GASTROINTESTINAL AGENTS

1. Introduction

Compounds used as gastrointestinal agents may be divided into classes according to general activity: agents for therapy of peptic ulcer and gastroesophageal reflux, laxatives, antidiarrheals, antiemetics, and pro-kinetic drugs. Most included drugs have been approved for marketing in the United States. Trade names are those used in the United States or in foreign countries. Many compounds are now available over the counter (OTC) as well as by prescription.

2. Antipeptic Ulcer and Gastro-Esophageal Reflux Therapy

The primary aim in antiulcer therapy and prevention and/or treatment of GERD is either prevention of acid secretion from the gastric parietal cells or neutralization of the acid before it comes into contact with the damaged areas of the gastrointestinal tract (1). Long established therapy of duodenal ulcers, prior to the introduction of potent gastric anti-secretory agents such as the histamine H_2 blockers and proton pump inhibitors (PPIs) consisted of restricted diet, antacids, and anticholinergics. Of these, only antacids have been shown conclusively to be effective. Antacids can encourage healing, but only when given in large and frequent doses. Antacids, are now used mainly as adjunctive therapy and generally available without a prescription and are indicated for short-term therapy of esophageal reflux (heartburn). Nonselective anticholinergics such as atropine [51-55-8], which enjoyed wide use prior to the availability of the more potent antisecretory agents, are only effective when given at doses high enough to produce objectionable side effects.

The therapy for peptic ulcers changed drastically upon the introduction of cimetidine in the United States in 1977. Cimetidine was the first of a series of agents that acted by antagonism of histamine induced gastric acid secretion. Since the approval of cimetidine [51481-61-9], three additional blockers have been approved for acute therapy of duodenal ulcers: famotidine [76824-35-6], nizatidine [76963-41-2], and ranitidine [66357-35-5].

Agents, which specifically prevent the secretion of hydrochloric acid by the gastric parietal cells act by selective inhibition of the proton pump (PPIs) (1). This enzyme is found only in gastric parietal cells and compounds inhibiting it have selective gastric anti-ecretory activity. The first compound marketed in the United States (ca 1992), omeprazole [73590-58-6], is a potent antisecretory agent and is used for acute therapy of ulcerative disease and esophagitis. Several other are now available include esomeprazole, [161973-10-0], lansoprazole [103577-45-3], pantoprazole [102625-70-7], and rabeprazole [117976-89-3]. These have found wide use, not only for treatment of peptic ulcer, but also for the treatment of gastroesophageal reflux, which is the major indication for their use. Gastroesophageal reflux disease (GERD) is now treated with PPIs which can significantly inhibit gastric acid production and decrease acidity of the gastric reflux into the esophagus, thereby decreasing heartburn. The market for this use is difficult to

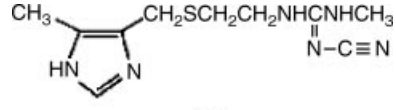
obtain, but it is well over a billion dollars per year for OTC (omeprazole) and multi-billion dollars for the rest that are still prescription only (2).

The treatment of peptic ulcers has changed dramatically since the confirmation of the importance of *Helicobacter pylori* in the etiology of the formation and maintenance of gastric and duodenal peptic ulcers (3). This organism has been shown to be able to survive the acid media of the stomach. Tissue biopsy studies have shown that colonization with *Helicobacter pylori* is associated with gastritis and peptic ulcers in the stomach and duodenum. Long term cures for peptic ulcers have been achieved using therapy which can eradicate *Helicobacter* from the gastrointestinal mucosa. Clinical trials have shown the effectiveness of combinations of PPIs and antibiotics in eliminating *Helicobacter* and induce healing of ulcers after several weeks of therapy. Specific combinations are not discussed in this article.

Drugs acting by mechanisms not related to inhibition of gastric acid secretion have been introduced into therapy in the United States. The two compounds falling into this category are sucralfate and misoprostol, which are discussed.

2.1. Antiulcer and Gastro-Esophageal Reflux Agents

Cimetidine. This agent, also known as Tagamet, Brumetidina, Eureceptor, Ulcomedina, Acibilin, Dyspame, Gastromet, Metracin, Ulcedine, [51481-61-9], 1-cyano-2-methyl-3-[2-[(5-methyl-1*H*-imidazol-4-yl) methylsulfanyl]ethyl] guanidine (**1**) is soluble in alcohol, slightly soluble in water, very slightly soluble in chloroform, and insoluble in ether. The hydrochloride is freely soluble in water, soluble in alcohol, very slightly soluble in chloroform, and practically insoluble in ether. The method of preparation of cimetidine is available in (see Ref. 4).



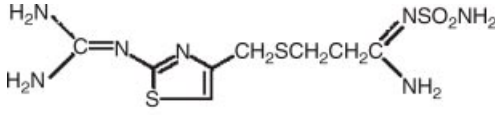
(1)

Mechanism of Action. Cimetidine was the first histamine-H_2 antagonist approved in the United States. Its mechanism of action is suppression of gastric acid secretion through the blockade of histamine H_2-receptors on the gastric parietal cells, thereby decreasing both basal and stimulated gastric acid secretion. Cimetidine has been reported to inhibit certain microsomal enzyme systems and reduce the liver metabolism of a large number of drugs. Cimetidine is a known inhibitor of many isozymes of the cytochrome P450 enzyme system (specifically CYP1A2, CYP2C9, CYP2C19 CYP2D6, CYP2E1, and CYP3A4). This inhibition forms the basis of the numerous drug interactions that occur between cimetidine and other drugs. Cimetidine may decrease metabolism of some drugs, such as oral contraceptives. There should be careful monitoring of patients on concomitant therapy with other drugs. Cimetidine interferes with estrogen metabolism, enhancing estrogen activity leading to gynecomastia. The development of longer-acting H_2-receptor antagonists with reduced adverse effects decreased the use of cimetidine and it is no longer among the more widely used H_2-receptor antagonists. It is available as tablets, liquid, and injection.

Uses. Cimetidine is used in the short-term treatment of active duodenal ulcer and of active benign gastric ulcer. It is used as a maintenance therapy for

duodenal ulcer patients at reduced dosage after healing of active ulcer and as therapy for erosive gastroesophageal reflux disease (GERD).

Famotidine. Famotidine is also known as Pepcid, Dispronil, Famodil, Famosan and other names [76824-35-6], (*N*′-(aminosulfonyl)-3-([[2-[(diaminomethylene) amino]-4-thiazolyl] methyl]thio) propanimidamide (**2**) is a white to pale yellow crystalline compound, freely soluble in glacial acetic acid, slightly soluble in methanol, very slightly soluble in water, and practically insoluble in ethanol. It may be prepared by the method described in (Ref. 5).



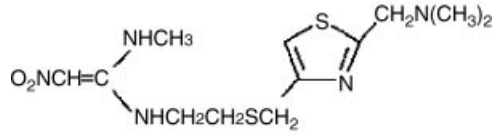
(2)

Generic preparations became available in 2001. It is now available as chewable tablets, gelcaps, tablets, injection, and oral suspension by prescription or OTC.

Mechanism of Action. Famotidine is a competitive histamine-H_2 antagonist that works primarily by inhibition of gastric acid secretion. It is three times more potent than ranitidine and 20 times more potent than cimetidine.

Uses. Famotidine is used in the short term treatment of active duodenal ulcer, of active benign gastric clucer, and of gastroesophageal reflux disease. It is also used as a maintenance therapy for duodenal ulcer patients at reduced dosage after healing of an active ulcer.

Nizatidine. Nizatidine is also known as Axid, Calmaxid, Chronizat, Gastrax, Naxidine, Nizax, Nizaxid, Zanizal [76963-41-2], *N*-[2-[[[2-[(Dimethylamino) methyl]-4-thiazolyl] methyl] thio]ethyl]-*N*′-methyl-2-nitro-1,1-ethenediamine (**3**) is an off-white to buff crystalline solid with a bitter taste and mild sulfur-like odor and soluble in water. Its method of synthesis is available in (Ref. 6).



(3)

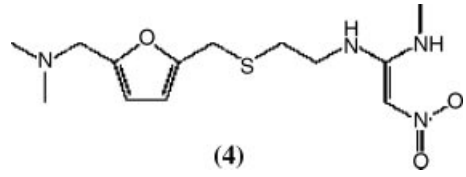
Nizatidine is available in oral formulations from a variety of manufacturers. It is available by prescription and OTC.

Mechanism of Action. Nizatidine is a histamine-H_2 antagonist that may inhibit alcohol dehydrogenase in the gastric mucosa and produce higher alcohol levels in the blood. In patients given very high (3900 mg) doses of aspirin daily, increases in serum salicylate levels have been seen when nizatidine, at 150 mg bid, is administered concurrently.

Uses. Nizatidine is used in the treatment of active duodenal ulcer, of active benign gastric clucer and of endoscopically diagnosed esophagitis, including erosive and ulcerative esophagitis, and associated heartburn due to GERD.

Ranitidine. Ranitidine is also known as Zantac, Tazac, Duractin, Gastrial, Microtid, Ptinolin, Ranidine, Raniogas. Ranitiget, Rantacid, [66357-35-5] [66357-59-3] (*E*)-*N*-(2-((5-((dimethyl aminomethyl) furan-2-yl)methylthio)ethyl)-*N*′-

methyl-2-nitroethene-1,1-diamine HCl (**4**). It is a white to pale yellow granular substance. It is freely soluble in water and acetic acid, soluble in methanol, sparingly soluble in ethanol, and practically insoluble in chloroform. It has a slightly bitter taste and a sulfur-like odor. It may be made by the method described in (Ref. 7).

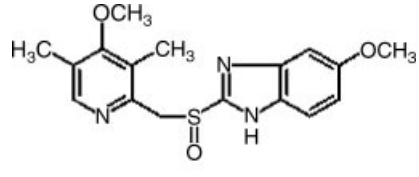


(4)

Mechanism of Action. Ranitidine is a histamine H_2-receptor antagonist that inhibits stomach acid production and is commonly used in the treatment of peptic ulcer and gastroesophageal reflux disease. Ranitidine was the second H_2-receptor antagonist approved for use in the United States. Although it may interact weakly with cytochrome P-450, this has not been a significant effect seen in clinical use. Drug interactions are less frequent than for cimetidine; however, interactions with nifedipine [21829-25-4], warfarin [81-81-2], theophylline [58-55-9], and metoprolol [37350-58-6] have been observed.

Uses. Ranitidine is used in oral administration for short-term therapy of active duodenal ulcers and for maintenance therapy using reduced daily dosage. It is also used in the treatment of pathological hypersecretory conditions, of gastroesophageal reflux, short-term treatment of benign gastric ulcers. Parenteral administration is used for some hospitalized patients with pathological hypersecretory conditions or intractable duodenal ulcers.

Omeprazole. Omeprazole is also known as Prilosec, Omepral, Omeprazon, Audazol, Omapren, Parizac, Zegerid, Mopral, Antra [73590-58-6] (5-methoxy-2-(((methoxy-3,5-dimethyl-2-pyridinyl)methyl)sulfinyl)-1*H*-benzimidazole) (**5**) is a white to off-white crystalline powder. It is a weak base freely soluble in ethanol and methanol, slightly soluble in acetone and isopropanol, and very slightly soluble in water and is rapidly degraded in acid media but has acceptable stability under alkaline conditions. The method of preparation is available in (8). It is now available from generic manufacturers under various trade names. Omeprazole was one of the most widely prescribed drugs internationally and is available over the counter in the US.



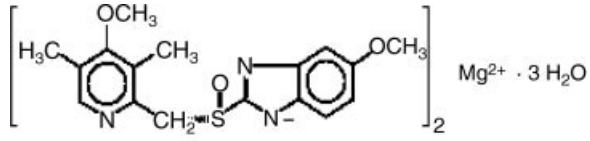
(5)

Mechanism of Action. Omeprazole is supplied as a delayed-release formulation to prevent degradation in the acid environment of the stomach. It was the first approved antisecretory agent that acts by suppression of gastric acid

secretion by specific inhibition of the adenosine triphosphatase (ATPase) enzyme system in the gastric parietal cell. It blocks the final step of gastric acid secretion and works independently of the means of gastric acid stimulation. Omeprazole has produced a dose-related increase in gastric carcinoid tumors in long-term tests in rats; however, there does not appear to be this risk in humans. Omeprazole inhibits microsomal P-450 monooxygenase and can be expected to interfere with the metabolism of some drugs.

Uses. Omeprazole is used in the short-term treatment of duodenal ulcers and for the short-term therapy of gastroesophageal reflux disease and severe erosive esophagitis.

Esomeprazole Sodium. Esomeprazole sodium is also known as Nexium, Esomeprazole, Esomperazole, Nexiam, [119141-88-7], (*S*)-5-methoxy-2[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1*H*-benzimidazole sodium (**6**). Esomeprazole is the *S*-isomer of omeprazole, which is a mixture of the *S* and *R*-isomers. Esomeprazole sodium is very soluble in water and freely soluble in ethanol (95%). Delayed release tablets contains the *S*-form magnesium salt [161973-10-0]. The magnesium salt is a white to slightly colored crystalline powder. It contains 3 moles of water of solvation and is slightly soluble in water. The stability of esomeprazole magnesium is a function of pH; it rapidly degrades in acidic media, but it has acceptable stability under alkaline conditions. Reconstituted solution of esomeprazole for injection depends on the reconstitution volume and is in the pH range of 9 to 11. The stability of esomeprazole sodium in aqueous solution is strongly pH dependent. The rate of degradation increases with decreasing pH. Preparation may be found in (Ref. 9).



(6)

Mechanism of Action. Esomeprazole is extensively metabolized in the liver by CYP2C19 and CYP3A4. *In vitro* and *in vivo* studies have shown that esomeprazole is not likely to inhibit CYPs 1A2, 2A6, 2C9, 2D6, 2E1 and 3A4. No clinically relevant interactions with drugs metabolized by these CYP enzymes would be expected. The metabolites of esomeprazole lack antisecretory activity. The major part of esomeprazole's metabolism is dependent upon the CYP2C19 isoenzyme, which forms the hydroxy and desmethyl metabolites. The remaining amount is dependent on CYP3A4 which forms the sulphone metabolite. CYP2C19 isoenzyme exhibits polymorphism in the metabolism of esomeprazole, since some 3% of Caucasians and 15–20% of Asians lack CYP2C19.

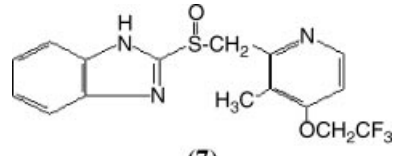
Esomeprazole is a proton pump inhibitor that suppresses gastric acid secretion by specific inhibition of the H+/K+-ATPase in the gastric parietal

cell. The *S*- and *R*-isomers of omeprazole are protonated and converted in the acidic compartment of the parietal cell forming the active inhibitor, the achiral sulfenamide. By acting specifically on the proton pump, esomeprazole blocks the final step in acid production, thus reducing gastric acidity.

An oral fluid formulation, esomeprazole magnesium for delayed-release oral suspension, has been approved by the FDA (November, 2006). Each packet contains esomeprazole granules and inactive granules that are mixed with water to form a suspension and are given by oral, nasogastric or gastric administration.

Uses. Esomeprazole sodium is indicated for the short-term treatment in the healing and symptomatic resolution of diagnostically confirmed erosive esophagitis and to maintain symptom resolution and healing of erosive esophagitis. It is used to treat heartburn and other symptoms associated with GERD. It is indicated for the reduction in the occurrence of gastric ulcers associated with continuous NSAID therapy in patients at risk for developing gastric ulcers in combination with amoxicillin and clarithromycin. It is used in treatment of patients with *H. pylori* infection and duodenal ulcer disease to eradicate *H. pylori*. Eradication of *H. pylori* has been shown to reduce the risk of duodenal ulcer recurrence. Intravenous treatment if esomeprazole is used in patients when therapy orally is not possible for the short-term treatment of GERD patients with a history of erosive esophagitis.

Lansoprazole. Lansoprazole is also known as Prevacid, Agopton, Lansox. Bamalite, Limpidex, Monolitum, Takepron, Agopton. Ogastro, Lanzor, Opiren, [103577-45-3] 2-[[[3-methyl-4-(2,2,2-trifluoroethoxy)-2-pyridyl] methyl] sulfinyl] benzimidazole (**7**) is a white to brownish-white odorless crystalline powder. Lansoprazole is freely soluble in dimethylformamide; soluble in methanol, sparingly soluble in ethanol; slightly soluble in ethyl acetate, dichloromethane and acetonitrile, very slightly soluble in ether, and practically insoluble in hexane and water. Lansoprazole is stable when exposed to light for up to two months. The rate of degradation of the compound in aqueous solution increases with decreasing pH. It is available as an orally suspension and tablet. The degradation half-life of the drug substance in aqueous solution at 25°C is approximately 0.5 hour at pH 5.0 and approximately 18 hours at pH 7.0. The method for preparation may be found in (Ref. 10).



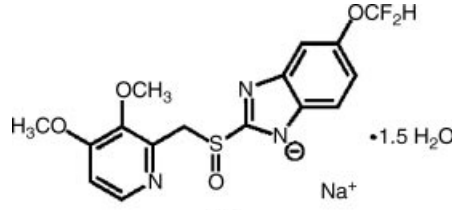
(7)

Mechanism of Action. Lansoprazole is a proton pump inhibitor that suppresses gastric acid secretion by specific inhibition of the H+/K+-ATPase in the gastric parietal cell. Lansoprazole is supplied as a delayed-release capsule, delayed-release orally disintegrating tablets or in a packet for delayed-release oral suspension.

Uses. Lansoprazole is used in the short-term treatment of active duodenal ulcer,symptomatic GERD (heartburn and other symptoms associated with

GERD), for healing and symptom relief of all grades of erosive esophagitis and maintenance of healing of erosive esophagitis, and for healing and symptom relief of active duodenal ulcer, *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence. It is used in combination with amoxicillin plus clarithromycin as triple therapy is indicated for the treatment of patients with *H. pylori* infection and duodenal ulcer disease. It can reduce the risk of NSAID-associated gastric ulcers in patients with a history of a documented gastric ulcer that require the use of an NSAID. Long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome.

Pantoprazole Sodium. Pantoprazole Sodium is also known as Protonix, Eupantol, Pantecta, Pantozol, Anagastra, Pantoloc, Pantopan, Peptazol, Ulcotenal, Inipomp, Pantorc, [102625-70-7] sodium 5-(difluoromethoxy)- 2- [[(3,4-dimethoxy- 2- pyridinyl) methyl] sulfinyl]- 1 *H*- benzimidazole sesquihydrate (**8**). Pantoprazole sodium sesquihydrate is a white to off- white crystalline powder and is racemic and has weakly basic and acidic properties. Pantoprazole sodium sesquihydrate is freely soluble in water, very slightly soluble in phosphate buffer at pH 7.4, and practically insoluble in *n*- hexane. The stability of the compound in aqueous solution is pH- dependent. The rate of degradation increases with decreasing pH. At ambient temperature, the degradation half-life is approximately 2.8 hours at pH 5.0 and approximately 220 hours at pH 7.8. It may be prepared as described in Ref. 11.



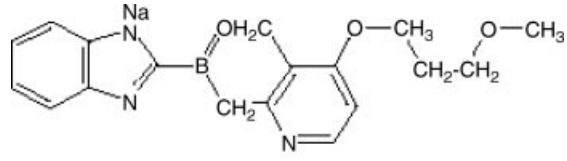
(8)

Mechanism of Action. Pantoprazole is prepared as an enteric-coated tablet so that absorption of pantoprazole begins only after the tablet leaves the stomach. It is extensively metabolized in the liver through the cytochrome P450 (CYP) system and metabolism is independent of the route of administration (intravenous or oral). The main metabolic pathway is demethylation, by CYP2C19, with subsequent sulfation; other metabolic pathways include oxidation by CYP3A4. There is no evidence that any of the pantoprazole metabolites have significant pharmacologic activity. CYP2C19 displays a known genetic polymorphism due to its deficiency in some sub-populations (eg, 3% of Caucasians and African-Americans and 17%–23% of Asians). Although these sub-populations of slow pantoprazole metabolizers have elimination half-life values of 3.5 to 10.0 hours, they still have minimal accumulation ($\leq$23%) with once daily dosing.

Pantoprazole is a proton pump inhibitor (PPI) that suppresses the final step in gastric acid production by covalently binding to the (H+,K+)-ATPase enzyme system at the secretory surface of the gastric parietal cell. This effect leads to inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus. The binding to the (H+,K+)-ATPase results in a duration of antisecretory effect that persists longer than 24 hours for all doses tested.

uses. Pantoprazole sodium is used in the short-term treatment of erosive esophagitis associated with gastroesophageal and of GERD. It is used in the maintenance of healing of erosive esophagitis and the long-term treatment of pathological hypersecretory conditions, including Zollinger-Ellison syndrome.

Rabeprazole Sodium. Rabeprazole sodium is also known as Aciphex, Pariet, Pariprazole sodium [117976-89-3], 2-[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl]-methyl]sulfinyl]-1*H*−benzimidazole sodium salt (**9**) is a white to slightly yellowish-white solid. It is very soluble in water and methanol, freely soluble in ethanol, chloroform and ethyl acetate and insoluble in ether and *n*-hexane. The stability of rabeprazole sodium is a function of pH; it is rapidly degraded in acid media, and is more stable under alkaline conditions. May be prepared by the method in Ref. 12.



(9)

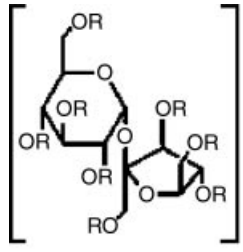
Mechanism of Action. It is administered as an enteric-coated to allow rabeprazole sodium, which is acid labile, to pass through the stomach relatively intact. Rabeprazole is 96.3% bound to human plasma proteins and is extensively metabolized. The thioether and sulphone are the primary metabolites measured in human plasma. These metabolites were not observed to have significant antisecretory activity. *In vitro* studies have demonstrated that rabeprazole is metabolized in the liver primarily by cytochromes P450 3A (CYP3A) to a sulphone metabolite and cytochrome P450 2C19 (CYP2C19) to desmethyl rabeprazole. The thioether metabolite is formed nonenzymatically by reduction of rabeprazole. CYP2C19 exhibits a known genetic polymorphism due to its deficiency in some sub-populations (eg, 3 to 5% of Caucasians and 17 to 20% of Asians.

It is a partially reversible proton pump inhibitor and suppresses gastric acid secretion by inhibiting the gastric H+, K+ATPase at the secretory surface of the gastric parietal cell. Rabeprazole blocks the final step of gastric acid secretion. In gastric parietal cells, rabeprazole is protonated, accumulates, and is transformed to an active sulfenamide.

Uses. Rabeprazole sodium is used in the short-term treatment in the healing and symptomatic relief of erosive or ulcerative gastroesophageal reflux disease (GERD) and in the healing and symptomatic relief of erosive or ulcerative gastroesophageal reflux disease. It maintains healing and reduction in relapse rates of heartburn symptoms in patients with erosive or ulcerative gastroesophageal reflux disease (GERD) and is used in the treatment of symptomatic GERD. It is also used in the healing of duodenal ulcers.

Sucralfate. Sucralfate is also know as Carafate, Sucramal, Antepsin, Ulcerban, Ulcerlmin, Ulcogant, Ulcar, [54182-58-0], 3,4,5-trisulfooxy-2-(sulfooxymethyl)-6- [3,4,5-trisulfooxy-2- (sulfooxymethyl) oxolan-2-yl] oxy-oxane; icosahydrate (**10**). It is a white amorphous powder soluble in dilute hydrochloric

acid and sodium hydroxide. It is practically insoluble in water, ethanol, and carbon tetrachloride. It may be prepared by the method described in Ref. 13.



$[A](OH)_3]x\ [H_2O]y$
(X = B to 10 end y = 22 to 31)

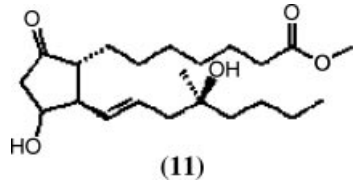
$R = SO_3Al(OH)_2$

(10)

Mechanism of Action. Sucralfate is a sucrose sulfate-aluminum complex that binds to the hydrochloric acid in the stomach and acts like an acid buffer with cytoprotective properties. Sucralfate is a locally acting substance that in an acidic environment (pH < 4), reacts with hydrochloric acid in the stomach to form a cross-linking, viscous, paste-like material capable of acting as an acid buffer for as long as 6 to 8 hours after a single dose. It also attaches to proteins on the surface of ulcers (such as albumin and fibrinogen) to form stable, insoluble complexes. These complexes serve as protective barriers at the ulcer surface, preventing further damage from acid, pepsin, and bile. In addition, it prevents back diffusion of hydrogen ions, and adsorbs both pepsin and bile acids. Recently, it has been indicated that sucralfate also stimulates the increase of prostaglandin E_2, epidermal growth factors (EGF, bFGF), and gastric mucus.

Uses. Sucralfate is used in the following: maintenance therapy for resolved duodenal ulcers; treatment of gastric ulcer not related to NSAID; aphthous ulcer and stomatitis due to radiation or chemotherapy; proctitis from radiation or ulcerative colitis; and stress ulcer prophylaxis rather than H_2 antagonists. It is also use as a protective agent against stricture formation after corrosive esophageal burns to enhance mucosal healing and suppress stricture formation.

Misoprostol. Misoprostol is also known as Cytotec, [59122-46-2], methyl 7-[3-hydroxy-2-(4-hydroxy-4-methyl-oct-1-enyl)-5-oxo-cyclopentyl]-heptanoate (**11**) this agent is a light yellow liquid that is soluble in water. The methods for preparation are available in Ref. 14.



(11)

Mechanism of Action. Misoprostol is a stable prostaglandin analog that has gastric antisecretory and cytoprotective activity. It is contraindicated in pregnant woman owing to abortifacient properties. Misoprostol stimulates increased secretion of the protective mucus that lines the gastrointestinal tract

and increases mucosal blood flow, thereby increasing mucosal integrity. It is often co-prescribed with nonsteroidal antiinflammatory drugs to prevent their common adverse effect of gastric ulceration (eg, with diclofenac in Arthrotec). There is a significant incidence of diarrhea and abdominal pain associated with the drug.

Uses. Misoprostol is used in the prevention of nonsteroidal (NSAIDs) antiinflammatory drugs, including aspirin)-induced gastric ulcers in patients at high risk of complications from gastric ulcer in elderly and patients with concomitant debilitating disease, as well as patients at high risk of developing gastric ulceration. It has not been shown to prevent duodenal ulcers in patients taking NSAIDs. It may be used to induce labor and as an abortifacient.

2.2. Antacids

Aluminum Hydroxide Gel. Also known as colloidal aluminum hydroxide, Amphogel, [21645-51-2] is a suspension. Each 100 g contain the equivalent of 3.6–4.4 g aluminum oxide [1344-28-1]. Aluminum hydroxide gel may contain a variety of flavoring agents. It is a white viscous suspension from which small amounts of water may separate on standing and is translucent in thin layers.

Preparation. Aluminum hydroxide gel may be prepared by a number of methods. The products vary widely in viscosity, particle size, and rate of solution. Such factors as degree of supersaturation, pH during precipitation, temperature, and nature and concentration of by-products present affect the physical properties of the gel.

In one manufacturing process, aluminum chloride is treated with a solution containing sodium carbonate and sodium bicarbonate. The product of this reaction is mixed with the precipitate obtained by reaction of a solution of aluminum chloride and ammonia. The mixed magma is dialyzed, the product mixed with sodium benzoate is added, and the mixture is then passed through a colloid mill.

Mechanism of Action. One gram of amphogel suspension raises the pH of 12.5–25 mL of simulated gastric juice, ie, 0.1 *N* HCl, to pH 3.5. The rate of neutralization is slow. Aluminum hydroxide gel is nontoxic, but has side effects, ie, constipation, nausea, or vomiting owing to astringent action or taste; hypophosphatemia and osteomalacia owing to interference with absorption; complexation with tetracycline; and interference with absorption of tetracycline and other classes of drugs.

Uses. Aluminum hydroxide gel is used as an antacid and in the treatment of phosphate nephrolithiasis.

Precipitated Calcium Carbonate. Precipitated calcium carbonate is also known as Tums, and a number other proprietary names [471-34-1]. It is a fine white microcrystalline powder without odor or taste and it is stable in air. An aqueous suspension is close to neutrality. It is practically insoluble in water, insoluble in alcohol, and dissolves with effervescence in dilute acetic, hydrochloric, and nitric acids.

Preparation. Calcium carbonate can be prepared by the double decomposition of calcium chloride and sodium carbonate in aqueous solution. Its density and fineness are governed by the concentration of the solutions. Heavy and light forms are available.

Mechanism of Action. One gram of neutralizes 110 mL of 0.1 *N* HCl in 10 min, and 162 mL within 2 hours. Long-term therapy, including large doses of taken with milk or other sources of phosphate, may cause renal pathology, ie, milk–alkali syndrome, and systemic alkalosis, ie, 7–19% of calcium is absorbed; increased urinary calcium may favor calcific renal stones; and calcium carbonate may be constipating and rebound gastric secretion may occur with high doses that neutralize gastric contents, ie, greater than 2 g.

Uses. It is an effective gastric antacid for use in peptic ulcer disease and GERD.

Magnesia and Alumina Suspension. Magnesia and alumina suspension is a mixture of salts, available as Maalox, Mylanta, Gelusil, and Aludrox, contains magnesium hydroxide, [1309-42-8], and variable amounts of aluminum oxide in the form of aluminum hydroxide and hydrated aluminum oxide, ie, 2.9–4.2% magnesium hydroxide and 2.0–2.4% aluminum oxide, for a mixture of 4.9–6.6% combined magnesium hydroxide and aluminum oxide. This mixture may contain a flavoring and antimicrobial agents in a total amount not to exceed 0.5%.

Preparation. The magnesia and alumina suspension is prepared by treatment of an aqueous solution, containing aluminum and magnesium salt in the desired proportion, with sodium hydroxide. The co-precipitated aluminum and magnesium hydroxides are collected by filtration, washed free of soluble salts, and stabilized by the addition of a suitable hexatol. It is available both as liquid and tablet formulations.

Uses. Magnesia and alumina suspension is used for the therapy of duodenal ulcers when given at high doses at frequent intervals.

Magnesium Oxide. Magnesia, [1309-48-4], is available in a very bulky white powder known as light magnesium oxide, or a relatively dense white powder known as heavy magnesium oxide. It absorbs moisture and carbon dioxide when exposed to air. It is practically insoluble in water, insoluble in alcohol, and soluble in dilute acids.

Light or heavy magnesium carbonate is exposed to a red heat, and carbon dioxide and water are expelled leaving light or heavy magnesium oxide. The calcining temperature also influences the density; higher temperatures yield more compact forms.

Mechanism of Action. Magnesium oxide is an effective nonsystemic antacid, ie, it is converted to the hydroxide. It does not neutralize gastric acid excessively nor does it liberate carbon dioxide. The light form is preferable to the heavy for administration in liquids because it is suspended more readily. One gram of magnesium oxide neutralizes 87 mL of 0.1 *N* HCl in 10 min, and 305 mL in 2 h.

Uses. Magnesium oxide is used for conditions requiring a gastric antacid.

Magnesium Trisilicate. Magnesium trisilicate [39365-87-2], is a compound of magnesium oxide and silicon dioxide with varying proportions of water. It contains not less than 20% magnesium oxide, nor less than 45% silicon dioxide, ie, magnesium silicate hydrate. It is a fine, white, odorless, tasteless powder free from grittiness, its suspension is neutral or only slightly alkaline, it is insoluble in water and alcohol, and it is decomposed readily by mineral acids with the liberation of silicic acid.

Preparation. Magnesium trisilicate is prepared by precipitation of a solution of sodium silicate of the proper composition, ie, to ratio equal to 1:1.5, using a solution of magnesium chloride or sulfate. The precipitate of the magnesium trisilicate is filtered, washed, and dried at a low temperature.

Mechanism of Action. Magnesium trisilicate is a nonsystemic antacid and an adsorbent. It has a slow onset of activity and is a relatively weak antacid. It may cause diarrhea in large doses owing to soluble magnesium salts. One gram of magnesium trisilicate neutralizes 10 mL of 0.1 *N* HCl in 10 min, and 15 mL in 2 h.

Uses. Magnesium trisilicate is used for conditions requiring a gastric antacid.

Magaldrate. Also known as aluminum magnesium hydroxide, Riopan and other proprietary names, [39366-43-3] (tetrakis(hydroxymagnesium) decahydroxydialuminatedihydrate contains the equivalent of 28–39% magnesium oxide and 17–25% aluminum oxide. It is a white, odorless, crystalline powder insoluble in water and alcohol, and soluble in dilute solutions of mineral acids.

Preparation. Magaldrate is prepared by precipitation from aqueous solutions of sodium or potassium aluminate and a magnesium salt under controlled conditions of concentration and temperature. The precipitated product is collected by filtration, washed to remove soluble by-products, and dried.

Mechanism of Action. Magaldrate is an antacid having somewhat more efficacy than aluminum hydroxide. It does not appear to disturb electrolyte balance or bowel function.

Uses. Magaldrate is used for conditions requiring a gastric antacid.

Sodium Bicarbonate. Sodium bicarbonate, [144-55-8], is a white crystalline powder. It is odorless, has a saline and slightly alkaline taste, and is stable in dry air, but slowly decomposes in moist air. Its solubility is one gram in 10 mL water; in hot water it is converted into carbonate, and it is insoluble in alcohol.

Preparation. Sodium bicarbonate may be prepared by the ammonia-salt (Solvay) process. Carbon dioxide is passed through a solution of sodium chloride in ammonia water. Sodium bicarbonate is precipitated and the ammonium chloride remains in solution. The ammonium chloride is heated with lime to regenerate ammonia.

Mechanism of Action. Sodium bicarbonate is a gastric antacid that may cause systemic alkalosis on overdose and may contribute to edema owing to sodium retention. Sodium bicarbonate also is an ingredient of many effervescent mixtures, alkaline solutions, etc. One gram of $NaHCO_3$ neutralizes 115 mL 0.1 *N* HCl.

Uses. Sodium bicarbonate is used for conditions requiring a gastric antacid and in the treatment of systemic acidosis because both deficient ions are present in the same molecule. It can be used topically as a moist paste or in solution as an antipruritic.

2.3. Economic Aspects. GERD and peptic ulcer disease are among the most highly prevalent diseases in the developed world. With approximately 15 million chronic GERD sufferers in the U.S. alone, it is estimated that between 10 to 15 percent of these patients can be served by noninvasive therapies. In 2000, $8.3 billion was spent in the U.S. on prescription drugs that treat heartburn, the primary symptom of the disease. GERD is one of the most common conditions in the U.S., with 44% of adults suffering at least one episode per month.

The incidence of nocturnal GERD symptoms in the overall population has been reported to be as high as 10%. In 2003, $13.5 billion was spent on PPIs in the U.S., making them the second biggest-selling drug class after cholesterol-lowering agents.

The estimated prescription market for antisecretory agents is over $6 billion annually in the United States, whereas the more difficult to estimate OTC market is in the range of $3 billion annually. The market for anti-ulcer and antireflux agents is large and is comprised of both prescription and over the counter products. Due to a series of patent expirations over the next 5 years, it is forecast that this market will experience a decline in sales due to increasing generic competition and a low level of new product introductions through 2010.

Helicobacter pylori is now recognized as one of the most important causes of gastric and duodenal ulcers, which affect at least 10% of the North American population at one point in their lives. It is believed to cause a spectrum of diseases in humans, including gastritis, ulcer disease (gastric and duodenal), gastric cancer, and gastric lymphoma. The U.S. market for therapies for the eradication of *Helicobacter pylori* is in excess of $160 million.

3. Laxatives

Laxatives facilitate the passage and elimination of feces (15). The use of laxatives should be limited to those conditions in which they are warranted and usually should not be used chronically. Uses include the removal of hardened and dry stools causing partial or complete intestinal obstruction, the softening of stools in patients for whom straining could be harmful, as preparation prior to diagnostic tests, and symptomatic treatment of patients with constipation predominant irritable bowel syndrome (IBS). Laxatives have traditionally been classified as bulking agents, contact, saline or osmotic; and lubricant. Emollient or lubricant laxatives such as mineral oil are not discussed herein. Bulking agents containing indigestible fiber appear to have the most physiological mechanism of action and should be the agent of choice unless purgation is needed. The signs and symptoms associated with chronic idiopathic constipation such as abdominal pain, discomfort, bloating, straining, and hard or lumpy stools may be the result of abnormal colonic motility that can delay the transit of intestinal contents and impede the evacuation of rectal contents. There has been a revival of interest in development of compounds with selective laxative activity for the symptomatic treatment of constipation predominate irritable bowel syndrome. Recently a compound with a unique mechanism of action, lubiprostone, was approved for marketing in the U.S. The market for laxatives has been mainly from OTC sales. However, due to the increase interest in the use of newer agents available only by prescription, sales will probably increase dramatically. There is an unmet need for safe and effective compounds for the treatment of chronic constipation seen in patients with constipation predominant irritable bowel syndrome.

3.1. Bulk Laxatives

Polycarbophil Calcium. Polycarbophil calcium is also known as Carbofil, Sorboquel, Mitrolan, Sorboquel, Quival, Carbopol EX 55, Noveon. [9003-97-8], is a copolymer of acrylic acid and divinyl glycol (1,5-hexadiene-3,4-diol)) consists of

white-to-creamy white granules having a slight ester-like odor. It is a synthetic, loosely cross-linked, hydrophilic resin of the polycarboxylic type, marketed as a stool normalizer and used in the treatment of both constipation and diarrhea. It swells to contain a maximum of 1.5% water, but is insoluble in water and most organic solvents.

Preparation. It is prepared by copolymerization of acrylic acid and divinyl glycerol in a hot salt slurry using azobisisobutyronitrile as the initiator. It is most active in the slightly acid or alkaline medium of the small bowel and colon.

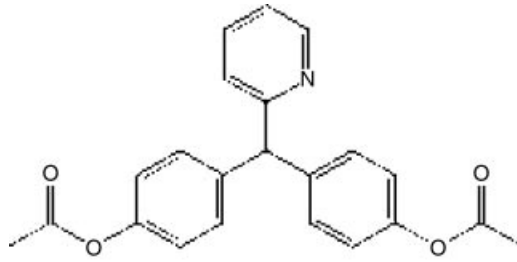
Uses. Polycarbophil calcium relieves constipation and helps restore and maintain regularity.

Psyllium Hydrophilic Mucciloid. Metamucil, or psyllium hydrophilic mucciloid, is a white-to-cream colored, slightly granular powder having little or no odor and a slightly acidic taste. It is made from the mucilaginous portion, ie, outer epidermis, of blond psyllium seeds.

Uses. Psyllium hydrophilic mucciloid is used as a bulking agent in the chronic therapy of several gastrointestinal disorders. It is indicated for use when a high fiber intake is recommended.

3.2. Contact Laxatives

Bisacodyl. Bisacodyl is also known as Dulcolax, Fleets, Alophen, Correctol, [603-50-9], 4,4′-(2-pyridylmethylene) bisphenol diacetate (**12**) is a white to off-white crystalline powder. It is very soluble in water, freely soluble in chloroform and alcohol, soluble in methanol and benzene, and slightly soluble in diethyl ether. Bisacodyl may be prepared from 2-pyridine-carboxaldehyde by condensation with phenol and the aid of a dehydrant such as sulfuric acid. The resulting 4,4′-(pyridylmethylene)diphenol is esterified by treatment with acetic anhydride and anhydrous sodium acetate. Crystallization is from ethanol.



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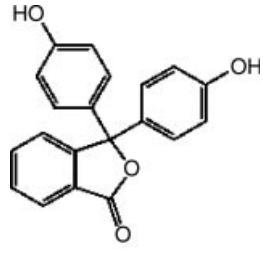
Uses. Bisacodyl is sold tablets, suppositories, or pediatric suppositories. Bisacodyl is a contact laxative that may be given orally or rectally. It is often used for evacuation of the bowel prior to surgery or diagnostic examination and may eliminate the need for a cleansing enema. Bisacodyl is used in the relief of constipation and for the management of neurogenic bowel dysfunction.

Phenolphthalein. Phenolphthalein is also known as (3,3-bis(4-hydroxyphenyl)-1-(3*H*)-1 isobenzofuranone), [77-09-8] (**13**). It is a white or faintly yellowish white crystalline powder, odorless and stable in air, and practically insoluble in water; one gram is soluble in 15 mL alcohol and 100 mL diethyl ether. Phenolphthalein may be prepared by mixing phenol, phthalic anhydride, and sulfuric acid, and heating at 120°C for 10–12 h. The product is extracted with boiling

water, then the residue dissolved in dilute sodium hydroxide solution, filtered, and precipitated with acid.



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Mechanism of Action. Phenolphthalein is a cathartic drug and was the basis of many OTC laxatives. Its action is mainly on the colon to produce a soft semifluid stool within six to eight hours. Its action may persist for several days owing to enterohepatic circulation and it may cause red urine if urine is alkaline. Phenolphthalein had been used for over a century as a laxative but has been removed from the market because of concerns over possible carcinogenicity. However, the small amounts usually used in experiments are harmless.

Cascara Sagrada. Cascara sagrada, also known as sacred bark, chitten, dogwood, coffeeberry, bearberry, bitter bark, and bearwood, is the dried bark of *Rhamnus Purshiana* DeCandolle. It is in the form of brown, purplish brown, or brownish red flattened or transversely curved pieces, 1- to 5-mm thick, and has a characteristic odor and bitter taste. It should be collected at least one year prior to use. The active constituents are aloe-emodin [481-72-1]; iso-emodin [476-62-0]; purshianin [1393-00-6]; and several resins. It is most useful when prepared as a fluid extract, and tends to be a mild laxative causing little discomfort. However, on prolonged use it may result in characteristic melanotic pigmentation of the rectal mucosa. The bitter taste can be lessened, owing to neutralization of the acid constituents, if the ground substance is moistened and mixed with magnesium or calcium hydroxide. This treatment may lessen the potency of the preparation.

Uses. Cascara sagrada is used as a cathartic.

Castor Oil. Castor oil, [8001-79-4], is the fixed oil obtained from the seeds of *Ricinus communis*. Pale yellowish or almost colorless, it is a transparent viscid liquid with a faint, mild odor and a bland taste followed by a slightly acrid and usually nauseating taste. Its specific gravity is between 0.945 and 0.965. Castor oil is soluble in alcohol, and miscible with anhydrous alcohol, glacial acetic acid, chloroform, and diethyl ether. It consists chiefly of the glycerides of ricinoleic acid [141-22-0], and isoricinoleic acid [73891-08-4], found in the small intestine. The seed contains a highly poisonous albumin (ricin) and base (ricinine).

Preparation. Castor oil may be obtained by cold expression of the decorticated seed. The oil is steamed under vacuum to eliminate odors and coagulate the toxic albumin. Fuller's earth or activated charcoal may be used for further purification.

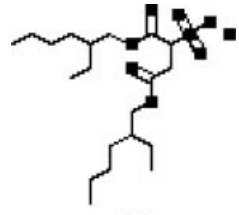
Mechanism of Action. Castor oil is a cathartic only after lipolysis in the small intestine liberating ricinoleic acid. Ricinoleic acid inhibits the absorption of water and electrolytes.

Uses. Castor oil is used for preparation of the large bowel for diagnostic procedures.

Docusate Calcium. Dioctyl calcium sulfosuccinate, [128-49-4], (calcium salt of 1,4-bis(2-ethylhexyl)ester butanedioic acid) is a white amorphous solid having the characteristic odor of octyl alcohol. It is very slightly soluble in water, and very soluble in alcohol, polyethylene glycol 400, and corn oil. It may be prepared directly from dioctyl sodium sulfosuccinate dissolved in 2-propanol, by reaction with a methanolic solution of calcium chloride.

Uses. Docusate calcium is used as a fecal softening agent and an emulsifier.

Docusate Sodium. Aerosol OT, Colace, and Doxinate are trade names of docusate sodium [577-11-7] (dioctyl sodium sulfosuccinate, sodium salt of 1,4-bis(2-ethylhexyl)ester butanedioic) (**14**). This white, wax-like, plastic solid, with a characteristic odor suggestive of octyl alcohol, is usually available in the form of pellets. One gram of the sodium salt slowly dissolves in about 70 mL water. Docusate sodium is freely soluble in alcohol and glycerol, very soluble in hexane, and decomposes in the presence of strong alkali. It may be prepared by treatment of maleic anhydride with 2-ethylhexanol to produce dioctyl maleate, which is allowed to react with sodium bisulfite under conditions conducive to saturation of the olefinic bond with simultaneous arrangement of the bisulfite to the sulfonate.



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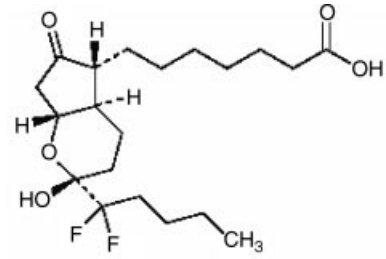
Uses. Docusate sodium is a surface-active agent for use as a fecal softener, and a wetting agent in industrial, pharmaceutical, cosmetic, and food applications.

Lubiprostone. Lubiprostone is also know as Amitza, RU 0211 and SPI 0211 [136790-76-6], (−)-7-[(2*R*,4a*R*,5*R*,7a*R*)-2-(1,1- difluoropentyl)-2-hydroxy-6-oxooctahydrocyclopenta[*b*]pyran-5-yl]heptanoic acid (**15**). Lubiprostone drug substance occurs as white, odorless crystals or crystalline powder and is very soluble in ether and ethanol, and practically insoluble in hexane and water. It may be made by the process noted in Ref. 16.



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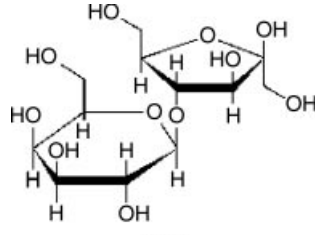
Mechanism of Action. Lubiprostone is a bicyclic fatty acid that acts as a chloride channel opener, increasing intestinal water secretion. Lubiprostone activates a specific chloride channel (CLC2), that is located in the apical intestinal membrane, thereby increasing intestinal fluid secretion. The increased fluid level softens the stool, promotes spontaneous bowel movements, and reduces abdominal discomfort/pain and bloating. Lubiprostone has low systemic availability following oral administration and concentrations of lubiprostone in plasma are below the level of quantization (10 pg/mL). The safety of lubiprostone in pregnancy has not been evaluated in humans. Lubiprostone enhances a chloride-rich intestinal fluid secretion without altering sodium and potassium concentrations in the serum. By increasing intestinal fluid secretion, accelerates the passage of stool. Patch clamp cell studies in human cell lines have indicated that the majority of the beneficial biological activity of lubiprostone and its metabolites is observed only on the apical (luminal) portion of the gastrointestinal epithelium.

Uses. Lubiprostone is used in the treatment of chronic idiopathic constipation in the adult population.

3.3. Saline or Osmotic Laxatives

Lactulose. Lactulose is also known as Generlac, Cephulac, Cholac, Chronolac, Constilac. Enulose. Acilac, and Heptalac [4618-18-2], 4-*O*-β-D-Galactopyranosyl-4-D-fructofuranose (**16**) may be made from lactose using the method described in Ref. 17.

Mechanism of Action. It is a synthetic disaccharide containing fructose and galactose that is not hydrolyzed by gastrointestinal enzymes in the small intestine, but is metabolized by colonic bacteria to short-chain organic acids. The increased osmotic pressure of these non-absorbable organic acids results in an accumulation of fluid in the colon. Lactulose may not be tolerated by patients because of an extremely sweet taste. It frequently produces flatulence and intestinal cramps. Lactulose is metabolized in the by bacterial flora to short chain fatty acids, acidifying the colonic contents. This favors the formation of the nonabsorbable $NH4^+$ from NH_3, trapping NH_3 in the colon and effectively reducing plasma NH_3 concentrations.



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Uses. Lactulose is used in the treatment of constipation. It is also used to treat hepatic encephalopathy, lactulose helps trap ammonia (NH_3) from the body. The effectiveness of lactulose is somewhat controversial, and whether or not its effects are through ammonia is also controversial as well.

Magnesium Citrate Solution. Also known as citrate of magnesia, magnesium citrate solution(3:2) [3344-18-1], contains in each 100 mL an amount of

magnesium citrate corresponding to 1.55–1.9 g of MgO, as well as potassium bicarbonate and flavorings. It is a colorless to slightly yellow, clear, effervescent liquid with a sweet, acidulous taste and a lemon flavor.

Preparation. In the preparation of a kilogram of magnesium citrate solution, anhydrous citric acid (49.4 g) is dissolved in 220 mL of hot purified water. Magnesium carbonate is added slowly and stirred until dissolved into 220 mL of purified water. The syrup is added and the mixed liquids heated to the boiling point. The lemon oil is triturated with talc and added to the hot mixture, which is filtered into a strong sterile bottle of appropriate size. Boiled purified water is added to make 770 mL. The bottle is stoppered with cotton and allowed to cool, potassium bicarbonate is added, and the bottle is closed securely. The mixture should be shaken occasionally and the bottle stored on its side in a cool place. Sodium bicarbonate (4.6 g) may be substituted for potassium bicarbonate, and the solution may also be further carbonated using carbon dioxide. The solution can be stabilized by sterilization or by the addition of 66 g citric acid and a quantity of magnesium carbonate equivalent to 13.2 g MgO. Precipitation on standing is increased by the presence of sucrose and decreased by sterilization.

Uses. Magnesium citrate solution is used as saline preoperative or prediagnostic cathartic. Usually packaged in a single-use container.

Magnesium Sulfate. Magnesium sulfate heptahydrate [10034-99-8] also known as bitter salts and Epsom salts, are small, colorless crystals, usually needlelike, having a cooling, saline, and bitter taste, that effloresce in warm, dry air. The heptahydrate loses 5 molecules of water at 100°C. An aqueous solution of magnesium sulfate is neutral, and one gram is soluble in 1 mL water, 0.2 mL boiling water, or 1 mL glycerol; the heptahydrate is sparingly soluble in ethanol.

Preparation. Magnesium sulfate heptahydrate may be prepared by neutralization of sulfuric acid with magnesium carbonate or oxide, or it can be obtained directly from natural sources. It occurs abundantly as a double salt and can also be obtained from the magnesium salts that occur in brines used for the extraction of bromine. The brine is treated with calcium hydroxide to precipitate magnesium hydroxide. Sulfur dioxide and air are passed through the suspension to yield magnesium sulfate.

Uses. Magnesium sulfate is used as a saline cathartic.

Sodium Phosphate. Sodium phosphate is also known as Phospho-Soda, Disodium phosphate heptahydrate, Visicol [7782-85-6] is a colorless or white granular salt that effloresces in warm dry air. One gram of the heptahydrate dissolves in 4 mL water, and is only slightly soluble in alcohol.

Preparation. Finely ground phosphatic material is mixed with a quantity of sulfuric acid a little in excess of the amount required to transform the phosphate into monobasic calcium phosphate. Bone phosphate or bone ash, obtained by heating bones to whiteness and which consists mainly of tribasic calcium phosphate and phosphorite (phosphate rock), may be used as a source of phosphatic materials. The mixture is leached with hot water, a concentrated solution of sodium carbonate sufficient to convert half of the phosphate into the dibasic sodium salt is added, and the mixture is boiled. After filtering, the solution is concentrated and the sodium phosphate allowed to crystallize.

Uses. Sodium phosphate is used as a saline cathartic mainly for preparation for diagnostic and surgical procedures.

Polyethylene Glycol Electrolyte Preparation. A mixture of osmotically balanced ingredients, made up of polyethylene glycol 3350 [25322-68-3] (a nonabsorbable osmotic agent), sodium chloride, sodium sulfate, potassium chloride, and sodium bicarbonate, is known as Colyte, GoLytely, and NuLytely. It is usually in a dry formulation to be made up to volume with cold water just prior to administration. The mixture provides complete gastrointestinal cleansing when given prior to endoscopic or x-ray diagnostic procedures. It is usually well tolerated with little change in blood electrolyte concentrations, but occasionally may cause nausea, vomiting, abdominal fullness, and cramps because of the large volume that must be ingested.

Uses. This mixture is used for gastrointestinal cleansing prior to endoscopic or x-ray diagnostic procedures.

4. Antidiarrheals

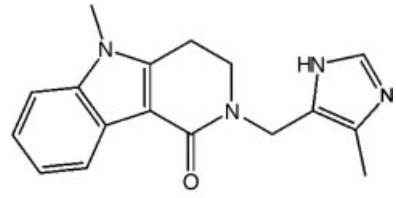
Diarrhea is a common problem that is usually self-limiting and of short duration. Increased accumulations of small intestinal and colonic contents are known to be responsible for producing diarrhea. The former may be caused by increased intestinal secretion which may be enterotoxin-induced, eg, cholera and, or hormone and drug-induced, eg, caffeine, prostaglandins, and laxatives; decreased intestinal absorption because of decreased mucosal surface area, mucosal disease, eg, tropical sprue, or osmotic deficiency, eg, disaccharidase or lactase deficiency; and rapid transit of contents. An increased accumulation of colonic content may be linked to increased colonic secretion owing to hydroxy fatty acid or bile acids, and exudation, eg, inflammatory bowel disease or amebiasis; decreased colonic absorption caused by decreased surface area, mucosal disease, and osmotic factors; and rapid transit, eg, irritable bowel syndrome.

Diagnosis and alleviation of the cause, if possible, is of primary importance. Often, however, this is not possible and therapy is used to alleviate the inconvenience and pain of diarrhea. These compounds usually only mask the underlying factors producing the problem. Diarrhea may cause significant dehydration and loss of electrolytes and is a particularly serious problem in infants. Antidiarrheals do not usually prevent the loss of fluids and electrolytes into the large bowel and, although these may prevent frequent defecation, often the serious imbalance of body electrolytes and fluids is not significantly affected. The therapy of acute and chronic diarrhea is discussed in Refs. 18,19.

Commonly used antidiarrheals work by one of two mechanisms: effects on net intestinal secretion, or a decrease in intestinal propulsive motility. Narcotic analgesics are constipating and are antidiarrheal owing to the effect on intestinal propulsion. This is not a smooth muscle relaxing activity but results from the increase in nonpropulsive phasic smooth muscle contractions, and is apparently the mechanism of such commonly used compounds as codeine sulfate [76-57-3], diphenoxylate, and loperamide. Some opiates also have been found to have effects on intestinal secretion. Bismuth subsalicylate (Pepto-Bismol) is effective and works by several mechanisms. Although drugs such as atropine, which have antispasmodic activity, have been used as antidiarrheals in the past, they are no longer considered useful or effective at doses not causing

significant side effects. Some drugs effective in the therapy of inflammatory bowel disease are also included even though they are not specifically antidiarrheal but are useful in chronic therapy of intestinal inflammation.

4.1. Alosetron Hydrochloride. Alosetron hydrochloride is also known as Lotronex [122852-42-0] 2,3,4,5-tetrahydro-5-methyl-2-[(5-methyl-1H-imidazol-4-yl)methyl]-1H-pyrido[4,3-b]indol-1-one, monohydrochloride (**17**). It is achiral and is a white to beige solid that has a solubility of 61 mg/mL in water, 42 mg/mL in 0.1 *M* hydrochloric acid, 0.3 mg/mL in pH 6 phosphate buffer, and 0.1 mg/mL in pH 8 phosphate buffer. The method of synthesis may be found in Ref. 20.



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Alosetron is a potent and selective antagonist of the serotonin 5-HT3 receptor. Alosetron was approved by the FDA for the management of severe diarrhea-predominant irritable bowel syndrome (IBS) in women only. It was withdrawn from the market in 2000 because of the occurrence of serious life-threatening adverse effects, but was reintroduced in 2002 with availability and use restrictions. The cumulative incidence of ishemic colitis was as 2 in 1000, while serious complications arising from constipation (obstruction, perforation, impaction, toxic megacolon, secondary colonic ischaemia, death) was 1 in 1000.

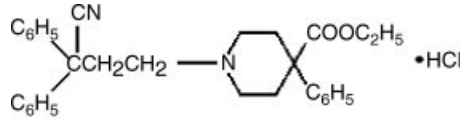
Uses. Alosetron hydrochloride is used in the treatment of diarrhea in patients with diarrhea predominant irritable bowel syndrome and is available only is controlled program. Its use is controlled because of the infrequent but serious gastrointestinal adverse events that have been reported.

4.2. Bismuth Subsalicylate. Also known as Pepto-Bismol, Stabisol, Vismut, Spiromak forte, [14882-18-9], (2-Hydroxybenzoato-O^1)-oxobismuth may be made by the process described in Ref. 21. Bismuth subsalicylate has been shown to bind toxins produced by several bacterial strains. It may also act as a result of its salicylate component on prostaglandin formation and have specific intestinal antisecretory activity. It has been found to be effective in the prevention and therapy of traveler's diarrhea and diarrhea of nonspecific origin. It is available as a suspension or tablet, and because it is radio-opaque it may interfere with radiological examination. It also may produce a grayish black discoloration of the stool that could be confused with melena.

Uses. Bismuth subsalicylate is used in the treatment of nausea, heartburn, indigestion, upset stomach, diarrhea and other temporary discomforts of the stomach and intestines. It is also the main ingredient of Kaopectate since 2003, replacing attapulgite.

4.3. Diphenoxylate Hydrochloride. Diphenoxylate hydrochloride is also known as Lomotil, [3810-80-8], 1-(3-Cyano-3,3-diphenylpropyl)-4-phenyl-4-piperidinecarboxylic acid monohydrochlorhydrate (**18**). It is a white, odorless,

crystalline powder that is soluble in methanol, sparingly soluble in ethanol and acetone, slightly soluble in water and isopropyl alcohol, freely soluble in chloroform, and practically insoluble in ether and hexane. The method of preparation for diphenoxylate hydrochloride is available in Ref. 22. Diphenoxylate hydrochloride is an antidiarrheal that acts through an opiate receptor. It has effects both on propulsive motility and intestinal secretion. Commercial forms are mixed with atropine to discourage abuse.



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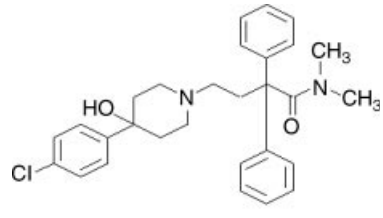
Uses. Diphenoxylate HCl with atropine sulfate is effective as adjunctive therapy in the management of diarrhea.

4.4. Loperamide. Loperamide is also known as Lopex, Imodium, Dimor, Pepto Diarrhea Control, Dissenten, Fortasec, Suprasec, Lopemid, Lopemin, Loperyl, Imosec, Tebloc, [53179-11-6], [34552-83-5] for HCL, 4-(4-Chlorophenyl)-4-hydroxy-*N*,*N*-dimethyl-*α*,*α*-diphenyl-1 piperidinebutanamide monohydrochloride **(19)** is practically insoluble in water (0.002%) at physiological pH. Its crystals are not affected by light and it is not hygroscopic. A method of synthesis may be found in (Ref. 23).



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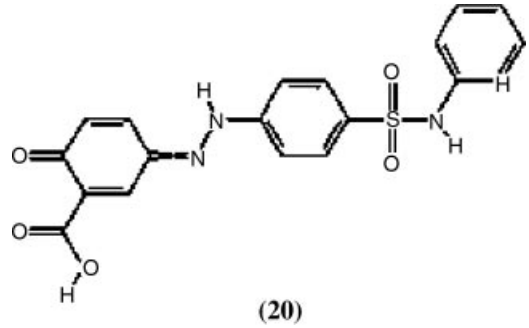
Mechanism of Action. Loperamide is an opiod receptor agonist and acts on the *mu* opioid receptors in themyenteric plexus in the small and large intestines; it does not appear to have effects on the brain.

It significantly inhibits gastrointestinal propulsive motility throughout the system apparently by interfering with acetylcholine release at nerve endings in the gastrointestinal nervous plexuses. It causes an increase in the amount of time for intraluminal contents to stay in the intestine, allowing for more water to be absorbed out of the fecal matter. Loperamide as well as other opioids inhibites intestinal secretion of electrolytes into the intestinal lumen. Loperamide does not cross the blood brain barrier and has no analgesic or addictive properties Loperamide does not need to be formulated with atropine and is available by prescription and OTC.

Uses. Loperamide is indicated for the control and symptomatic relief of acute nonspecific diarrhea and for chronic diarrhea associated with inflammatory bowel disease. It is also of use for treatment of diarrhea in patients with irri-

table bowel syndrome. It is also used for reducing the volume of discharge from ileostomies.

4.5. Sulfasalazine. Sulfasalazine is also known as Salicylazosulfapyridine or Azulfadine,Salazopyrin, Sulcolon, Accucol, Salazosulfapyridine, Salazopiridazin, Salazopyridin, Benzosulfa, Azopyrin, Azopyrine, Reupirin, Salisulf, Rorasul, Colo-Pleon, [599-79-1], (2-hydroxy-5-[[4[(2-pyridylamino) sulfonyl]-phenyl]azo] benzoic acid) (**20**) is a light brownish yellow-to-bright yellow fine powder that is practically tasteless and odorless, is very slightly soluble in ethanol, is practically insoluble in water, diethyl ether, chloroform, and benzene, and is soluble in aqueous solutions of alkali hydroxides. Sulfasalazine may be made by the synthesis described in Ref. 24. It is not used as an antidiarrheal as such, but is indicated for the treatment of inflammatory bowel diseases such as ulcerative colitis and Crohn's disease. Its action is purported to result from the breakdown in the colon to 5-aminosalicylic acid [89-57-6] (5-ASA) and sulfapyridine [144-83-2]. It may cause infertility in males, as well as producing idiosyncratic reactions in some patients. These reactions have been attributed to the sulfa component of the compound. The mechanism of 5-ASA is attributed to inhibition of the arachidonic acid cascade preventing leukotriene B*4* production and the ability to scavenge oxygen free radicals. The active component appears to be 5-aminosalicylic acid.



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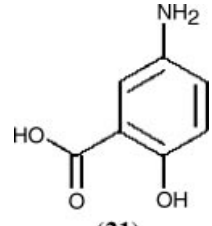
Mechanism of Action. Sulfasalazine, and its metabolite 5-ASA, are poorly absorbed. Its main mode of action is therefore believed to be inside the intestine. In Crohn's disease and ulcerative colitis, it is thought to be an antinflammatory drug that is essentially providing topical relief inside the intestine. Because sulfasalazine and its metabolite 5-ASA are poorly absorbed into the bloodstream, it is surprising that the drug is effective against symptoms outside of the intestine. One possible explanation is that, given that ulcerative colitis produces arthritic symptoms, it is possible that, in some cases, the arthritic symptoms are actually a product of unrecognized ulcerative colitis, which is effectively treated with sulfazalazine. The other metabolite, sulfapyridine, is absorbed into the blood, and is believed to be the source of the side-effects discussed below. It is possible that the sulfapyridine is responsible for some of the anti-arthritic effects of sulfasalazine.

Uses. Sulfasalazine is used in the treatment of inflammatory bowel disease and in the treatment of several types of arthritis, particularly rheumatoid arthritis. There ia a new treatment to reverse the scarring associated with

cirrhosis of the liver. Apparently, cells called myofibroblasts, that cause scar tissue to form in a diseased liver, also give off proteins that prevent the breakdown of the scar tissue. Sulfasalazine appears to retard the secretion of these proteins.

4.6. Mesalamine. Mesalamine is also known as Rowasa, Asacol, Canasa, Ipocal, Pentasa, Salofalk, Mesalazine, 5-aminosalicylic acid, 5-ASA, [89-57-6], 5-amino-2-hydroxybenzoic acid (**21**). It is a white to pinkish crystalline substance that is slightly soluble in cold water and alcohol, more soluble in hot water, and soluble in hydrochloric acid. It may be prepared by the reduction of *m*-nitrobenzoic acid with zinc dust and HCl. Mesalazine is a bowel-specific aminosalicylate drug that is metabolized in the gut and has its predominant actions there, thereby having fewer systemic side effects. As a derivative of salicylic acid, 5-ASA is also an antioxidant that traps free radicals, which are potentially damaging by-products of metabolism.



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Mechanism of Action. One proposed mechanism of action for its use in inflammatory bowel disease is 5-ASA is functioning as a free radical trap as well as an antiinflammatory drug. 5-ASA appears to be the active component of sulfasalazine without the sulfa component, and is free of the serious side effects seen with sulfasalazine. It is used orally, in a delay-release formulation, as a retention enema, and as a suppository. It is well tolerated in most patients.

It is formulated for oral ingestion as tablets or granules, and for rectal administration as rectal suppository, suspension or enema. Dosing depends on the preparation used, in particular, slow-release tablets may have quite different drug delivery characterists and are not interchangeable. Preparations that lower stool pH, such as lactulose, will affect the binding of mesalamine in the bowel and will therefore reduce its efficacy.

Uses. Mesalamine is use to treat inflammation of the digestive tract, Crohn's disease and mild to moderate ulcerative colitis.

4.7. Infliximab. Infliximab is also known as Remicade, Avakine, Immunoglobulin G, anti-(human tumor necrosis factor) (human-mouse monoclonal cA2 heavy chain), disulfide with human-mouse monoclonal cA2 light chain, dimer, [170277-31-3]. Infliximab is a chimeric IgG1κ monoclonal antibody with an approximate molecular weight of 149,100 daltons. It is composed of human constant and murine variable regions. Infliximab binds specifically to human tumor necrosis factor alpha (TNFα) with an association constant of 1010 M-1. Infliximab is produced by a recombinant cell line cultured by continuous perfusion and is purified by a series of steps that includes measures to inactivate and remove viruses (25).

Mechanism of Action. Infliximab neutralizes the biological activity of TNFα by binding with high affinity to the soluble and transmembrane forms of TNFα and inhibits binding of TNFα with its receptors. Infliximab does not neutralize TNFβ (lymphotoxin a), a related cytokine that utilizes the same receptors as TNFα. Biological activities attributed to TNFα include: induction of proinflammatory cytokines such as interleukins (IL) 1 and 6, enhancement of leukocyte migration by increasing endothelial layer permeability and expression of adhesion molecules by endothelial cells and leukocytes, activation of neutrophil and eosinophil functional activity, induction of acute phase reactants and other liver proteins, as well as tissue degrading enzymes produced by synoviocytes and/or chondrocytes. Cells expressing transmembrane TNFα bound by infliximab can be lysed *in vitro* or *in vivo*. Infliximab inhibits the functional activity of TNFα in a wide variety of *in vitro* bioassays utilizing human fibroblasts, endothelial cells, neutrophils, B and T lymphocytes and epithelial cells. Anti-TNFα antibodies reduce disease activity in the cotton-top tamarin colitis model, and decrease synovitis and joint erosions in a murine model of collagen-induced arthritis. Infliximab prevents disease in transgenic mice that develop polyarthritis as a result of constitutive expression of human TNFα, and when administered after disease onset, allows eroded joints to heal, was first approved in the United States for the treatment of Crohn's disease in 1998 and later approved for the treatment of ulcerative colitis in September 2005. With this new expanded indication for maintenance therapy in ulcerative colitis, infliximab is now the only biologic indicated for inducing and maintaining clinical remission of both types of IBD.

Tuberculosis invasive fungal infections, and other opportunistic infections, have been observed in patients receiving infliximab. Some of these infections have been fatal. Antituberculosis treatment of patients with a reactive tuberculin skin test reduces the risk of TB reactivation in patients receiving treatment with infliximab, however, active tuberculosis has developed in patients receiving infliximab who were tuberculin skin test negative prior to receiving infliximab.

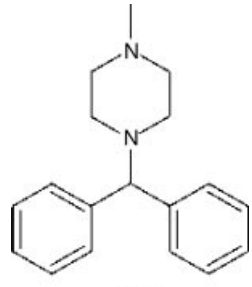
Uses. Infliximab is indicated for reducing signs and symptoms and inducing and maintaining clinical remission in adult and pediatric patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy. It is indicated for reducing the number of draining and fistulas and maintaining fistula closure in adult patients with fistulizing Crohn's disease and for the treatment of rheumatoid arthritis and ankylosing spondylitis. It is used to maintain clinical remission and mucosal healing in patients with moderately to severely active ulcerative colitis (UC), who have had an inadequate response to conventional therapy.

5. Antiemetics

Nausea and vomiting are frequent symptoms of disease and can be produced by a number of causes, eg, pregnancy, chemotherapy, motion sickness, radiation, and gastrointestinal infections. In most cases, it is self-limiting, however, in those cases in which fluid and electrolyte loss are significant, the control of emesis is required. Drugs may act at a variety of physiological locations, eg, blockade of

dopamine in the CNS, effects at the chemoreceptor trigger zone, vestibular apparatus, serotonin (5-HT_3) receptors or neurokinin 1 receptors (26). The use of antiemetics to prevent the nausea and vomiting of chemotherapy or radiation has become an important area of drug development. This class of therapy has expanded greatly over the last decade and now amounts to a market well in excess of a billion dollars. Their high price and resistance of insurance companies to cover the costs have limited the expansion of their use. $5HT_3$ antagonists have been shown to have great utility in the prevention of nausea and vomiting due to chemotherapy and radiation. The current global market size for these types of anti-emetics is estimated at over $2 billion per annum.

5.1. Cyclizine Hydrochloride. Cyclizine hydrochloride is also known as Valoid, Marezine, Marzine, Emoquil. [303-25-3] 1-(Diphenylmethyl)-4-methylpiperazine monohydrochloride (**22**) is a white crystalline powder, or small colorless crystals, that is odorless or nearly so and has a bitter taste. One gram of cyclizine hydrochloride is soluble in 115 mL water, 115 mL ethanol, and 5 mL chloroform. It is insoluble in diethyl ether. It may be made by the synthesis shown in Ref. 27.



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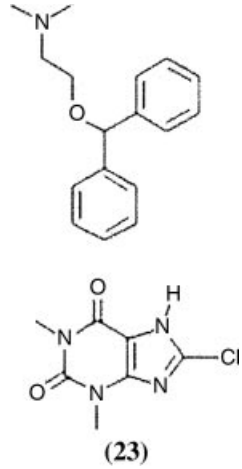
This compound has antihistaminic activity and is useful in the therapy of motion sickness. It may also be effective in the control of post-operative nausea and vomiting. It is classified as FDA Category B for Pregnancy (no demonstrated risks shown in animal studies), however, there have not been any controlled trials in pregnant women. Large doses may cause drowsiness and dry mouth owing to decreased secretion of saliva.

Mechanism of Action. Cyclizine is a piperazine derivative with histamine H_1-receptor antagonist. The precise mechanism of action in inhibiting the symptoms of motion sickness is not well understood. It may have effects directly on the labyrinthine apparatus and on the chemoreceptor trigger zone and has a central anticholinergic, action.

Uses. Marezine is used in the treatment of nausea and vomiting and in the prevention and treatment of motion sickness.

5.2. Dimenhydrinate. Dimenhydrinate is also known as Dramamine, Gravol and many other names, [523-87-5] 2-benzhydryloxy-*N*,*N*-dimethyl-ethanamine; 8-chloro-1,3-dimethyl-7*H*-purine-2,6-dione (**23**) is a salt of two drugs: diphenhydramine(+) and 8-chlorotheophyllinate(−), a clorinated form of theophylline. The chlorination provides the necessary charge to associate with diphenhydramine as a solid. Dimenhydrinate is a white crystalline, odorless powder, sparingly soluble in water, freely soluble in ethanol and chloroform,

and sparingly soluble in diethyl ether. Dimenhydrinate is prepared by combining dimethylaminoethyl benzhydryl ester with 8-chlorotheophylline and refluxing in an isopropyl alcohol solution. The crystalline precipitate of dimenhydrinate that forms on cooling is collected by filtration, washed with cold ethyl acetate, and dried. It is closely related to diphenhydramine HCl a commononly used antihistamine availabe OTC. The differences relate to the weight-for-weight potency (50 mg dimenhydrinate contains 29 mg of the drug diphenhydramine). A delay in onset action is caused by the time for dissociation into diphenhydramine and its counterion in the body before it is active. It was thought that by combining the antiemetic effects of diphenhydramine with a stimulant, the extreme drowsiness induced by the former could be mitigated somewhat by the latter. Actually, the sedation caused by diphenhydramine is substantially stronger than the stimulation caused by hlorotheophyllinate.



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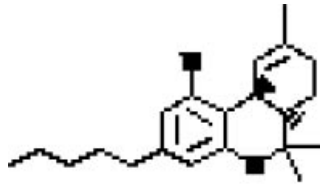
Uses. Diphenhydrinate is used as antinauseant in motion sickness, and for syndromes associated with vertigo such as Meniere's syndrome, radiation sickness, and vestibular dysfunction

5.3. Dronabinol. Dronabinol is also known as Marinol, [1972-08-3], (6*aR-trans*)-6*a*,7,8,10*a*-tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo(B,D) pyran-1-ol. Dronabinol (**24**) is synthetic delta-9-tetrahydrocannabinol (delta-9-THC). Delta-9-tetrahydrocannabinol is also a naturally occurring component of *Cannabis sativa L.* (Marijuana). It is a light yellow resinous oil that is sticky at room temperature and hardens upon refrigeration. It is insoluble in water and is formulated in sesame oil. It has a pKa of 10.6 and an octanol-water partition coefficient: 6,000:1 at pH 7. It is a controlled substance, formulated in sesame oil and encapsulated in soft gelatin capsules for oral administration. This agent may be habit forming and can be expected to produce disturbing psychomimetic reactions. Marinol is the only FDA approved cannabinoid. In 1999, Marinol was rescheduled from Schedule II to III of the controlled substance act, reflecting a finding that THC had a potential for abuse less than that of LSD, cocaine and heroin. See Ref. 28 for synthesis.



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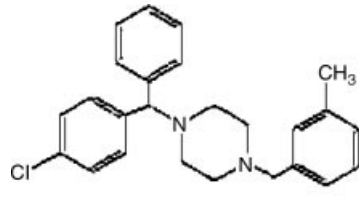
Uses. Dronabinol is used as an appetite stimulant, primarily for AIDS and chemotherapy patients. It is indicated for the treatment of the nausea and vomiting produced by cancer chemotherapy in patients who have failed to respond adequately to other conventional treatments.

5.4. Meclizine Hydrochloride. Meclizine hydrochloride is also known as Piperazine, Antivert, Bonine, Bonamine, Bonikraft, Emetostop, Medivert, Sea-Legs [31884-77-2], 1-[(4-chlorophenyl)- phenyl-methyl]-4- [(3-methylphenyl) methyl]piperazine (**25**). It is a white or slightly yellowish crystalline powder with a slight odor and no taste. The hydrochloride is practically insoluble in water and ether. It is freely soluble in chloroform, pyridine, methylacetamide, and mild acid alcohol–water mixtures, and is slightly soluble in dilute acids or alcohol. See Ref. 29 for synthesis.



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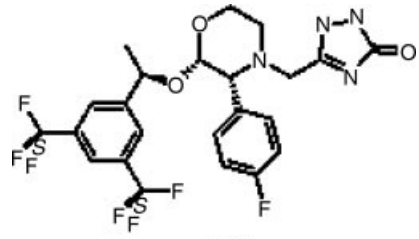
Uses. Meclizine Inhibits the symptoms motion sickness such as nausea, vomiting, and dizziness. It relieves vertigo experienced as a result of inner ear infections or other conditions.

5.5. Aprepitant. Aprepitant is also known as Emend, [170729-80-3], 5-[[(2*R*,3*S*)-2-[(1*R*)-1-[3,5-bis(trifluoromethyl) phenyl]ethoxy]-3-(4-fluorophenyl)-4-morpholinyl]methyl]-1,2-dihydro-3*H*-1,2,4-triazol-3-one (**26**). It is a white to off-white crystalline solid that is practically insoluble in water. It is sparingly soluble in ethanol and isopropyl acetate and slightly soluble in acetonitrile. An efficient stereoselective synthesis of aprepitant is described (30).



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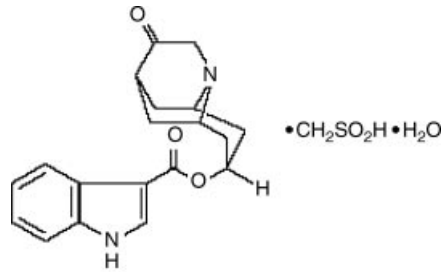
Mechanism of Action. Aprepitant is the first of a class of compounds that are substance P/neurokinin 1 (NK-1) receptor antagonists. They are

believed to work through a novel mechanism, which primarily blocks nausea and vomiting signals to the brain. This mechanism is distinct from how current antiemetics act and represent a new class of therapy for the management of post operative nausea and vomiting. Aprepitant has little or no affinity for serotonin (5-HT_3), dopamine, and corticosteroid receptors, the targets of existing therapies for chemotherapy-induced nausea and vomiting and postoperative nausea and vomiting. Aprepitant has been shown in animal models to inhibit emesis induced by cytotoxic chemotherapeutic agents, such as cisplatin, via central actions. Animal and human Positron Emission Tomography (PET) studies with aprepitant have shown that it crosses the blood brain barrier and occupies brain NK1 receptors. Animal and human studies show that aprepitant augments the antiemetic activity of the 5-HT_3 receptor antagonist ondansetron and the corticosteroid dexamethasone and inhibits both the acute and delayed phases of cisplatin-induced emesis. It is effective after oral administration. It produces a dose –dependant inhibition of CYP3A4 and should be used with caution in patients receiving concomitant orally administered drugs that are primarily metabolized through CYP3A4. Co-administration with warfarin may result in a clinically significant decrease in international normalized ratio of prothrombin time.

Uses. Aprepitant is used in combination with other antiemetic agents, is indicated for prevention of: acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy, including high-dose cisplatin. It is used to treat nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy and in the prevention of postoperative nausea and vomiting.

5.6. Dolasetron Mesylate. Dolasetron mesylate is also known as Anzemet, [115956-12-2], (2a,6a,8a,9ab)-octahydro-3-oxo-2,6-methano-2*H*-quinolizin-8-yl-l*H*- indole-3-carboxylate monomethanesulfonate, monohydrate (**27**). Dolasetron mesylate monohydrate is a white to off-white powder that is freely soluble in water and propylene glycol, slightly soluble in ethanol, and slightly soluble in normal saline.

Mechanism of Action. It is a highly specific and selective serotonin (5-HT_3) receptor antagonist both *in vitro* and *in vivo*. It is a serotonin 5-HT_3 receptor antagonist used to treat nausea and vomiting and following chemotherapy. Its main affect is to reduce the activity of the vagus nerve, which is a nerve that activates the vomiting center in the medulla oblongata. It does not have much effect on vomiting due to motion sickness. This drug does not have any effect on dopamine receptors or muscarinic receptors. It is only admisitered parenterally. See Ref. 31 for synthesis.



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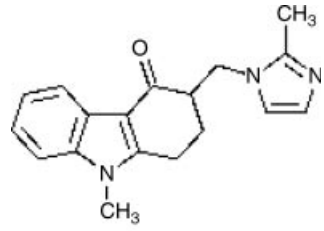
Uses. Dolasetron is used in the treatment of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy, including high dose cisplatin. It is also used in the treatment and prevention of postoperative nausea and vomiting.

5.7. Ondansetron HCl. Ondansetron HCl is known as Zofran, Cipla, Emeset, Emetron, Ondemet [99614-02-5], (+/−) 1,2,3,9-Tetrahydro-9-methyl-3-((2-methyl-1*H*-imidazol-1-yl)methyl)-4H-carbazol-4-one,monohydrochloride, dihydrate (**28**) is a white to off-white powder that is soluble in water and normal saline. It may be prepared by the method found in Ref. 32.



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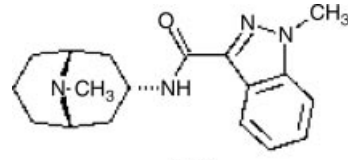
Mechanism of Action. Ondansetron was the first of a novel class of antiemetic, which has selective serotonin (5-HT_3) antagonistic activity. It is particularly useful in emesis induced by cytotoxic chemotherapeutic agents such as cisplatin. It lacks the high incidence of dystonic reaction seen with antiemetics that have dopamine-blocking activity. Side effects are infrequent other than a significant incidence of constipation. It is available for use by injection for the prevention of nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy. GSK's patent expires at he end of 2006.

Ondansetron was developed in 1984 by scientists working at Glaxo's laboratories. After several attempts the company successfully filed for U.S. patent protection for the drug in 1986. Ondansetron was granted FDA approval in January 1991. Its effects are thought to be on both peripheral and central nerves. One part is to reduce the activity of the vagus nerve, that activates the vomiting center in the medulla, the other is a antagonism of serotonin receptors in the chemoreceptor trigger zone. It may also have effects on peripheral receptors in the myenteric plexus of the stomach. It does not appear to be effective on vomiting due to motion sickness nor have effects on dopamine or muscarinic receptors. Ondansetron is a well-tolerated drug with few side effects. Headache, constipation, and dizziness are the most commonly reported side effects associated with its use. Although highly effective, its high cost limits its use to controlling postoperative nausea and vomiting. There have been no significant drug interactions reported with this drug's use. It is broken down by the hepatic cytochrome P450 system and it has little effect on the metabolism of other drugs broken down by this system.

Uses. Ondansetron is the primary drug used to treat and prevent chemotherapy-induced nausea and vomiting and in post-operative and post-radiation nausea and vomiting. It is also a possible therapy for nausea and vomiting due to acute or chronic medical illness or acute gastroenteritis.

5.8. Granisetron. Granisetron is also known as Kytril, [109889-09-0], Granisetron HCL[107007-99-8], *endo*-N-(9-methyl-9-azabicyclo [3.3.1] non-3-yl)-1-methyl-1*H*-indazole- 3-carboxamide hydrochloride (**29**). May be prepared by method in Ref. 33. Granisetron is a white to off-white solid that is readily soluble in water and normal saline at 20°C. Granisetron breaks down slowly, staying in the body for a long time. One dose usually lasts 4 to 9 hours and is usually administered once or twice daily. This drug is removed from the body by the liver and kidneys.



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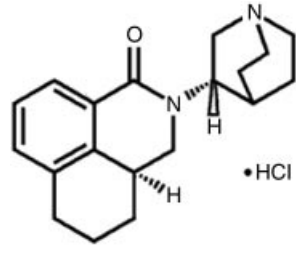
Mechanism of Action. Its pharmacology and mechanism of action is similar to that of Ondansetron. Granisetron is expected to go generic in 2007/2008. The drug was approved in the United Kingdom in 1991 and in United States in 1994.

Uses. Granisetron HCL is used to treat chemotherapy-induced nausea and vomiting and for post-operative and post-radiation nausea and vomiting. It is also a possible therapy for nausea and vomiting due to acute or chronic medical illness or acute gastroenteritis. It is used in the treatment of cyclic vomiting syndrome although there are no formal trials to confirm efficacy.

5.9. Palonosetron Hydrochloride. Palonosetron hydrochloride is also known as Aloxi, Onicita, Onicit, [135729-61-2], (3aS)-2-[(S)-1-Azabicyclo [2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1*H*benz[*de*]isoquinoline hydrochloride (**30**) is a white to off-white crystalline powder. It is freely soluble in water, soluble in propylene glycol, and slightly soluble in ethanol and 2-propanol. It is an antiemetic and antinauseant agent with selective and strong binding affinity to serotonin the 5-HT_3 receptor. Palonosetron hydrochloride exists as a single isomer. It is only available as a sterile, clear, colorless, nonpyrogenic, isotonic, buffered solution for intravenous administration. See Ref. 34 for synthesis.



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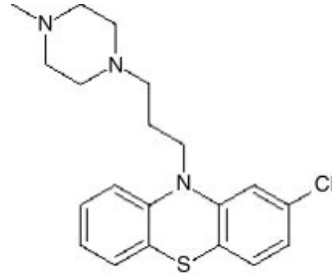
Uses. Palonosetron is used in the prevention of acute nausea and vomiting associated with initial and repeat courses of moderately and highly emetogenic cancer chemotherapy and of delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy.

5.10. Prochlorperazine. Prochlorperazine is also known as Compazine, Buccastem, Stemetil, and many other names, [58-38-8], 2-Chloro-10-[3-(4-methyl-1-piperazinyl)-propyl]-10*H*-phenothiazine maleate (**31**) is a white or pale yellow crystalline powder. It is almost completely odorless, its saturated solution is acidic to litmus, it is practically insoluble in water and ethanol, and it is slightly soluble in warm chloroform. It may be made by the synthesis described in, Ref. 35.

Prochlorperazine is available as an oral liquid, tablets, and suppositories, as well as in an injectable form. Available in the UK as Buccastem M as formulation for buccal use as an OTC-treatment for migraine. In this indication it blocks the CTZ in the brain, which is responsible for causing severe nausea and emesis.



(31)

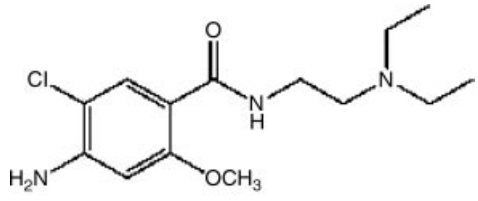
Uses. Prochlorperazine maleate [84-02-6] is an effective antiemetic and tranquilizing agent. It is not particularly effective for motion sickness. Adverse reactions that may occur include extra pyramidal reactions, motor restlessness, dystonias, tardive dyskinesia, and contact dermatitis. Prochlorperazine is also a significant phenothiazine antipsychotic. Prochlorperazine is used in the treatment of vertigo and as an antiemetic for nausea and vomiting caused by cancer treatment and surgical procedures.

6. Prokinetics

Prokinetics are a relatively new class of agent that can augment propulsive motility of the gastrointestinal tract. The aim of programs to develop agents with specific activity on different portions of the gastrointestinal tract has resulted in the development of specific gastro prokinetics and colonic prokinetics. Cisapride [81098-60-4] (Propulsid) had been accepted by the FDA for the treatment of gastroesophageal reflux and also found to be useful in diabetic gastroparesis and other disease in which delayed gastric emptying is a problem. Janssen Pharmaceutica withdrew the compound from the U.S. market as of July 14, 2000. Use of cisapride was associated with 341 reports of heart rhythm abnormalities including 80 reports of deaths. Most of these adverse events occurred in patients who were taking other medications or suffering from underlying conditions known to increase risk of cardiac arrhythmia associated with cisapride. Cisapride can in some cases produce the long QT syndrome which predisposes to arrhythmias.

Gastroprokinetic agents in most cases increase the barrier pressure of the lower esophageal sphincter decreasing reflux and increase esophageal acid clearance making them useful for therapy of esophageal reflux (heartburn) and erosive esophagitis. Recently Tegaserod [145158-71-01] has been approved for treatment of chronic constipation and has found use in the treatment of IBS. The prevalent hypothesis of the mechanism of action of many prokinetics is an agonistic activity on the serotonin (5-HT_4) receptors on the nervous network in the gastrointestinal tract (36).

6.1. Metoclopramide Dihydrochloride. Metoclopramide dihydrochloride is also knowns as Reglan, Cerucal, Maxolon, Metaclopramide, Primperan, Rimetin, [364-62-54] [54143-57-6] amino-5-chloro-*N*-(2-(diethylamino)ethyl)-2-methoxybenzamide (**32**) is a white crystalline powder soluble in water. It may be made by the method described in Ref. 37.



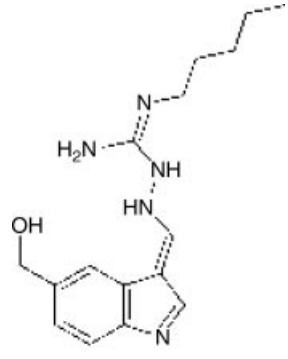
(32)

Mechanism of Action. Metoclopramide is an effective antiemetic, which may work due either to its central dopamine- D_2 blocking activity or a mixed 5-HT_3 receptor antagonist/5-HT_4 receptors agonist blocking activity. It also stimulates propulsive motility of the upper gastrointestinal tract, probably due to stimulation of 5-HT_4 receptors. The prokinetic activity of metoclopramide is mediated by D2 receptor antagonist activity and 5-HT_4 receptor agonist activity. The prokinetic activity itself may also contribute to the anti-emetic effectiveness. Interactions with concomitant medication may occur due to increased gastric emptying. Metoclopramide increases propulsive motility of the jejunum and duodenum, increases tone and amplitude of gastric contractions, and relaxes the pyloric sphincter and duodenal bulb. Use is often limited due to extra-pyramidal symptoms presenting primarily as acute dystonic reactions. These side effects may be partially alleviated by administration of anticholinergics with central activity. The anti-emetic action of metoclopramide is due to its antagonist activity at D_2 receptors in the chemoreceptor trigger zone preventing nausea and vomiting triggered by most stimuli. At higher doses, 5-HT_3 antagonist activity may also contribute to the anti-emetic effect.

Uses. Metoclopramide dihydrochloride is used in the prevention and treatment of nausea and vomiting due to emetogenic cancer chemotherapy and in the prevention of postoperative nausea and vomiting. Symptomatic esophageal reflux, diabetic gastroparesis, small bowel intubation, and radiological examination can be treated with metoclopramide dihydrochloride. It is used as prokinetic activity for treamtent of gastric stasis due to gastric surgery or diabetic gastroparesis, as an aid in gastrointestinal radiology by increasing transit in barium studies, and as an aid in difficult small intestinal intubation. It

inhibits the action of prolactin inhibiting hormone metoclopramide has sometimes been used to stimulate lactation.

6.2. Tegaserod. Tegaserod also known as Zelnorm,(in the U.S.) or Zelmac (in other countries [145158-71-01] [189188-57-6], 3-(5-methoxy-1H-indol-3-ylmethylene)-*N*-pentylcarbazimidamide hydrogen maleate (**33**). Tegaserod as the maleate salt is a white to off-white crystalline powder and is slightly soluble in ethanol and very slightly soluble in water. It may be synthesized according to the data in Ref. 38.



(33)

Mechanism of Action. Both the enteric nervous system, which acts to integrate and process information in the gut, and 5-hydroxytryptamine (5-HT, serotonin) are thought to represent key elements in the etiology of both IBS and idiopathic constipation. Approximately 95% of serotonin is found throughout the gastrointestinal tract, primarily stored in enterochromaffin cells but also in enteric nerves acting as a neurotransmitter. Serotonin has been shown to be involved in regulating motility, visceral sensitivity and intestinal secretion. Investigations suggest an important role of serotonin (5-HT_4) receptors in the maintenance of gastrointestinal functions in humans. Tegaserod is a 5-HT_4 receptor partial agonist that binds with high affinity at human 5-HT_4 receptors, whereas it has no appreciable affinity for 5-HT_3 or dopamine receptors. It has moderate affinity for 5-HT_1 receptors. Tegaserod, by acting as an agonist at neuronal 5-HT_4 receptors, triggers the release of further neurotransmitters such as calcitonin gene-related peptide from sensory neurons. The activation of 5-HT_4 receptors in the gastrointestinal tract stimulates the peristaltic reflex and intestinal secretion, as well as inhibits visceral sensitivity. *In vivo* studies showed that tegaserod enhanced basal motor activity and normalized impaired motility throughout the gastrointestinal tract. In addition, studies demonstrated that tegaserod moderated visceral sensitivity during colorectal distension in animals.

Uses. Tegaserod is a treatment for irritable bowel syndrome with constipation and chronic idiopathic constipation are both lower gastrointestinal dysmotility disorders. It relieves the abdominal discomfort, bloating and constipation of chronic constipation.

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