other starches, pre-gelatinized starch, clays, other algins, other celluloses, gums (like gellan), low-substituted hydroxypropyl cellulose, or mixtures thereof,

LUBRICANTS: calcium stearate, magnesium stearate, mineral oil, light mineral oil, glycerin, sorbitol, mannitol, polyethylene glycol, other glycols, stearic acid, sodium lauryl sulfate, sodium stearyl fumarate, vegetable based fatty acids lubricant, talc, hydrogenated vegetable oil (*e.g.*, peanut oil, cottonseed oil, sunflower oil, sesame oil, olive oil, corn oil and soybean oil), zinc stearate, ethyl oleate, ethyl laurate, agar, syloid silica gel (AEROSIL 200, W.R. Grace Co., Baltimore, MD USA), a coagulated aerosol of synthetic silica (Deaussa Co., Plano, TX USA), a pyrogenic silicon dioxide (CAB-O-SIL, Cabot Co., Boston, MA USA), or mixtures thereof,

ANTI-CAKING AGENTS: calcium silicate, magnesium silicate, silicon dioxide, colloidal silicon dioxide, talc, or mixtures thereof,

ANTIMICROBIAL AGENTS: benzalkonium chloride, benzethonium chloride, benzoic acid, benzyl alcohol, butyl paraben, cetylpyridinium chloride, cresol, chlorobutanol, dehydroacetic acid, ethylparaben, methylparaben, phenol, phenylethyl alcohol, phenoxyethanol, phenylmercuric acetate, phenylmercuric nitrate, potassium sorbate, propylparaben, sodium benzoate, sodium dehydroacetate, sodium propionate, sorbic acid, thimersol, thymo, or mixtures thereof, and

COATING AGENTS: sodium carboxymethyl cellulose, cellulose acetate phthalate, ethylcellulose, gelatin, pharmaceutical glaze, hydroxypropyl cellulose, hydroxypropyl methylcellulose (hypromellose), hydroxypropyl methyl cellulose phthalate, methylcellulose, polyethylene glycol, polyvinyl acetate phthalate, shellac, sucrose, titanium dioxide, carnauba wax, microcrystalline wax, gellan gum,

maltodextrin, methacrylates, microcrystalline cellulose and carrageenan or mixtures thereof.

The formulation can also include other excipients and categories thereof including but not limited to L-histidine, Pluronic®, Poloxamers (such as Lutrol® and Poloxamer 188), ascorbic acid, glutathione, permeability enhancers (e.g. lipids, sodium cholate, acylcarnitine, salicylates, mixed bile salts, fatty acid micelles, chelators, fatty acid, surfactants, medium chain glycerides), protease inhibitors (e.g. soybean trypsin inhibitor, organic acids), pH lowering agents and absorption enhancers effective to promote bioavailability (including but not limited to those described in US6086918 and US5912014), creams and lotions (like maltodextrin and carrageenans); materials for chewable tablets (like dextrose, fructose, lactose monohydrate, lactose and aspartame, lactose and cellulose, maltodextrin, maltose, mannitol, microcrystalline cellulose and guar gum, sorbitol crystalline); parenterals (like mannitol and povidone); plasticizers (like dibutyl sebacate, plasticizers for coatings, polyvinylacetate phthalate); powder lubricants (like glyceryl behenate); soft gelatin capsules (like sorbitol special solution); spheres for coating (like sugar spheres); spheronization agents (like glyceryl behenate and microcrystalline cellulose); suspending/gelling agents (like carrageenan, gellan gum, mannitol, microcrystalline cellulose, povidone, sodium starch glycolate, xanthan gum); sweeteners (like aspartame, aspartame and lactose, dextrose, fructose, honey, maltodextrin, maltose, mannitol, molasses, sorbitol crystalline, sorbitol special solution, sucrose); wet granulation agents (like calcium carbonate, lactose anhydrous, lactose monohydrate, maltodextrin, mannitol, microcrystalline cellulose, povidone, starch), caramel, carboxymethylcellulose sodium, cherry cream flavor and cherry flavor, citric acid anhydrous, citric acid, confectioner's sugar, D&C Red No. 33, D&C Yellow #10 Aluminum Lake, disodium edetate, ethyl alcohol 15%, FD& C Yellow No. 6 aluminum lake, FD&C Blue #1 Aluminum Lake, FD&C Blue No. 1, FD&C blue no. 2 aluminum lake, FD&C Green No.3, FD&C Red No. 40, FD&C Yellow No. 6 Aluminum Lake, FD&C Yellow No. 6, FD&C Yellow No.10, glycerol palmitostearate, glyceryl monostearate, indigo carmine, lecithin, manitol,

methyl and propyl parabens, mono ammonium glycyrrhizinate, natural and artificial orange flavor, pharmaceutical glaze, poloxamer 188, Polydextrose, polysorbate 20, polysorbate 80, polyvidone, pregelatinized corn starch, pregelatinized starch, red iron oxide, saccharin sodium, sodium carboxymethyl ether, sodium chloride, sodium citrate, sodium phosphate, strawberry flavor, synthetic black iron oxide, synthetic red iron oxide, titanium dioxide, and white wax.

Solid oral dosage forms may optionally be treated with coating systems (e.g. Opadry® fx film coating system, for example Opadry® blue (OY-LS-20921), Opadry® white (YS-2-7063), Opadry® white (YS-1-7040), and black ink (S-1-8106)).

The agents either in their free form or as a salt can be combined with a polymer such as polylactic-glycoloic acid (PLGA), poly-(I)-lactic-glycolic-tartaric acid (P(I)LGT) (WO 01/12233), polyglycolic acid (U.S. 3,773,919), polylactic acid (U.S. 4,767,628), poly(ε-caprolactone) and poly(alkylene oxide) (U.S. 20030068384) to create a sustained release formulation. Such formulations can be used in implants that release an agent over a period of a few days, a few weeks or several months depending on the polymer, the particle size of the polymer, and the size of the implant (see, e.g., U.S. 6,620,422). Other sustained release formulations and polymers for use in are described in EP 0 467 389 A2, WO 93/24150, U.S. 5,612,052, WO 97/40085, WO 03/075887, WO 01/01964A2, U.S. 5,922,356, WO 94/155587, WO 02/074247A2, WO 98/25642, U.S. 5,968,895, U.S. 6,180,608, U.S. 20030171296, U.S. 20020176841, U.S. 5,672,659, U.S. 5,893,985, U.S. 5,134,122, U.S. 5,192,741, U.S. 5,192,741, U.S. 4,668,506, U.S. 4,713,244, U.S. 5,445,832 U.S. 4,931,279, U.S. 5,980,945, WO 02/058672, WO 9726015, WO 97/04744, and US20020019446. In such sustained release formulations microparticles (Delie and Blanco-Prieto 2005 Molecule 10:65-80) of peptide are combined with microparticles of polymer. One or more sustained release implants can be placed in the large intestine, the small intestine or both. U.S. 6,011,011 and WO 94/06452 describe a sustained release formulation providing either polyethylene glycols (i.e. PEG 300

and PEG 400) or triacetin. WO 03/053401 describes a formulation which may both enhance bioavailability and provide controlled releaseof the agent within the GI tract. Additional controlled release formulations are described in WO 02/38129, EP 326 151, U.S. 5,236,704, WO 02/30398, WO 98/13029; U.S. 20030064105, U.S. 20030138488A1, U.S. 20030216307A1, U.S. 6,667,060, WO 01/49249, WO 01/49311, WO 01/49249, WO 01/49311, and U.S. 5,877,224.

The agents can be administered, e.g., by intravenous injection, intramuscular injection, subcutaneous injection, intraperitoneal injection, topical, sublingual, intraarticular (in the joints), intradermal, buccal, ophthalmic (including intraocular), intranasaly (including using a cannula), intraspinally, intrathecally, or by other routes. The agents can be administered orally, (e.g., as a tablet or cachet, gel, pellet, paste, syrup, bolus, electuary, slurry, capsule, powder, lyophilized powder, granules, sachet, as a solution or a suspension in an aqueous liquid or a non-aqueous liquid, as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion, via a micellar formulation (see, e.g. WO 97/11682) via a liposomal formulation (see, e.g., EP 736299,WO 99/59550 and WO 97/13500), via formulations described in WO 03/094886, via bilosome (bile-salt based vesicular system), via a dendrimer) or in some other form containing a predetermined amount of the active ingredient. The agents can also be administered transdermally (i.e. via reservoir-type or matrix-type patches, microneedles, thermal poration, hypodermic needles, iontophoresis, electroporation, ultrasound or other forms of sonophoresis, jet injection, or a combination of any of the preceding methods (Prausnitz et al. 2004, Nature Reviews Drug Discovery 3:115-124)). The agents can be administered using high-velocity transdermal particle injection techniques using the hydrogel particle formulation described in U.S. 20020061336. Additional particle formulations are described in WO 00/45792, WO 00/53160, and WO 02/19989. An example of a transdermal formulation containing plaster and the absorption promoter dimethylisosorbide can be found in WO 89/04179. WO 96/11705 provides formulations suitable for transdermal administration. The agents can be administered in the form a suppository or by other vaginal or rectal means. The agents can be administered in a

transmembrane formulation as described in WO 90/07923. The agents can be administed non-invasively via the dehydrated particicles described in U.S. 6,485,706. The agent can be administered in an enteric-coated drug formulation as described in WO 02/49621. The agents can be administered intranassaly using the formulation described in U.S. 5,179,079. Formulations suitable for parenteral injection are described in WO 00/62759. The agents can be administered using the casein formulation described in U. S. 20030206939 and WO 00/06108. The agents can be administered using the particulate formulations described in U.S. 20020034536.

The agents can be incorporated into microemulsions, which generally are thermodynamically stable, isotropically clear dispersions of two immiscible liquids, such as oil and water, stabilized by an interfacial film of surfactant molecules (Encyclopedia of Pharmaceutical Technology (New York: Marcel Dekker, 1992), volume 9). For the preparation of microemulsions, surfactant (emulsifier), co-surfactant (co-emulsifier), an oil phase and a water phase are necessary. Suitable surfactants include any surfactants that are useful in the preparation of emulsions, e.g., emulsifiers that are typically used in the preparation of creams. The co-surfactant (or "co-emulsifer") is generally selected from the group of polyglycerol derivatives, glycerol derivatives and fatty alcohols. Preferred emulsifier/co-emulsifier combinations are generally although not necessarily selected from the group consisting of: glyceryl monostearate and polyoxyethylene stearate; polyethylene glycol and ethylene glycol palmitostearate; and caprilic and capric triglycerides and oleoyl macrogolglycerides. The water phase includes not only water but also, typically, buffers, glucose, propylene glycol, polyethylene glycols, preferably lower molecular weight polyethylene glycols (e.g., PEG 300 and PEG 400), and/or glycerol, and the like, while the oil phase will generally comprise, for example, fatty acid esters, modified vegetable oils, silicone oils, mixtures of mono-di- and triglycerides, mono- and di-esters of PEG (e.g., oleoyl macrogol glycerides), etc.

The agents of the invention can be incorporated into pharmaceutically-acceptable nanoparticle, nanosphere, and nanocapsule formulations (Delie and Blanco-Prieto 2005 Molecule 10:65-80). Nanocapsules can generally entrap compounds in a stable and reproducible way (Henry-Michelland et al., 1987; Quintanar-Guerrero et al., 1998; Douglas et al., 1987). To avoid side effects due to intracellular polymeric overloading, ultrafine particles (sized around 0.1 μm) can be designed using polymers able to be degraded in vivo (e.g. biodegradable polyalkyl-cyanoacrylate nanoparticles). Such particles are described in the prior art (Couvreur et al, 1980; 1988; zur Muhlen et al., 1998; Zambaux et al. 1998; Pinto-Alphandry et al., 1995 and U.S. Pat. No. 5,145,684).

The agents of the invention can be formulated with pH sensitive materials which may include those described in WO04041195 (including the seal and enteric coating described therein) and pH-sensitive coatings that achieve delivery in the colon including those described in US4910021 and WO9001329. US4910021 describes using a pH-sensitive material to coat a capsule. WO9001329 describes using pH-sensitive coatings on beads containing acid, where the acid in the bead core prolongs dissolution of the pH-sensitive coating. U. S. Patent No. 5,175, 003 discloses a dual mechanism polymer mixture composed of pH-sensitive enteric materials and film-forming plasticizers capable of conferring permeability to the enteric material, for use in drug-delivery systems; a matrix pellet composed of a dual mechanism polymer mixture permeated with a drug and sometimes covering a pharmaceutically neutral nucleus; a membrane-coated pellet comprising a matrix pellet coated with a dual mechanism polymer mixture envelope of the same or different composition; and a pharmaceutical dosage form containing matrix pellets. The matrix pellet releases acid-soluble drugs by diffusion in acid pH and by disintegration at pH levels of nominally about 5.0 or higher. The agents of the invention may be formulated in the pH triggered targeted control release systems described in WO04052339. The agents of the invention may be formulated according to the methodology described in any of WO03105812 (extruded hyrdratable polymers); WO0243767 (enzyme cleavable membrane translocators); WO03007913 and WO03086297

(mucoadhesive systems); WO02072075 (bilayer laminated formulation comprising pH lowering agent and absorption enhancer); WO04064769 (amidated peptides); WO05063156 (solid lipid suspension with pseudotropic and/or thixotropic properties upon melting); WO03035029 and WO03035041 (erodible, gastric retentive dosage forms); US5007790 and US5972389 (sustained release dosage forms); WO04112711 (oral extended release compositions); WO05027878, WO02072033, and WO02072034 (delayed release compositions with natural or synthetic gum); WO05030182 (controlled release formulations with an ascending rate of release); WO05048998 (microencapsulation system); US Patent 5,952, 314 (biopolymer); US5108758 (glassy amylose matrix delivery); US 5840860 (modified starch based delivery). JP10324642 (delivery system comprising chitosan and gastric resistant material such as wheat gliadin or zein); US5866619 and US6368629 (saccharide containing polymer); US 6531152 (describes a drug delivery system containing a water soluble core (Ca pectinate or other water-insoluble polymers) and outer coat which bursts (eg hydrophobic polymer-Eudragrit)); US 6234464; US 6403130 (coating with polymer containing casein and high methoxy pectin; WO0174175 (Maillard reaction product); WO05063206 (solubility increasing formulation); WO04019872 (transferring fusion proteins). The agents of the invention may be formulated using gastrointestinal retention system technology (GIRES; Merrion Pharmaceuticals). GIRES comprises a controlled–release dosage form inside an inflatable pouch, which is placed in a drug capsule for oral administration. Upon dissolution of the capsule, a gas-generating system inflates the pouch in the stomach where it is retained for 16-24 hours, all the time releasing agents of the invention.

The agents of the invention can be formulated in an osmotic device including the ones disclosed in US4503030, US5609590 and US5358502. US4503030 discloses an osmotic device for dispensing a drug to certain pH regions of the gastrointestinal tract. More particularly, the invention relates to an osmotic device comprising a wall formed of a semi-permeable pH sensitive composition that surrounds a compartment containing a drug, with a passageway through the wall connecting the exterior of the

device with the compartment. The device delivers the drug at a controlled rate in the region of the gastrointestinal tract having a pH of less than 3.5, and the device self-destructs and releases all its drug in the region of the gastrointestinal tract having a pH greater than 3.5, thereby providing total availability for drug absorption. U. S. Patent Nos. 5,609, 590 and 5, 358,502 disclose an osmotic bursting device for dispensing a beneficial agent to an aqueous environment. The device comprises a beneficial agent and osmagent surrounded at least in part by a semi-permeable membrane. The beneficial agent may also function as the osmagent. The semi-permeable membrane is permeable to water and substantially impermeable to the beneficial agent and osmagent. A trigger means is attached to the semi-permeable membrane (e. g. , joins two capsule halves). The trigger means is activated by a pH of from 3 to 9 and triggers the eventual, but sudden, delivery of the beneficial agent. These devices enable the pH-triggered release of the beneficial agent core as a bolus by osmotic bursting.

The agents of the invention may be formulated based on the invention described in U. S. Patent No. 5,316, 774 which discloses a composition for the controlled release of an active substance comprising a polymeric particle matrix, where each particle defines a network of internal pores. The active substance is entrapped within the pore network together with a blocking agent having physical and chemical characteristics selected to modify the release rate of the active substance from the internal pore network. In one embodiment, drugs may be selectively delivered to the intestines using an enteric material as the blocking agent. The enteric material remains intact in the stomach but degrades under the pH conditions of the intestines. In another embodiment, the sustained release formulation employs a blocking agent, which remains stable under the expected conditions of the environment to which the active substance is to be released. The use of pH-sensitive materials alone to achieve site-specific delivery is difficult because of leaking of the beneficial agent prior to the release site or desired delivery time and it is difficult to achieve long time lags before release of the active ingredient after exposure to high pH (because of rapid dissolution or degradation of the pH-sensitive materials).

The agents may also be formulated in a hybrid system which combines pH-sensitive materials and osmotic delivery systems. These hybrid devices provide delayed initiation of sustained-release of the beneficial agent. In one device a pH-sensitive matrix or coating dissolves releasing osmotic devices that provide sustained release of the beneficial agent see U. S. Patent Nos. 4,578, 075, 4,681, 583, and 4,851, 231. A second device consists of a semipermeable coating made of a polymer blend of an insoluble and a pH-sensitive material. As the pH increases, the permeability of the coating increases, increasing the rate of release of beneficial agent see U. S. Patent Nos. 4,096, 238,4, 503,030, 4, 522, 625, and 4,587, 117.

The agents of the invention may be formulated in terpolumers according to U. S. Patent No. 5,484, 610 which discloses terpolymers which are sensitive to pH and temperature which are useful carriers for conducting bioactive agents through the gastric juices of the stomach in a protected form. The terpolymers swell at the higher physiologic pH of the intestinal tract causing release of the bioactive agents into the intestine. The terpolymers are linear and are made up of 35 to 99 wt % of a temperature sensitive component, which imparts to the terpolymer LCST (lower critical solution temperature) properties below body temperatures, 1 to 30 wt % of a pH sensitive component having a pKa in the range of from 2 to 8 which functions through ionization or deionization of carboxylic acid groups to prevent the bioactive agent from being lost at low pH but allows bioactive agent release at physiological pH of about 7.4 and a hydrophobic component which stabilizes the LCST below body temperatures and compensates for bioactive agent effects on the terpolymers. The terpolymers provide for safe bioactive agent loading, a simple procedure for dosage form fabrication and the terpolymer functions as a protective carrier in the acidic environment of the stomach and also protects the bioactive agents from digestive enzymes until the bioactive agent is released in the intestinal tract.

The agents of the invention may be formulated in pH sensitive polymers according to those described in U.S. Patent No. 6,103,865. U.S. Patent No. 6,103,865 discloses pH-sensitive polymers containing sulfonamide groups, which can be

changed in physical properties, such as swellability and solubility, depending on pH and which can be applied for a drug-delivery system, bio-material, sensor, and the like, and a preparation method therefore. The pH-sensitive polymers are prepared by introduction of sulfonamide groups, various in pKa, to hydrophilic groups of polymers either through coupling to the hydrophilic groups of polymers, such as acrylamide, N, N- dimethylacrylamide, acrylic acid, N-isopropylacrylamide and the like or copolymerization with other polymerizable monomers. These pH-sensitive polymers may have a structure of linear polymer, grafted copolymer, hydrogel or interpenetrating network polymer.

The agents of the invention may be formulated according U.S. Patent No. 5,656,292 which discloses a composition for pH dependent or pH regulated controlled release of active ingredients especially drugs. The composition consists of a compactable mixture of the active ingredient and starch molecules substituted with acetate and dicarboxylate residues. The preferred dicarboxylate acid is succinate. The average substitution degree of the acetate residue is at least 1 and 0. 2-1. 2 for the dicarboxylate residue. The starch molecules can have the acetate and dicarboxylate residues attached to the same starch molecule backbone or attached to separate starch molecule backbones. The present invention also discloses methods for preparing said starch acetate dicarboxylates by transesterification or mixing of starch acetates and starch dicarboxylates respectively.

The agents of the invention may be formulated according to the methods described in U. S. Patent Nos. 5,554, 147,5, 788, 687, and 6,306, 422 which disclose a method for the controlled release of a biologically active agent wherein the agent is released from a hydrophobic, pH-sensitive polymer matrix. The polymer matrix swells when the environment reaches pH 8.5, releasing the active agent. A polymer of hydrophobic and weakly acidic comonomers is disclosed for use in the controlled release system. Also disclosed is a specific embodiment in which the controlled release system may be used. The pH-sensitive polymer is coated onto a latex catheter used in ureteral catheterization. A ureteral catheter coated with a pH-

sensitive polymer having an antibiotic or urease inhibitor trapped within its matrix will release the active agent when exposed to high pH urine.

The agents of the invention may be formulated in/with bioadhesive polymers according to U.S. Patent No. 6,365, 187. Bioadhesive polymers in the form of, or as a coating on, microcapsules containing drugs or bioactive substances which may serve for therapeutic, or diagnostic purposes in diseases of the gastrointestinal tract, are described in U.S. Patent No. 6,365,187. The polymeric microspheres all have a bioadhesive force of at least 11 mN/cm^2 (110 N/m2) Techniques for the fabrication of bioadhesive microspheres, as well as a method for measuring bioadhesive forces between microspheres and selected segments of the gastrointestinal tract in vitro are also described. This quantitative method provides a means to establish a correlation between the chemical nature, the surface morphology and the dimensions of drug-loaded microspheres on one hand and bioadhesive forces on the other, allowing the screening of the most promising materials from a relatively large group of natural and synthetic polymers which, from theoretical consideration, should be used for making bioadhesive microspheres. Solutions of medicament in buffered saline and similar vehicles are commonly employed to generate an aerosol in a nebulizer. Simple nebulizers operate on Bernoulli's principle and employ a stream of air or oxygen to generate the spray particles. More complex nebulizers employ ultrasound to create the spray particles. Both types are well known in the art and are described in standard textbooks of pharmacy such as Sprowls' American Pharmacy and Remington's The Science and Practice of Pharmacy. Other devices for generating aerosols employ compressed gases, usually hydrofluorocarbons and chlorofluorocarbons, which are mixed with the medicament and any necessary excipients in a pressurized container, these devices are likewise described in standard textbooks such as Sprowls and Remington.

The agents can be a free acid or base, or a pharmacologically acceptable salt thereof. Solids can be dissolved or dispersed immediately prior to administration or earlier. In some circumstances the preparations include a preservative to prevent the growth

of microorganisms. The pharmaceutical forms suitable for injection can include sterile aqueous or organic solutions or dispersions which include, e.g., water, an alcohol, an organic solvent, an oil or other solvent or dispersant (e.g., glycerol, propylene glycol, polyethylene glycol, and vegetable oils). The formulations may contain antioxidants, buffers, bacteriostats, and solutes that render the formulation isotonic with the blood of the intended recipient, and aqueous and non-aqueous sterile suspensions that can include suspending agents, solubilizers, thickening agents, stabilizers, and preservatives. Pharmaceutical agents can be sterilized by filter sterilization or by other suitable means. The agent can be fused to immunoglobulins or albumin, or incorporated into a lipsome to improve half-life. The agent can also be conjugated to polyethylene glycol (PEG) chains. Methods for pegylation and additional formulations containing PEG-conjugates (i.e. PEG-based hydrogels, PEG modified liposomes) can be found in Harris and Chess, Nature Reviews Drug Discovery 2: 214-221 and the references therein. Agents can also be modified with alkyl groups (e.g., C1-C20 straight or branched alkyl groups); fatty acid radicals; and combinations of PEG, alkyl groups and fatty acid radicals (see U.S. Patent No. 6,309,633; Soltero et al., 2001 Innovations in Pharmaceutical Technology 106-110). The agent can be administered via a nanocochleate or cochleate delivery vehicle (BioDelivery Sciences International). The agents can be delivered transmucosally (i.e. across a mucosal surface such as the vagina, eye or nose) using formulations such as that described in U.S. 5,204,108. The agents can be formulated in microcapsules as described in WO 88/01165. The agent can be administered intra-orally using the formulations described in U.S. 20020055496, WO 00/47203, and U.S. Patent No. 6,495,120. The agent can be delivered using nanoemulsion formulations described in WO 01/91728A2.

Controlled release formulations

In general, one can provide for controlled release of the agents described herein through the use of a wide variety of polymeric carriers and controlled release systems including erodible and non-erodible matrices, osmotic control devices, various reservoir devices, enteric coatings and multiparticulate control devices.

Matrix devices are a common device for controlling the release of various agents. In such devices, the agents described herein are generally present as a dispersion within the polymer matrix, and are typically formed by the compression of a polymer/drug mixture or by dissolution or melting. The dosage release properties of these devices may be dependent upon the solubility of the agent in the polymer matrix or, in the case of porous matrices, the solubility in the sink solution within the pore network, and the tortuosity of the network. In one instance, when utilizing an erodible polymeric matrix, the matrix imbibes water and forms an aqueous-swollen gel that entraps the agent. The matrix then gradually erodes, swells, disintegrates or dissolves in the GI tract, thereby controlling release of one or more of the agents described herein. In non-erodible devices, the agent is released by diffusion through an inert matrix.

Agents described herein can be incorporated into an erodible or non-erodible polymeric matrix controlled release device. By an erodible matrix is meant aqueous-erodible or water-swellable or aqueous-soluble in the sense of being either erodible or swellable or dissolvable in pure water or requiring the presence of an acid or base to ionize the polymeric matrix sufficiently to cause erosion or dissolution. When contacted with the aqueous environment of use, the erodible polymeric matrix imbibes water and forms an aqueous-swollen gel or matrix that entraps the agent described herein. The aqueous-swollen matrix gradually erodes, swells, disintegrates or dissolves in the environment of use, thereby controlling the release of a compound described herein to the environment of use.

The erodible polymeric matrix into which an agent described herein can be incorporated may generally be described as a set of excipients that are mixed with the agent following its formation that, when contacted with the aqueous environment of use imbibes water and forms a water-swollen gel or matrix that entraps the drug form. Drug release may occur by a variety of mechanisms, for example, the matrix may disintegrate or dissolve from around particles or granules of the agent or the agent may dissolve in the imbibed aqueous solution and diffuse from the tablet, beads or granules of the device. One ingredient of this water-swollen matrix is the water-swellable, erodible, or soluble polymer, which may generally be described as an osmopolymer, hydrogel or water-swellable polymer. Such polymers may be linear, branched, or crosslinked. The polymers may be homopolymers or copolymers. In certain embodiments, they may be synthetic polymers derived from vinyl, acrylate, methacrylate, urethane, ester and oxide monomers. In other embodiments, they can be derivatives of naturally occurring polymers such as polysaccharides (e.g. chitin, chitosan, dextran and pullulan; gum agar, gum arabic, gum karaya, locust bean gum, gum tragacanth, carrageenans, gum ghatti, guar gum, xanthan gum and scleroglucan), starches (e.g. dextrin and maltodextrin), hydrophilic colloids (e.g. pectin), phosphatides (e.g. lecithin), alginates (e.g. ammonium alginate, sodium, potassium or calcium alginate, propylene glycol alginate), gelatin, collagen, and cellulosics. Cellulosics are cellulose polymer that has been modified by reaction of at least a portion of the hydroxyl groups on the saccharide repeat units with a compound to form an ester-linked or an ether-linked substituent. For example, the cellulosic ethyl cellulose has an ether linked ethyl substituent attached to the saccharide repeat unit, while the cellulosic cellulose acetate has an ester linked acetate substituent. In certain embodiments, the cellulosics for the erodible matrix comprises aqueous-soluble and aqueous-erodible cellulosics can include, for example, ethyl cellulose (EC), methylethyl cellulose (MEC), carboxymethyl cellulose (CMC), CMEC, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), cellulose acetate (CA), cellulose propionate (CP), cellulose butyrate (CB), cellulose acetate butyrate (CAB), CAP, CAT, hydroxypropyl methyl cellulose (HPMC), HPMCP, HPMCAS, hydroxypropyl methyl cellulose acetate trimellitate

(HPMCAT), and ethylhydroxy ethylcellulose (EHEC). In certain embodiments, the cellulosics comprises various grades of low viscosity (MW less than or equal to 50,000 daltons, for example, the Dow Methocel™ series E5, E15LV, E50LV and K100LY) and high viscosity (MW greater than 50,000 daltons, for example, E4MCR, E10MCR, K4M, K15M and K100M and the Methocel™ K series) HPMC. Other commercially available types of HPMC include the Shin Etsu Metolose 90SH series.

The choice of matrix material can have a large effect on the maximum drug concentration attained by the device as well as the maintenance of a high drug concentration. The matrix material can be a concentration-enhancing polymer, for example, as described in WO05/011634.

Other materials useful as the erodible matrix material include, but are not limited to, pullulan, polyvinyl pyrrolidone, polyvinyl alcohol, polyvinyl acetate, glycerol fatty acid esters, polyacrylamide, polyacrylic acid, copolymers of ethacrylic acid or methacrylic acid (EUDRAGITO, Rohm America, Inc., Piscataway, New Jersey) and other acrylic acid derivatives such as homopolymers and copolymers of butylmethacrylate, methylmethacrylate, ethylmethacrylate, ethylacrylate, (2-dimethylaminoethyl) methacrylate, and (trimethylaminoethyl) methacrylate chloride.

The erodible matrix polymer may contain a wide variety of the same types of additives and excipients known in the pharmaceutical arts, including osmopolymers, osmagens, solubility-enhancing or-retarding agents and excipients that promote stability or processing of the device.

Alternatively, the agents of the present invention may be administered by or incorporated into a non-erodible matrix device. In such devices, an agent described herein is distributed in an inert matrix. The agent is released by diffusion through the inert matrix. Examples of materials suitable for the inert matrix include insoluble plastics (e.g methyl acrylate-methyl methacrylate copolymers, polyvinyl chloride, polyethylene), hydrophilic polymers (e.g. ethyl cellulose, cellulose acetate, crosslinked polyvinylpyrrolidone (also known as crospovidone)), and fatty

compounds (e.g. carnauba wax, microcrystalline wax, and triglycerides). Such devices are described further in Remington: The Science and Practice of Pharmacy, 20th edition (2000).

Matrix controlled release devices may be prepared by blending an agent described herein and other excipients together, and then forming the blend into a tablet, caplet, pill, or other device formed by compressive forces. Such compressed devices may be formed using any of a wide variety of presses used in the fabrication of pharmaceutical devices. Examples include single-punch presses, rotary tablet presses, and multilayer rotary tablet presses, all well known in the art. See for example, Remington: The Science and Practice of Pharmacy, 20th Edition, 2000. The compressed device may be of any shape, including round, oval, oblong, cylindrical, or triangular. The upper and lower surfaces of the compressed device may be flat, round, concave, or convex.

In certain embodiments, when formed by compression, the device has a strength of at least 5 Kiloponds (Kp)/cm^2 (for example, at least 7 Kp/cm^2). Strength is the fracture force, also known as the tablet hardness required to fracture a tablet formed from the materials, divided by the maximum cross-sectional area of the tablet normal to that force. The fracture force may be measured using a Schleuniger Tablet Hardness Tester, Model 6D. The compression force required to achieve this strength will depend on the size of the tablet, but generally will be greater than about 5 kP/cm^2. Friability is a well-know measure of a device's resistance to surface abrasion that measures weight loss in percentage after subjecting the device to a standardized agitation procedure. Friability values of from 0.8 to 1.0% are regarded as constituting the upper limit of acceptability. Devices having a strength of greater than 5 kP/cm^2 generally are very robust, having a friability of less than 0. 5%. Other methods for forming matrix controlled-release devices are well known in the pharmaceutical arts. See for example, Remington: The Science and Practice of Pharmacy, 20th Edition, 2000.

As noted above, the agents described herein may also be incorporated into an osmotic control device. Such devices generally include a core containing one or more agents as described herein and a water permeable, non-dissolving and non-eroding coating surrounding the core which controls the influx of water into the core from an aqueous environment of use so as to cause drug release by extrusion of some or all of the core to the environment of use. In certain embodiments, the coating is polymeric, aqueous-permeable, and has at least one delivery port. The core of the osmotic device optionally includes an osmotic agent which acts to imbibe water from the surrounding environment via such a semi-permeable membrane. The osmotic agent contained in the core of this device may be an aqueous-swellable hydrophilic polymer or it may be an osmogen, also known as an osmagent. Pressure is generated within the device which forces the agent(s) out of the device via an orifice (of a size designed to minimize solute diffusion while preventing the build-up of a hydrostatic pressure head).

Osmotic agents create a driving force for transport of water from the environment of use into the core of the device. Osmotic agents include but are not limited to water-swellable hydrophilic polymers, and osmogens (or osmagens). Thus, the core may include water-swellable hydrophilic polymers, both ionic and nonionic, often referred to as osmopolymers and hydrogels. The amount of water-swellable hydrophilic polymers present in the core may range from about 5 to about 80 wt% (including for example, 10 to 50 wt%). Nonlimiting examples of core materials include hydrophilic vinyl and acrylic polymers, polysaccharides such as calcium alginate, polyethylene oxide (PEO), polyethylene glycol (PEG), polypropylene glycol (PPG), poly (2-hydroxyethyl methacrylate), poly (acrylic) acid, poly (methacrylic) acid, polyvinylpyrrolidone (PVP) and crosslinked PVP, polyvinyl alcohol (PVA), PVA/PVP copolymers and PVA/PVP copolymers with hydrophobic monomers such as methyl methacrylate, vinyl acetate, and the like, hydrophilic polyurethanes containing large PEO blocks, sodium croscarmellose, carrageenan, hydroxyethyl cellulose (HEC), hydroxypropyl cellulose (HPC), hydroxypropyl methyl cellulose (HPMC), carboxymethyl cellulose (CMC) and carboxyethyl cellulose (CEC), sodium alginate, polycarbophil, gelatin, xanthan gum, and sodium

starch glycolat. Other materials include hydrogels comprising interpenetrating networks of polymers that may be formed by addition or by condensation polymerization, the components of which may comprise hydrophilic and hydrophobic monomers such as those just mentioned. Water-swellable hydrophilic polymers include but are not limited to PEO, PEG, PVP, sodium croscarmellose, HPMC, sodium starch glycolate, polyacrylic acid and crosslinked versions or mixtures thereof.

The core may also include an osmogen (or osmagent). The amount of osmogen present in the core may range from about 2 to about 70 wt% (including, for example, from 10 to 50 wt%). Typical classes of suitable osmogens are water-soluble organic acids, salts and sugars that are capable of imbibing water to thereby effect an osmotic pressure gradient across the barrier of the surrounding coating. Typical useful osmogens include but are not limited to magnesium sulfate, magnesium chloride, calcium chloride, sodium chloride, lithium chloride, potassium sulfate, sodium carbonate, sodium sulfite, lithium sulfate, potassium chloride, sodium sulfate, mannitol, xylitol, urea, sorbitol, inositol, raffinose, sucrose, glucose, fructose, lactose, citric acid, succinic acid, tartaric acid, and mixtures thereof. In certain embodiments, the osmogen is glucose, lactose, sucrose, mannitol, xylitol, sodium chloride, including combinations thereof.

The core may include a wide variety of additives and excipients that enhance the performance of the dosage form or that promote stability, tableting or processing. Such additives and excipients include tableting aids, surfactants, water- soluble polymers, pH modifiers, fillers, binders, pigments, disintegrants, antioxidants, lubricants and flavorants. Nonlimiting examples of additives and excipients include but are not limited to those described elsewhere herein as well as microcrystalline cellulose, metallic salts of acids (e.g. aluminum stearate, calcium stearate, magnesium stearate, sodium stearate, zinc stearate), pH control agents (e.g. buffers, organic acids, organic acid salts, organic and inorganic bases), fatty acids, hydrocarbons and fatty alcohols (e.g. stearic acid, palmitic acid, liquid paraffin, stearyl alcohol, and palmitol), fatty acid esters (e.g. glyceryl (mono-and di-)

stearates, triglycerides, glyceryl (palmiticstearic) ester, sorbitan esters (e.g. sorbitan monostearate, saccharose monostearate, saccharose monopalmitate, sodium stearyl fumarate), polyoxyethylene sorbitan esters), surfactants (e.g. alkyl sulfates (e.g. sodium lauryl sulfate, magnesium lauryl sulfate), polymers (e.g. polyethylene glycols, polyoxyethylene glycols, polyoxyethylene, polyoxypropylene ethers, including copolymers thereof), polytetrafluoroethylene), and inorganic materials (e.g. talc, calcium phosphate), cyclodextrins, sugars (e.g. lactose, xylitol), sodium starch glycolate). Nonlimiting examples of disintegrants are sodium starch glycolate (e. g., Explotab™ CLV, (microcrystalline cellulose (e. g., Avicel™), microcrystalline silicified cellulose (e.g., ProSolv™), croscarmellose sodium (e. g., Ac-Di-Sol™). When the agent described herein is a solid amorphous dispersion formed by a solvent process, such additives may be added directly to the spray-drying solution when forming an agent described herein/concentration-enhancing polymer dispersion such that the additive is dissolved or suspended in the solution as a slurry, Alternatively, such additives may be added following the spray-drying process to aid in forming the final controlled release device.

A nonlimiting example of an osmotic device consists of one or more drug layers containing an agent described herein, such as a solid amorphous drug/polymer dispersion, and a sweller layer that comprises a water-swellable polymer, with a coating surrounding the drug layer and sweller layer. Each layer may contain other excipients such as tableting aids, osmagents, surfactants, water-soluble polymers and water-swellable polymers.

Such osmotic delivery devices may be fabricated in various geometries including bilayer (wherein the core comprises a drug layer and a sweller layer adjacent to each other), trilayer (wherein the core comprises a sweller layer sandwiched between two drug layers) and concentric (wherein the core comprises a central sweller agent surrounded by the drug layer). The coating of such a tablet comprises a membrane permeable to water but substantially impermeable to drug and excipients contained within. The coating contains one or more exit passageways or ports in

communication with the drug-containing layer(s) for delivering the drug agent. The drug-containing layer(s) of the core contains the drug agent (including optional osmagents and hydrophilic water-soluble polymers), while the sweller layer consists of an expandable hydrogel, with or without additional osmotic agents.

When placed in an aqueous medium, the tablet imbibes water through the membrane, causing the agent to form a dispensable aqueous agent, and causing the hydrogel layer to expand and push against the drug-containing agent, forcing the agent out of the exit passageway. The agent can swell, aiding in forcing the drug out of the passageway. Drug can be delivered from this type of delivery system either dissolved or dispersed in the agent that is expelled from the exit passageway.

The rate of drug delivery is controlled by such factors as the permeability and thickness of the coating, the osmotic pressure of the drug-containing layer, the degree of hydrophilicity of the hydrogel layer, and the surface area of the device. Those skilled in the art will appreciate that increasing the thickness of the coating will reduce the release rate, while any of the following will increase the release rate: increasing the permeability of the coating; increasing the hydrophilicity of the hydrogel layer; increasing the osmotic pressure of the drug-containing layer; or increasing the device's surface area.

Other materials useful in forming the drug-containing agent, in addition to the agent described herein itself, include HPMC, PEO and PVP and other pharmaceutically acceptable carriers. In addition, osmagents such as sugars or salts, including but not limited to sucrose, lactose, xylitol, mannitol, or sodium chloride, may be added. Materials which are useful for forming the hydrogel layer include sodium CMC, PEO (e.g. polymers having an average molecular weight from about 5,000,000 to about 7,500,000 daltons), poly (acrylic acid), sodium (polyacrylate), sodium croscarmellose, sodium starch glycolat, PVP, crosslinked PVP, and other high molecular weight hydrophilic materials.

In the case of a bilayer geometry, the delivery port(s) or exit passageway(s) may be located on the side of the tablet containing the drug agent or may be on both sides of the tablet or even on the edge of the tablet so as to connect both the drug layer and the sweller layer with the exterior of the device. The exit passageway(s) may be produced by mechanical means or by laser drilling, or by creating a difficult-to-coat region on the tablet by use of special tooling during tablet compression or by other means.

The osmotic device can also be made with a homogeneous core surrounded by a semipermeable membrane coating, as in US3845770. The agent described herein can be incorporated into a tablet core and a semipermeable membrane coating can be applied via conventional tablet-coating techniques such as using a pan coater. A drug delivery passageway can then be formed in this coating by drilling a hole in the coating, either by use of a laser or mechanical means. Alternatively, the passageway may be formed by rupturing a portion of the coating or by creating a region on the tablet that is difficult to coat, as described above. In one embodiment, an osmotic device comprises: (a) a single-layer compressed core comprising: (i) an agent described herein, (ii) a hydroxyethylcellulose, and (iii) an osmagent, wherein the hydroxyethylcellulose is present in the core from about 2.0% to about 35% by weight and the osmagent is present from about 15% to about 70% by weight; (b) a water-permeable layer surrounding the core; and (c) at least one passageway within the water-permeable layer (b) for delivering the drug to a fluid environment surrounding the tablet. In certain embodiments, the device is shaped such that the surface area to volume ratio (of a water-swollen tablet) is greater than 0.6 mm^{-1} (including, for example, greater than 1.0 mm^{-1}). The passageway connecting the core with the fluid environment can be situated along the tablet band area. In certain embodiments, the shape is an oblong shape where the ratio of the tablet tooling axes, i.e., the major and minor axes which define the shape of the tablet, are between 1.3 and 3 (including, for example, between 1.5 and 2.5). In one embodiment, the combination of the agent described herein and the osmagent have an average ductility from about 100 to about 200 Mpa, an average tensile strength from about

0.8 to about 2.0 Mpa, and an average brittle fracture index less than about 0.2. The single-layer core may optionally include a disintegrant, a bioavailability enhancing additive, and/or a pharmaceutically acceptable excipient, carrier or diluent.

In certain embodiments, entrainment of particles of agents described herein in the extruding fluid during operation of such osmotic device is desirable. For the particles to be well entrained, the agent drug form is dispersed in the fluid before the particles have an opportunity to settle in the tablet core. One means of accomplishing this is by adding a disintegrant that serves to break up the compressed core into its particulate components. Nonlimiting examples of standard disintegrants include materials such as sodium starch glycolate (e. g. , Explotab™ CLV), microcrystalline cellulose (e. g., Avicel™), microcrystalline silicified cellulose (e. g., ProSolv™) and croscarmellose sodium (e. g., Ac-Di-Sol™), and other disintegrants known to those skilled in the art. Depending upon the particular formulation, some disintegrants work better than others. Several disintegrants tend to form gels as they swell with water, thus hindering drug delivery from the device. Non-gelling, non-swelling disintegrants provide a more rapid dispersion of the drug particles within the core as water enters the core. In certain embodiments, non-gelling, non-swelling disintegrants are resins, for example, ion-exchange resins. In one embodiment, the resin is Amberlite™ IRP 88 (available from Rohm and Haas, Philadelphia, PA). When used, the disintegrant is present in amounts ranging from about 1-25% of the core agent.

Water-soluble polymers are added to keep particles of the agent suspended inside the device before they can be delivered through the passageway(s) (e.g., an orifice). High viscosity polymers are useful in preventing settling. However, the polymer in combination with the agent is extruded through the passageway(s) under relatively low pressures. At a given extrusion pressure, the extrusion rate typically slows with increased viscosity. Certain polymers in combination with particles of the agent described herein form high viscosity solutions with water but are still capable of being extruded from the tablets with a relatively low force. In contrast, polymers

having a low weight-average, molecular weight (< about 300,000) do not form sufficiently viscous solutions inside the tablet core to allow complete delivery due to particle settling. Settling of the particles is a problem when such devices are prepared with no polymer added, which leads to poor drug delivery unless the tablet is constantly agitated to keep the particles from settling inside the core. Settling is also problematic when the particles are large and/or of high density such that the rate of settling increases.

In certain embodiments, the water-soluble polymers for such osmotic devices do not interact with the drug. In certain embodiments the water-soluble polymer is a non-ionic polymer. A nonlimiting example of a non-ionic polymer forming solutions having a high viscosity yet still extrudable at low pressures is Natrosol™ 250H (high molecular weight hydroxyethylcellulose, available from Hercules Incorporated, Aqualon Division, Wilmington, DE; MW equal to about 1 million daltons and a degree of polymerization equal to about 3,700). Natrosol 250H™ provides effective drug delivery at concentrations as low as about 3% by weight of the core when combined with an osmagent. Natrosol 250H™ NF is a high-viscosity grade nonionic cellulose ether that is soluble in hot or cold water. The viscosity of a 1% solution of Natrosol 250H using a Brookfield LVT (30 rpm) at 25°C is between about 1, 500 and about 2,500 cps.

In certain embodiments, hydroxyethylcellulose polymers for use in these monolayer osmotic tablets have a weight-average, molecular weight from about 300,000 to about 1.5 million. The hydroxyethylcellulose polymer is typically present in the core in an amount from about 2.0% to about 35% by weight.

Another example of an osmotic device is an osmotic capsule. The capsule shell or portion of the capsule shell can be semipermeable. The capsule can be filled either by a powder or liquid consisting of an agent described herein, excipients that imbibe water to provide osmotic potential, and/or a water-swellable polymer, or optionally solubilizing excipients. The capsule core can also be made such that it has a bilayer

or multilayer agent analogous to the bilayer, trilayer or concentric geometries described above.

Another class of osmotic device useful in this invention comprises coated swellable tablets, for example, as described in EP378404. Coated swellable tablets comprise a tablet core comprising an agent described herein and a swelling material, preferably a hydrophilic polymer, coated with a membrane, which contains holes, or pores through which, in the aqueous use environment, the hydrophilic polymer can extrude and carry out the agent. Alternatively, the membrane may contain polymeric or low molecular weight water-soluble porosigens. Porosigens dissolve in the aqueous use environment, providing pores through which the hydrophilic polymer and agent may extrude. Examples of porosigens are water-soluble polymers such as HPMC, PEG, and low molecular weight compounds such as glycerol, sucrose, glucose, and sodium chloride. In addition, pores may be formed in the coating by drilling holes in the coating using a laser or other mechanical means. In this class of osmotic devices, the membrane material may comprise any film-forming polymer, including polymers which are water permeable or impermeable, providing that the membrane deposited on the tablet core is porous or contains water-soluble porosigens or possesses a macroscopic hole for water ingress and drug release. Embodiments of this class of sustained release devices may also be multilayered, as described, for example, in EP378404.

When an agent described herein is a liquid or oil, such as a lipid vehicle formulation, for example as described in WO05/011634, the osmotic controlled-release device may comprise a soft-gel or gelatin capsule formed with a composite wall and comprising the liquid formulation where the wall comprises a barrier layer formed over the external surface of the capsule, an expandable layer formed over the barrier layer, and a semipermeable layer formed over the expandable layer. A delivery port connects the liquid formulation with the aqueous use environment. Such devices are described, for example, in US6419952, US6342249, US5324280, US4672850, US4627850, US4203440, and US3995631.

The osmotic controlled release devices of the present invention can also comprise a coating. In certain embodiments, the osmotic controlled release device coating exhibits one or more of the following features: is water-permeable, has at least one port for the delivery of drug, and is non-dissolving and non-eroding during release of the drug formulation, such that drug is substantially entirely delivered through the delivery port(s) or pores as opposed to delivery primarily via permeation through the coating material itself. Delivery ports include any passageway, opening or pore whether made mechanically, by laser drilling, by pore formation either during the coating process or *in situ* during use or by rupture during use. In certain embodiments, the coating is present in an amount ranging from about 5 to 30 wt% (including, for example, 10 to 20 wt%) relative to the core weight.

One form of coating is a semipermeable polymeric membrane that has the port(s) formed therein either prior to or during use. Thickness of such a polymeric membrane may vary between about 20 and 800 μm (including, for example, between about 100 to 500 μm). The diameter of the delivery port (s) may generally range in size from 0.1 to 3000 μm or greater (including, for example, from about 50 to 3000 μm in diameter). Such port(s) may be formed post-coating by mechanical or laser drilling or may be formed *in situ* by rupture of the coatings; such rupture may be controlled by intentionally incorporating a relatively small weak portion into the coating. Delivery ports may also be formed *in situ* by erosion of a plug of water-soluble material or by rupture of a thinner portion of the coating over an indentation in the core. In addition, delivery ports may be formed during coating, as in the case of asymmetric membrane coatings of the type disclosed in US5612059 and US5698220. The delivery port may be formed *in situ* by rupture of the coating, for example, when a collection of beads that may be of essentially identical or of a variable agent are used. Drug is primarily released from such beads following rupture of the coating and, following rupture, such release may be gradual or relatively sudden. When the collection of beads has a variable agent, the agent may be chosen such that the beads rupture at various times following administration, resulting in the overall release of drug being sustained for a desired duration.

Coatings may be dense, microporous or asymmetric, having a denser region supported by a thick porous region such as those disclosed in US5612059 and US5698220. When the coating is dense the coating can be composed of a water-permeable material. When the coating is porous, it may be composed of either a water-permeable or a water-impermeable material. When the coating is composed of a porous water-impermeable material, water permeates through the pores of the coating as either a liquid or a vapor. Nonlimiting examples of osmotic devices that utilize dense coatings include US3995631 and US3845770. Such dense coatings are permeable to the external fluid such as water and may be composed of any of the materials mentioned in these patents as well as other water-permeable polymers known in the art.

The membranes may also be porous as disclosed, for example, in US5654005 and US5458887 or even be formed from water-resistant polymers. US5120548 describes another suitable process for forming coatings from a mixture of a water-insoluble polymer and a leachable water-soluble additive. The porous membranes may also be formed by the addition of pore-formers as disclosed in US4612008. In addition, vapor-permeable coatings may even be formed from extremely hydrophobic materials such as polyethylene or polyvinylidene difluorid that, when dense, are essentially water-impermeable, as long as such coatings are porous. Materials useful in forming the coating include but are not limited to various grades of acrylic, vinyls, ethers, polyamides, polyesters and cellulosic derivatives that are water-permeable and water-insoluble at physiologically relevant pHs, or are susceptible to being rendered water-insoluble by chemical alteration such as by crosslinking. Nonlimiting examples of suitable polymers (or crosslinked versions) useful in forming the coating include plasticized, unplasticized and reinforced cellulose acetate (CA), cellulose diacetate, cellulose triacetate, CA propionate, cellulose nitrate, cellulose acetate butyrate (CAB), CA ethyl carbamate, CAP, CA methyl carbamate, CA succinate, cellulose acetate trimellitate (CAT), CA dimethylaminoacetate, CA ethyl carbonate, CA chloroacetate, CA ethyl oxalate, CA methyl sulfonate, CA butyl sulfonate, CA p-toluene sulfonate, agar acetate, amylose

triacetate, beta glucan acetate, beta glucan triacetate, acetaldehyde dimethyl acetate, triacetate of locust bean gum, hydroxiated ethylene-vinylacetate, EC, PEG, PPG, PEG/PPG copolymers, PVP, HEC, HPC, CMC, CMEC, HPMC, HPMCP, HPMCAS, HPMCAT, poly (acrylic) acids and esters and poly- (methacrylic) acids and esters and copolymers thereof, starch, dextran, dextrin, chitosan, collagen, gelatin, polyalkenes, polyethers, polysulfones, polyethersulfones, polystyrenes, polyvinyl halides, polyvinyl esters and ethers, natural waxes and synthetic waxes. In various embodiments, the coating agent comprises a cellulosic polymer, in particular cellulose ethers, cellulose esters and cellulose ester-ethers, i.e., cellulosic derivatives having a mixture of ester and ether substituents, the coating materials are made or derived from poly (acrylic) acids and esters, poly (methacrylic) acids and esters, and copolymers thereof, the coating agent comprises cellulose acetate, the coating comprises a cellulosic polymer and PEG, the coating comprises cellulose acetate and PEG.

Coating is conducted in conventional fashion, typically by dissolving or suspending the coating material in a solvent and then coating by dipping, spray coating or by pan-coating. In certain embodiments, the coating solution contains 5 to 15 wt% polymer. Typical solvents useful with the cellulosic polymers mentioned above include but are not limited to acetone, methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate, methyl isobutyl ketone, methyl propyl ketone, ethylene glycol monoethyl ether, ethylene glycol monoethyl acetate, methylene dichloride, ethylene dichloride, propylene dichloride, nitroethane, nitropropane, tetrachloroethane, 1,4-dioxane, tetrahydrofuran, diglyme, water, and mixtures thereof. Pore-formers and non- solvents (such as water, glycerol and ethanol) or plasticizers (such as diethyl phthalate) may also be added in any amount as long as the polymer remains soluble at the spray temperature. Pore-formers and their use in fabricating coatings are described, for example, in US5612059. Coatings may also be hydrophobic microporous layers wherein the pores are substantially filled with a gas and are not wetted by the aqueous medium but are permeable to water vapor, as disclosed, for example, in US5798119. Such hydrophobic but water-vapor

permeable coatings are typically composed of hydrophobic polymers such as polyalkenes, polyacrylic acid derivatives, polyethers, polysulfones, polyethersulfones, polystyrenes, polyvinyl halides, polyvinyl esters and ethers, natural waxes and synthetic waxes. Hydrophobic microporous coating materials include but are not limited to polystyrene, polysulfones, polyethersulfones, polyethylene, polypropylene, polyvinyl chloride, polyvinylidene fluoride and polytetrafluoroethylene. Such hydrophobic coatings can be made by known phase inversion methods using any of vapor-quench, liquid quench, thermal processes, leaching soluble material from the coating or by sintering coating particles. In thermal processes, a solution of polymer in a latent solvent is brought to liquid-liquid phase separation in a cooling step. When evaporation of the solvent is not prevented, the resulting membrane will typically be porous. Such coating processes may be conducted by the processes disclosed, for example, in US4247498, US4490431 and US4744906. Osmotic controlled-release devices may be prepared using procedures known in the pharmaceutical arts. See for example, Remington: The Science and Practice of Pharmacy, 20th Edition, 2000.

As further noted above, the agents described herein may be provided in the form of microparticulates, generally ranging in size from about 10μm to about 2mm (including, for example, from about 100μm to 1mm in diameter). Such multiparticulates may be packaged, for example, in a capsule such as a gelatin capsule or a capsule formed from an aqueous-soluble polymer such as HPMCAS, HPMC or starch; dosed as a suspension or slurry in a liquid ; or they may be formed into a tablet, caplet, or pill by compression or other processes known in the art. Such multiparticulates may be made by any known process, such as wet- and dry-granulation processes, extrusion/spheronization, roller-compaction, melt-congealing, or by spray-coating seed cores. For example, in wet-and dry- granulation processes, the agent described herein and optional excipients may be granulated to form multiparticulates of the desired size. Other excipients, such as a binder (e. g., microcrystalline cellulose), may be blended with the agent to aid in processing and forming the multiparticulates. In the case of wet granulation, a binder such as microcrystalline cellulose may be included in the granulation fluid to aid in forming a suitable multiparticulate. See, for example, Remington : The Science and Practice of Pharmacy, 20"Edition, 2000. In any case, the resulting particles may themselves constitute the therapeutic composition or they may be coated by various film-forming materials such as enteric polymers or water-swellable or water-soluble polymers, or they may be combined with other excipients or vehicles to aid in dosing to patients.

Suitable pharmaceutical compositions in accordance with the invention will generally include an amount of the active compound(s) with an acceptable pharmaceutical diluent or excipient, such as a sterile aqueous solution, to give a range of final concentrations, depending on the intended use. The techniques of preparation are generally well known in the art, as exemplified by Remington's Pharmaceutical Sciences (18th Edition, Mack Publishing Company, 1995).

Kits

The agents described herein and combination therapy agents can be packaged as a kit that includes single or multiple doses of two or more agents, each packaged or

formulated individually, or single or multiple doses of two or more agents packaged or formulated in combination. Thus, one or more agents can be present in first container, and the kit can optionally include one or more agents in a second container. The container or containers are placed within a package, and the package can optionally include administration or dosage instructions. A kit can include additional components such as syringes or other means for administering the agents as well as diluents or other means for formulation.

Thus, the kits can comprise: a) a pharmaceutical composition comprising a compound described herein and a pharmaceutically acceptable carrier, vehicle or diluent; and b) a container or packaging. The kits may optionally comprise instructions describing a method of using the pharmaceutical compositions in one or more of the methods described herein (e.g. gastrointestinal motility disorders, IBS (e.g. d-IBS), IBD, Crohn's disease, duodenogastric reflux, dyspepsia, functional dyspepsia, nonulcer dyspepsia, a functional gastrointestinal disorder, functional heartburn, gastroesophageal reflux disease (GERD), gastroparesis, irritable bowel syndrome, ulcerative colitis, diarrhea, and disorders and conditions associated with diarrhea as described, for example, herein. The kit may optionally comprise a second pharmaceutical composition comprising one or more additional agents including but not limited to those including analgesic peptides and compounds, a phosphodiesterase inhibitor, an agent used to treat gastrointestinal and other disorders (including those described herein), an anti-diarrheal agent, an anti-obesity agent, an agent that activates soluble guanylate cyclase and a pharmaceutically acceptable carrier, vehicle or diluent. The pharmaceutical composition comprising the compound described herein and the second pharmaceutical composition contained in the kit may be optionally combined in the same pharmaceutical composition.

A kit includes a container or packaging for containing the pharmaceutical compositions and may also include divided containers such as a divided bottle or a divided foil packet. The container can be, for example a paper or cardboard box, a

glass or plastic bottle or jar, a re-sealable bag (for example, to hold a "refill" of tablets for placement into a different container), or a blister pack with individual doses for pressing out of the pack according to a therapeutic schedule. It is feasible that more than one container can be used together in a single package to market a single dosage form. For example, tablets may be contained in a bottle which is in turn contained within a box.

An example of a kit is a so-called blister pack. Blister packs are well known in the packaging industry and are being widely used for the packaging of pharmaceutical unit dosage forms (tablets, capsules, and the like). Blister packs generally consist of a sheet of relatively stiff material covered with a foil of a preferably transparent plastic material. During the packaging process, recesses are formed in the plastic foil. The recesses have the size and shape of individual tablets or capsules to be packed or may have the size and shape to accommodate multiple tablets and/or capsules to be packed. Next, the tablets or capsules are placed in the recesses accordingly and the sheet of relatively stiff material is sealed against the plastic foil at the face of the foil which is opposite from the direction in which the recesses were formed. As a result, the tablets or capsules are individually sealed or collectively sealed, as desired, in the recesses between the plastic foil and the sheet. Preferably the strength of the sheet is such that the tablets or capsules can be removed from the blister pack by manually applying pressure on the recesses whereby an opening is formed in the sheet at the place of the recess. The tablet or capsule can then be removed via said opening.

It maybe desirable to provide a written memory aid containing information and/or instructions for the physician, pharmacist or subject regarding when the medication is to be taken. A "daily dose" can be a single tablet or capsule or several tablets or capsules to be taken on a given day. When the kit contains separate compositions, a daily dose of one or more compositions of the kit can consist of one tablet or capsule while a daily dose of another one or more compositions of the kit can consist of several tablets or capsules. A kit can take the form of a dispenser designed to

dispense the daily doses one at a time in the order of their intended use. The dispenser can be equipped with a memory-aid, so as to further facilitate compliance with the regimen. An example of such a memory-aid is a mechanical counter which indicates the number of daily doses that have been dispensed. Another example of such a memory-aid is a battery-powered micro-chip memory coupled with a liquid crystal readout, or audible reminder signal which, for example, reads out the date that the last daily dose has been taken and/or reminds one when the next dose is to be taken.

Methods to increase chemical and/or physical stability of the agents the described herein are found in U.S. 6,541,606, U.S. 6,068,850, U.S. 6,124,261, U.S. 5,904,935, and WO 00/15224, U.S. 20030069182 (via the additon of nicotinamide), U.S. 20030175230A1, U.S. 20030175230A1, U.S. 20030175239A1, U.S. 20020045582, U.S. 20010031726, WO 02/26248, WO 03/014304, WO 98/00152A1, WO 98/00157A1, WO 90/12029, WO 00/04880, and WO 91/04743, WO 97/04796 and the references cited therein.

Methods to increase bioavailability of the agents described herein are found in U.S. 6,008,187, U.S. 5,424,289, U.S. 20030198619, WO 90/01329, WO 01/49268, WO 00/32172, and WO 02/064166. Glycyrrhizinate can also be used as an absorption enhancer (see, e.g., EP397447). WO 03/004062 discusses Ulex europaeus I (UEAl) and UEAI mimetics which may be used to target the agents of the invention to the GI tract.

The agents described herein can be fused to a modified version of the blood serum protein transferrin. U.S. 20030221201, U.S. 20040023334, U.S. 20030226155, WO 04/020454, and WO 04/019872 discuss the manufacture and use of transferrin fusion proteins. Transferrin fusion proteins may improve circulatory half life and efficacy, decrease undesirable side effects and allow reduced dosage.

Dosage

The dose range for adult humans is generally from 0.005 mg to 10 g/day orally. Tablets or other forms of presentation provided in discrete units may conveniently contain an amount of compound of the invention which is effective at such dosage or as a multiple of the same, for instance, units containing 5 mg to 500 mg, usually around 10 mg to 200 mg. The precise amount of compound administered to a patient will be the responsibility of the attendant physician. However, the dose employed will depend on a number of factors, including the age and sex of the patient, the precise disorder being treated, and its severity.

The precise amount of each of the two or more active ingredients in a dosage unit will depend on the desired dosage of each component. Thus, it can be useful to create a dosage unit that will, when administered according to a particular dosage schedule (e.g., a dosage schedule specifying a certain number of units and a particular timing for administration), deliver the same dosage of each component as would be administered if the patient was being treated with only a single component. In other circumstances, it might be desirable to create a dosage unit that will deliver a dosage of one or more components that is less than that which would be administered if the patient was being treated only with a single component. Finally, it might be desirable to create a dosage unit that will deliver a dosage of one or more components that is greater than that which would be administered if the patient was being treated only with a single component. The pharmaceutical composition can include additional ingredients including but not limited to the excipients described herein. In certain embodiments, one or more therapeutic agents of the dosage unit may exist in an extended or control release formulation and additional therapeutic agents may not exist in extended release formulation. For example, an agent described herein may exist in a controlled release formulation or extended release formulation in the same dosage unit with another agent that may or may not be in either a controlled release or extended release formulation. Thus, in certain embodiments, it may be desirable to provide for the immediate release of one or

more of the agents described herein, and the controlled release of one or more other agents.

In certain embodiments the dosage unit and daily dose are equivalent. In certain embodiments the dosage unit and the daily dose are not equivalent. In various embodiments, the dosage unit is administered twenty minutes prior to food consumption, twenty minutes after food consumption, with food at anytime of the day, without food at anytime of the day, with food after an overnight fast (e.g. with breakfast), at bedtime after a low fat snack. In various embodiments, the dosage unit is administered once a day, twice a day, three times a day, four times a day, five times a day, six times a day.

When two or more active ingredients are combined in single dosage form, chemical interactions between the active ingredients may occur. For example, acidic and basic active ingredients can react with each other and acidic active ingredients can facilitate the degradation of acid labile substances. Thus, in certain dosage forms, acidic and basic substances can be physically separated as two distinct or isolated layers in a compressed tablet, or in the core and shell of a press-coated tablet. Additional agents that are compatible with acidic as well as basic substances, have the flexibility of being placed in either layer. In certain multiple layer compositions at least one active ingredient can be enteric-coated. In certain embodiments thereof at least one active ingredient can be presented in a controlled release form. In certain embodiments where a combination of three or more active substances are used, they can be presented as physically isolated segments of a compressed mutlilayer tablet, which can be optionally film coated.

The therapeutic combinations described herein can be formulated as a tablet or capsule comprising a plurality of beads, granules, or pellets. All active ingredients including the vitamins of the combination are formulated into granules or beads or pellets that are further coated with a protective coat, an enteric coat, or a film coat to avoid the possible chemical interactions. Granulation and coating of granules or

beads is done using techniques well known to a person skilled in the art. At least one active ingredient can present in a controlled release form. Finally these coated granules or beads are filled into hard gelatin capsules or compressed to form tablets.

The therapeutic combinations described herein can be formulated as a capsule comprising microtablets or minitablets of all active ingredients. Microtablets of the individual agents can be prepared using well known pharmaceutical procedures of tablet making like direct compression, dry granulation or wet granulation. Individual microtablets can be filled into hard gelatin capsules. A final dosage form may comprise one or more microtablets of each individual component. The microtablets may be film coated or enteric coated.

The therapeutic combinations described herein can be formulated as a capsule comprising one or more microtablets and powder, or one or more microtablets and granules or beads. In order to avoid interactions between drugs, some active ingredients of a said combination can be formulated as microtablets and the others filled into capsules as a powder, granules, or beads. The microtablets may be film coated or enteric coated. At least one active ingredient can be presented in controlled release form.

The therapeutic combinations described herein can be formulated wherein the active ingredients are distributed in the inner and outer phase of tablets. In an attempt to divide chemically incompatible components of proposed combination, few interacting components are converted in granules or beads using well known pharmaceutical procedures in prior art. The prepared granules or beads (inner phase) are then mixed with outer phase comprising the remaining active ingredients and at least one pharmaceutically acceptable excipient. The mixture thus comprising inner and outer phase is compressed into tablets or molded into tablets. The granules or beads can be controlled release or immediate release beads or granules, and can further be coated using an enteric polymer in an aqueous or non-aqueous system, using methods and materials that are known in the art.

The therapeutic combinations described herein can be formulated as single dosage unit comprising suitable buffering agent. All powdered ingredients of said combination are mixed and a suitable quantity of one or more buffering agents is added to the blend to minimize possible interactions.

The agents described herein, alone or in combination, can be combined with any pharmaceutically acceptable carrier or medium. Thus, they can be combined with materials that do not produce an adverse, allergic or otherwise unwanted reaction when administered to a patient. The carriers or mediums used can include solvents, dispersants, coatings, absorption promoting agents, controlled release agents, and one or more inert excipients (which include starches, polyols, granulating agents, microcrystalline cellulose, diluents, lubricants, binders, disintegrating agents, and the like), etc. If desired, tablet dosages of the disclosed compositions may be coated by standard aqueous or nonaqueous techniques.

Analgesic Agents in combitherapy

The agents described herein can be used in combination therapy with an analgesic agent, e.g., an analgesic compound or an analgesic peptide. These peptides and compounds can be administered with the agents of the invention (simultaneously or sequentially). They can also be optionally covalently linked or attached to an agent described herein to create therapeutic conjugates. Among the useful analgesic agents are: Ca channel blockers, 5HT receptor antagonists (for example 5HT3, 5HT4 and 5HT1 receptor antagonists), opioid receptor agonists (loperamide, fedotozine, and fentanyl), NK1 receptor antagonists, CCK receptor agonists (e.g., loxiglumide), NK1 receptor antagonists, NK3 receptor antagonists, norepinephrine-serotonin reuptake inhibitors (NSRI), vanilloid and cannabanoid receptor agonists, and sialorphin. Analgesics agents in the various classes are described in the literature.

Among the useful analgesic peptides are sialorphin-related peptides, including those comprising the amino acid sequence QHNPR (SEQ ID NO:), including: VQHNPR

(SEQ ID NO:); VRQHNPR (SEQ ID NO:); VRGQHNPR (SEQ ID NO:); VRGPQHNPR (SEQ ID NO:); VRGPRQHNPR (SEQ ID NO:); VRGPRRQHNPR (SEQ ID NO:); and RQHNPR (SEQ ID NO:). Sialorphin-related peptides bind to neprilysin and inhibit neprilysin-mediated breakdown of substance P and Met-enkephalin. Thus, compounds or peptides that are inhibitors of neprilysin are useful analgesic agents which can be administered with the agents of the invention in a co-therapy or linked to the agents of the invention, e.g., by a covalent bond. Sialophin and related peptides are described in U.S. Patent 6,589,750; U.S. 20030078200 A1; and WO 02/051435 A2.

Opioid receptor antagonists and agonists can be administered with the agents of the invention in co-therapy or linked to the agent of the invention, e.g., by a covalent bond. For example, opioid receptor antagonists such as naloxone, naltrexone, methyl nalozone, nalmefene, cypridime, beta funaltrexamine, naloxonazine, naltrindole, and nor-binaltorphimine are thought to be useful in the treatment of IBS. It can be useful to formulate opioid antagonists of this type is a delayed and sustained release formulation such that initial release of the antagonist is in the mid to distal small intestine and/or ascending colon. Such antagonists are described in WO 01/32180 A2. Enkephalin pentapeptide (HOE825; Tyr-D-Lys-Gly-Phe-L-homoserine) is an agonist of the mu and delta opioid receptors and is thought to be useful for increasing intestinal motility (*Eur. J. Pharm.* 219:445, 1992), and this peptide can be used in conjunction with the agents of the invention. Also useful is trimebutine which is thought to bind to mu/delta/kappa opioid receptors and activate release of motilin and modulate the release of gastrin, vasoactive intestinal peptide, gastrin and glucagons. Kappa opioid receptor agonists such as fedotozine, asimadoline, and ketocyclazocine, and compounds described in WO 03/097051 A2 can be used with or linked to the agents of the invention. In addition, mu opioid receptor agonists such as morphine, diphenyloxylate, frakefamide (H-Tyr-D-Ala-Phe(F)-Phe-NH_2; WO 01/019849 A1) and loperamide can be used.

Tyr-Arg (kyotorphin) is a dipeptide that acts by stimulating the release of met-enkephalins to elicit an analgesic effect (*J. Biol. Chem* 262:8165, 1987). Kyotorphin can be used with or linked to the agents of the invention.

Chromogranin-derived peptide (CgA 47–66; see, e.g., Ghia et al. 2004 Regulatory Peptides 119:199) can be used with or linked to the agents of the invention.

CCK receptor agonists such as caerulein from amphibians and other species are useful analgesic agents that can be used with or linked to the agents of the invention.

Conotoxin peptides represent a large class of analgesic peptides that act at voltage gated Ca channels, NMDA receptors or nicotinic receptors. These peptides can be used with or linked to the agents of the invention.

Peptide analogs of thymulin (FR Application 2830451) can have analgesic activity and can be used with or linked to the agents of the invention.

CCK (CCKa or CCKb) receptor antagonists, including loxiglumide and dexloxiglumide (the R-isomer of loxiglumide) (WO 88/05774) can have analgesic activity and can be used with or linked to the agents of the invention.

Other useful analgesic agents include 5-HT4 agonists such as tegaserod (Zelnorm®), mosapride, metoclopramide, zacopride, cisapride, renzapride, benzimidazolone derivatives such as BIMU 1 and BIMU 8, and lirexapride. Such agonists are described in: EP1321142 A1, WO 03/053432A1, EP 505322 A1, EP 505322 B1, US 5,510,353, EP 507672 A1, EP 507672 B1, and US 5,273,983.

Calcium channel blockers such as ziconotide and related compounds described in, for example, EP625162B1, US 5,364,842, US 5,587,454, US 5,824,645, US 5,859,186, US 5,994,305, US 6,087,091, US 6,136,786, WO 93/13128 A1, EP 1336409 A1, EP 835126 A1, EP 835126 B1, US 5,795,864, US 5,891,849, US

6,054,429, WO 97/01351 A1, can be used with or linked to the agents of the invention.

Various antagonists of the NK-1, NK-2, and NK-3 receptors (for a review see Giardina et al. 2003 *Drugs* 6:758) can be can be used with or linked to the agents of the invention.

NK1 receptor antagonists such as: aprepitant (Merck & Co Inc), vofopitant, ezlopitant (Pfizer, Inc.), R-673 (Hoffmann-La Roche Ltd), SR-48968 (Sanofi Synthelabo), CP-122,721 (Pfizer, Inc.), GW679769 (Glaxo Smith Kline), TAK-637 (Takeda/Abbot), SR-14033, and related compounds described in, for example, EP 873753 A1, US 20010006972 A1, US 20030109417 A1, WO 01/52844 A1, can be used with or linked to the agents of the invention.

NK-2 receptor antagonists such as nepadutant (Menarini Ricerche SpA), saredutant (Sanofi-Synthelabo), GW597599 (Glaxo Smith Kline), SR-144190 (Sanofi-Synthelabo) and UK-290795 (Pfizer Inc) can be used with or linked to the agents of the invention.

NK3 receptor antagonists such as osanetant (SR-142801; Sanofi-Synthelabo), SSR-241586, talnetant and related compounds described in, for example, WO 02/094187 A2, EP 876347 A1, WO 97/21680 A1, US 6,277,862, WO 98/11090, WO 95/28418, WO 97/19927, and Boden et al. (*J Med Chem.* 39:1664-75, 1996) can be used with or linked to the agents of the invention.

Norepinephrine-serotonin reuptake inhibitors (NSRI) such as milnacipran and related compounds described in WO 03/077897 A1 can be used with or linked to the agents of the invention.

Vanilloid receptor antagonists such as arvanil and related compouds described in WO 01/64212 A1 can be used with or linked to the agents of the invention.

The analgesic peptides and compounds can be administered with cGMP and analogs thereof (simultaneously or sequentially). The analgesic agents can also be covalently linked to cGMP and analogs thereof to create therapeutic conjugates. Where the analgesic is a peptide and is covalently linked to an agent described herein the resulting agent may also include at least one cleavage site.

In addition to sialorphin-related peptides, analgesic peptides include: AspPhe, endomorphin-1, endomorphin-2, nocistatin, dalargin, lupron, ziconotide, and substance P.

Other Agents for Use in Combitherapy

Also within the invention are pharmaceutical compositions comprising cGMP or an analog thereof and a second therapeutic agent. The second therapeutic agent can be administered to treat any condition for which it is useful, including conditions that are not considered to be the primary indication for treatment with the second therapeutic agent. The second therapeutic agent can be administered simultaneously or sequentially. The second therapeutic agent can be covalently linked to cGMP and analogs thereof to create a therapeutic conjugate, e.g., via a linker.

Examples of additional therapeutic agents to treat gastrointestinal and other disorders include:

agents used to treat diarrhea including but not limited to: Octreotide, antiperistaltic agents (e.g. Loperamide (Imodium, Pepto Diarrhea)), Tamoxifen, bulking agent, anti-estrogens (e.g. droloxifene, TAT-59, and raloxifene), tormentil root extract (Potentilla tormentilla) from the family Rosaceae, bismuth subsalicylate (e.g. Pepto-Bismol™), diphenoxylate, diphenoxylate with atropine (Lomotil, Lomocot), oat bran, psyllium, calcium carbonate, astringents (e.g., tannins), cholestyramine (Questran, Cholybar), anticholinergics (e.g., atropine (Co-Phenotrope, Diarsed, Diphenoxylate, Lofene, Logen, Lonox, Vi-Atro, atropine sulfate injection),

hyoscyamine, and metoclopramide), spasmolytics such as Reasec™(Janssen), α2-adrenergic agonists such as clonidine (Catapresan™), somatostatin, encephalin, morphine analogs, lidamidine, Xifaxan® (rifaximin; Salix Pharmaceuticals Ltd), , TZP-201(Tranzyme Pharma Inc.), the neuronal acetylcholine receptor (nAChR) blocker AGI-004 (AGI therapeutics), opium derivatives and astringents.

acid reducing agents such as proton pump inhibitors (e.g., omeprazole (Prilosec®), esomeprazole (Nexium®), lansoprazole (Prevacid®), pantoprazole (Protonix®) and rabeprazole (Aciphex®)) and Histamine H2-receptor antagonist (also known as H2 receptor blockers including cimetidine, ranitidine, famotidine and nizatidine);

complete or partial 5HT (e.g. 5HT1, 5HT2, 5HT3, 5HT4) receptor agonists or antagonists (including 5HT1A antagonists (e.g. AGI-001 (AGI therapeutics)), 5HT2B antagonists (e.g. PGN1091 and PGN1164 (Pharmagene Laboratories Limited)), 5HT4 receptor agonists (such as tegaserod (ZELNORM®), prucalopride, mosapride, metoclopramide, zacopride, cisapride, renzapride, benzimidazolone derivatives such as BIMU 1 and BIMU 8, and lirexapride); 5HT3 receptor agonists such as MKC-733; and 5HT3 receptor antagonists such as DDP-225 (MCI-225; Dynogen Pharmaceuticals, Inc.), cilansetron (Calmactin®), alosetron (Lotronex®), Ondansetron HCl (Zofran®), Dolasetron (ANZEMET®), palonosetron (Aloxi®), Granisetron (Kytril®), YM060(ramosetron; Astellas Pharma Inc.) and ATI-7000 (Aryx Therapeutics, Santa Clara CA) (5HT agonists and antagonists are described in, for example: EP1321142 A1, WO 03/053432A1, EP 505322 A1, EP 505322 B1, US 5,510,353, EP 507672 A1, EP 507672 B1, and US 5,273,983));

muscarinic receptor agonists;

anti-inflammatory agents;

antispasmodics including anticholinergic drugs (like dicyclomine (e.g. Colimex®, Formulex®, Lomine®, Protylol®, Viscerol®, Spasmoban®, Bentyl®, Bentylol®), hyoscyamine (e.g. IB-Stat®, Nulev®, Levsin®, Levbid®, Levsinex Timecaps®, Levsin/SL®, Anaspaz®, A-Spas S/L®, Cystospaz®, Cystospaz-M®, Donnamar®, Colidrops Liquid Pediatric®, Gastrosed®, Hyco Elixir®, Hyosol®, Hyospaz®, Hyosyne®, Losamine®, Medispaz®, Neosol®, Spacol®, Spasdel®, Symax®, Symax SL®), Donnatal (e.g. Donnatal Extentabs®), clidinium (e.g. Quarzan, in combination with Librium = Librax), methantheline (e.g. Banthine), Mepenzolate (e.g. Cantil), homatropine (e.g. hycodan, Homapin), Propantheline bromide (e.g. Pro-Banthine), Glycopyrrolate (e.g. Robinul®, Robinul Forte®), scopolamine (e.g. Transderm-Scop®, Transderm-V®), hyosine-N-butylbromide (e.g. Buscopan®), Pirenzepine (e.g. Gastrozepin®), dicycloverine (e.g. Merbentyl®) , glycopyrronium bromide (e.g. Glycopyrrolate®), hyoscine hydrobromide, hyoscine methobromide, methanthelinium, and octatropine); peppermint oil; and direct smooth muscle relaxants like cimetropium bromide, mebeverine (DUSPATAL®, DUSPATALIN®, COLOFAC MR®, COLOTAL®), otilonium bromide (octilonium), pinaverium (e.g. Dicetel® (pinaverium bromide; Solvay S.A.)), Spasfon® (hydrated phloroglucinol and trimethylphloroglucinol) and trimebutine (including trimebutine maleate (Modulon®);

antidepressants, including but not limited to those listed herein, as well as tricyclic antidepressants like amitriptyline (Elavil®), desipramine (Norpramin®), imipramine (Tofranil®), amoxapine (Asendin®), nortriptyline; the selective serotonin reuptake inhibitors (SSRI's) like paroxetine (Paxil®), fluoxetine (Prozac®), sertraline (Zoloft®), and citralopram (Celexa®); and others like doxepin (Sinequan®) and trazodone (Desyrel®);

centrally-acting analgesic agents such as opioid receptor agonists, opioid receptor antagonists (e.g., naltrexone);

agents for the treatment of Inflammatory bowel disease;

agents for the treatment of Crohn's disease and/or ulcerative colitis (e.g., alequel (Enzo Biochem, Inc.; Farmingsale, NY), the anti-inflammatory peptide RDP58 (Genzyme, Inc.; Cambridge, MA), and TRAFICET-EN™ (ChemoCentryx, Inc.; San Carlos, CA);

agents that treat gastrointestinal or visceral pain;

PDE (phosphodiesterase) inhibitors including but not limited to those disclosed herein;

Corticotropin Releasing Factor (CRF) receptor antagonists (including NBI-34041 (Neurocrine Biosciences, San Diego, CA), CRH9-41, astressin, R121919 (Janssen Pharmaceutica), CP154,526, NBI-27914, Antalarmin, DMP696 (Bristol-Myers Squibb) CP-316,311 (Pfizer, Inc.), SB723620 (GSK), GW876008 (Neurocrine/Glaxo Smith Kline), ONO-2333Ms (Ono Pharmaceuticals), TS-041 (Janssen), AAG561 (Novartis) and those disclosed in US 5,063,245, US 5,861,398, US20040224964, US20040198726, US20040176400, US20040171607, US20040110815, and US20040006066);

glucagon-like peptides (glp-1) and analogues thereof (including exendin-4 and GTP-010 (Gastrotech Pharma A)) and inhibitors of DPP-IV (DPP-IV mediates the inactivation of glp-1);

tofisopam, enantiomerically-pure R-tofisopam, and pharmaceutically-acceptable salts thereof (US 20040229867);

the tricyclic anti-depressant of the dibenzothiazepine type (e.g. Dextofisopam® (Vela Pharmaceuticals), tianeptine (Stablon®) and other agents described in U.S. 6,683,072;

(E)-4 (1,3bis(cyclohexylmethyl)-1,2,34,-tetrahydro-2,6-diono-9H-purin-8-yl)cinnamic acid nonaethylene glycol methyl ether ester and related compounds described in WO 02/067942;

the probiotic PROBACTRIX® (The BioBalance Corporation; New York, NY) which contains microorganisms useful in the treatment of gastrointestinal disorders;

anxiolytic drugs including but not limited toAtivan (lorazepam), alprazolam (Xanax®), chlordiazepoxide/clidinium (Librium®, Librax®), clonazepam (Klonopin®), clorazepate (Tranxene®), diazepam (Valium®), estazolam (ProSom®), flurazepam (Dalmane®), oxazepam (Serax®), prazepam (Centrax®), temazepam (Restoril®), triazolam (Halcion®);

Bedelix® (Montmorillonite beidellitic; Ipsen Ltd), Solvay SLV332 (ArQule Inc), YKP (SK Pharma), Asimadoline (Tioga Pharmaceuticals/Merck), AGI-003 (AGI Therapeutics);
the serotonin modulator AZD7371 (AstraZeneca Plc);

M3 muscarinic receptor antagonists such as darifenacin (Enablex; Novartis AG and zamifenacin (Pfizer); and

herbal and natural therapies including but not limited to acidophilus, chamomile tea, evening primrose oil, fennel seeds,wormwood, and comfrey.

The agents described herein can be used in combination therapy with an anti-obesity agent. Suitable such agents include, but are not limited to:

11β HSD-1 (11-beta hydroxy steroid dehydrogenase type 1) inhibitors, such as BVT 3498, BVT 2733, 3-(1-adamanty1)-4-ethyl-5-(ethy1thio)- 4H-1,2,4-triazole, 3-(1-adamantyl)-5-(3,4,5-trimethoxypheny1)-4-methy1-4H-1,2,4-triazole, 3-

adamantanyl-4,5,6,7,8,9,10,11,12,3a-decahydro-1,2,4-triazolo[4,3-a][11]annulene, and those compounds disclosed in WO01/90091, WO01/90090, WO01/90092 and WO02/072084;

5HT antagonists such as those in WO03/037871, WO03/037887, and the like;

5HT1a modulators such as carbidopa, benserazide and those disclosed in US6207699, WO03/031439, and the like;

5HT2c (serotonin receptor 2c) agonists, such as BVT933, DPCA37215, IK264, PNU 22394, WAY161503, R-1065, SB 243213 (Glaxo Smith Kline) and YM 348 and those disclosed in US3914250, WO00/77010, WO02/36596, WO02/48124, WO02/10169, WO01/66548, WO02/44152, WO02/51844, WO02/40456, and WO02/40457;

5HT6 receptor modulators, such as those in WO03/030901, WO03/035061, WO03/039547, and the like;

acyl-estrogens, such as oleoyl-estrone, disclosed in del Mar-Grasa, M. et al., Obesity Research, 9:202-9 (2001) and Japanese Patent Application No. JP 2000256190;

anorectic bicyclic compounds such as 1426 (Aventis) and 1954 (Aventis), and the compounds disclosed in WO00/18749, WO01/32638, WO01/62746, WO01/62747, and WO03/015769;

CB 1 (cannabinoid-1 receptor) antagonist/inverse agonists such as rimonabant (Acomplia; Sanofi), SR-147778 (Sanofi), SR-141716 (Sanofi), BAY 65-2520 (Bayer), and SLV 319 (Solvay), and those disclosed in patent publications US4973587, US5013837, US5081122, US5112820, US5292736, US5532237, US5624941, US6028084, US6509367, US6509367, WO96/33159, WO97/29079, WO98/31227, WO98/33765, WO98/37061, WO98/41519, WO98/43635, WO98/43636, WO99/02499, WO00/10967, WO00/10968, WO01/09120, WO01/58869, WO01/64632, WO01/64633, WO01/64634, WO01/70700,

WO01/96330, WO02/076949, WO03/006007, WO03/007887, WO03/020217, WO03/026647, WO03/026648, WO03/027069, WO03/027076, WO03/027114, WO03/037332, WO03/040107, WO03/086940, WO03/084943 and EP658546;

CCK-A (cholecystokinin-A) agonists, such as AR-R 15849, GI 181771 (GSK), JMV-180, A-71378, A-71623 and SR146131 (Sanofi), and those described in US5739106;

CNTF (Ciliary neurotrophic factors), such as GI-181771 (Glaxo-SmithKline), SR146131 (Sanofi Synthelabo), butabindide, PD170,292, and PD 149164 (Pfizer);

CNTF derivatives, such as Axokine® (Regeneron), and those disclosed in WO94/09134, WO98/22128, and WO99/43813;

dipeptidyl peptidase IV (DP-IV) inhibitors, such as isoleucine thiazolidide, valine pyrrolidide, NVP-DPP728, LAF237, P93/01, P 3298, TSL 225 (tryptophyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid; disclosed by Yamada et al, Bioorg. & Med. Chem. Lett. 8 (1998) 1537-1540), TMC-2A/2B/2C, CD26 inhibtors, FE 999011, P9310/K364, VIP 0177, SDZ 274-444, 2-cyanopyrrolidides and 4-cyanopyrrolidides as disclosed by Ashworth et al, Bioorg. & Med. Chem. Lett., Vol. 6, No. 22, pp 1163-1166 and 2745-2748 (1996) and the compounds disclosed patent publications. WO99/38501, WO99/46272, WO99/67279 (Probiodrug), WO99/67278 (Probiodrug), WO99/61431 (Probiodrug), WO02/083128, WO02/062764, WO03/000180, WO03/000181, WO03/000250, WO03/002530, WO03/002531, WO03/002553, WO03/002593, WO03/004498, WO03/004496,WO03/017936, WO03/024942, WO03/024965, WO03/033524, WO03/037327 and EP1258476;

growth hormone secretagogue receptor agonists/antagonists, such as NN703, hexarelin, MK-0677 (Merck), SM-130686, CP-424391 (Pfizer), LY 444,711 (Eli Lilly), L-692,429 and L-163,255, and such as those disclosed in USSN 09/662448, US provisional application 60/203335, US6358951, US2002049196, US2002/022637, WO01/56592 and WO02/32888;

H3 (histamine H3) antagonist/inverse agonists, such as thioperamide, 3-(1H-imidazol-4-yl)propyl N-(4-pentenyl)carbamate), clobenpropit, iodophenpropit, imoproxifan, GT2394 (Gliatech), and A331440, O-[3-(1H-imidazol-4-yl)propanol]carbamates (Kiec-Kononowicz, K. et al., Pharmazie, 55:349-55 (2000)), piperidine-containing histamine H3-receptor antagonists (Lazewska, D. et al., Pharmazie, 56:927-32 (2001), benzophenone derivatives and related compounds (Sasse, A. et al., Arch. Pharm.(Weinheim) 334:45-52 (2001)), substituted N-phenylcarbamates (Reidemeister, S. et al., Pharmazie, 55:83-6 (2000)), and proxifan derivatives (Sasse, A. et al., J. Med. Chem.. 43:3335-43 (2000)) and histamine H3 receptor modulators such as those disclosed in WO02/15905, WO03/024928 and WO03/024929;

leptin derivatives, such as those disclosed in US5552524, US5552523, US5552522, US5521283, WO96/23513, WO96/23514, WO96/23515, WO96/23516, WO96/23517, WO96/23518, WO96/23519, and WO96/23520;

leptin, including recombinant human leptin (PEG-OB, Hoffman La Roche) and recombinant methionyl human leptin (Amgen);

lipase inhibitors, such as tetrahydrolipstatin (orlistat/Xenical®), Triton WR1339, RHC80267, lipstatin, teasaponin, diethylumbelliferyl phosphate, FL-386, WAY-121898, Bay-N-3176, valilactone, esteracin, ebelactone A, ebelactone B, and RHC 80267, and those disclosed in patent publications WO01/77094, US4598089, US4452813, USUS5512565, US5391571, US5602151, US4405644, US4189438, and US4242453;

lipid metabolism modulators such as maslinic acid, erythrodiol, ursolic acid uvaol, betulinic acid, betulin, and the like and compounds disclosed in WO03/011267;

Mc4r (melanocortin 4 receptor) agonists, such as CHIR86036 (Chiron), ME-10142, ME-10145, and HS-131 (Melacure), and those disclosed in PCT publication Nos. WO99/64002, WO00/74679, WO01/991752, WO01/25192, WO01/52880, WO01/74844, WO01/70708, WO01/70337, WO01/91752, WO02/059095,

WO02/059107, WO02/059108, WO02/059117, WO02/06276, WO02/12166, WO02/11715, WO02/12178, WO02/15909, WO02/38544, WO02/068387, WO02/068388, WO02/067869, WO02/081430, WO03/06604, WO03/007949, WO03/009847, WO03/009850, WO03/013509, and WO03/031410;

Mc5r (melanocortin 5 receptor) modulators, such as those disclosed in WO97/19952, WO00/15826, WO00/15790, US20030092041;

melanin-concentrating hormone 1 receptor (MCHR) antagonists, such as T-226296 (Takeda), SB 568849, SNP-7941 (Synaptic), and those disclosed in patent publications WO01/21169, WO01/82925, WO01/87834, WO02/051809, WO02/06245, WO02/076929, WO02/076947, WO02/04433, WO02/51809, WO02/083134, WO02/094799, WO03/004027, WO03/13574, WO03/15769, WO03/028641, WO03/035624, WO03/033476, WO03/033480, JP13226269, and JP1437059;

mGluR5 modulators such as those disclosed in WO03/029210, WO03/047581, WO03/048137, WO03/051315, WO03/051833, WO03/053922, WO03/059904, and the like;

serotoninergic agents, such as fenfluramine (such as Pondimin® (Benzeneethanamine, N-ethyl-alpha-methyl-3-(trifluoromethyl)-, hydrochloride), Robbins), dexfenfluramine (such as Redux® (Benzeneethanamine, N-ethyl-alpha-methyl-3-(trifluoromethyl)-, hydrochloride), Interneuron) and sibutramine ((Meridia®, Knoll/Reductil™) including racemic mixtures, as optically pure isomers (+) and (-), and pharmaceutically acceptable salts, solvents, hydrates, clathrates and prodrugs thereof including sibutramine hydrochloride monohydrate salts thereof, and those compounds disclosed in US4746680, US4806570, and US5436272, US20020006964, WO01/27068, and WO01/62341;

NE (norepinephrine) transport inhibitors, such as GW 320659, despiramine, talsupram, and nomifensine;

NPY 1 antagonists, such as BIBP3226, J-115814, BIBO 3304, LY-357897, CP-671906, GI-264879A, and those disclosed in US6001836, WO96/14307, WO01/23387, WO99/51600, WO01/85690, WO01/85098, WO01/85173, and WO01/89528;

NPY5 (neuropeptide Y Y5) antagonists, such as 152,804, GW-569180A, GW-594884A, GW-587081X, GW-548118X, FR235208, FR226928, FR240662, FR252384, 1229U91, GI-264879A, CGP71683A, LY-377897, LY-366377, PD-160170, SR- 120562A, SR-120819A, JCF-104, and H409/22 and those compounds disclosed in patent publications US6140354, US6191160, US6218408, US6258837, US6313298, US6326375, US6329395, US6335345, US6337332, US6329395, US6340683, EP01010691, EP-01044970, WO97/19682, WO97/20820, WO97/20821, WO97/20822, WO97/20823, WO98/27063, WO00/107409, WO00/185714, WO00/185730, WO00/64880, WO00/68197, WO00/69849, WO/0113917, WO01/09120, WO01/14376, WO01/85714, WO01/85730, WO01/07409, WO01/02379, WO01/23388, WO01/23389, WO01/44201, WO01/62737, WO01/62738, WO01/09120, WO02/20488, WO02/22592, WO02/48152, WO02/49648, WO02/051806, WO02/094789, WO03/009845, WO03/014083, WO03/022849, WO03/028726 and Norman et al., J. Med. Chem. 43:4288-4312 (2000);

opioid antagonists, such as nalmefene (REVEX ®), 3-methoxynaltrexone, naloxone, and naltrexone (e.g. PT901; Pain Therapeutics, Inc.) and those disclosed in WO00/21509;

orexin antagonists, such as SB-334867-A and those disclosed in patent publications WO01/96302, WO01/68609, WO02/44172, WO02/51232, WO02/51838, WO02/089800, WO02/090355, WO03/023561, WO03/032991, and WO03/037847;

PDE inhibitors (e.g. compounds which slow the degradation of cyclic AMP (cAMP) and/or cyclic GMP (cGMP) by inhibition of the phosphodiesterases, which can lead to a relative increase in the intracellular concentration of cAMP and cGMP; possible

PDE inhibitors are primarily those substances which are to be numbered among the class consisting of the PDE3 inhibitors, the class consisting of the PDE4 inhibitors and/or the class consisting of the PDE5 inhibitors, in particular those substances which can be designated as mixed types of PDE3/4 inhibitors or as mixed types of PDE3/4/5 inhibitors) such as those disclosed in patent publications DE1470341, DE2108438, DE2123328, DE2305339, DE2305575, DE2315801, DE2402908, DE2413935, DE2451417, DE2459090, DE2646469, DE2727481, DE2825048, DE2837161, DE2845220, DE2847621, DE2934747, DE3021792, DE3038166, DE3044568, EP000718, EP0008408, EP0010759, EP0059948, EP0075436, EP0096517, EP0112987, EP0116948, EP0150937, EP0158380, EP0161632, EP0161918, EP0167121, EP0199127, EP0220044, EP0247725, EP0258191, EP0272910, EP0272914, EP0294647, EP0300726, EP0335386, EP0357788, EP0389282, EP0406958, EP0426180, EP0428302, EP0435811, EP0470805, EP0482208, EP0490823, EP0506194, EP0511865, EP0527117, EP0626939, EP0664289, EP0671389, EP0685474, EP0685475, EP0685479, JP92234389, JP94329652, JP95010875, US4963561, US5141931, WO9117991, WO9200968, WO9212961, WO9307146, WO9315044, WO9315045, WO9318024, WO9319068, WO9319720, WO9319747, WO9319749, WO9319751, WO9325517, WO9402465, WO9406423, WO9412461, WO9420455, WO9422852, WO9425437, WO9427947, WO9500516, WO9501980, WO9503794, WO9504045, WO9504046, WO9505386, WO9508534, WO9509623, WO9509624, WO9509627, WO9509836, WO9514667, WO9514680, WO9514681, WO9517392, WO9517399, WO9519362, WO9522520, WO9524381, WO9527692, WO9528926, WO9535281, WO9535282, WO9600218, WO9601825, WO9602541, WO9611917, DE3142982, DE1116676, DE2162096, EP0293063, EP0463756, EP0482208, EP0579496, EP0667345 US6331543, US20050004222 (including those disclosed in formulas I-XIII and paragraphs 37-39, 85-0545 and 557-577), WO9307124, EP0163965, EP0393500, EP0510562, EP0553174, WO9501338 and WO9603399, as well as PDE5 inhibitors (such as RX-RA-69, SCH-51866, KT-734, vesnarinone, zaprinast, SKF-96231, ER-21355, BF/GP-385, NM-702 and sildenafil (Viagra™)), PDE4 inhibitors (such as etazolate, ICI63197, RP73401, imazolidinone (RO-20-1724), MEM 1414 (R1533/R1500;

Pharmacia Roche), denbufylline, rolipram, oxagrelate, nitraquazone, Y-590, DH-6471, SKF-94120, motapizone, lixazinone, indolidan, olprinone, atizoram, KS-506-G, dipamfylline, BMY-43351, atizoram, arofylline, filaminast, PDB-093, UCB-29646, CDP-840, SKF-107806, piclamilast, RS-17597, RS-25344-000, SB-207499, TIBENELAST, SB-210667, SB-211572, SB-211600, SB-212066, SB-212179, GW-3600, CDP-840, mopidamol, anagrelide, ibudilast, amrinone, pimobendan, cilostazol, quazinone and N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy4-difluoromethoxybenzamide, PDE3 inhibitors (such as ICI153, 100, bemorandane (RWJ 22867), MCI-154, UD-CG 212, sulmazole, ampizone, cilostamide, carbazeran, piroximone, imazodan, CI-930, siguazodan, adibendan, saterinone, SKF-95654, SDZ-MKS-492, 349-U-85, emoradan, EMD-53998, EMD-57033, NSP-306, NSP-307, revizinone, NM-702, WIN-62582 and WIN-63291, enoximone and milrinone, PDE3/4 inhibitors (such as benafentrine, trequinsin, ORG-30029, zardaverine, L-686398, SDZ-ISQ-844, ORG-20241, EMD-54622, and tolafentrine) and other PDE inhibitors (such as vinpocetin, papaverine, enprofylline, cilomilast, fenoximone, pentoxifylline, roflumilast, tadalafil(Cialis®), theophylline, and vardenafil(Levitra®);

Neuropeptide Y2 (NPY2) agonists include but are not limited to: peptide YY and fragments and variants thereof (e.g. YY3–36 (PYY3-36)(N. Engl. J. Med. 349:941, 2003; IKPEAPGE DASPEELNRY YASLRHYLNL VTRQRY (SEQ ID NO:XXX)) and PYY agonists such as those disclosed in WO03/026591, WO03/057235, and WO03/027637;

serotonin reuptake inhibitors, such as, paroxetine, fluoxetine (Prozac™), fluvoxamine, sertraline, citalopram, and imipramine, and those disclosed in US6162805, US6365633, WO03/00663, WO01/27060, and WO01/162341;

thyroid hormone β agonists, such as KB-2611 (KaroBioBMS), and those disclosed in WO02/15845, WO97/21993, WO99/00353, GB98/284425, U.S. Provisional Application No. 60/183,223, and Japanese Patent Application No. JP 2000256190;

UCP-1 (uncoupling protein-1), 2, or 3 activators, such as phytanic acid, 4-[(E)-2-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-napthalenyl)-1-propenyl]benzoic acid (TTNPB), retinoic acid, and those disclosed in WO99/00123;

β3 (beta adrenergic receptor 3) agonists, such as AJ9677/TAK677 (Dainippon/Takeda), L750355 (Merck), CP331648 (Pfizer), CL-316,243, SB 418790, BRL-37344, L-796568, BMS-196085, BRL-35135A, CGP12177A, BTA-243, GW 427353, Trecadrine, Zeneca D7114, N-5984 (Nisshin Kyorin), LY-377604 (Lilly), SR 59119A, and those disclosed in US5541204, US5770615, US5491134, US5776983, US488064, US5705515, US5451677, WO94/18161, WO95/29159, WO97/46556, WO98/04526 and WO98/32753, WO01/74782, WO02/32897, WO03/014113, WO03/016276, WO03/016307, WO03/024948, WO03/024953 and WO03/037881;

noradrenergic agents including, but not limited to, diethylpropion (such as Tenuate® (1-propanone, 2-(diethylamino)-1-phenyl-, hydrochloride), Merrell), dextroamphetamine (also known as dextroamphetamine sulfate, dexamphetamine, dexedrine, Dexampex, Ferndex, Oxydess II, Robese, Spancap #1), mazindol ((or 5-(p-chlorophenyl)-2,5-dihydro-3H-imidazo[2,1-a]isoindol-5-ol) such as Sanorex®, Novartis or Mazanor®, Wyeth Ayerst), phenylpropanolamine (or Benzenemethanol, alpha-(1-aminoethyl)-, hydrochloride), phentermine ((or Phenol, 3-[[4,5-duhydro-1H-imidazol-2-yl)ethyl](4-methylpheny-l)amino], monohydrochloride) such as Adipex-P®, Lemmon, FASTIN®, Smith-Kline Beecham and Ionamin®, Medeva), phendimetrazine ((or (2S,3S)-3,4-Dimethyl-2phenylmorpholine L-(+)-tartrate (1:1)) such as Metra® (Forest) , Plegine® (Wyeth-Ayerst), Prelu-2® (Boehringer Ingelheim), and Statobex® (Lemmon), phendamine tartrate (such as Thephorin® (2,3,4,9-Tetrahydro-2-methyl-9-phenyl-1H-indenol[2,1-c]pyridine L-(+)-tartrate (1:1)), Hoffmann-LaRoche), methamphetamine (such as Desoxyn®, Abbot ((S)--N, (alpha)-dimethylbenzeneethanamine hydrochloride)), and phendimetrazine tartrate (such as Bontril® Slow-Release Capsules, Amarin (-3,4-Dimethyl-2-phenylmorpholine Tartrate);

fatty acid oxidation upregulator/inducers such as Famoxin® (Genset);

monamine oxidase inhibitors including but not limited to befloxatone, moclobemide, brofaromine, phenoxathine, esuprone, befol, toloxatone, pirlindol, amiflamine, sercloremine, bazinaprine, lazabemide, milacemide, caroxazone and other certain compounds as disclosed by WO01/12176; and

other anti-obesity agents such as 5HT-2 agonists, ACC (acetyl-CoA carboxylase) inhibitors such as those described in WO03/072197, alpha-lipoic acid (alpha-LA), AOD9604, appetite suppressants such as those in WO03/40107, ATL-962 (Alizyme PLC), benzocaine, benzphetamine hydrochloride (Didrex), bladderwrack (focus vesiculosus), BRS3 (bombesin receptor subtype 3) agonists, bupropion, caffeine, CCK agonists, chitosan, chromium, conjugated linoleic acid, corticotropin-releasing hormone agonists, dehydroepiandrosterone, DGAT1 (diacylglycerol acyltransferase 1) inhibitors, DGAT2 (diacylglycerol acyltransferase 2) inhibitors, dicarboxylate transporter inhibitors, ephedra, exendin-4 (an inhibitor of glp-1) FAS (fatty acid synthase) inhibitors (such as Cerulenin and C75), fat resorption inhibitors (such as those in WO03/053451, and the like), fatty acid transporter inhibitors, natural water soluble fibers (such as psyllium, plantago, guar, oat, pectin), galanin antagonists, galega (Goat's Rue, French Lilac), garcinia cambogia, germander (teucrium chamaedrys), ghrelin antibodies and ghrelin antagonists (such as those disclosed in WO01/87335, and WO02/08250), peptide hormones and variants thereof which affect the islet cell secretion, such as the hormones of the secretin/gastric inhibitory peptide (GIP)/vasoactive intestinal peptide (VIP)/pituitary adenylate cyclase activating peptide (PACAP)/glucagon-like peptide II (GLP-II)/glicentin/glucagon gene family and/or those of the adrenomedullin/amylin/calcitonin gene related peptide (CGRP) gene family includingGLP-1 (glucagon-like peptide 1) agonists (e.g. (1) exendin-4, (2) those GLP-1 molecules described in US20050130891 including GLP-1(7-34), GLP-1(7-35), GLP-1(7-36) or GLP-1(7-37) in its C-terminally carboxylated or amidated form or as modified GLP-1 peptides and modifications thereof including those described in paragraphs 17-44 of

US20050130891,and derivatives derived from GLP-1-(7-34)COOH and the corresponding acid amide are employed which have the following general formula:

R-NH-HAEGTFTSDVSYLEGQAAKEFIAWLVK-$CONH_2$

wherein R=H or an organic compound having from 1 to 10 carbon atoms. Preferably, R is the residue of a carboxylic acid. Particularly preferred are the following carboxylic acid residues: formyl, acetyl, propionyl, isopropionyl, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl.) and glp-1 (glucagon-like peptide-1), glucocorticoid antagonists, glucose transporter inhibitors, growth hormone secretagogues (such as those disclosed and specifically described in US5536716), interleukin-6 (IL-6) and modulators thereof (as in WO03/057237, and the like), L-carnitine, Mc3r (melanocortin 3 receptor) agonists, MCH2R (melanin concentrating hormone 2R) agonist/antagonists, melanin concentrating hormone antagonists, melanocortin agonists (such as Melanotan II or those described in WO 99/64002 and WO 00/74679), nomame herba, phosphate transporter inhibitors, phytopharm compound 57 (CP 644,673), pyruvate, SCD-1 (stearoyl-CoA desaturase-1) inhibitors, T71 (Tularik, Inc., Boulder CO), Topiramate (Topimax®, indicated as an anti-convulsant which has been shown to increase weight loss), transcription factor modulators (such as those disclosed in WO03/026576), β-hydroxy steroid dehydrogenase-1 inhibitors (β -HSD-1), β-hydroxy-β-methylbutyrate, p57 (Pfizer), Zonisamide (Zonegran™, indicated as an anti-epileptic which has been shown to lead to weight loss), and the agents disclosed in US20030119428 paragraphs 20-26.

The agents described herein useful in the treatment of obesity can be administered as a cotherapy with electrostimulation (US20040015201).

The agents described herein can be used in combination therapy with agents that activate soluble guanylate cyclase, for example those described in US20040192680.

The agents described herein can be used in combination therapy with a phosphodiesterase inhibitor. PDE inhibitors are those compounds which slow the degradation of cyclic AMP (cAMP) and/or cyclic GMP (cGMP) by inhibition of the phosphodiesterases, which can lead to a relative increase in the intracellular concentration of cAMP and/or cGMP. Possible PDE inhibitors are primarily those substances which are to be numbered among the class consisting of the PDE3 inhibitors, the class consisting of the PDE4 inhibitors and/or the class consisting of the PDE5 inhibitors, in particular those substances which can be designated as mixed types of PDE3/4 inhibitors or as mixed types of PDE3/4/5 inhibitors. By way of example, those PDE inhibitors may be mentioned such as are described and/or claimed in the following patent applications and patents: DE1470341, DE2108438, DE2123328, DE2305339, DE2305575, DE2315801, DE2402908, DE2413935, DE2451417, DE2459090, DE2646469, DE2727481, DE2825048, DE2837161, DE2845220, DE2847621, DE2934747, DE3021792, DE3038166, DE3044568, EP000718, EP0008408, EP0010759, EP0059948, EP0075436, EP0096517, EP0112987, EP0116948, EP0150937, EP0158380, EP0161632, EP0161918, EP0167121, EP0199127, EP0220044, EP0247725, EP0258191, EP0272910, EP0272914, EP0294647, EP0300726, EP0335386, EP0357788, EP0389282, EP0406958, EP0426180, EP0428302, EP0435811, EP0470805, EP0482208, EP0490823, EP0506194, EP0511865, EP0527117, EP0626939, EP0664289, EP0671389, EP0685474, EP0685475, EP0685479, JP92234389, JP94329652, JP95010875, U.S. Pat. Nos. 4,963,561, 5,141,931, WO9117991, WO9200968, WO9212961, WO9307146, WO9315044, WO9315045, WO9318024, WO9319068, WO9319720, WO9319747, WO9319749, WO9319751, WO9325517, WO9402465, WO9406423, WO9412461, WO9420455, WO9422852, WO9425437, WO9427947, WO9500516, WO9501980, WO9503794, WO9504045, WO9504046, WO9505386, WO9508534, WO9509623, WO9509624, WO9509627, WO9509836, WO9514667, WO9514680, WO9514681, WO9517392, WO9517399, WO9519362, WO9522520, WO9524381, WO9527692, WO9528926, WO9535281, WO9535282, WO9600218, WO9601825, WO9602541, WO9611917, DE3142982, DE1116676, DE2162096, EP0293063, EP0463756, EP0482208, EP0579496, EP0667345 US6,331,543,

US20050004222 (including those disclosed in formulas I-XIII and paragraphs 37-39, 85-0545 and 557-577) and WO9307124, EP0163965, EP0393500, EP0510562, EP0553174, WO9501338 and WO9603399. PDE5 inhibitors which may be mentioned by way of example are RX-RA-69, SCH-51866, KT-734, vesnarinone, zaprinast, SKF-96231, ER-21355, BF/GP-385, NM-702 and sildenafil (Viagra®). PDE4 inhibitors which may be mentioned by way of example are RO-20-1724, MEM 1414 (R1533/R1500; Pharmacia Roche), DENBUFYLLINE, ROLIPRAM, OXAGRELATE, NITRAQUAZONE, Y-590, DH-6471, SKF-94120, MOTAPIZONE, LIXAZINONE, INDOLIDAN, OLPRINONE, ATIZORAM, KS-506-G, DIPAMFYLLINE, BMY-43351, ATIZORAM, AROFYLLINE, FILAMINAST, PDB-093, UCB-29646, CDP-840, SKF-107806, PICLAMILAST, RS-17597, RS-25344-000, SB-207499, TIBENELAST, SB-210667, SB-211572, SB-211600, SB-212066, SB-212179, GW-3600, CDP-840, MOPIDAMOL, ANAGRELIDE, IBUDILAST, AMRINONE, PIMOBENDAN, CILOSTAZOL, QUAZINONE and N-(3,5-dichloropyrid-4-yl)-3-cyclopropylmethoxy4-difluoromethoxybenzamide. PDE3 inhibitors which may be mentioned by way of example are SULMAZOLE, AMPIZONE, CILOSTAMIDE, CARBAZERAN, PIROXIMONE, IMAZODAN, CI-930, SIGUAZODAN, ADIBENDAN, SATERINONE, SKF-95654, SDZ-MKS-492, 349-U-85, EMORADAN, EMD-53998, EMD-57033, NSP-306, NSP-307, REVIZINONE, NM-702, WIN-62582 and WIN-63291, ENOXIMONE and MILRINONE. PDE3/4 inhibitors which may be mentioned by way of example are BENAFENTRINE, TREQUINSIN, ORG-30029, ZARDAVERINE, L-686398, SDZ-ISQ-844, ORG-20241, EMD-54622, and TOLAFENTRINE. Other PDE inhibitors include: cilomilast, pentoxifylline, roflumilast, tadalafil(Cialis®), theophylline, and vardenafil(Levitra®), zaprinast (PDE5 specific).

Adenosine 3',5'-cyclic monophosphate (cAMP) and analogues thereof can be administered with the agents of the invention in co-therapy. Analogues of cAMP include, but are not limited to, those that have modifications to the purine ring system, to the ribose, or to the phosphate group. Thus, analogues of cAMP useful in

the present invention include, but are not limited to, dibutyryl adenosine 3',5'-cyclic monophosphate (db cAMP), 8-bromo-adenosine 3',5'-cyclic monophosphate (8-bromo cAMP) Rp-adenosine 3',5'-cyclic monophosphate (Rp-cAMP) and Sp-adenosine 3',5'-cyclic monophosphate (Sp-cAMPS) (the S isomer of cAMP). The purine ring system is a commonly studied site for modification as it is essential for cyclic nucleotide recognition by its dependent kinase. Ogreid et al., 1985, Eur. J. Biochem. 150:219-227; Corbin et al., 1986, J. Biol. Chem. 261:1208-1214; Ogreid et al., 1989, Eur. J. Biochem. 181:19-31. Modifications to the purine ring system can be made in either the pyrimidine portion or the imidazole portion. For example, modifications to the pyrimidine portion of the ring system (positions 1, 2 or 6) alter binding affinity in direct correlation to the changes in tertiary structure or hydrophilic interactions; in contrast, modifications to the imidazole portion of the system (position 8) seem to regulate binding through a combination of electronic, steric and hydophobic forces. Corbin et al., 1986, J. Biol. Chem. 261:1208-1214. Although most substituents at position 8 reduce the affinity of the analog for its respective kinase, a few, notably 8-Br cAMP, have the opposite effect. Ogreid et al., 1989, Eur. J. Biochem. 181:19-31. This is thought due either to electronic effects in the case of electron withdrawing groups or the direct interaction of the substituent with the binding site. Corbin et al., 1986, J. Biol. Chem. 261:1208-1214. Analogues of cAMP may comprise simultaneous modifications to the purine ring system, the ribose or to the phosphate group. For example, modifications to the either the purine ring system or the ribose are often combined with a substitution of one of the exocyclic oxygens of the phosphate group by sulfur. Sulfur replacement at either the equatorial or axial position (Sp or Rp isomer, respectively) increases not only the lipophilicity of the compound but also induces its resistance to hydrolysis by phosphodiesterase. Braumann et al., 1985, J. Chromatogr. 350: 105-108; Eckstein, 1985, Ann. Rev. Biochem. 54:367-402; Schaap et al., 1993, J. Biol. Chem. 268:6323-6331. Analogues of cAMP are listed in the catalog at the website of BIOLOG Life Science Institute, Bremen, Germany, the address of which is BIOLOG.de. The analogue of cAMP may be cell membrane permeable.

Methods of Treatment

cGMP and analogs thereof can be used alone or in combination therapy for the treatment or prevention of gastrointestinal related disorders including: Crohn's disease, dyspepsia (including functional dyspepsia or nonulcer dyspepsia), duodenogastric reflux, functional bowel disorder, irritable bowel disorder (IBD), functional gastrointestinal disorders, functional heartburn, gastroesophageal reflux disease (GERD), gastrointestinal motility disorders, gastroparesis (e.g. idopathic gastroparesis), hypertrophic pyloric stenosis, Inflammatory bowel disease, irritable bowel syndrome (IBS, e.g.. d-IBS or alternating IBS), and ulcerative colitis. cGMP and analogs thereof can be used alone or in combination therapy to treat a patient suffering from or susceptible to GI disorders relating to damage to the GI tract stemming from impact or surgical intervention. cGMP and analogs thereof can be used alone or in combination therapy to treat patients at risk for or having particular diseases associated with hypermotility. cGMP and analogs thereof can be used alone or in combination therapy to prevent and/or treat GI disorders characterized by at least one of nausea, vomiting, heartburn, postprandial discomfort, diarrhea, indigestion or related symptoms. cGMP and analogs thereof can be used alone or in combination therapy to prevent and/or treat GI disorders associated with at least one of diabetes, anorexia nervosa, bulimia, achlorhydria, achalasia, anal fissure, irritable bowel syndrome, intestinal pseudoobstruction, scleroderma and gastrointestinal damage.

cGMP and analogs thereof can be used alone or in combination therapy for the treatment, prevention or reduction of visceral pain associated with a gastrointestinal disorder or pain associated with another disorder.

cGMP and analogs thereof can be used alone or in combination therapy for the treatment or prevention of obesity-related disorders (e.g., disorders that are associated with, caused by, or result from obesity). Examples of obesity-related disorders include overeating and bulimia, hypertension, diabetes, elevated plasma insulin concentrations and insulin resistance, dyslipidemias, hyperlipidemia,

endometrial, breast, prostate and colon cancer, osteoarthritis, obstructive sleep apnea, cholelithiasis, gallstones, heart disease, abnormal heart rhythms and arrhythmias, myocardial infarction, congestive heart failure, coronary heart disease, sudden death, stroke, polycystic ovarian disease, craniopharyngioma, the Prader-Willi Syndrome, Frohlich's syndrome, GH-deficient subjects, normal variant short stature, Turner's syndrome, and other pathological conditions showing reduced metabolic activity or a decrease in resting energy expenditure as a percentage of total fat-free mass, e.g., children with acute lymphoblastic leukemia. The agents of the invention may be used to reduce or control body weight (or fat) or to prevent and/or treat obesity or other appetite related disorders related to the excess consumption of food, ethanol and other appetizing substances. The agents may be used to modulate lipid metabolism, reduce body fat (e.g. via increasing fat utilization) or reduce (or suppress) appetite (e.g. via inducing satiety). Further examples of obesity-related disorders are metabolic syndrome, also known as syndrome X, insulin resistance syndrome, sexual and reproductive dysfunction, such as infertility, hypogonadism in males and hirsutism in females, gastrointestinal motility disorders, such as obesity-related gastroesophageal reflux, respiratory disorders, such as obesity-hypoventilation syndrome (Pickwickian syndrome), cardiovascular disorders, inflammation, such as systemic inflammation of the vasculature, arteriosclerosis, hypercholesterolemia, hyperuricaemia, lower back pain, gallbladder disease, gout, and kidney cancer. The agents of the present invention are also useful for reducing the risk of secondary outcomes of obesity, such as reducing the risk of left ventricular hypertrophy.

cGMP and analogs therof can be used alone or in combination therapy to prevent and/or treat diarrhea (e.g. chronic diarrhea, and disorders and conditions associated with diarrhea (e.g. scours, diarrhea associated with a functional digestive disorder, exudative diarrhea, non-exudative diarrhea, decreased absorption diarrhea, non-decreased absorption diarrhea, inflammatory diarrhea, non-inflammatory diarrhea, secretory diarrhea, non-secretory diarrhea, early chemotherapy related diarrhea, late chemotherapy related diarrhea, drug-induced diarrhea, bacteria-induced diarrhea,

viral-induced diarrhea, protozoa-induced diarrhea, HIV associated diarrhea, Highly Active Anti-Retroviral Therapy associated diarrhea, antibiotic associated diarrhea, nasogastric tube feeding associated diarrhea, diarrhea associated with rapid narcotic detoxification, and diarrhea associated with a neuroendocrine tumor.

cGMP and analogs thereof can be used alone or in combination therapy for the treament or prevention of anorexia, hyperthyroidism, other weight loss disorders and correcting fat malabsorption (steatorrhea) and loss of body mass in, for example, HIV-positive patients being treated with High Activity Antiretroviral drugs (HAART).

cGMP and analogs thereof can be used alone or in combination therapy for the treatment or prevention of cancer, pre-cancerous growths, or metastatic growths. For example, they can be used for the prevention or treatment of: colorectal/local metastasized colorectal cancer, intestinal polyps, gastrointestinal tract cancer, lung cancer, cancer or pre-cancerous growths or metastatic growths of epithelial cells, polyps, breast, colorectal, lung, ovarian, pancreatic, prostatic, renal, stomach, bladder, liver, esophageal and testicular carcinoma, carcinoma (e.g., basal cell, basosquamous, Brown-Pearce, ductal carcinoma, Ehrlich tumor, Krebs, Merkel cell, small or non-small cell lung, oat cell, papillary, bronchiolar, squamous cell, transitional cell, (Walker), leukemia (e.g., B-cell, T-cell, HTLV, acute or chronic lymphocytic, mast cell, myeloid), histiocytonia, histiocytosis, Hodgkin's disease, non-Hodgkin's lymphoma, plasmacytoma, reticuloendotheliosis, adenoma, adeno-carcinoma, adenofibroma, adenolymphoma, ameloblastoma, angiokeratoma, angiolymphoid hyperplasia with eosinophilia, sclerosing angioma, angiomatosis, apudoma, branchionia, malignant carcinoid syndrome, carcinoid heart disease, carcinosarcoma, cementoma, cholangioma, cholesteatoma, chondrosarcoma, chondroblastoma, chondrosarcoma, chordoma, choristoma, craniopharyngioma, chrondrorna, cylindroma, cystadenocarcinoma, cystadenoma, cystosarconia phyllodes, dysgenninoma, ependymoma, Ewing sarcoma, fibroma, fibrosarcoma, giant cell tumor, ganglioneuroma, glioblastoma, glomangioma, granulosa cell tumor,

gynandroblastoma, hamartoma, hemangioendothelioma, hemangioma, hemangiopericytoma, hemangiosarcoma, hepatoma, islet cell tumor, Kaposi sarcoma, leiomyoma, leiomyosarcoma, leukosarcoma, Leydig cell tumor, lipoma, liposarcoma, lymphaugioma, lymphangiomyoma, lymphangiosarcoma, medulloblastoma, meningioma, mesenchymoma, mesonephroma, mesothelioma, myoblastoma, myoma, myosarcoma, myxoma, myxosarcoma, neurilemmoma, neuroma, neuroblastoma, neuroepithelioma, neurofibroma, neurofibromatosis, odontoma, osteoma, osteosarcoma, papilloma, paraganglioma, paraganglionia. nonchroinaffin, pinealoma, rhabdomyoma, rhabdomyosarcoma, Sertoli cell tumor, teratoma, theca cell tumor, and other diseases in which cells have become dysplastic, immortalized, or transformed.

cGMP and analogs thereof can be used alone or in combination therapy for the treatment or prevention of: Familial Adenomatous Polyposis (FAP) (autosomal dominant syndrome) that precedes colon cancer, hereditary nonpolyposis colorectal cancer (HNPCC), and inherited autosomal dominant syndrome.

For treatment or prevention of cancer, pre-cancerous growths and metastatic growths, cGMP and analogs thereof can be used in combination therapy with radiation or chemotherapeutic agents, an inhibitor of a cGMP-dependent phosphodiesterase or a selective cyclooxygenase-2 inhibitor. A number of selective cyclooxygenase-2 inhibitors are described in US20010024664, U.S. Pat. No. 5,380,738, U.S. Pat. No. 5,344,991, U.S. Pat. No. 5,393,790, U.S. Pat. No. 5,434,178, U.S. Pat. No. 5,474,995, U.S. Pat. No. 5,510,368, WO02/062369, WO 96/06840, WO 96/03388, WO 96/03387, WO 96/19469, WO 96/25405, WO 95/15316, WO 94/15932, WO 94/27980, WO 95/00501, WO 94/13635, WO 94/20480, and WO 94/26731, the disclosures of which are herein incorporated by reference. [Pyrazol-1-yl]benzenesulfonamides have also been described as inhibitors of cyclooxygenase-2.

cGMP and analogs thereof can be used alone or in combination therapy in the treatment or prevention of inflammation. Thus, they can be used alone or in combination with an inhibitor of cGMP-dependent phosphodiesterase or a selective cyclooxygenase-2 inhibitor for treatment of: organ inflammation, IBD (e.g, Crohn's disease, ulcerative colitis), asthma, nephritis, hepatitis, pancreatitis, bronchitis, cystic fibrosis, ischemic bowel diseases, intestinal inflammations/allergies, coeliac disease, proctitis, eosnophilic gastroenteritis, mastocytosis, and other inflammatory disorders. cGMP and analogs thereof can be used alone or in combination therapy in the treatment or prevention of gastrointestinal tract inflammation (e.g. inflammation associated with a gastrointestinal disorder, gastrointestinal tract infection, or another disorder).

What is claimed is:

1. A method for treating a gastrointestinal disorder in a human patient comprising administering to the patient a composition comprising an effective amount of guanosine 3', 5'-cyclic monophosphate or a pharmaceutically acceptable salt thereof.

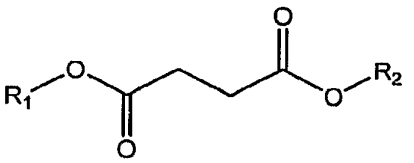
2. The method of claim 1 wherein the composition comprises guanosine 3', 5'-cyclic monophosphate or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

3. The method of claim 1 wherein the composition consists essentially of guanosine 3', 5'-cyclic monophosphate or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

4. The method of claim 1 wherein the composition consists of guanosine 3', 5'-cyclic monophosphate pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

5. The method of any of claims 1-4 wherein the gastroinstestinal disorder is selected from irritable bowel syndrome, irritable bowel disorder, a gastrointestinal motility disorder, Crohn's disease, duodenogastric reflux, dyspepsia, functional dyspepsia, nonulcer dyspepsia, a functional gastrointestinal disorder, functional heartburn, gastroesophageal reflux disease, gastroparesis, and ulcerative colitis.

6. The method of any of claims 1-5 further comprising administering a compound of Formula II



Formula II

wherein R_1 and R_2 are independently selected from H and a $C_1 - C_6$ alkyl. In various embodiments R_1 ans R_2 are both H, both methyl,both ethyl or a pharmaceutically acceptable salt thereof.

7. The method of claim 6 wherein both R_1 and R_2 are H.

8. A method for decreasing stool frequency comprising administering to a human patient a composition comprising an effective amount of guanosine 3', 5'-cyclic monophosphate or a pharmaceutically acceptable salt thereof.

9. The method of any of claims 1-8 wherein the composition is administered orally.

10. The method of any of claims 1-8 wherein the composition is administered rectally.

11. The method of any of claims 1-10 wherein the patient is suffering from irritable bowel syndrome.

12. The method of claim 11 wherein the patient is suffering from diarrhea-predominant irritable bowel syndrome.

13. The method of any of claims 1-10 wherein the patient is suffering from a gastrointestinal motility disorder.

14. The method of any of claims 1-10 wherein the patient is suffering from Crohn's disease.

15. The method of any of claims 1-10 wherein the patient is suffering from duodenogastric reflux.

16. The method of any of claims 1-10 wherein the patient is suffering from dyspepsia.

17. The method of any of claims 1-10 wherein the patient is suffering from functional dyspepsia.

18. The method of any of claims 1-10 wherein the patient is suffering from nonulcer dyspepsia.

19. The method of any of claims 1-10 wherein the patient is suffering from a functional gastrointestinal disorder.

20. The method of any of claims 1-10 wherein the patient is suffering from functional heartburn.

21. The method of any of claims 1-10 wherein the patient is suffering from gastroesophageal reflux disease.

22. The method of any of claims 1-10 wherein the patient is suffering from gastroparesis.

23. The method of any of claims 1-10 wherein the patient is suffering from post-operative diarrhea.

24. The method of any of claims 1-10 wherein the patient is suffering from ulcerative colitis.

25. The method of any of claims 1-10 wherein the patient is suffering from diarrhea.

26. The method of claim 25 wherein the patient is suffering from a disorder selected from: scours, diarrhea associated with a functional digestive disorder,

exudative diarrhea, non-exudative diarrhea, decreased absorption diarrhea, non-decreased absorption diarrhea, inflammatory diarrhea, non-inflammatory diarrhea, secretory diarrhea, non-secretory diarrhea, early chemotherapy related diarrhea, late chemotherapy related diarrhea, drug-induced diarrhea, bacteria-induced diarrhea, viral-induced diarrhea, protozoa-induced diarrhea, HIV associated diarrhea, Highly Active Anti-Retroviral Therapy associated diarrhea, antibiotic associated diarrhea, nasogastric tube feeding associated diarrhea, diarrhea associated with rapid narcotic detoxification, and diarrhea associated with a neuroendocrine tumor.

27. The method of claim 25 wherein the diarrhea is caused by an infectious agent.

28. The method of any of claims 1-4 wherein the composition contains at least 1% by weight guanosine 3', 5'-cyclic monophosphate pharmaceutically acceptable salt thereof.

29. The method of any of claims 1-4 wherein the composition contains at least 5% by weight guanosine 3', 5'-cyclic monophosphate pharmaceutically acceptable salt thereof.

30. The method of any of claims 1-4 wherein the composition contains at least 10% by weight guanosine 3', 5'-cyclic monophosphate pharmaceutically acceptable salt thereof.

31. The method of any of claims 1-4 wherein the composition contains at least 50% by weight guanosine 3', 5'-cyclic monophosphate pharmaceutically acceptable salt thereof.

32. A method for treating a patient suffering from colon cancer comprising administering to the patient a composition comprising an effective amount of guanosine 3', 5'-cyclic monophosphate or a pharmaceutically acceptable salt thereof.

33. The method of claim 32 wherein the composition comprises guanosine 3', 5'-cyclic monophosphate or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

34. The method of claim 32 wherein the composition consists essentially of guanosine 3', 5'-cyclic monophosphate or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

35. The method of claim 32 wherein the composition consists of guanosine 3', 5'-cyclic monophosphate pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

36. The method of any of claims 32-35 wherein the composition contains at least 1% by weight guanosine 3', 5'-cyclic monophosphate pharmaceutically acceptable salt thereof.

37. The method of any of claims 32-35 wherein the composition contains at least 5% by weight guanosine 3', 5'-cyclic monophosphate pharmaceutically acceptable salt thereof.

38. The method of any of claims 32-35 wherein the composition contains at least 10% by weight guanosine 3', 5'-cyclic monophosphate pharmaceutically acceptable salt thereof.

39. The method of any of claims 32-35 wherein the composition contains at least 50% by weight guanosine 3', 5'-cyclic monophosphate pharmaceutically acceptable salt thereof.

40. A method for treating a gastrointestinal disorder in a human patient comprising administering to the patient a composition comprising an effective amount of an agent selected from: i) guanosine 3', 5'-cyclic monophosphate or a

pharmaceutically acceptable salt thereof or ii) a guanosine 3', 5'-cyclic monophosphate analog or a pharmaceutically acceptable salt thereof., the method comprising:

(a) identifying a patient as suffering from a gastrointestinal disorder; and

(b) administering an amount of the agent.

41. A method for treating a gastrointestinal disorder in a human patient comprising administering to the patient a composition comprising an effective amount of guanosine 3', 5'-cyclic monophosphate or a pharmaceutically acceptable salt thereof.

42. The method of claim 40 wherein the guanosine 3', 5'-cyclic monophosphate analog is selected from: 8-(4-chlorophenylthio)guanosine 3',5'-cyclic monophosphate, dibutyryl guanosine 3',5'-cyclic monophosphate (db cGMP), 8-bromo-guanosine 3',5'-cyclic monophosphate (8-bromo cGMP), 8-(4-chlorophenylthio)-guanosine 3',5'-cyclic monophosphate (8-(4, chlorophenylthio) cGMP, Rp-guanosine 3',5'-cyclic monophosphate (Rp-cGMP) and Sp-guanosine 3',5'-cyclic monophosphate (Sp-cGMPS), cyclic guanosine-3',5'-triphosphate, cyclic guanosine-3',5'-diphosphate, cyclic guanosine-3',5'-triphosphate, cyclic deoxyguanosine-3',5'-monophosphate, cyclic deoxyguanosine-3',5'diphosphate, cyclic deoxyguanosine-3',5'-triphosphate, cyclic guanosine-2',3'-monophosphate, cyclic guanosine-2,3'-diphosphate, cyclic guanosine-2',3'-triphosphate, cyclic 2-(N-methyl)-guanosine-3',5'-monophosphate, cyclic 2-(N-methyl)-guanosine-3',5'-diphosphate, cyclic 2-(N-methyl)-guanosine-3',5'-triphosphate, cyclic 2-(N-methyl)-deoxyguanosine-3',5'-monophosphate, cyclic 2-(N-methyl)-doxyguanosine-3',5'-diphosphate, cyclic 2-(N-methyl)-deoxyguanosine-3',5'-triphosphate, cyclic 2-(N-methyl)-guanosine-2',3'-monophosphate, cyclic 2-(N-methyl)-guanosine-2',3'-diphosphate, cyclic 2-(N-methyl)-guanosine-2',3'-triphosphate, cyclic 7-(N-methyl)-guanosine-3',5'-monophosphate, cyclic 7-(N-methyl)-guanosine-3',5'-diphosphate, cyclic 7-(N-methyl)-guanosine-3',5'-triphosphate, cyclic 7-(N-methyl)-deoxyguanosine-3',5'-monophosphate, cyclic 7-(N-methyl)-deoxyguanosine-3',5'-

diphosphate, cyclic 7-(N-methyl)-deoxyguanosine-3',5'-triphosphate, cyclic 7-(N-methyl)-guanosine-2',3'-monophosphate, cyclic 7-(N-methyl)-guanosine-2',3'-diphosphate, cyclic 7-(N-methyl)-guanosine-2',3'-triphosphate, cyclic 2,7-(N,N'-dimethyl)-guanosine-3',5'-monophosphate, cyclic 2,7-(N,N'-dimethyl)-guanosine-3',5'-diphosphate, cyclic 2,7-(N,N'-dimethyl)-guanosine-3',5'-triphosphate, cyclic 2,7-(N,N'-dimethyl)-deoxyguanosine-3',5'-monophosphate, cyclic 2,7-(N,N'-dimethyl)-deoxyguanosine-3',5'-diphosphate, cyclic 2,7-(N,N'-dimethyl)-deoxyguanosine-3',5'-triphosphate, cyclic 2,7-(N,N'-dimethyl)-guanosine-2',3'-monophosphate, cyclic 2,7-(N,N'-dimethyl)-guanosine-2',3'-diphosphate, and cyclic 2,7-(N,N'-dimethyl)-guanosine-2',3'-triphosphate

43. The method of claim 40 wherein the composition comprises guanosine 3', 5'-cyclic monophosphate or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

44. The method of claim 40 wherein the composition consists essentially of guanosine 3', 5'-cyclic monophosphate or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

45. The method of claim 40 wherein the composition consists of guanosine 3', 5'-cyclic monophosphate pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

46. The method of any of claims 40-45 wherein the gastroinstestinal disorder is selected from irritable bowel syndrome, irritable bowel disorder, a gastrointestinal motility disorder, Crohn's disease, duodenogastric reflux, dyspepsia, functional dyspepsia, nonulcer dyspepsia, a functional gastrointestinal disorder, functional heartburn, gastroesophageal reflux disease, gastroparesis, and ulcerative colitis.

47. The method of any of claims 40-46 further comprising administering a second therapeutic agent.

48. A method for treating a gastrointestinal disorder selected from gastrointestinal pain, visceral pain, chronic visceral hypersensitivity, dyspepsia or hypersensitivity to colorectal distension in a human patient comprising administering to the patient a composition comprising an effective amount of an agent selected from: i) guanosine 3', 5'-cyclic monophosphate or a pharmaceutically acceptable salt thereof or ii) a guanosine 3', 5'-cyclic monophosphate analog or a pharmaceutically acceptable salt thereof, the method comprising:

(a) identifying a patient as suffering from gastrointestinal pain, visceral pain, chronic visceral hypersensitivity, dyspepsia or hypersensitivity to colorectal distension; and

(b) administering an amount of the agent.

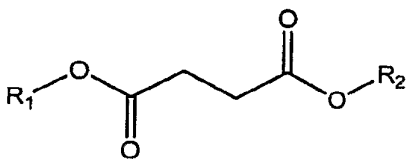
49. A method for treating a disorder selected from: gastrointestinal pain, visceral pain, chronic visceral hypersensitivity, dyspepsia or hypersensitivity to colorectal distension
in a human patient comprising administering to the patient a composition comprising an effective amount of an agent selected from: i) guanosine 3', 5'-cyclic monophosphate or a pharmaceutically acceptable salt thereof or ii) a guanosine 3', 5'-cyclic monophosphate analog or a pharmaceutically acceptable salt thereof.

50. The method of claim 49 wherein the composition comprises guanosine 3', 5'-cyclic monophosphate or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

51. The method of claim 49 wherein the composition consists essentially of guanosine 3', 5'-cyclic monophosphate or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

52. The method of claim 49 wherein the composition consists of guanosine 3', 5'-cyclic monophosphate pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier or diluent.

53. The method of any of claims 49-52 further comprising administering a compound of Formula II



Formula II

wherein R_1 and R_2 are independently selected from H and a $C_1 - C_6$ alkyl. In various embodiments R_1 ans R_2 are both H, both methyl,both ethyl or a pharmaceutically acceptable salt thereof.

54. The method of any of claims 1-53 wherein the composition comprising an effective amount of an agent selected from: i) guanosine 3', 5'-cyclic monophosphate or a pharmaceutically acceptable salt thereof or ii) a guanosine 3', 5'-cyclic monophosphate analog or a pharmaceutically acceptable salt thereof is not administered together with any active ingredient or pharmaceutical agent.