Abstract: The present invention provides compositions to be used in conditions in which the reduction of gastric acidity or inhibition of gastric acid secretion is beneficial. The compositions comprise one or more endoperoxide-bearing compounds effective in the inhibition of gastric acid secretion or in reducing gastric acidity. The compositions of the present invention preferably further comprise a substituted bemidimazole H+ZK+-ATPase proton pump inhibitor (PPJ) or ffe blocker in order to obtain more effective reduction of gastric acidity or inhibition of gastric acid secretion.
COMPOSITIONS AND METHODS FOR INHIBITING GASTRIC ACIDITY USING ENDOPEROXIDE BRIDGE-CONTAINING COMPOUNDS

This application claims the benefit of and priority to U.S. Provisional Application Nos. 60/795,165 filed April 27, 2006; 60/843,705 filed September 12, 2006; and 60/860,803 filed November 24, 2006, the contents of each which are expressly incorporated herein by reference thereto.

FIELD OF THE INVENTION

The present invention relates to novel oral compositions for inhibition of gastric acidity comprising endoperoxide bridge-containing compounds. The present invention further relates to a method of using such compositions to reduce gastric acidity in a mammal.

BACKGROUND OF THE INVENTION

The treatment of a wide number of pathological conditions is characterized by the need to suppress gastric acid secretion. Such conditions include, but are not limited to Zollinger/Ellison syndrome (ZES), gastroesophageal reflux disease (GERD), peptic ulcer disease, duodenal ulcers, esophagitis, and the like. Conditions such as reflux esophagitis can have serious complications and represent some of the most prevalent diseases in industrialized nations.

Presently, the main therapies employed in the treatment of GERD and peptic ulcer diseases include agents for reducing the stomach acidity, for example by using the histamine H$_2$-receptor antagonists or proton pump inhibitors (PPIs). PPIs act by inhibiting the parietal cell H$^+$/K$^+$ ATPase proton pumps responsible for acid secretion from these cells. PPIs, such as omeprazole, and its pharmaceutically acceptable salts are disclosed for example in EP 05129, EP 124495 and US Patent No. 4,255,431.

PPI agents are acid-labile pro-drugs that are usually administered in enteric-coated granules and are weak bases. Following absorption in the small intestine, PPIs preferentially accumulate within the acidic milieu of the acid-secreting parietal cells. The acid environment within the acid milieu of parietal cells causes the conversion of the pro-drugs into the active sulfenamides, which are the active agents that bind and inhibit the parietal cell H$^+$/K$^+$ ATPase pumps. PPIs inhibit only activated pumps once they have fused into the membrane of the secretory canaliculus. Thus, pre-activation of parietal cells is
required for the conversion of PPIs to its active protonated form and inhibition of acid secretion. The pre-activation of parietal cells is usually achieved by meal ingestion that initiates gastrin-dependent parietal cell activation. Indeed, patients are instructed to take PPI one hour prior to meal intake in order to ensure that parietal cells are activated when the PPI reaches the parietal cells via blood stream.

Despite their well-documented efficacy, PPIs have notable limitations such as the need for meal-dependent administration of the drug, the slow onset of full pharmacological action in patients, incomplete control of nocturnal acid secretion that is associated with heartburn pain in GERD patients and inter-patient variability in pharmacokinetics that may have significant interactions with other drugs. Thus, an improvement of PPI-mediated activity is a well-recognized challenge in gastroenterology.

Artemisinin is an anti-malarial drug isolated by Chinese scientists in 1972 from Artemisia annua L. The endoperoxide moiety of artemisinin and its analogs has been found to be necessary for the anti-malarial activity, and analogs lacking this group have been found to be inactive. In the presence of heme, the endoperoxide bridge undergoes reductive decomposition to form a free radical and electrophilic intermediates (Meshnick, Int. J. Parasitology, 32 (2002) 1655). It was recently proposed that artemisinin possesses its anti-parasite activity by inhibition of specific P-type ATPase (Eckstein-Ludwig et al., Nature, Vol. 424, 957).

Because of the low water solubility of the natural substance artemisinin, attempts have been made to convert it to a variety of synthetic derivatives in order to improve the pharmaceutical availability. Known analogs of artemisinin that have higher solubility in water are dihydroartemisinin, artemether, artesunate, arteether, propylcarbonate dihydroartemisinin and artelinic acid.

Artemisinin or artemisinin analogs were reported to be effective in various disorders. These include skin disorders such as psoriasis, blistering skin diseases, viral warts, and hemorrhoids (U.S. Patent No. 4,978,676). U.S. Patent No. 5,219,880 discloses the use of artemisinin or artemisinin analogs in the treatment of warts, molluscum contagiosum and hemorrhoids. U.S. Patent No. 5,225,427 discloses certain 10-substituted ether derivatives of dihydroartemisinin alleged to exhibit anti-malarial and anti/protozoal activity. Artemisinin has been shown to be toxic to cancer cells in vitro at 20-180 μM range (Sun et al., "Antitumor Activities of 4 Derivatives of Artemisic Acid and Artemisinin B in vitro," Chung-Kuo-Yao-Li-Hsueh-Pao  13:541-543 (1992)). U.S. Patent No. 5,578,637 discloses that the anticancer activity of compounds having an endoperoxide moiety such as
artemisinin and its analogs, is substantially enhanced both in vitro and in vivo when administered under conditions which enhance intracellular iron concentrations. WO04071506 discloses the use of Artemisinin and/or artemisinin derivatives for treating tumors induced by oncogenic viruses and for treating viral infections as well as treatment of cervical disorders associated with virus infection (e.g., cervical cancer and cervical dysplasia). This publication further discloses a method of killing or inhibiting growth of cells that are infected by oncogenic viruses such as BPV, HTLV-I, herpes virus (e.g., EBV or CMV), SV40-like viruses, hepatitis virus, or adenovirus. WO04041176 discloses the use of sesquiterpene lactone endoperoxides to treat hepatitis C infections, yellow fever, dengue fever, bovine viral diarrhea and classical swine fever. Foglio et al. disclose that dihydro-epideoxyartemannuin B and deoxyartemisinin provided gastric cytoprotection by decreasing the ulcerative lesion index produced by ethanol and indomethacin in rats (Planta Med. 2002, 68 515-518).

The development of an effective treatment for pathologies in which inhibition of gastric acid secretion is required would fulfill a long felt need. Despite the wide-spread use of PPIs, a need still exist for increasing the PPI efficacy, e.g., improved control of night time acid secretion, more rapid onset of activity, greater effect at reduced dosage and meal-independent administration. Applicants' invention disclosed herein meets many of these long felt needs.

SUMMARY OF THE INVENTION

It is the object of the present invention to provide compositions to be used in conditions in which the reduction of gastric acidity or inhibition of gastric acid secretion is beneficial.

The compositions of the present invention comprise one or more endoperoxide-bearing compounds effective in the inhibition of gastric acidity. The compositions of the present invention preferably further comprise a substituted benzimidazole H⁺/K⁺-ATPase proton pump inhibitor (PPI) or H₂ blocker in order to obtain more effective reduction of gastric acidity or inhibition of gastric acid secretion.

In a preferred embodiment, the endoperoxide-bearing compounds of the present invention have a sesquiterpene structure, particularly an oxygenated tricyclic sesquiterpene structure with an endoperoxide group, and preferably those which are sesquiterpene lactones or alcohols, carbonates, esters, ethers and sulfonates thereof. It will be apparent that other endoperoxide-bearing compounds may be useful for the present invention. Examples of
other suitable endoperoxide-bearing compounds include for example: hydroxy, hydroperoxy or peroxy derivative of a polyunsaturated fatty acid, trioxolanes, spiro and dispiro 1,2,4-trioxolanes, byciclo (3,2,2) endoperoxides, trioxanes, 3-substituted trioxanes, ozonides, 2,3 bicyclo (3.3.1) nonanes, 1,2,4-trioxanes, 1,2,4,5-tetraoxanes, terpenes and substituted terpenes.

In a more preferred embodiment, the endoperoxide-bearing compound to be used in the present invention is a sesquiterpene compound, or a pharmaceutically acceptable salt thereof, according to formula (I):

\[
\text{R} = \text{CO- or R is CR}_1
\]

wherein \( R_1 \) is hydrogen, hydroxyl, alkyl, \(-\text{OR}_2\), \(-\text{COR}_2\), \(-\text{COOR}_2\), \(-\text{CO}(\text{CH}_2)_n\), \(-\text{COOH}\), \(-\text{SOOR}_2\), a halogen atom, an optionally substituted cycloalkyl, aryl, C-linked heteroaryl or heterocyclylalkyl group,

wherein \( R_2 \) is alkyl or aryl and \( n \) is 1 to 6,

or wherein \( R_1 \) is \( \text{NR}_1\text{R}_2 \); where \( R^1 \) represents a hydrogen atom or an optionally substituted alkyl, alkenyl or alkynyl group; \( R^2 \) represents an optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl or aralkyl group; or \( R^1 \) and \( R^2 \) together with the interjacent nitrogen atom represent an optionally substituted heterocyclic group or an amino group derived from an optionally substituted amino acid ester.

Any alkyl, alkenyl or alkynyl group, unless otherwise specified, may be linear or branched and may contain up to 12, preferably up to 6, and especially up to 4 carbon atoms. Preferred alkyl groups are methyl, ethyl, propyl and butyl. Preferred alkenyl and alkynyl groups include propenyl, butenyl, propynyl and butynyl groups. When an alkyl moiety forms part of another group, for example the alkyl moiety of an aralkyl group it is preferred that it contains up to 6, especially up- to 4, carbon atoms. Preferred alkyl moieties are methyl and ethyl.
An aryl group may be any aromatic hydrocarbon group and may contain from 6 to 24, preferably 6 to 18, more preferably 6 to 16, and especially 6 to 14, carbon atoms. Preferred aryl groups include phenyl, naphthyl, anthryl, phenanthryl and pyryl groups, especially a phenyl or naphthyl, and particularly a phenyl, group.

An aralkyl group may be any alkyl group substituted by an aryl group. A preferred aralkyl group contains from 7 to 30, particularly 7 to 24 and especially 7 to 18, carbon atoms, particularly preferred aralkyl groups being benzyl, naphthylmethyl, anthrylmethyl, phenanthrylmethyl and pyrylmethyl groups. A particularly preferred aralkyl group is a benzyl group.

A cycloalkyl group may be any saturated cyclic hydrocarbon group and may contain in from 3 to 12, preferably 3 to 8, and especially 3 to 6, carbon atoms. Preferred cycloalkyl groups are cyclopropyl, cyclopentyl and cyclohexyl groups.

A heteroaryl group may be any aromatic monocyclic or polycyclic ring system which contains at least one heteroatom. Preferably, a heteroaryl group is a 5-18-membered, particularly a 5- to 14-membered, and especially a 5- to 10-membered, aromatic ring system containing at least one heteroatom selected from oxygen, sulphur and nitrogen atoms. Preferred heteroaryl groups include pyridyl, pyryl, thiopyrlyl, pyrryol, furyl, thiencyl, indoliny1, isoindoliny1, indoliziny1, imidazolyl, pyridony1, pyron1, pyrimidy1, pyrazinyl, oxazolyl, thiazolyl, puriny1, quinoliny1, isoquinoliny1, quinoxalinyl, pyridaziny1, benzofurany1, benzoazolyl and acridiny1 groups. A C-linked heteroaryl group is therefore a heteroaryl group as defined above which is linked to the tetracyclic 1,2,4-trioxane moiety of a compound of general formula I via a carbon atom in the heteroaromatic ring system.

A heterocyclic group may be any monocyclic or polycyclic ring system which contains at least one heteroatom and may be unsaturated or partially or fully saturated. The term "heterocyclic" thus includes heteroaryl groups as defined above as well as non-aromatic heterocyclic groups. Preferably, a heterocyclic group is a 3- to 18-membered, particularly a 3- to 14-membered, especially a 5- to 10-membered, ring system containing at least one heteroatom selected from oxygen, sulphur and nitrogen atoms. Preferred heterocyclic groups include the specific heteroaryl groups named above as well as pyrany1, piperidiny1, pyrrlydinyl, dioxany1, piperaziny1, morpholiny1, thiomorpholiny1, morpholinosulphonyl, tetrahydroisoquinoliny1 and tetrahydrofurany1 groups.

A heterocyclylalkyl group may be any alkyl group substituted by a heterocyclic group. Preferably, the heterocyclic moiety is a 3- to 18-membered, particularly a 3- to 14-
membered, and especially a 5- to 10-membered, heterocyclic group as defined above and the alkyl moiety is a C_{1-6} alkyl, preferably C_{1-4} alkyl, and especially methyl, group.

An amino acid may be any \(\alpha\)-amino acid, such as glycine, alanine, valine, leucine, isoleucine, serine, threonine, cysteine, cystine, methionine, aspartic acid, glutamic acid, asparagine, glutamine, lysine, hydroxylysine, arginine, histidine, phenylalanine, tyrosine, tryptophan, proline, hydroxyproline or phenylglycine, and includes both D- and L-configurations. An amino acid ester may be any ester of such an amino acid, alkyl esters, particularly C_{1-4} alkyl esters, being especially preferred.

Other artemisinin derivatives that may be used in conditions in which the reduction of gastric acidity or inhibition of gastric acid secretion is beneficial are disclosed in US patent publications US 2005/0119232, 2005/0038024, 2002/0055528, US patent 6,984,640, US patent 6,649,647, Haynes RK, "From artemisinin to new artemisinin antimalarials: biosynthesis, extraction, old and new derivatives, stereochemistry and medicinal chemistry requirements" Curr Top Med Chem. 2006;6(5):509-37, all incorporated herein by reference.

Examples of such preferred compounds include artemisinin; C-10 derivatives of artemisinin, dihydroartemisinin; carbonate, sulfonate, ester and ether derivatives of dihydroartemisinin, notably arteether, arteether, arteflene, artesunate, artesunate salts, dihydroartemisinin propyl carbonate, C-10 thiomorpholinyl or morpholinosulphonyl derivatives of artemisinin (artemisone), 12(\beta\text{ or } \alpha)-\text{Dihydroartemisininoxymethyl(}\text{ox})\text{yl, bis-ether artelinc acid, 2-}\{12(\beta\text{ or } \alpha)-\text{Dihydroartemisininoxymethyl(}l\text{-ethyl})\text{phenoxy propionic acids, and dihydroxydihydroartemisinin.}\)

Advantageously, other compounds that possess an endoperoxide group may be successfully used in the disclosed method, although in a non-limiting preferred embodiment the endoperoxide compounds are those disclosed herein.

An example of one is a sesquiterpene compound, which includes, for example, artemisinin, where \(R\) of Formula (I) is C=O, dihydroartemisinin (\(R_1\) is OH), artesunic acid (\(R_1\) is OCO(CH\text{=})\text{)h}_2\text{CO}_2\text{H}), and artesunate, arteether (\(R_1\) is OCH\text{=}h) and arteether (\(R_1\) is OC\text{=}h\text{h}_2\text{H}).

Pharmaceutically acceptable salts according to the present invention include the alkali or alkaline metal salts, preferably sodium or potassium, with sodium being the most preferred. Also included in the present invention are any possible conformers or isomers of the active compounds such as the alpha or beta isomers of dihydroartemisinin, arteether or
arteether. Also included in the present invention are various dimers of the active compounds such as dimers of dihydroartemisinin.

In a preferred embodiment, the compositions of the present invention comprise the endoperoxide-bearing compound in combination with one or more active agents for reducing gastric acid secretion or gastric acidity or for the relief of symptoms associated with heartburns or gastric ulcers as a means of further enhancing clinical efficacy. Such agents are for example an inhibitor of gastric acid secretion, a proton pump inhibitor (either irreversible or reversible proton pump inhibitor), an \( \beta \)-blocker such as cimetidine, famotidine, nizatidine, and ranitidine, buffering agents, antacids, sucralfate, antibacterial agents, a non-steroidal anti-inflammatory (NSAID) drug or bismuth-containing compounds. The inventors of the present invention have surprisingly found that the combination of an endoperoxide-bearing compound such as artemisinin or artesunate in combination with a PPI such as pantoprazole or omeprazole or with \( \text{H}_2 \) Blocker such as ranitidine showed better inhibition of gastric acid secretion compared to PPI, \( \text{H}_2 \) blocker or artesunate alone.

In such embodiment, the active ingredients of the present invention may be formulated in a single dosage form, preferably oral dosage form, more preferably oral solid dosage form. Such oral dosage forms may contain one or both of the drugs in immediate or sustained release form such as in a gastric retention form. Thus, in one embodiment the PPI and/or \( \text{H}_2 \) blocker and the endoperoxide-bearing compound may be formulated as multilayered tablets, suspension tablets, effervescent tablets, powder, pellets, granules, hard gelatin capsules comprising multiple beads, or soft gelatin capsules containing a lipid-based vehicle. Liquid dosage forms such as suspensions may be used as well. In another embodiment, the endoperoxide-bearing compound is combined with antacids in an effervescent tablet, fast-integrating tablet or chewable tablet which provide both immediate relief for heartburn episodes with prolonged effect on gastric acid secretion.

The active ingredients of the present invention might also be administered via parenteral routs of administration such as intravenous administration and subcutaneous injection, rectal administration, transdermal administration, buccal administration or nasal administration.

According to one preferred embodiment, the solid dosage form of the present invention is a capsule or a multi-layered tablet containing particles of both PPI and/or \( \text{H}_2 \) blocker and the endoperoxide-bearing compound. The release of either PPI and/or \( \text{H}_2 \) blocker particles, the endoperoxide-bearing compound, or both PPI and/or \( \text{H}_2 \) blocker particles and the particles of the endoperoxide-bearing compound may be delayed by enteric
pH-dependent release polymers or non-enteric time-dependent release polymers, such that
the releasing time in the stomach is extended.

The active ingredients of the present invention may also be formulated in separate
dosage forms. For example, the endoperoxide-bearing compound may be formulated in an
oral suspension or a solid dosage form such as capsules, tablets, suspension tablets, or
effervescent tablets and the PPI and/or H₂ blocker may be formulated in a separate solid
dosage form, preferably capsules or tablets comprising pellets with enteric pH-dependent
release polymers or non-enteric time-dependent release polymers. The separate dosage
forms may be provided as a kit containing pellets of the endoperoxide-bearing compound in
one dosage form and pellets of PPI and/or H₂ blocker in a separate dosage form. The PPI
and/or H₂ blocker and the endoperoxide-bearing compound can be administered
simultaneously and/or sequentially.

The active ingredients of the present invention may also be formulated in a dosage
form suitable for parenteral administration such as intravenous administration and
subcutaneous injection. It is also possible that one of the active ingredients is administered
orally (such as in tablets or capsules) and the second active ingredient is administered
parenterally for example by intravenous, subcutaneous or rectal administration. Although
any suitable route of administration is acceptable, it is preferred to administer the
compositions orally. The active compounds are typically combined with a pharmaceutically
acceptable carrier to form a pharmaceutical composition. The pharmaceutically acceptable
carrier can contain a physiologically acceptable compound that acts, for example, to
stabilize the composition or to increase the absorption of the agent.

In another embodiment, the present invention is directed to a method of treating a
subject suffering from a disorder in which suppression of gastric acid secretion or reduction
of gastric acidity is required or a disorder normally treated by suppression of gastric acid
secretion. The method comprises administering to the subject a pharmaceutical composition
according to the present invention.

The compositions of the present invention may be used for preventing or treating
pathologies in a mammal in which inhibition of gastric acid secretion or reduction of gastric
acidity is required. Preferably the mammal is human. The compositions of the present
invention are effective both in treating the pathologies and in minimizing the risk of
development of such pathologies before onset of symptoms.

The pharmaceutical compositions of the present invention may be used in a wide
number of pathological conditions that are treated by suppression of gastric acid secretion.
Such conditions include, but are not limited to Zollinger/Ellison syndrome (ZES), gastroesophageal reflux disease (GERD), esophagitis, peptic ulcer diseases, duodenal ulcers, gastritis and gastric erosions, dyspepsia, NSAJD- induced gastropathy, acute upper GI bleeding and the like. The pharmaceutical compositions of the present invention may also be used as prophylaxis or treatment for mucosal damage in patients undergoing cancer chemotherapy. The compositions may be used in order to provide symptom relief and prophylaxis against upper GI ulceration in patients receiving cancer chemotherapy. Further, the compositions may be used in conditions in which elevation of gastric pH is required such as when acid-susceptible drugs are administered.

In one embodiment, the endoperoxide-bearing compounds are formulated in a composition designed to act locally in the stomach following oral administration in order to reduce gastric acidity. Since the preferred compounds such as artemisinin or the active derivatives thereof are not soluble in the acidic conditions of the gastric fluid, it is necessary to preserve its solubility in the stomach in order to permit the active compound to act locally.

Thus, the compositions may further comprise an agent that maintains the solubility of the endoperoxide-bearing compound in the gastric fluids. This enables the endoperoxide-bearing compound to act locally in the stomach. Such agents are preferably alkaline agents or antacids that when dissolved in the gastric juice are capable of elevating the pH of the gastric fluids to a pH in which at least significant proportion of the endoperoxide-bearing compound remains soluble in the gastric fluids.

The compositions may further comprise one or more agents that accelerate the solubility and the stability of the endoperoxide-bearing compound in aqueous environment. Such agents are for example cyclodextrin analogs that form complexes with artemisinin or its derivatives, thereby improving the aqueous solubility of the complex and the stability of the endoperoxide bridge in aqueous environment.

In another embodiment, the compositions may further comprise one or more gastric-retention agents. These gastric-retention agents enable the active compound to act locally in the stomach for extended time periods sufficient to induce reduction in gastric acid secretion. Such gastric retention agents may be for example one or more polymers that swell in the stomach via the absorption of water from the gastric fluid, thereby increasing the size of the particles to promote gastric retention in the stomach. The active ingredient is slowly released from the particles by diffusion or following slow erosion of the particles in the stomach.
According to another embodiment, the compositions of the present invention are formulated to permit systemic absorption of the endoperoxide-bearing compound in the intestine. In order to accelerate the absorption of the endoperoxide-bearing compound in the intestine, the compositions may comprise vehicle such as vegetable oil suitable for liquid formulations that increase the absorption in the intestine.

These and further embodiments will be apparent from the detailed description and examples that follow.

**BRIEF DESCRIPTION OF THE FIGURES**

**Figures 1A and 1B** demonstrate the effect of artesunate, pantoprazole and the combination thereof on gastric output (Figure 1A) and pH of gastric fluid in rats (Figure 1B).

**Figures 2A and 2B** demonstrate the effect of Artemisinin or pantoprazole on gastric output (Figure 2A) and pH of gastric fluid (Figure 2B).

**Figures 3A and 3B** demonstrate the dose response of artesunate on gastric output (Figure 3A) and gastric pH (Figure 3B).

**Figures 4A and 4B** demonstrate the effect of artesunate, ranitidine and the combination thereof on gastric output (Figure 4A) and pH of gastric fluid in rats (Figure 4B).

**Figures 5A and 5B** demonstrate the effect of intravenous artesunate on gastric output (Figure 5A) and pH of gastric fluid (Figure 5B).

**Figures 6A and 6B** demonstrate the effect of intravenous artesunate and/or subcutaneous indomethacin on gastric output (Figure 6A) and pH of gastric fluid (Figure 6B).

**Figures 7A and 7B** demonstrate the effect of oral artesunate and omeprazole on gastric output (Figure 7A) and pH of gastric fluid (Figure 7B).

**Figures 8A and 8B** demonstrate the effect of oral artesunate (20 mg/kg and 40 mg/kg) and pantoprazole on gastric output (Figure 8A) and pH of gastric fluid (Figure 8B).

**Figures 9A and 9B** demonstrate the effect of intravenous artesunate (15, 30 and 60 mg/kg) on gastric output (Figure 9A) and pH of gastric fluid (Figure 9B).
DETAILED DESCRIPTION OF THE INVENTION

The compositions of the present invention comprise one or more endoperoxide-bearing compounds effective in the inhibition of gastric acid secretion or reduction of gastric acidity. The compositions of the present invention preferably further comprise a substituted benzimidazole H⁺/K⁺-ATPase proton pump inhibitor (PPI) and/or H₂ blocker in order to obtain more effective inhibition of gastric acid secretion or gastric acidity.

In a preferred embodiment, the present invention relates to a composition comprising an endoperoxide-containing sesquiterpene compound, such as, for example, artemisinin, artesunate or an active derivative thereof. These compounds are efficient at inhibiting gastric acid secretion or reducing gastric acidity.

Without being bound by theory, it is possible that artemisinin or the active derivative thereof possess its anti-acid activity via inhibition of the H⁺/K⁺-ATPase proton pump in parietal cells. A similar mechanism was suggested by Eckstein-Ludwig et al (Nature, Vol. 424, 957) who showed that artemisinin possesses its anti-parasite activity by inhibition of specific P-type ATPase.

In connection with the present invention, compounds may be employed, in general, that possess an endoperoxide group. Preferred endoperoxide compounds are set forth hereinabove, although as will be apparent from the present specification that other endoperoxide-bearing compounds not specifically mentioned should also be useful.

The compositions of the present invention may further comprise a PPI that acts as an irreversible inhibitor of the gastric H⁺/K⁺-ATPase proton pump. The PPI used in the present invention can be any substituted benzimidazole compound having H⁺, K⁺-ATPase inhibiting activity. For the purposes of this invention, the term "PPI" shall mean any substituted benzimidazole possessing pharmacological activity as an inhibitor of H⁺,K⁺-ATPase, including, but not limited to, omeprazole, lansoprazole, pantoprazole, rabeprazole, donotoprazole, perprazole (s-omeprazole magnesium), habeprazole, ransoprazole, pariprazole, tenatoprazole and leminoprazole in neutral form or a salt form, a single enantiomer or isomer or other derivative or an alkaline salt of an enantiomer of the same.

Examples of gastric H⁺/K⁺-ATPase proton pump inhibitors that may be used in the present invention are disclosed for example in US Patent 6,093,738 that describes novel thiadiazole compounds that are effective as proton pumps inhibitors. European Patent Nos. 322133 and 404322 disclose quinazoline derivatives, European Patent No. 259174 describes quinoline derivatives, and WO 91/13337 and US Patent 5,750,531 disclose pyrimidine derivatives, as proton pump inhibitors. Suitable proton pump inhibitors are also disclosed.

Numerous proton pump inhibitors are known to those of skill in the art. Thus, for example, US Patent 6,093,738 describes novel thiadiazole compounds that are effective as proton pump inhibitors. European Patent Nos. 322133 and 404322 disclose quinazoline derivatives, European Patent No. 259174 describes quinoline derivatives, and WO 91/13337 and US Patent 5,750,531 disclose pyrimidine derivatives, as proton pump inhibitors. Suitable proton pump inhibitors are also disclosed for example in EP-A1-174726, EP-A1-166287, GB 2 163 747 and W090/06925, W091/19711, W091/19712, W094/27988 and W095/01977. In general, any proton pump inhibitor that is activated within the acid canaliculi and inhibits the activity of the H⁺/K⁺-adenosine triphosphatase (ATPase) proton pump may be used in combination with the endoperoxide-containing compound of the present invention. Particularly preferred PPIs include, but are not limited to omeprazole, esomeprazole, rabeprazole, lansoprazole, tenatoprazole and pantoprazole and derivatives or analogues thereof.

The compositions of the present invention may further comprise an H₂ blocker. By the term "H₂ blockers" it is referred to herein in a broad sense and is meant to include those agents that inhibit or block the secretion of gastric acid by binding to a specific histamine receptor on the parietal cell membrane located in the stomach. Exemplary of H₂ blockers contemplated by the present invention are cimetidine, ranitidine, nizatidine and famotidine.

Histamine H₂ receptor blocking agents (referred to herein as H₂ blockers) are a class of drugs which act as antagonists of the histamine H₂ receptor. H₂ blockers are currently sold as prescription drugs in the United States for the treatment of medical conditions such as active duodenal ulcer, and pathological hypersecretory conditions such as Zollinger-Ellison syndrome and systemic mastocytosis. Some H₂ blockers have also been approved for the prophylactic treatment of reflux esophagitis. H₂ blockers are effective means of inhibiting gastric acid secretion. Such compounds have a delayed onset, generally one to two hours after ingestion, and a long duration of action.

Suitable H₂ blockers include, without limitation, the commercially available compounds, cimetidine (TAGAMET®, sold by SmithKline Beecham), famotidine (PEPCID®, sold by Merck, Sharp & Dohme), ranitidine (ZANTAC®, sold by Glaxo), nizatidine (AXID®, sold by Eli Lilly) as well as others reported in the literature such as etintidine, lupitidine, mifentidine, niperotidine, roxatidine, sufotidine, tuvatidine and zaltidine.
The compositions of the present invention optionally comprise a PPI and/or H₂ blocker in an effective amount to achieve a pharmacological effect or therapeutic improvement without undue adverse side effects. A therapeutic improvement includes but is not limited to: raising of gastric pH, treatment of gastrointestinal bleeding, or improvement or elimination of symptoms. According to a preferred embodiment, the typical daily dose of the PPI varies and will depend on various factors such as the individual requirements of the patients and the disease to be treated. In general, the daily dose of PPI will be in the range of 1-400 mg. A preferred standard approximate amount of a PPI present in the composition is typically about 20-40 mg of omeprazole, about 30 mg lansoprazole, about 40 mg pantoprazole, about 20 mg rabeprazole, and the pharmacologically equivalent doses of the following PPIs: habeprazole, pariprazole, donoprazole, ransoprazole, perprazole (s-omeprazole magnesium), tenatoprazole and leminoprazole.

With respect to the H₂ blockers, the amount included in the single dosages is believed to be in the range of 10-500 mg, more preferably 50-300 mg per dosage unit, administered, for example, 1 to 4 times per day, preferably once or twice per day.

The compositions of the present invention may further comprise a reversible proton pump inhibitor (potassium competitive acid blockers such as AZ0865, CS526, Revaprazan and Soraprazan), sucralfate, a buffering agent, antacid, a non-steroidal anti-inflammatory (NSAID) drug and a bismuth-containing compound.

With respect to NSAID drugs, long-term use of nonsteroidal anti-inflammatory drugs are associated with serious and sometimes fatal gastrointestinal side effects such as stomach ulcers and bleeding. At particular risk are people who take NSAIDs for a year or longer, such as for relief from the symptoms of chronic arthritis. These side effects are caused primarily by the reduction of prostaglandin formation by inhibiting the enzyme cyclooxygenase. Without being bound by theory, it is possible that artemisinin or the active derivative thereof may increase prostaglandin levels in the stomach, thus providing advantage of the combination of artemisinin or the active derivative thereof with NSAID.

The compositions of the present invention may include one or more of the following active drugs in combination with the endoperoxide-bearing compounds: an antibacterial agent, an inhibitor of gastric acid secretion, a proton pump inhibitor (PPI), potassium-competitive acid blockers, an H₂ blocker, sucralfate, a buffering agent, antacid, an non-steroidal anti-inflammatory (NSAID) drug and a bismuth-containing compound.

The compositions of the present invention may also include one or more of the following active drugs in combination with the endoperoxide-bearing compounds: mucosal
protective drags (e.g., sucralfate, rebamipide, teprenone etc.), mucosal covering drags (e.g., sodium alginate, azunol preparation etc.), tissue repair accelerating drags (e.g., aceglutamide aluminum, aldioxia, gefalnate etc.), mucus production accelerating drags (e.g., proglumide, teprenone, secretin, aldioxia etc.), mucosal microcirculation improving drugs (e.g., cetaxate hydrochloride, benexate, sulpirid etc.), prostaglandin synthesis accelerating drugs (e.g., sofalcone) and prostaglandin preparations (e.g., ornoprostil, misoprostol, enprostil etc.) and the like.

The present invention further relates to a method of treating a subject suffering from a disorder in which suppression of gastric acid secretion or reduction of gastric acidity is required, or a disorder normally treated by suppression of gastric acid secretion. The method comprises administering to the subject a pharmaceutical composition comprising one or more endoperoxide-bearing compounds as gastric acid secretion inhibitors and optionally a PPI and/or an H₂ blocker, a reversible proton pump inhibitor, sucralfate, a buffering agent, antacid, a non-steroidal anti-inflammatory (NSAID) drug and a bismuth-containing compound.

The compositions of the present invention may be used for preventing or treating pathologies in a mammal in which inhibition of gastric acid secretion or reducing gastric acidity is required. The compositions of the present invention are effective both in treating the pathologies and in minimizing the risk of development of such pathologies before onset. Such pathologies include for example: reflux esophagitis, gastritis, duodenitis, gastric ulcer and duodenal ulcer. Furthermore, the compositions of the present invention may be used for treatment or prevention of other gastrointestinal disorders where gastric acid inhibitory effect is desirable, e.g. in patients on nonsteroidal anti-inflammatory drugs (NSAID) therapy (including low dose aspirin), in patients with Non Ulcer Dyspepsia, in patients with symptomatic gastroesophageal reflux disease (GERD), and in patients with gastrinomas. They may also be used in patients in intensive care situations, in patients with acute upper gastrointestinal bleeding such as bleeding peptic ulcers, in patients with nonvariceal upper gastrointestinal bleeding, for prevention of stress-related mucosal bleeding, in conditions of pre-and postoperatively to prevent aspiration of gastric acid and to prevent and treat stress ulceration. Further, they may be useful in the treatment of Helicobacter infections and diseases related to these. Other conditions well suited for treatment include, but are not limited to Zollinger-Ellison syndrome (ZES), Werner's syndrome, chronic pancreatitis and systemic mastocytosis.
The pharmaceutical compositions of the present invention may also be used as prophylaxis or treatment for mucosal damage in patients undergoing cancer chemotherapy. Thus, the compositions may be used in order to provide symptom relief and prophylaxis against upper GI ulceration in patients receiving cancer chemotherapy. Further, the compositions may be used in any other condition in which elevation of gastric pH is required such as when acid-labile drugs are administered and there is a risk that the acidic conditions in the stomach will damage the drugs. Thus, the compositions of the present invention may be used in combination with any acid-labile drug in order to protect the acid-labile drug from the acidic conditions in the stomach.

The oral compositions may further comprise mucosal protectants, such as bismuth-containing compounds and sucralfate. Bismuth-containing compounds are well known, being used widely to treat a variety of gastrointestinal disorders such as nausea, heartburn, and diarrhea. One such product is liquid Pepto-Bismol (sold by The Procter & Gamble Company). This product contains bismuth/subsalicylate and a methylcellulose/magnesium aluminum silicate suspension system. Another is Pabizol with Paregoric (sold by Rexall) which is a liquid suspension said to contain, in addition to opium, bismuth subsalicylate (17.0 mg/ml), aluminum magnesium silicate (8.83 mg/ml), and hydroxypropylmethylcellulose (6.7 mg/ml). These and other bismuth-containing compositions are described generally in "Handbook of Nonprescription Drugs, 8th Edition" (American Pharmaceutical Association, Washington, D.C.; 1986), pages 73-74.

The oral compositions may further comprise an antibacterial agent for the treatment of ulcers associated with Helicobacter sp infection (e.g. Helicobacter pylori). Such antibacterial agents include, for example, amoxicillin, clarithromycin or other macrolides, metronidazole and related antibiotics, tetracycline, quinolones, rifabutin or furazolidone.

The PPIs used in the present invention can be used in neutral form or in the form of a salt (e.g., an alkaline salt), such as for instance the Mg\(^{2+}\), Ca\(^{2+}\), Na\(^{+}\), K\(^{+}\), or Li\(^{+}\) salts, preferably the Mg\(^{2+}\) salts. Further where applicable, the compounds can be used in racemic form or in the form of an enantiomer thereof, or salts of the racemates or the single enantiomers. Furthermore, the H\(_2\) blockers used in the present invention can be used in the form of specific polymorphic crystalline forms, such as Form 1 or Form 2 polymorphs of ranitidine.

AUPPIs are acid-labile drugs, therefore the PPI particles in the present composition are preferably formulated as pH-dependent enteric-coated granules or time-dependent release polymers in order to avoid contact with the gastric juice in the stomach.
Non-limiting examples of suitable pH-dependent enteric-coated polymers to be used in the present invention are: cellulose acetate phthalate, hydroxypropynethylcellulose phthalate, polyvinylacetate phthalate, methacrylic acid copolymer, shellac, hydroxypropylmethylcellulose succinate, cellulose acetate trimellitate, and mixtures of any of the foregoing. A suitable commercially available enteric material, for example, is sold under the trademark Eudragit L 100-55. This coating can be spray coated onto the substrate.

The active ingredients of the present invention (e.g. the PPI and the endoperoxide-bearing compounds) may be coated with suitable non-enteric time-dependent release coatings such as for example: film-forming compounds such as cellulosic derivatives, such as methylcellulose, hydroxypropyl methylcellulose (HPMC), hydroxyethylcellulose, and/or acrylic polymers including the non-enteric forms of the Eudragit brand polymers. Other film-forming materials may be used alone or in combination with each other or with the ones listed above. These other film forming materials generally include polyvinylpyrrolidone), Zein, poly(ethylene glycol), poly(ethylene oxide), polyvinyl alcohol), polyvinyl acetate), and ethyl cellulose, as well as other pharmaceutically acceptable hydrophilic and hydrophobic film-forming materials. These film-forming materials may be applied to the substrate cores using water as the vehicle or, alternatively, a solvent system. Hydro-alcoholic systems may also be employed to serve as a vehicle for film formation.

Other materials which are suitable for making the time-dependent release coating of the invention include, by way of example and without limitation, chitosan and its derivatives such as trimethylchitosan, water soluble polysaccharide gums such as carrageenan, fucoidan, gum ghatti, tragacanth, arabinogalactan, pectin, and xanthan; water-soluble salts of polysaccharide gums such as sodium alginate, sodium tragacanthin, and sodium gum ghattate; water-soluble hydroxyalkylicellulose wherein the alkyl member is straight or branched of 1 to 7 carbons such as hydroxymethylcellulose, hydroxyethylcellulose, and hydroxypropylcellulose; synthetic water-soluble cellulose-based lamina formers such as methyl cellulose and its hydroxyalkyl methylcellulose cellulose derivatives such as a member selected from the group consisting of hydroxyethyl methylcellulose, hydroxypropyl methylcellulose, and hydroxybutyl methylcellulose; other cellulose polymers such as sodium carboxymethylcellulose; and other materials known to those of ordinary skill in the art. Other lamina forming materials that can be used for this purpose include polyvinylpyrrolidone), polyvinylalcohol, polyethylene oxide, a blend of gelatin and
polyvinylpyrrolidone, gelatin, glucose, saccharides, povidone, copovidone, poly(vinylpyrrolidone)-poly(vinyl acetate) copolymer.

It is also possible to add buffering agents to the enteric-coated formulation in order to facilitate the release of the PPI from the enteric-coated pellets, thereby enhancing the absorption of the PPI in blood. Specifically, a buffering agent such as for example sodium bicarbonate may be added in an amount sufficient to provide a pH above 5 in the stomach. For example, between 300 to 2,000 mg of sodium bicarbonate may be added to the formulation. If fast absorption of PPI in blood is required, it is possible to use non-enteric PPI pellets in the present formulations. In this case, the stability of the PPI in the stomach will be preserved due to the buffering agent that provides a pH above 5 in the stomach.

The active compounds used in the methods of the present invention may be administered by intravenous, parenteral, rectal, transdermal or oral means. In preferred embodiments of the present invention, the pharmaceutical compositions are administered orally. Such oral dosage forms may contain the active compound in immediate or sustained release form.

In one embodiment, the endoperoxide-bearing compounds are formulated in a composition designed to act locally in the stomach following oral administration to reduce acid secretion. Since the preferred compounds such as artemisinin or the active derivatives thereof are not soluble in the acidic conditions of the gastric fluid, it is necessary to preserve its solubility in the stomach in order to permit the active compound to act locally. Thus, the compositions may further comprise agents that maintain the solubility of the endoperoxide-bearing compound in the gastric fluids. Such agents are preferably alkaline agents or antacids that when dissolved in the gastric juice are capable of elevating the pH of the gastric fluids to a pH in which at least significant proportion of the endoperoxide-bearing compound remains soluble in the gastric fluids.

Buffering agents to be used in the present invention include for example: sodium or potassium bicarbonate, magnesium oxide, hydroxide or carbonate, magnesium lactate, magnesium glucomate, aluminium hydroxide, aluminium, calcium, sodium or potassium carbonate, phosphate or citrate, di-sodium carbonate, disodium hydrogen phosphate, a mixture of aluminium glycinate and a buffer, calcium hydroxide, calcium lactate, calcium carbonate, calcium bicarbonate, and other calcium salts. It is noted that while sodium bicarbonate dissolves easily in water, calcium carbonate is water-insoluble and is slowly soluble only in acidic environment. Therefore, calcium carbonate may be useful when sustained dissolution of the alkaline agent in the stomach is desired.
Examples of antacids to be used in the present invention include one or more of the following: alumina, calcium carbonate, and sodium bicarbonate; alumina and magnesia; alumina, magnesia, calcium carbonate, and simethicone; alumina, magnesia, and magnesium carbonate; alumina, magnesia, magnesium carbonate, and simethicone; alumina, magnesia, and simethicone; alumina, magnesium alginate, and magnesium carbonate; alumina and magnesium carbonate; alumina, magnesium carbonate, and simethicone; alumina, magnesium carbonate, and sodium bicarbonate; alumina and magnesium trisilicate; alumina, magnesium trisilicate, and sodium bicarbonate; alumina and simethicone; alumina and sodium bicarbonate; aluminum carbonate, basic; aluminum carbonate, basic, and simethicone; aluminum hydroxide; calcium carbonate; calcium carbonate and magnesia; calcium carbonate, magnesia, and simethicone; calcium carbonate and simethicone; calcium and magnesium carbonates; magaldrate; magaldrate and simethicone; magnesium carbonate and sodium bicarbonate; magnesium hydroxide; magnesium oxide.

The oral dosage forms may be in the form of tablets, capsules, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsions, multiparticulate formulations, syrups, elixirs, and the like.

Suitable pharmaceutically acceptable carriers include but are not limited to water, salt solutions, alcohols, gum arabic, vegetable oils, benzyl alcohols, polyethylene glycols, gelate, carbohydrates such as lactose, amylose or starch, magnesium stearate talc, silicic acid, viscous paraffin, perfume oil, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxymethylcellulose, polyvinylpyrrolidone, etc. The pharmaceutical preparations can be sterilized and if desired mixed with auxiliary agents, e.g., lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure buffers, coloring, flavoring and/or aromatic substances and the like. For oral application, particularly suitable are tablets, dragees, liquids, drops, suppositories, or capsules, caplets and gelcaps.

The compositions intended for oral use may be prepared according to any method known in the art and such compositions may contain one or more agents selected from the group consisting of inert, non-toxic pharmaceutically excipients which are suitable for the manufacture of tablets. Such excipients include, for example an inert diluent such as lactose; granulating and disintegrating agents such as cornstarch; binding agents such as starch; and lubricating agents such as magnesium stearate. The tablets may be uncoated or they may be coated by known techniques for elegance or to delay the release of the active.
ingredients. Formulations for oral use may also be presented as hard gelatin capsules wherein the active ingredient is mixed with an inert diluent.

The present invention also includes a pharmaceutical kit, preferably an oral pharmaceutical kit. The kit typically comprises as active ingredients a pharmaceutically effective amount of: (i) one or more endoperoxide-bearing compounds according to the present invention; and (ii) a substituted benzimidazole H+/K⁺-ATPaSe proton pump inhibitor and/or an H₂ blocker. In one embodiment, the active ingredients are formulated in separate dosage unit forms. The kit may be used to treat or prevent a disorder in a subject in which suppression of gastric acid secretion or reducing gastric acidity is required by administering to a subject the active ingredients. The one or more endoperoxide-bearing compounds are typically administered simultaneously, prior to or following the administration of the PPI and/or an H₂ blocker.

The compositions of the endoperoxide-bearing compounds of the invention generally comprise an amount of the endoperoxide compounds sufficient to suppress gastric acid secretion or to reduce gastric acidity, together with a pharmaceutically acceptable carrier. The compositions are typically administered to a human or other animal subject in an amount to localize a sufficient amount of the endoperoxide-bearing compounds at the stomach to facilitate the anti-acid effect. Any pharmaceutically acceptable carrier may be generally used for this purpose, provided that the carrier does not significantly interfere with the stability or bioavailability of the sesquiterpene compounds of the invention.

The particles may be formed into a packed mass for ingestion by conventional techniques. For instance, the particles may be encapsulated as a "hard-filled capsule" using known encapsulating procedures and materials. The encapsulating material should be highly soluble in gastric fluid so that the particles are rapidly dispersed in the stomach after the capsule is ingested.

In another embodiment, the active ingredients of the present invention are packaged in compressed tablets. The term "compressed tablet" generally refers to a plain, uncoated tablet for oral ingestion, prepared by a single compression or by pre-compaction tapping followed by a final compression. Such solid forms can be manufactured as is well known in the art. Tablet forms can include, for example, one or more of lactose, mannitol, corn starch, potato starch, microcrystalline cellulose, acacia, gelatin, colloidal silicon dioxide, croscarmellose sodium, talc, magnesium stearate, stearic acid, and other excipients, colorants, diluents, buffering agents, moistening agents, preservatives, flavoring agents, and pharmaceutically compatible carriers. The manufacturing processes may employ one, or a
combination of four established methods: (1) dry mixing; (2) direct compression; (3) milling; and (4) non-aqueous granulation. Lachman et al., The Theory and Practice of Industrial Pharmacy (1986). Such tablets may also comprise film coatings, which preferably dissolve upon oral ingestion or upon contact with diluent.

In another alternative, the compositions of the present invention are formulated in compressed forms, such as suspension tablets and effervescent tablets, such that upon reaction with water or other diluents, the aqueous form of the composition is produced for oral administration. These forms are particularly useful for medicating children and the elderly and others in a way that is much more acceptable than swallowing or chewing a tablet. The present pharmaceutical tablets or other solid dosage forms disintegrate the alkaline agent with minimal shaking or agitation.

The term "suspension tablets" as used herein refers to compressed tablets which rapidly disintegrate after they are placed in water, and are readily dispersible to form a suspension containing a precise dosage of the PPI and the parietal cell activator. To achieve rapid disintegration of the tablet, a disintegrant such as croscarmellose sodium may be added to the formulation. The disintegrant may be blended in compressed tablet formulations either alone or in combination with microcrystalline cellulose, which is well known for its ability to improve compressibility of difficult to compress tablet materials. Microcrystalline cellulose, alone or co-processed with other ingredients, is also a common additive for compressed tablets and is well known for its ability to improve compressibility of difficult to compress tablet materials. It is commercially available under the Avicel trademark.

The suspension tablet composition may, in addition to the ingredients described above, contain other ingredients often used in pharmaceutical tablets, including flavoring agents, sweetening agents, flow aids, lubricants or other common tablet adjuvants, as will be apparent to those skilled in the art. Other disintegrants, such as crospovidone and sodium starch glycolate may be employed, although croscarmellose sodium is preferred.

The compositions of the invention can be administered in any effective pharmaceutically acceptable form to warm blooded animals, including human and other animal subjects, e.g., oral, suppository, parenteral, or infusible dosage forms, or in any other manner effective to deliver the agents to the target tissue. The route of administration will preferably be designed to optimize delivery and localization of the agents to the target tissue.
Compositions designed for injection may comprise pharmaceutically acceptable sterile aqueous or nonaqueous solutions, suspensions or emulsions. Examples of suitable nonaqueous carriers, diluents, solvents, or vehicles include propylene glycol, polyethylene glycol, vegetable oils, such as olive oil, and injectable organic esters such as ethyl oleate. Such compositions may also comprise adjuvants such as preserving, wetting, emulsifying, and dispensing agents. They may be sterilized, for example, by filtration through a bacteria-retaining filter, or by incorporating sterilizing agents into the compositions. They can also be manufactured in the form of sterile solid compositions that can be dissolved or suspended in sterile water, saline, or other injectable medium prior to administration.

Solid dosage forms for oral administration include capsules, tablets, pills, suppositories, powders, and granules. In solid dosage forms, the compositions may be admixed with at least one inert diluent such as sucrose, lactose, or starch, and may additionally comprise lubricating agents, buffering agents, enteric coatings, and other components well known to those skilled in the art.

The concentrations of the endoperoxide-containing compounds in the formulations to be applied in the practice of the present invention will generally range up to the maximally tolerated dosage, but the concentrations are not critical and may vary widely. For artemisinin and its analogs, however, best results will be obtained using formulations containing the compounds at levels of from about 0.1 to about 100 mg per kilogram of body weight per day, preferably from about 1 to about 100 mg per kilogram of body weight per day, and most preferably from about 1 to about 20 mg per kilogram of body weight per day. The precise amounts employed by the attending physician will vary, of course, depending on the compound, route of administration, and physical condition of the patient and other factors. The daily dosage may be administered as a single dosage or may be divided into multiple doses for administration. The amount of the compound actually administered for treatment will be a therapeutically effective amount, which term is used herein to denote the amount needed to produce a substantial clinical improvement or an amount sufficient to inhibit growth of the bacteria in the subject. Optimal amounts will vary with the method of administration, and will generally be in accordance with the amounts of conventional medicaments administered in the same or a similar form. Oral administration, for instance, may typically be done from once to three times a day.

The following examples are presented in order to more fully illustrate certain embodiments of the invention. They should in no way, however, be construed as limiting the broad scope of the invention. One skilled in the art can readily devise many variations and
modifications of the principles disclosed herein without departing from the scope of the invention.

**EXAMPLES**

The following examples are not intended to limit the scope of the invention, but merely to illustrate representative possibilities concerning the present invention.

*Example 1: Artesunate is capable of reducing gastric acidity and to enhance the effect of pantoprazole on gastric acid secretion*

To study the effect of artesunate on gastric acidity, an experimental model of conscious pylorus-ligated rats was used. This experimental model permits the analysis of the effect of drugs on gastric acidity in conscious animals and avoids the effect of anesthesia on gastric acid secretion. Artesunate alone (ASN, 49 mg/kg corresponding to 127 mmol/kg), pantoprazole alone (3 mg/kg) and combination of artesunate with pantoprazole were administered by oral gavage. Water was administered as a placebo. Ninety minutes later the animals were anesthetized using anesthetic gas machine for a short period (5 minutes) that is sufficient to perform the pylorus ligation procedure and to close the abdomen. The animals were then placed back into their cage for additional 3.5 hours after which the animals were sacrificed. The ligature was placed around the esophagus, the stomach removed and gastric content was collected. Following centrifugation, the gastric output and the pH of the gastric juice samples was determined. Data is presented as average ± SEM of gastric output (in mEq) or pH values. The number of animals was 6-8 in each experimental group.

As can be seen in Figure IA, artesunate (ASN) alone significantly reduced the gastric output as compared to the placebo group. Pantoprazole (PAN) alone also effectively reduced gastric output. Administration of artesunate in combination with pantoprazole resulted in almost complete inhibition of gastric output. Figure IB further demonstrates that treatment with artesunate alone led to increased gastric pH. The combination of artesunate with pantoprazole was more effective in increasing the gastric pH than artesunate or pantoprazole alone.
Example 2: Artemisinin is capable of reducing gastric acidity

The effect of Artemisinin, another endoperoxide-bearing compound on gastric output was examined following administration by oral gavage. As can be seen in Figure 2A, Artemisinin alone (AMS, 36 mg/kg corresponding to 127 mmol/kg) significantly reduced the gastric output as compared to the placebo group (AMS 0). Pantoprazole (PAN) alone also effectively reduced gastric output compared to placebo (PAN 0). Figure 2B further demonstrates that treatment with Artemisinin alone led to increased gastric pH.

Example 3: Dose response of artesunate in reducing gastric acidity secretion following administration by oral gavage

The dose response of artesunate in reducing gastric acidity was examined. As can be seen in Figure 3A, 90 mg/ml artesunate was more effective than 30 mg/ml and 10 mg/ml in reducing gastric acid output. Similarly, the higher dose of artesunate was most effective in elevating the pH in the stomach (Figure 3B).

Example 4: Administration of artesunate in combination with ranitidine resulted in complete inhibition of gastric output

The effect of oral artesunate alone (ASN, 90 mg/kg), ranitidine injection alone (RAN, 10 mg/kg) and combination of oral artesunate with ranitidine injection (RAN, ASN) was tested as well. As can be seen in Figure 4A, artesunate alone (ASN) significantly reduced the gastric output as compared to the placebo group. Ranitidine alone (RAN) also effectively reduced gastric output. Administration of artesunate in combination with ranitidine (RAN, ASN) resulted in complete inhibition of gastric output. Figure 4B further demonstrates that treatment with a combination of artesunate and ranitidine was much more effective in increasing the gastric pH compared to artesunate or ranitidine alone.

Example 5: Intravenous artesunate is capable of inhibiting gastric acid secretion

Animals were anesthetized using anesthetic gas machine for a short period (5 minutes) that is sufficient to perform pylorus ligation and to administer artesunate (40 mg/kg) by intravenous injection. Sodium bicarbonate was administered as a placebo. The animals were then placed back into their cages for additional 3.5 hours after which the animals were sacrificed and gastric content was collected.

As can be seen in Figure 5A, intravenous administration of artesunate (ASN) significantly reduced the gastric output as compared to the placebo group. Figure 5B further
demonstrates that treatment with intravenous artesunate led to increased gastric pH. These results indicate that artesunate is capable of inhibiting gastric acid output following systemic administration of the drug.

**Example 6: The effect of intravenous artesunate in combination with indomethacin on gastric acid output.**

Animals were anesthetized using anesthetic gas machine for a short period (5 minutes) that is sufficient to perform pylorus ligation and to administer artesunate (ASN, 40 mg/kg) by intravenous injection and/or indomethacin subcutaneously (INDO, 9.3 mg/kg). Sodium bicarbonate was administered as a placebo. The animals were then placed back into their cage for additional 3.5 hours after which the animals were sacrificed and gastric content was collected.

As can be seen in Figure 6A, indomethacin reversed the effect of artesunate in reducing gastric acid output. Indomethacin is a nonselective inhibitor of cyclooxygenase (COX) 1 and 2, enzymes that participate in prostaglandin synthesis from arachidonic acid. In addition, indomethacin itself led to a significant increase in gastric acid output (probably due to its inhibitory effect on the synthesis of prostaglandins). These results might indicate that the inhibitory effect of artesunate on gastric acid output in the stomach is mediated by increase in prostaglandin release. However, since indomethacin itself has a prominent effect on acid secretion, it is also possible that artesunate reduces acid output via different mechanism. The average pH levels in gastric juice following the treatment with artesunate alone, indomethacin alone or the combination thereof is demonstrated in Figure 6B.

**Example 7: Administration of oral artesunate (45 mg/kg) in combination with omeprazole (10 mg/kg) resulted in complete inhibition of gastric output**

The effect of oral artesunate alone (ASN, 45 mg/kg), omeprazole alone (OMP, 10 mg/kg) or the combination thereof (Combo) was tested. As can be seen in Figure 7A, artesunate (ASN) alone significantly reduced the gastric output as compared to the placebo group. Omeprazole (OMP) alone also effectively reduced gastric output. Administration of artesunate in combination with omeprazole (Combo) resulted in 80% inhibition of gastric output. Figure 7B further demonstrates that treatment with a combination of artesunate and omeprazole was much more effective in increasing the gastric pH compared to artesunate or omeprazole alone.
Example 8: The effect of oral artemesunate (20 mg/kg and 40 mg/kg) and pantoprazole (3 mg/kg) on gastric output and pH of gastric fluid.

The effect of oral artemesunate alone (ASN, 20 mg/kg or 40 mg/kg) in combination with pantoprazole (PAN, 3 mg/kg) was tested. As can be seen in Figure 8A, pantoprazole (PAN) alone effectively reduced gastric output. Administration of 20 mg/kg or 40 mg/kg of artemesunate in combination with pantoprazole resulted in total inhibition of gastric output. Figure 8B further demonstrates that treatment with a combination of artemesunate and pantoprazole was much more effective in increasing the gastric pH compared to pantoprazole alone.

Example 9: The effect of intravenous artemesunate (15, 30 and 60 mg/kg) on gastric output and pH of gastric fluid

Animals were anesthetized using anesthetic gas machine for a short period (5 minutes) that is sufficient to perform pylorus ligation and to administer artemesunate (15, 30 or 60 mg/kg) by intravenous injection. Sodium bicarbonate was administered as a placebo. The animals were then placed back into its cage for additional 3.5 hours after which the animals were sacrificed and gastric content was collected.

As can be seen in Figure 9A, intravenous administration of artemesunate (ASN) significantly reduced the gastric output as compared to the placebo group already with 15 mg/kg of artemesunate. Figure 9B further demonstrates that treatment with intravenous artemesunate led to increased gastric pH already with 15 mg/kg of artemesunate.

Example 10: Oral formulations comprising artemesunate and optionally a proton pump inhibitor (PPI) and/or ranitidine:

Hard gelatin capsules of artemesunate alone

Hard gelatin capsules may contain granules of artemesunate in an immediate release or delayed release formulation. The granules may be packed into a hard gelatin capsule in an amount corresponding to 250 mg artemesunate per capsule. Optionally, granules of between 300 to 2,000 mg of sodium bicarbonate may be added in order to permit local activity of artemesunate in the stomach.

Hard gelatin capsules of artemesunate and PPI and/or ranitidine

Hard gelatin capsules may contain a mixed granules population of artemesunate and PPI and/or ranitidine. Artemesunate and ranitidine granules are in an immediate release or delayed release formulation and PPI is formulated as enteric-coated granules or time-
dependent release coating (delayed release). Granules may be packed into a hard gelatin capsule in an amount corresponding to 40 mg PPI and/or 150 mg ranitidine and 250 mg artesunate per capsule. Optionally, granules of between 300 to 2,000 mg of sodium bicarbonate may be added.

A) Immediate release artesunate formulation:
- 40 mg enteric-coated (Eudragit) or time-dependent release coated (HPMC) PPI granules and/or 150 mg ranitidine granules
- 250 mg artesunate granules
- Diluent

B) Delayed release artesunate formulation:
- 40 mg enteric-coated or time-dependent release coated PPI granules and/or 150 mg ranitidine granules
- 250 mg artesunate granules (HPMC coated)
- Diluent

For the delayed release artesunate formulation, artesunate solution is sprayed on inert beads in a fluid bed apparatus. After drying, the artesunate beads are further coated with hydroxypropyl methylcellulose (HPMC) to form the final granules. The rate of artesunate release is determined by the thickness and erosion rate of the HPMC layer.

Tablets or caplets of artesunate and PPI and/or ranitidine

The pharmaceutical composition may be in the form of tablet or more preferably caplet. The caplet contains a mixed granules population of artesunate (immediate release or delayed release, as mentioned above), enteric-coated or time-dependent release coated PPI (stable under compression pressure) and/or ranitidine and a wide variety of conventional tableting aid agents to be compressed into a caplet formulation.

Minitabs in hard gelatin capsule of artesunate and PPI and/or ranitidine (Rastric retentive dosage form)

Artesunate is granulated with a combination of Polyox WSR N60 and HPMC K100M. These granules are further combined with lactose and HPMC and later on compressed into mini-tabs with the ability of fast swelling into size, big enough to enable gastric retention. The polymeric matrix controls the artesunate release into the stomach.

The artesunate mini-tabs are mixed with enteric-coated PPI and/or ranitidine pellets and filled into hard gelatin capsules. Following disintegration of the capsules gelatinic body, the PPI and/or ranitidine pellets pass though the stomach to the duodenum, where the
enteric coat will dissolve. The artesunate mini-tabs remain in the stomach and slowly release their content in a controlled release gastro retentive manner.

**Press coated tablet of artesunate and PPI and/or ranitidine**

The tablet's internal core is composed of artesunate combined with a mixture of hydrogels aimed for controlled release and prompt swelling of the dosage form. The expanded core has gastro-retentive properties. Mixtures of gums like: xantan gum, gellan gum, together with cellulose derivatives such as sodium carboxymethylcellulose or HPMC may be applied.

The core is further coated with an external layer composed of enteric-coated PPI and/or ranitidine pellets (stable under compression pressure) together with appropriate filler, which disintegrates immediately after digestion and promptly releases the PPI and/or ranitidine. The final product is a tablet composed of an internal controlled-release core of artesunate and an outer layer, immediate release type with the enteric-coated or time-dependent release coated PPI and/or ranitidine.

**Powder for oral suspension of artesunate or artesunate and PPI and/or ranitidine**

Powder for oral suspension is comprised of artesunate or artesunate and enteric-coated or time-dependent release coated PPI granules and/or ranitidine granules. Artesunate granules may be in immediate release or delayed release formulation (as mentioned above). PPI are formulated as enteric-coated or time-dependent release coated granules (delayed release). The composition comes in individual packets to be constituted with water. When mixed with water, powder becomes a uniform liquid suspension.

**Injectable preparation of artesunate**

Artesunate liquid solution is prepared by dissolving 60 mg artesunate in 5% sodium bicarbonate and shaking vigorously till the solution becomes clear. The solution is further mixed with normal saline. To prepare a dose form for intravenous administration, the resulting solution is dispensed into sealable translucent plastic bags for use in intravenous administration of the compound.

Any and all publications and patent applications mentioned in this specification are indicative of the level of skill of those skilled in the art to which this invention pertains. All publications and patent applications are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.
It will be appreciated by a person skilled in the art that the present invention is not limited by what has been particularly shown and described hereinabove. Rather, the scope of the invention is defined by the claims that follow.
CLAIMS

1. A method of treating or preventing a disorder in a subject in which suppression of gastric acid secretion or reducing of gastric acidity is required, comprising administering to a subject in need of such treatment a therapeutically effective amount of an endoperoxide-bearing compound, wherein the compound being in an amount sufficient to reduce gastric acid secretion or reduce gastric acidity in the subject.

2. The method of claim 1, wherein the endoperoxide-bearing compound is selected from the group consisting of: sesquiterpene lactones and alcohols, carbonates, esters, ethers sulfonates and pharmaceutically acceptable salts thereof, trioxolanes, bicyclo endoperoxides, trioxanes, tetraoxanes, terpenes, and substituted terpenes.

3. The method of claim 2, wherein the endoperoxide-bearing compound is according to formula (I):

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\begin{align*}
\text{wherein } R \text{ is } -\text{CO-} & \quad \text{or } R \text{ is } -\text{CR}_1 \\
\text{wherein } R_1 \text{ is hydrogen, hydroxyl, alkyl, } -\text{OR}_2, -\text{COR}_2, -\text{COR}_2, -\text{COOR}_2, -\text{CO(CH}_2)_n \text{, COOH, } -\text{SOOR}_2, \text{ a halogen atom, an optionally substituted cycloalkyl, aryl, C-linked heteroaryl or heterocyclylalkyl group,} \\
\text{wherein } R_2 \text{ is alkyl or aryl and } n \text{ is 1 to 6,} \\
\text{or wherein } R_1 \text{ is } NR^1R^2; \text{ where } R^1 \text{ represents a hydrogen atom or an optionally substituted alkyl, alkenyl or alkynyl group; } R^2 \text{ represents an optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl or aralkyl group; or } R^1 \text{ and } R^2 \text{ together with the interjacent nitrogen atom represent an optionally substituted heterocyclic group or an amino group derived from an optionally substituted amino acid ester.}
\end{align*}
\]
4. The method of claim 3, wherein the endoperoxide-bearing compound is a sesquiterpene selected from the group consisting of: artemisinin, dihydroartemisinin, artemether, arteether, artelene, artesunate, dihydroxydihydroartemisinin, artelinic acid, artemisone and dihydroartemisinin propyl carbonate.

5. The method of claim 1, further comprising administering to the subject a therapeutically effective amount of at least one active agent selected from the group consisting of: an antibacterial agent, an inhibitor of gastric acid secretion, a proton pump inhibitor (PPI), potassium-competitive acid blockers, an H$_2$ blocker, sucralfate, a buffering agent, antacid, a non-steroidal anti-inflammatory (NSAID) drug and a bismuth-containing compound.

6. The method of claim 5, wherein the PPI is selected from the group consisting of: rabeprazole, omeprazole, esomeprazole, lansoprazole, pantoprazole, leminoprazole, tenatoprazole, single enantiomers thereof, alkaline salts thereof, and mixtures thereof.

7. The method of claim 5, wherein the antibacterial agent is selected from the group consisting of: amoxicillin, a macrolide, metronidazole, tetracycline, quinolones, rifabutin, and furazolidone.

8. The method of claim 1, wherein the disorder is selected from the group consisting of: reflux esophagitis, gastritis, duodenitis, gastric ulcer, duodenal ulcer, pathologies associated with nonsteroidal anti-inflammatory drugs (NSAID), non-ulcer Dyspepsia, gastro-esophageal reflux disease, gastrinomas, acute upper gastrointestinal bleeding, stress ulceration, Helicobacter pylori infections, Zollinger-Ellison syndrome (ZES), Werner's syndrome, systemic mastocytosis and chronic pancreatitis.

9. The method of claim 1, wherein the subject is a human subject.

10. The method of claim 6, wherein the endoperoxide-bearing compound is administered simultaneously, prior to or following the administration of the PPI.
11. The method of claim 10, wherein the endoperoxide-bearing compound is administered by intravenous, parenteral, rectal, transdermal, buccal, nasal or oral means.

12. The method of claim 11, wherein the oral composition is in the form of a tablet, a capsule, solution, powder for suspension, dispersion, or emulsion.

13. The method of claim 6, wherein the compound according to formula (I) is artemisinin or artesunate, and the PPI is omeprazole or pantoprazole.

14. The method of claim 5, wherein the H₂ blocker is selected from the group consisting of: cimetidine, famotidine, ranitidine, nizatidine, etintidine, lupitidine, mifentidine, niperotidine, roxatidine, sufotidine, tuvatidine and zaltidine.

15. A composition for reducing gastric acid secretion or gastric acidity in a mammal, comprising an effective amount of a endoperoxide-bearing compound in combination with at least one active agent selected from the group consisting of: an antibacterial agent, an inhibitor of gastric acid secretion, a proton pump inhibitor (PPI), a reversible proton pump inhibitor (a potassium competitive acid blocker), an H₂ blocker, sucralfate, a buffering agent, antacid and a bismuth-containing compound, a mucosal protective drug, a mucosal covering drug, a mucus production accelerating drug, a prostaglandin synthesis accelerating drug and a prostaglandin preparation.

16. The composition of claim 15, wherein the endoperoxide-bearing compound is selected from the group consisting of: sesquiterpene lactones and alcohols, carbonates, esters, ethers sulfonates and pharmaceutically acceptable salts thereof, trioxolanes, byciclo endoperoxides, trioxanes, tetraoxanes, terpenes, and substituted terpenes.
17. The composition of claim 16, wherein the endoperoxide-bearing compound is according to formula (I):

![Chemical Structure](image)

(I)

wherein R is -CO- or R_{i}S -CR_{i}^{-}

wherein R_{i} is hydrogen, hydroxyl, alkyl, -OR_{2}, -COR_{2}, -COR_{2}, -COOR_{2}, -C0(CH_{2})_{n}, -COOH, -SOOR_{2}, a halogen atom, an optionally substituted cycloalkyl, aryl, C-linked heteroaryl or heterocyclalkyl group.

wherein R_{j} is alkyl or aryl and n is 1 to 6, or wherein R_{j} is NR_{j}^{1}R_{j}^{2}; where R_{j}^{1} represents a hydrogen atom or an optionally substituted alkyl, alkenyl or alkynyl group; R_{j}^{2} represents an optionally substituted alkyl, alkenyl, alkynyl, cycloalkyl, aryl or aralkyl group; or R_{j}^{1} and R_{j}^{2} together with the interjacent nitrogen atom represent an optionally substituted heterocyclic group.

18. The composition of claim 17, wherein the endoperoxide-bearing compound is a sesquiterpene selected from the group consisting of: artemisinin, dihydroartemisinin, artemether, arteether, arteflene, artesunate, dihydroxydihydroartemisinin, artelinic acid, artemisone and dihydroartemisinin propyl carbonate.

19. The composition of claim 15, wherein the PPI is selected from the group consisting of: rabeprazole, omeprazole, esomeprazole, lansoprazole, pantoprazole, leminoprazole, tenatoprazole, single enantiomers thereof, alkaline salts thereof, and mixtures thereof.

20. The composition of claim 15, wherein the antibacterial agent is selected from the group consisting of: amoxicillin, a macrolide, metronidazole, tetracycline, quinolones, rifabutin, and furazolidone.
21. The composition of claim 15, wherein the composition is in the form of a tablet, a capsule, solution, powder for suspension, dispersion, or emulsion.

22. The composition of claim 17, wherein the compound according to formula (I) is artemisinin or artesunate.

23. The composition of claim 15, wherein the H₂ blocker is selected from the group consisting of: cimetidine, famotidine, ranitidine, nizatidine, etintidine, lupitidine, mifentidine, niperotidine, roxatidine, sufotidine, tuvatidine and zaltidine.
FIGURE 1A

Average Gastric Acid output

FIGURE 1B

Average pH of Gastric Fluid
FIGURE 2A

Average Gastric Acid output

FIGURE 2B

Average pH of Gastric Fluid
FIGURE 3A

Median Gastric Acid output

mEq

Placebo 10 mg/ml 30 mg/ml 90 mg/ml

FIGURE 3B

Median pH of Gastric Fluid

pH

Placebo, 30 mg/ml

10 mg/ml 90 mg/ml
Average Gastric Acid output

FIGURE 6A

Average pH of Gastric Fluid

FIGURE 6B
FIGURE 7A

Average Gastric Acid output

mEq

Placebo  ASN  OMP  Combo

FIGURE 7B

Average pH of Gastric Fluid

pH

Placebo  ASN  OMP  Combo
Average gastric acid output

![Graph showing average gastric acid output with bars for PLAC, PAN 3, PAN 3 ASN 20, and PAN 3 ASN 40.]

Average pH of Gastric Fluid

![Graph showing average pH of gastric fluid with bars for PLAC, PAN 3, PAN 3 ASN 20, and PAN 3 ASN 40.]

FIGURE 8A

FIGURE 8B
Average gastric acid output

Average pH of Gastric Fluid

FIGURE 9A

FIGURE 9B