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Annual Update 2003: Gastrointestinal Drugs

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Abstract

This month's Annual Update 2003 is dedicated to Gastrointestinal Drugs and is comprised of a compendium of 175 drugs for the treatment of gastrointestinal diseases, disorders of the pancreas and diseases of the liver and biliary tract. The table of drugs includes products which have been launched for the first time since 2002 and others that were previously marketed for another indication and are now being studied or have been introduced for a gastrointestinal condition. Products featured in the monograph updates section include adefovir dipivoxil, alicaforsen sodium, alosetron hydrochloride, almivopan hydrate, atlizumab, elvucitabine, emtricitabine, entecavir, natalizumab, pioglitazone hydrochloride, prucalopride, ramoplanin, renzapride hydrochloride, tegaserod maleate, tenatoprazole, vapreotide acetate, visilizumab and Z-338.

Introduction

This month's Annual Update 2003 is dedicated to Gastrointestinal Drugs and is comprised of a compendium of 175 drugs for the treatment of gastrointestinal diseases, disorders of the pancreas and diseases of the liver and biliary tract. The table of drugs includes products which have been launched for the first time since 2002 and others that were previously marketed for another indication and are now being studied or have been introduced for a gastrointestinal condition. Products featured in the monograph updates section include adefovir dipivoxil, alicaforsen sodium, alosetron hydrochloride, almivopan hydrate, atlizumab, elvucitabine, emtricitabine, entecavir, natalizumab, pioglitazone hydrochloride, prucalopride, ramoplanin, renzapride hydrochloride, tegaserod maleate, tenatoprazole, vapreotide acetate, visilizumab and Z-338.

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Drug	Source	Condition	Phase
683699	GlaxoSmithKline	Inflammatory bowel disease	I
5D12	Tanox	Crohn's disease	I/II
ABT-874	Abbott	Crohn's disease	II
Activax	AntexBiologics	Diarrhea	I
Adalimumab[2]	Abbott	Crohn's disease	II/III
Adefovir Dipivoxil[2]	Gilead	Hepatitis B	L-2002
AJM-300	Ajinomoto	Irritable bowel syndrome	I
Albumin Interferon Alfa	Human Genome Sciences	Hepatitis C	I
Alicaforsen Sodium[2]	Isis Pharmaceuticals	Crohn's disease	III
	Isis Pharmaceuticals	Ulcerative colitis	II
Alosetron Hydrochloride[2]	GlaxoSmithKline	Irritable bowel syndrome	L-2002
Alvimopan Hydrate[2]	Adolor/GlaxoSmithKline	Constipation (opioid-induced)	III
	Adolor/GlaxoSmithKline	Postoperative ileus	III
ANA-245	Anadys	Hepatitis C	I
Anti-Hepatitis B Hyperimmune	Cangene	Hepatitis B	Prereg.
Artofisopam	Vela Pharmaceuticals	Irritable bowel syndrome	II
Asimadoline	Merck KGaA	Irritable bowel syndrome	II
Atlizumab[2]	Chugai/Roche	Crohn's disease	II
Atvogen	HemispheRx	Hepatitis B	II
AU-224	Abbott	Constipation	II
AZD-0865	AstraZeneca	Gastroesophageal reflux disease	I
AZD-3355	AstraZeneca	Gastroesophageal reflux disease	I
Beclometasone Dipropionate[1]	Chiesi	Ulcerative colitis	III
Bile Salt-Stimulated Lipase	PPL	Pancreatic insufficiency	II
Body Protection Compound-15	Pliva	Ulcerative colitis	II
Budesonide[1]	West Pharmaceutical Services	Crohn's disease	I
	West Pharmaceutical Services	Ulcerative colitis	I
BXT-51072	Oxis	Inflammatory bowel disease	II
Campylobacter jejuni Vaccine	AntexBiologics	Diarrhea	II
CBP-1011	InKine	Crohn's disease	III
	InKine	Ulcerative colitis	II
CC-1088	Celgene	Crohn's disease	II
CC-7085	Celgene	Inflammatory bowel disease	I
CDP-870	Celltech/Pharmacia	Crohn's disease	II
Cellegesic[1]	Cellegy	Hemorrhoids	II
	Cellegy	Fissure, anal	III
CH-100	Cathay Herbal/Univ. Newcastle (Australia)	Hepatitis C	II
Cilansetron[2]	Solvay	Irritable bowel syndrome	III
CNI-1493	Cytokine PharmaSciences	Crohn's disease	II
CP-461	Cell Pathways	Crohn's disease	II
CpG-7909	Coley Pharmaceuticals	Hepatitis B	I/II
DA-9601	Dong-A	Gastritis	III
Daclizumab[1]	Protein Design Labs	Ulcerative colitis	II
DDB-S	Daewoo Pharmaceuticals	Hepatitis, viral	II
Dexloxiglumide[2]	Forest/Rotta	Irritable bowel syndrome	III
Diltiazem Hydrochloride[1]	SLA Pharma/Solvay	Fissure, anal	III
DNA Hepatitis B Vaccine	GlaxoSmithKline/Chiron Vaccines	Hepatitis B	I
Doramapimod	Boehringer Ingelheim	Crohn's disease	II
DPC-333	Bristol-Myers Squibb	Inflammatory bowel disease	II
Dronabinol/Cannabidiol	GW Pharmaceuticals	Inflammatory bowel disease	I
E-3309	Eisai	Ulcer, *Helicobacter pylori*	I
E-3620	Eisai	Gastritis	II
	Eisai	Irritable bowel syndrome	II
EHC-18	Enzo/Biochem	Hepatitis C	I/II
EHT-899	Enzo/Biochem	Hepatitis B	II
Elvucitabine[2]	Achillion	Hepatitis B	II
Emtricitabine[1,2]	Gilead	Hepatitis B	III
Entecavir[2]	Bristol-Myers Squibb	Hepatitis B	III
ETEC Vaccine	Iomai	Diarrhea	II
Etiprednol Dicloacetate	Ivax	Crohn's disease	II
	Ivax	Ulcerative colitis	II
Fontolizumab	Protein Design Labs	Crohn's disease	II
Gastrimmune[2]	Aphton/Aventis Pasteur	Gastroesophageal reflux disease	II
HBsAg, SBAS4	GlaxoSmithKline	Hepatitis B	Prereg.
Helicide	Axcan	Ulcer, *Helicobacter pylori*	R-2003
Helicobacter pylori Vaccine	Antex Biologics	Ulcer, *Helicobacter pylori*	II
	Iomai	Ulcer, *Helicobacter pylori*	I
	Acambis/Aventis Pasteur	Ulcer, *Helicobacter pylori*	II

Continuation

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Drug	Source	Condition	Phase
Hepatitis A and Hepatitis B Vaccine	GlaxoSmithKline	Hepatitis A and B	R-2002
Hepatitis B Pharmaccine	Oxxon Pharmaccines	Hepatitis B	II
Hepatitis B Vaccine	GlaxoSmithKline	Hepatitis B	III
Hepatitis C Immune Globulin (Human)	Nabi Biopharmaceuticals	Hepatitis C	I/II
Hepatitis E Vaccine	GlaxoSmithKline/NCI	Hepatitis E	II
Hepavir B	Ribapharm	Hepatitis B	I
Histamine Dihydrochloride	Maxim	Hepatitis C	II
Hydrocortisone Acetate[1]	Schwarz	Ulcerative colitis	L-2002
	Schwarz	Ulcerative colitis	L-2002
Hyoscyamine Sulfate[1]	InKine	Irritable bowel syndrome	L-2002
Icatibant	Jerini	Cirrhosis	II
IDN-6556	Idun	Hepatitis C	I
Ilaprazole[2]	Il-Yang	Gastroesophageal reflux disease	II
Infliximab[1]	Centocor/Schering-Plough	Ulcerative colitis	III
INKP-100[1]	InKine	Constipation	I
InnoVax C	Innogenetics/Rhein Biotech	Hepatitis C	II
Interferon Alfa (Intranasal)[1]	Nastech	Hepatitis B	I
Interferon Alfa-n1[1]	Sumitomo Pharmaceuticals	Cirrhosis	II
Interferon Alfa-n3[1]	HemispheRx	Hepatitis C	II/III
Interferon Beta[1]	Daiichi Pharmaceutical/Toray	Cirrhosis	II/III
Interferon Beta-1a[1]	Serono	Crohn's disease	II
	Serono	Ulcerative colitis	II
	Serono	Hepatitis C	III
Interferon Gamma-1b[1]	InterMune	Fibrosis, hepatic	II
Interferon Omega	BioMedicines	Hepatitis C	II
ISIS-14803	Isis Pharmaceuticals	Hepatitis C	II
ISS-1018	Dynavax	Hepatitis B	II
Itriglumide[2]	Rotta	Ulcer, peptic	I
JTK-003	Japan Tobacco	Hepatitis C	II
JTK-109	Japan Tobacco	Hepatitis C	I
LB-80380	LG Chem	Hepatitis B	I
LDP-02	Genentech/Millennium	Crohn's disease	II
	Genentech/Millennium	Ulcerative colitis	II
Levovirin	Ribapharm/Roche	Hepatitis C	I
LTβR-Ig	Biogen	Inflammatory bowel disease	I
Lubiprostone	Sucampo Pharmaceuticals	Constipation	III
	Sucampo Pharmaceuticals	Constipation (opioid-induced)	II
	Sucampo Pharmaceuticals	Irritable bowel syndrome	II
	Sucampo Pharmaceuticals	Postoperative ileus	II
MCC-478	Mitsubishi Pharma/Lilly	Hepatitis B	I/II
ME-3738	Meiji Seika	Hepatitis, viral	II
Merimepodib[2]	Vertex	Hepatitis C	II
Mesalamine[1]	Axcan	Ulcerative colitis	III
	Axcan	Crohn's disease	III
Metanicotine	Falk Pharma/Targacept	Ulcerative colitis	I
Methylnaltrexone Bromide[2]	Progenics	Constipation	III
	Progenics	Postoperative ileus	II
Mitemcinal[2]	Chugai	Gastroesophageal reflux disease	II
	Chugai	Gastroparesis	II
MIV-210	Medivir/GlaxoSmithKline	Hepatitis B	I
Mivotilate	Yuhan/Grelan	Hepatitis B	II
Mosapride Citrate[1,2]	Takeda	Gastroparesis	II
NAA-004	Nobex	Inflammatory bowel disease	IND Filed
Naltrexone Hydrochloride[1]	Pain Therapeutics	Irritable bowel syndrome	I/II
Natalizumab[2]	Biogen/Elan	Crohn's disease	III
NCX-1015	NicOx	Inflammatory bowel disease	I
Nepadutant	Menarini	Irritable bowel syndrome	II
NM-283	Idenix	Hepatitis C	I/II
Nolpitantium Besilate	Sanofi-Synthélabo	Inflammatory bowel disease	II
OC-108	Mitsubishi Pharma	Hemorrhoids	Prereg.
Omeprazole[1,2]	Mitsubishi Pharma	Gastritis	Prereg.
Omeprazole/Sodium Bicarbonate	Santarus	Ulcer, bleeding	Phase III
Onercept	Serono	Crohn's disease	Phase II
Ono-4817	Ono	Inflammatory bowel disease	I
OPC-6535	Otsuka	Ulcerative colitis	II
Opebacan	Xoma	Crohn's disease	II
P-54	Phytopharm	Crohn's disease	II
	Phytopharm	Ulcerative colitis	II

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Drug	Source	Condition	Phase
Peginterferon Alfa-2a[1]	Roche	Hepatitis B	III
PEGylated Interferon Alfacon-1	InterMune	Hepatitis C	I
Phenylephrine[1]	SLA Pharma/Solvay	Incontinence, fecal	III
Picroliv[2]	Central Drug Research Institute	Hepatitis, viral	II
Pioglitazone Hydrochloride[1,2]	Natl Inst. Diabetes Digest Kidney Dis	Steatohepatitis, nonalcoholic	II
Polaprezinc[1,2]	Zeria	Gastritis	Prereg.
Porfimer Sodium[1]	Axcan	Barrett's esophagus	L-2003
Prednisolone Sodium Metasulfobenzoate	Alizyme	Ulcerative colitis	III
Prucalopride[2]	Janssen	Constipation	III
	Janssen	Irritable bowel syndrome	III
QR-334	Quigley Pharma	Sialorrhea	II
R-105266	Sankyo/Ube	Ulcer, peptic	I
R-1479	Roche	Hepatitis C	I
R-1518	Roche	Hepatitis C	I
Ramoplanin[2]	Genome Therapeutics	Diarrhea	II
Ramosetron Hydrochloride[1,2]	Yamanouchi	Irritable bowel syndrome	II
RDP-58	SangStat	Diarrhea (chemotherapy-induced)	IND Filed
	SangStat	Crohn's disease	II
	SangStat	Ulcerative colitis	II
Recombinant Hepatitis B Vaccine	Aventis Pasteur MSD	Hepatitis B	L-2002
Renzapride Hydrochloride[2]	Alizyme	Irritable bowel syndrome	II
Repifermin	GlaxoSmithKline	Ulcerative colitis	II
Revaprazan	Yuhan	Ulcer, peptic	III
rhIL-18bp	Serono	Crohn's disease	I
Rotavirus Vaccine	GlaxoSmithKline/Avant	Diarrhea	II
	Merck & Co.	Diarrhea	III
RU-8811	Sucampo Pharmaceuticals	Steatohepatitis, nonalcoholic	II
S-3013	Shionogi	Inflammatory bowel disease	II
Saredutant[2]	Sanofi-Synthélabo	Irritable bowel syndrome	II
SB-723620	GlaxoSmithKline	Irritable bowel syndrome	I
Shigella sonnei Vaccine	AntexBiologics	Diarrhea	I
SLV-317	Solvay	Irritable bowel syndrome	I
Somatropin	Serono	Short-bowel syndrome	Prereg.
Soraprazan	Altana Pharma	Ulcer, gastrointestinal	II
SPD-476[1]	Shire	Ulcerative colitis	II
SPD-480[1]	Shire	Ulcerative colitis	II
SR-121463A	Sanofi-Synthélabo	Cirrhosis	II
STA-5326	Synta Pharmaceuticals	Crohn's disease	I
Stannsoporfin	WellSpring Pharmaceutical	Hyperbilirubinemia	III
T-487	Tularik	Inflammatory bowel disease	I
Tacrolimus[1,2]	Fujisawa	Ulcerative colitis	III
Talnetant	GlaxoSmithKline	Irritable bowel syndrome	II
Teduglutide	NPS Pharmaceuticals	Short-bowel syndrome	II
Tegaserod Maleate[1,2]	Novartis/Bristol-Myers Squibb	Irritable bowel syndrome	L-2001
	Novartis/Bristol-Myers Squibb	Constipation	III
	Novartis/Bristol-Myers Squibb	Gastroesophageal reflux disease	II
	Novartis/Bristol-Myers Squibb	Dyspepsia	II
Telbivudine	Idenix	Hepatitis B	III
Tenatoprazole[2]	Negma	Ulcer, peptic	Clinical
TheraCLEC Lipase	Altus Biologics	Pancreatic insufficiency	I
TJN-219	Tsumura	Hemorrhoids	II
Tolevamer Sodium	Genzyme General	Diarrhea	II
R-14035	Tanabe Seiyaku/GlaxoSmithKline	Inflammatory bowel disease	I
Transvax Hepatitis C Vaccine	InterCell	Hepatitis C	II
Ursodeoxycholic Acid[1]	Axcan	Steatohepatitis, nonalcoholic	II
	Axcan	Cholangitis, sclerosing	III
	Mitsubishi Pharma	Hepatitis C	III
Valtorcitabine Dihydrochloride	Idenix	Hepatitis B	I/II
Vapaliximab	BioTie Therapies	Crohn's disease	I
	BioTie Therapies	Ulcerative colitis	I
Vapreotide Acetate[2]	Debiopharm/H3 Pharma	Cirrhosis	Prereg.
Viramidine Hydrochloride	Ribapharm	Hepatitis C	II
Visilizumab[2]	Protein Design Labs	Ulcerative colitis	I
VX-702	Vertex	Crohn's disease	I
XTL-001	XTL Biopharmaceuticals	Hepatitis B	II
XTL-002	XTL Biopharmaceuticals	Hepatitis C	II
Z-205	Zeria	Gastroparesis	II
Z-338[2]	Zeria/Yamanouchi	Dyspepsia	II
Z-360	Zeria	Gastroesophageal reflux disease	I
	Zeria	Ulcer, peptic	I

[1]Launched for another indication. [2]Monograph previously published in Drugs of the Future.

Compendium of Gastrointestinal Drugs

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Diarrhea

Diarrhea, defined as abnormally frequent discharge of semisolid or liquid fecal matter from the bowel, is a common problem that usually lasts a day or two and goes away on its own without any special treatment. The average adult has a bout of diarrhea about four times a year. However, prolonged diarrhea can be a sign of other problems. Diarrhea may be caused by a temporary problem, like a bacterial or virus infection, parasite or food intolerance, or it may be a symptom of a chronic problem, such as an intestinal disease (inflammatory bowel disease, celiac disease or irritable bowel syndrome). People who visit foreign countries are at risk for traveler's diarrhea, which is caused by eating food or drinking water contaminated with bacteria, viruses or parasites. Traveler's diarrhea is a particular problem for people visiting developing countries.

The most serious potential consequence of diarrhea is dehydration. Dehydration is particularly dangerous in children and the elderly, and it must be treated promptly to avoid serious health problems. Diarrheal diseases are responsible for 2,000-8,000 deaths a year in the U.S. and over 3 million globally.

In most cases, replacing lost fluid to prevent dehydration is the only treatment necessary. Medicines that stop diarrhea may be helpful in some cases, but they are not recommended for people whose diarrhea is from a bacterial infection or parasite. Patients with this form of diarrhea should be treated with antibiotics. Viral causes are either treated with medication or left to run their course, depending on the severity and type of the virus.

Antibiotics

Ramoplanin is an investigational new drug in clinical development by Genome Therapeutics. A novel product of microbial fermentation first discovered by Vicuron Pharmaceuticals, ramoplanin is a member of a new class of antibiotics known as glycolipodepsipeptides. Genome Therapeutics has acquired development and commercialization rights to ramoplanin for North America from Vicuron Pharmaceuticals. Ramoplanin has potent *in vitro* bactericidal activity targeted against Gram-positive bacteria, including many antibiotic resistant strains such as vancomycin-resistant enterococci (VRE), methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Staphylococcus aureus* (VRSA). It is also bactericidal *in vitro* against *Clostridium difficile*. Because it is not absorbed systemically from the gastrointestinal tract following oral dosing and exerts its bactericidal activity in the gastrointestinal tract, ramoplanin represents a potential new concept for managing certain pathogens commonly found in the hospital and carried in patients' gastrointestinal tracts. Ramoplanin, which has Fast Track status from the FDA, is currently being studied for two indications: a phase III clinical trial for the prevention of VRE bloodstream infections and a phase II study for treating *C. difficile*-associated diarrhea.

Vaccines

Antex Biologics' **Activax™** is a multicomponent vaccine designed to prevent and eradicate travelers' diarrhea caused by *Shigella*, *Campylobacter jejuni* and enterotoxigenic *Escherichia coli* (ETEC) bacteria. The three component vaccines are also being developed as potential individual pathogen-specific vaccines. All three components have entered clinical testing and sufficient data have been collected to proceed to clinical trials with the combination vaccine.

Rotavirus infection is one of the most common causes of severe diarrhea in young children. In the severest of cases, children suffer 10-20 episodes of diarrhea each day, rapidly becoming dehydrated. As many as 600,000 children, most in developing countries, die each year as a consequence of rotavirus infection. Vaccines are considered an especially promising approach to the prevention of this devastating disease.

Vaccine strategies are being widely explored for the prevention and treatment of diarrheal diseases, as indicated in Table I.

Table I: Vaccines in development for the prevention and treatment of diarrhea.

Drug Name	Source	Description	Status (indication)
RotaTeq™	Merck & Co.	Pentavalent rotavirus vaccine	Phase III (rotavirus infection in children)
Campyvax™	Antex Biologics	Inactivated whole cell *C. jejuni* vaccine preparation	Phase II (traveler's diarrhea caused by *C. jejuni*)
ETEC vaccine	Iomai	Vaccine consisting of recombinant CS6 subunit of ETEC colonization factor plus heat-labile enterotoxin as an adjuvant, administered using transcutaneous immunization (TCI) technology	Phase II (traveler's diarrhea caused by ETEC)
Rotarix™	GlaxoSmithKline/Avant	Live, attenuated human rotavirus vaccine	Phase II (rotavirus infection in children)
Activax™	Antex Biologics	Combination vaccine against *Campylobacter*, *Shigella* and ETEC based on the nutriment signal transduction (NST) technology	Phase I (traveler's diarrhea)
Shigella vaccine	Antex Biologics	*S. sonnei* vaccine based on the NST technology	Phase I (traveler's diarrhea caused by *S. sonnei*)

Toxin-binding polymers

Clostridium difficile is a highly infectious Gram-positive anaerobic bacteria which is often responsible for colitis and resulting mild to moderate diarrhea in patients who have been treated with broad-spectrum oral antibiotics. Approximately 20% of hospitalized patients become infected with *C. difficile*, and about 30% of these will experience diarrhea. *C. difficile* should be suspected in any patient who has received antibiotic therapy within the previous 2 months or who develops diarrhea 72 h or more after being hospitalized.

Genzyme General is evaluating the toxin-binding polymer **tolevamer sodium** in phase II trials. This product is targeted to the prevention and treatment of *C. difficile* colitis.

Antiinflammatory agents

SangStat is currently evaluating **RDP-58** in phase I studies for the treatment of chemotherapy-induced diarrhea associated with irinotecan and 5-FU. RDP-58, an inhibitor of tumor necrosis factor-alpha and other inflammatory cytokines, is also in clinical development for the indication of inflammatory bowel disease (IBD), as discussed elsewhere in this article.

Constipation

Constipation is a condition in which bowel movements are infrequent or incomplete. People who are constipated may find it difficult and painful to have a bowel movement. Other symptoms of constipation include feeling bloated, uncomfortable and sluggish.

Constipation is one of the most common gastrointestinal complaints in the U.S., resulting in about 2 million doctor visits annually and affecting nearly everyone at some point in their lives. Americans spend millions of dollars each year on laxatives.

One important category of constipation is that induced by opioid therapy, as in the case of cancer patients or other patients with advanced illnesses who must receive chronic therapy with opioids to control their pain. This particular form of bowel dysfunction results from opioids' concomitant effects on peripheral receptors, which are not required for analgesia.

In most cases, modifications to diet (*i.e.*, increasing fiber intake) and lifestyle are sufficient to correct constipation. Pharmacotherapeutics for constipation include laxatives, stool softeners and lubricants. Drug therapy should be attempted only when dietary and lifestyle changes have failed, due to the risk of becoming dependent on laxatives and other drugs.

Laxatives

InKine Pharmaceutical's Visicol® (**INKP-100**), which is marketed as a purgative for colonoscopy, is now being studied in clinical trials as a potential treatment for constipation. The company is now enrolling patients in an open-label dose-ranging trial of Visicol® tablets to relieve the symptoms of constipation, including functional constipation (constipation not associated with other medical conditions) or constipation-predominant irritable bowel syndrome (IBS). In this study, adult patients are treated for up to 4 weeks with from 2-12 Visicol® tablets daily.

Serotonergic agents

Assuming positive results of ongoing phase III trials, Novartis plans to file a supplementary NDA later in 2003 requesting permission to market **tegaserod maleate** for the treatment of chronic constipation. Tegaserod (Zelnorm™/Zelmac®), a 5-HT_4 receptor agonist, has been

marketed since 2001 with Bristol-Myers Squibb for the treatment of constipation-predominant IBS.

Prucalopride, another 5-HT_4 agonist, is in phase III clinical trials at Janssen for the treatment of chronic constipation. This product is also being developed for the indication of constipation-predominant IBS, as discussed elsewhere in this review.

Abbott's **AU-224**, a 5-HT_4 agonist with potent prokinetic effects, is in phase II testing for the treatment of constipation.

Opioid antagonists

Progenics has initiated a pivotal phase III trial of the opioid antagonist **methylnaltrexone bromide** for the reversal of opioid-induced constipation. The trial will enroll 150 patients with advanced medical illness who are receiving chronic opioids. Single subcutaneous doses of methylnaltrexone or placebo will be assessed for their ability to induce laxation within 4 hours. Patients completing the double-blind portion of the study are eligible to receive the study drug in a 4-week open-label phase. Results are expected by the end of 2003. Methylnaltrexone blocks peripheral opioid receptors, which cause the side effects often associated with opioid use. However, as the drug does not cross the blood-brain barrier, it does not interfere with the central opioid receptors mediating pain relief.

Alvimopan hydrate, a mu opioid antagonist from Adolor, is being developed in collaboration with GlaxoSmithKline for the treatment of acute and chronic indications. Its efficacy in reversing the severe constipating effects of chronic opioid therapy is the subject of ongoing phase III trials.

Chloride channel activators

Sucampo is taking an alternative approach to the treatment of constipation with the chloride channel activator **lubiprostone** (SPI-0211). Phase III clinical trial results presented at the 2003 Digestive Disease Week demonstrated that the compound is safe and significantly more effective than placebo in improving all constipation variables measured in the study. The compound is also in phase II testing for the related indication of opioid-induced bowel dysfunction.

Fecal incontinence

Fecal incontinence is the uncontrollable loss of wind or bowel movements. It may range in severity from urgency to complete passive incontinence (unconscious loss of bowel movements). The condition is more common in women than men, but may occur in both genders and in any age group.

SLA Pharma, in collaboration with Solvay, is evaluating **phenylephrine gel** (Incostop®) in phase III trials as a potential treatment for passive fecal incontinence. Phenylephrine may benefit patients with this condition by improving resting anal sphincter tone.

Sialorrhea

Sialorrhea (excess secretion by the salivary glands) is a condition that affects patients suffering from diverse diseases including amyotrophic lateral sclerosis, cerebral palsy, Parkinson's disease and muscular dystrophy, among others. Although there is no published data summarizing all the patients suffering from this condition, sialorrhea may affect several million patients annually suffering from these diverse diseases.

The goal of treatment is to reduce drooling while maintaining a moist, healthy oral cavity, thereby avoiding the complication of xerostomia. Available therapies include the use of anticholinergic drugs, speech therapy, prosthetic devices, behavioral therapy, biofeedback, radiation therapy and various surgical procedures. No single therapy has been documented to resolve sialorrhea satisfactorily in all patients, without side effects. Rather, a combination of therapies is often required.

QR-334, a botanical composition in development by Quigley Pharma, is in phase II clinical testing for the treatment of sialorrhea. QR-334 includes ingredients obtainable from turmeric extract, ginger root powder and horseradish root powder.

Gastroesophageal reflux disease

Gastroesophageal reflux disease (GERD) has only been recognized as a distinct disease entity in the last 10-15 years. GERD is defined as damage to the mucosa (esophagitis) or symptoms arising as a result of reflux of gastric contents into the distal esophagus. The commonly accepted, working diagnosis of GERD is of heartburn and/or acid regurgitation twice a week or more.

According to the American College of Gastroenterology, about 60 million Americans report symptoms of heartburn – the predominant symptom of the condition – at least once a month. According to the Johns Hopkins Medical Institutions, one-third of the population in the U.S. suffers from GERD, with 3-7% of the population suffering from frank esophageal reflux disease.

Given the high prevalence of GERD, both direct and indirect costs are substantial. The American Gastroenterological Association has estimated the total yearly costs of U.S. physician office visits for GERD to be USD 603.1 million, the total costs of inpatient treatment to be about USD 2.5 billion and the total costs of drug medications around USD 5.9 billion.

The primary goals of therapy for GERD are to relieve and to maintain relief from symptoms, to heal mucosal injury where this is present and to prevent complications.

Drugs marketed for the treatment of GERD include antacids, acid suppressants (*i.e.*, proton pump inhibitors and histamine H_2 antagonists) and prokinetic agents (*i.e.*, dopamine antagonists and serotonin 5-HT_4 receptor agonists). In the most severe of cases, laparoscopy or open surgery may be required to tighten the lower esophageal sphincter muscles and prevent reflux.

Proton pump inhibitors

Proton pump inhibitors block the hydrogen-potassium adenosine triphosphatase (H^+/K^+-ATPase) enzyme system (the "proton pump") in gastric parietal cells, thereby suppressing gastric acid secretion. These drugs, which have well documented safety and efficacy, are considered the drugs of choice for managing acid-related disorders and are recommended as the mainstay of therapy for GERD by the American College of Gastroenterology.

Only one new proton pump inhibitor is known to be in development for the GERD indication at this time: the Korean pharmaceutical company Il-Yang is evaluating **ilaprazole** (IY-81149) in phase II trials for the treatment of GERD.

Serotonergic agents

Activation of 5-HT_4 receptors results in enhanced clearance and gastric emptying, speeding intestinal and colonic transit. Several classes of 5-HT_4 receptor agonists are being studied in clinical trials for a range of potential indications, including IBS, chemotherapy-induced emesis, GERD and anxiety.

Tegaserod maleate, marketed since 2001 by Novartis and Bristol-Myers Squibb for the treatment of IBS, is now in phase II development for the treatment of GERD. The company plans to introduce the drug for this new indication by the year 2006.

Motilin receptor agonists

The observation that the gastrointestinal side effects of the antibiotic erythromycin (diarrhea and vomiting) are related to the drug's marked prokinetic effects in the gut has led to a search for synthetic analogues that are structurally related to erythromycin but without its antibacterial effects. These compounds, known as motilides, are classified as motilin receptor agonists because of their action on motilin, a gastrointestinal peptide hormone which induces well-coordinated contractions throughout the gastrointestinal tract.

Chugai's motilin receptor agonist **mitemcinal** is in phase II testing in the U.S. It is targeted to the recovery of gastrointestinal motility in patients with GERD.

CCK_B antagonists

The peptide hormone and neurotransmitter cholecystokinin (CCK) is widely distributed throughout the gastrointestinal tract and central nervous system, where it is involved in the regulation of various biological functions. The action of CCK is mediated by two distinct receptor subtypes: CCK_A (also known as CCK_1) and CCK_B (also known as CCK_2), identified by pharmacological action and molecular cloning. CCK_A receptors are found in peripheral tissues such as gallbladder, pancreas and ileum, as well as in discrete brain areas. CCK_B receptors are present throughout the brain and are also found in the stomach, where they are indistinguishable from the gastrin receptors as demonstrated by the analysis of genomic DNA. The biological roles of the peripheral CCK_A receptors are well characterized and include gallbladder contraction, enzyme secretion and gut motility. Peripheral CCK_B receptors principally mediate the stimulation of gastric acid secretion and regulate gastric mucosal hypertrophy.

Although no compounds with this mechanism of action have yet reached the market, several are in the early stages of clinical testing, including one that is being evaluated for the treatment of GERD. Zeria's **Z-360** is in phase I testing for this indication.

Gastrin-targeted immunotherapy

Aphton has received approval to initiate clinical trials with G17DT (**Gastrimmune**, anti-gastrin 17 immunogen) in Europe in patients suffering from GERD, although patient enrollment has not yet begun. Prior to the initiation of this trial, Aphton agreed with the FDA to conduct toxicology and other preclinical studies in the U.S. GERD is widely treated with agents based on reducing acid secretion. However, these agents do not treat the underlying physiological mechanisms associated with the condition, which is now widely accepted to be transient lower esophageal sphincter relaxations (TLESRs) occurring in conjunction with acid reflux. Gastrin 17 has been shown to increase episodes of TLESRs, which Aphton believes may be attenuated following the reduction of gastrin 17 with its antigastrin immunotherapy. Gastrimmune is being developed in collaboration with Aventis Pasteur.

Miscellaneous drugs

In addition to the major therapeutic groups and drug classes described above, at least two less easily classified drugs are known to be in active development for the treatment of GERD at this time. These products, both from AstraZeneca, are the reversible acid pump inhibitor **AZD-0865** and **AZD-3355**, an inhibitor of TLESRs. Both are reported to be in phase I clinical testing.

Barrett's esophagus

Barrett's esophagus is a condition that results from prolonged heartburn in which the normal lining of the lower part of the esophagus is replaced, over time, by another type of lining normally present in the stomach. Barrett's esophagus is clearly recognizable at endoscopy. Typically, Barrett's esophagus develops during the process of healing after a chronic injury to the esophageal mucosa, such as the injury caused by the reflux of gastric juice in the esophagus. Continued reflux may cause dysplastic changes progressing from low-grade to high-grade dysplasia. Such dysplasia may lead to esophageal adenocarcinoma, a life-threatening condition.

It is estimated that 25,000-35,000 people in North America suffer from high-grade dysplasia associated with Barrett's esophagus, and approximately 5,000-7,000 new patients in North America are diagnosed with this condition each year.

Axcan announced in August 2003 that it has received approval from the U.S. FDA for the use of Photofrin™ (**porfimer sodium**) photodynamic therapy (PDT) in the ablation of high-grade dysplasia (HGD) in Barrett's esophagus patients who do not undergo esophagectomy. Photofrin™ PDT was also granted orphan drug designation for this indication, which guarantees a 7-year marketing exclusivity. Photofrin™ PDT has also been approved and launched in Canada for the ablation of HGD in Barrett's esophagus patients, and is under review in Europe for a similar indication.

Peptic ulcer

A peptic ulcer is a mucosal break, 3 mm or greater in size, that can involve the stomach (gastric ulcer) or duodenum (duodenal ulcer). In gastric ulcerations, lesions of the gastric mucosal lining produce symptoms of abdominal pain such as nausea, abdominal indigestion and vomiting (especially blood). The pain associated with gastric ulcer is typically relieved by antacids or milk, and characteristically occurs several hours after a meal and is worsened by lack of eating. These symptoms are often accompanied by changes in the consistency or frequency of stools, weight loss or fatigue.

Approximately 25 million Americans suffer from peptic ulcer (gastric and duodenal combined) at some time in their life, and each year there are 500,000-850,000 new cases of peptic ulcer disease and more than 1 million related hospitalizations. In the U.S. alone annual healthcare costs for peptic ulcer disease are estimated to approach USD 13.9 billion per year.

The choice of treatment depends on the suspected etiology of the ulcer. Nonpharmacological treatment of ulcer includes the avoidance of alcohol, smoking, aspirin, antiinflammatory drugs and caffeine. Pharmacological approaches to ulcer eradication address eliminating the *Helicobacter pylori* bacteria using triple or double combination therapies. In the absence of *H. pylori* organism, ulcer-healing medications such as antacids, histamine H_2 receptor antagonists or proton pump inhibitors are effective in most patients. Stress-induced ulcers respond to H_2 receptor antagonists, antisecretory agents or sucralfate. NSAID-associated ulcers are typically treated with antacid therapy and H_2 receptor antagonists.

Proton pump inhibitors

Proton pump inhibitors (PPIs) exhibit more potent and longer-lasting inhibition of gastric acid secretion as compared with H_2 receptor antagonists. This is primarily due to differences in their mechanism of action. PPIs block H_2-, gastrin-, and cholinergic-mediated sources of acid production and inhibit gastric secretion at the final common pathway of the H^+/K^+ adenosine triphosphatase (ATPase) proton pump. Several PPIs are marketed for the treatment of gastric ulcer, and new compounds with this mechanism of action continue to be developed. **Tenatoprazole**, a PPI originally discovered by Mitsubishi Pharma, has been outlicensed to the French company Negma; the latter is developing it in clinical trials as a treatment for peptic ulcer.

Sankyo and codevelopment partner Ube are preparing to initiate phase I testing of **CS-526** (R-105266), another PPI for treating gastric ulcer, in the U.S. and Europe.

Anti-H. pylori therapy

Discovered in 1983, *H. pylori* is now recognized as the predominant cause of ulcers. Scientists estimate that this spiral-shaped bacterium leads to 90% of duodenal ulcers and 80% of gastric ulcers. Because of its association with stomach cancers, the microorganism has been classified as a class I carcinogen by the World Health Organization.

Therapy for *H. pylori* infection consists of 10-14 days of one or two effective antibiotics, such as amoxicillin, tetracycline, metronidazole or clarithromycin, plus either ranitidine bismuth citrate, bismuth subsalicylate or a PPI. Acid suppression by an H_2 blocker or PPI in conjunction with the antibiotics helps alleviate ulcer-related symptoms, helps heal gastric mucosal inflammation and may enhance efficacy of the antibiotics against *H. pylori* at the gastric mucosal surface. At least eight *H. pylori* treatment regimens have been approved by the FDA; however, several other combinations have been used successfully.

A variety of potential anti-*H. pylori* strategies have been devised in recent years and are under active investigation, as shown in Table II.

Axcan has received approval from the Therapeutic Products Directorate of Health Canada for **Helicide™** (bismuth biskalcitrate/metronidazole/tetracycline hydrochloride), a patented single-capsule triple therapy administered in combination with a PPI for the eradication of *H. pylori*. Helicide™ is highly effective in eradicating metronidazole-resistant strains of *H. pylori*, whereas the

Table II: Anti-H. pylori agents in active development for the treatment of gastric ulcer.

Drug Name	Source	Description	Status
Helicide™	Axcan	Single-capsule triple therapy containing metronidazole, tetracycline and colloidal bismuth citrate	R-2003
Helivax™	Antex Biologics (acquired by BioPort)	Inactivated, multivalent, whole-cell vaccine designed to prevent and treat infections caused by *H. pylori*	Phase II
H. pylori vaccine	Acambis/Aventis Pasteur	Vaccine based on *H. pylori* urease as vaccine antigen	Phase II
E-3309	Eisai	Undisclosed	Phase I
H. pylori vaccine	Iomai	*H. pylori* vaccine administered using TCI technology	Phase I

widely prescribed omeprazole, amoxicillin and clarithromycin combination is not as effective against clarithromycin-resistant strains of *H. pylori*. Axcan expects to obtain U.S. marketing approval later in 2003.

CCK_B antagonists

As mentioned in the section on GERD, no CCK_B antagonists have yet reached the market. However, Zeria's **Z-360** and Rotta's **itriglumide** are both in phase I clinical testing for the treatment of gastric ulcer.

Acid pump antagonists

Acid pump inhibitors represent a new class of acid inhibitors that are undergoing clinical evaluation for the treatment of ulcers and other acid-related gastrointestinal disorders. The acid pump antagonist **soraprazan** (Altana Pharma) has progressed to phase II evaluation for the treatment of acid-induced gastrointestinal diseases. Positive results regarding proof of concept and tolerability were obtained from the first two phase IIa trials.

Yuhan is developing another acid pump antagonist designated **revaprazan** (YH-1885) for the treatment of peptic ulcer. The product is currently in phase III, with launch in Korea anticipated during 2004.

Bleeding ulcer

Santarus has begun a phase III clinical trial of its initial product candidate **SAN-05** (omeprazole/sodium bicarbonate, Acitrel™), to compare the efficacy of oral delivery of SAN-05 to intravenous cimetidine for the prevention of upper gastrointestinal bleeding in critically ill adult patients. SAN-05 combines omeprazole, a widely used PPI, with an antacid (sodium bicarbonate) in an immediate-release formulation as a powder for suspension. Cimetidine, a histamine H_2 receptor blocker, is the only drug approved by the FDA for this indication. The phase III trial has enrolled 359 patients in 50 centers across the U.S. Clinical endpoints will be the occurrence of clinically significant bleeding and gastric pH levels, plus safety and tolerability, and the results are expected in the third quarter of 2003. Santarus also intends to evaluate several dose formulations and pursue additional indications for this product candidate relating to other upper gastrointestinal diseases and disorders in future studies.

Gastritis

Gastritis includes a multitude of disorders that involve inflammatory changes in the gastric mucosa. These may include erosive gastritis caused by alcohol, NSAIDs or some other noxious irritant, reflux gastritis from exposure to bile and pancreatic fluids, hemorrhagic gastritis, infectious gastritis (*e.g.*, that caused by *H. pylori*) and gastric mucosal atrophy. The presentations of gastritis and peptic ulcer disease are often indistinguishable, and their management is generally the same.

Proton pump inhibitors

Daiichi Pharmaceutical is developing the PPI **omeprazole** (Omeprazon™), a gold standard in the treatment of peptic ulcer, for the new indication of gastritis. The product is preregistered in Japan for this indication.

Cytoprotectants

Zeria's cytoprotective agent **polaprezinc** (Promac™), marketed since 1994 for the treatment of peptic ulcer, is under regulatory review in Japan for the new indication of gastritis.

Serotonergic agents

Eisai is developing the dual-action 5-HT_4 agonist/5-HT_3 antagonist **E-3620** as a potential agent for gastritis. Phase II trials are under way for this indication.

Natural products and herbal remedies

Dong-A's **DA-9601**, an extract of dried aerial parts of *Artemisia asiatica*, is in phase III testing in the Republic of

Korea. It is designed as a treatment for acute and chronic gastritis and for alcoholic gastritis.

Functional dyspepsia

Functional dyspepsia, also known as nonulcer dyspepsia, is a common upper abdominal disorder characterized by symptoms of early satiety, upper abdominal pain, fullness, bloating, nausea and vomiting without any evidence of organic disease. Delayed gastric emptying, impaired gastric accommodation and visceral hypersensitivity are known to be involved in the pathogenesis of this disorder.

Nonulcer dyspepsia may be treated with antacids, H_2 receptor antagonists, PPIs or prokinetic agents. If *H. pylori* infection is detected, antibacterial therapy may be indicated.

Prokinetic agents

Prokinetic agents, which accelerate gastric emptying, are commonly used in the treatment of functional dyspepsia. Zeria's **Z-338**, a potent new prokinetic agent, has reached phase II testing in Europe for this indication. Z-338 increases gastrointestinal motility by promoting the release of acetylcholine, and is expected to be effective in relieving subjective symptoms in patients with functional gastrointestinal disorders. Zeria and Yamanouchi recently signed an agreement granting the latter development and marketing rights for Z-338 in the U.S. and Canada.

Tegaserod maleate, marketed by Novartis and Bristol-Myers Squibb since 2001 for the treatment of IBS, is now in phase II development for the treatment of functional dyspepsia. The company plans to introduce the 5-HT_4 partial agonist for this new indication by the year 2005.

Short bowel syndrome

Diseases that affect the ability of the gastrointestinal tract to absorb nutrients and water, such as IBD, have a particularly significant impact on health. The use of chemo- and radiation therapies and NSAIDs can also cause damage in the intestine. In some cases, disease or physical damage can be so severe that removal of all or part of the intestine is required. When a significant length of the intestinal tract is removed, the resulting condition is called short bowel syndrome. The condition is characterized by symptoms related to inefficient absorption of nutrients and fluids.

Currently the standard treatment for short bowel syndrome involves careful management of dietary intake, or where appropriate, parenteral nutrition. Surgical transplant of the intestine may also be performed for this condition. There are an estimated 10,000-20,000 patients in the U.S. who are receiving long-term intravenous parenteral nutrition for short bowel syndrome.

Teduglutide (ALX-0600) is NPS Pharmaceuticals' proprietary analog of the naturally occurring peptide, glucagon-like peptide 2 (GLP-2). GLP-2 is a hormone that regulates the growth, proliferation and maintenance of the mucosal lining of the small intestine. Preclinical studies have indicated that treatment with GLP-2 could produce a significant increase in both the mass and absorptive surface area of the inner lining of the small bowel. Intestinal absorption has been demonstrably improved following therapeutic administration of GLP-2 in animals. In addition, GLP-2 appears to have biological activity exclusively in the gastrointestinal system, with no major organs or tissues affected. NPS scientists have found that a small, but key change in the amino acid sequence of the natural hormone increases teduglutide's potency to 3 times the activity of the natural peptide. In addition, teduglutide is more stable than the natural peptide and, thus, potentially more useful as a therapy for diseases of the gastrointestinal tract. Teduglutide, which has orphan drug status for this indication, is in phase II testing for the treatment of short bowel syndrome.

The FDA's Gastrointestinal Drugs Advisory Committee announced in June 2003 that it had decided not to recommend approval at this time of Serono's Serostim® (**somatropin [rDNA origin]**) for use in the treatment of short bowel syndrome in patients receiving specialized nutritional support. The decision was partly based on the fact that the majority of study patients were treated in a single specialty treatment center. Serono presented data to the committee from a pivotal study evaluating the change in total parenteral nutrition requirements in adult patients with short bowel syndrome who were dependent on parenteral nutrition. In the double-blind, controlled, parallel-group phase III study, 41 patients were randomized to a specialized diet supplemented with oral glutamine alone, Serostim® with a specialized diet alone or Serostim® with a specialized diet with glutamine. The results of the study were positive, with total parenteral nutrition volume, total parenteral nutrition calories and frequency of infusion decreasing significantly more in the Serostim® plus specialized diet group as compared to the glutamine-supplemented specialized diet group. Reductions in the Serostim® plus glutamine-supplemented diet group as compared to the glutamine-supplemented specialized diet group were larger and highly significant. Serostim®, approved for the treatment of AIDS wasting or cachexia, has orphan drug designation for use alone or in combination with glutamine in the treatment of short bowel syndrome patients.

Gastroparesis

Gastroparesis, also called delayed gastric emptying, is a disorder in which the stomach takes too long to empty its contents. It commonly occurs in people with type 1 diabetes or type 2 diabetes, although it may also develop as

a result of postviral syndrome, anorexia nervosa, surgery of the stomach or vagus nerve, hypothyroidism or Parkinson's disease. Gastroparesis happens when the vagus nerve, which controls the movement of food through the digestive tract to the stomach, is damaged or stops working due to prolonged high blood glucose levels. The symptoms of gastroparesis range from mild to severe and may include heartburn, nausea, vomiting of undigested food, weight loss, abdominal bloating, early satiety, loss of appetite and gastroesophageal reflux.

When gastroparesis is caused by diabetes, proper control of blood glucose levels is fundamental. Other drugs used in the treatment of the disorder include metoclopramide, erythromycin and domperidone.

Prokinetic agents

The antibiotic erythromycin is sometimes used in the treatment of gastroparesis. The observation that the gastrointestinal side effects of erythromycin (diarrhea and vomiting) are related to the drug's marked prokinetic effects in the gut led to the discovery of a new class of synthetic compounds, the motilides, which are classified as motilin receptor agonists because of their action on motilin. **Mitemcinal**, a new motilin receptor agonist from Chugai, is in phase II clinical testing for the treatment of gastroparesis. As mentioned in an earlier section, this product is also under active investigation for the treatment of GERD.

Z-205, a novel prokinetic agent from Zeria, is also in phase II testing for the indication of gastroparesis.

The 5-HT_4 receptor agonist **mosapride citrate**, marketed (as Gasmotin®) for the treatment of GERD, is in phase II testing at Takeda for the treatment of gastroparesis.

Inflammatory bowel disease

Inflammatory bowel disease (IBD) is a serious disorder of the gastrointestinal tract in which tissue damage and inflammation lead to bowel impairment. Crohn's disease and ulcerative colitis are the most common forms of IBD. They both involve chronic inflammation and ulceration in the intestines, the result of an abnormal immune response. Chronic and abnormal activation of the immune system leads to tissue destruction in both diseases, although ulcerative colitis is generally limited to the rectum and colon, whereas Crohn's disease extends deeper into the intestinal wall and can involve the entire digestive tract, from the mouth to the anus. Other less common forms of IBD include microscopic (or lymphocytic) colitis, diversion colitis, fulminant colitis and toxic megacolon.

Up to 1 million Americans have IBD, according to an estimate by the Crohn's and Colitis Foundation of America. The estimated incidence of IBD in Western countries is approximately 1 in 1,000. IBD affects both sexes equally and can strike at any age, although it manifests most often between the ages of 15 and 35. The incidence of Crohn's disease has increased by as much as 6-fold in the past 25 years, while that of ulcerative colitis appears to have stabilized.

The annual economic impact of IBD in the U.S. alone is estimated at almost USD 2 billion.

The primary goal when treating a patient with IBD is to control active disease until a state of remission is obtained; the secondary goal is to maintain this state of remission. Evidence supports the use of local aminosalicylates to treat mild to moderate distal disease, while oral formulations are preferred in more severe disease. Corticosteroids are often administered to patients with severe disease, while fulminant attacks are controlled via intravenous ciclosporin or colectomy. None of the currently available drugs provides a cure, although they can help to control disease by suppressing destructive immune processes, promoting healing of intestinal tissues and relieving symptoms (diarrhea, abdominal pain and fever).

Aminosalicylates

The mechanisms underlying the antiinflammatory activity of aminosalicylate compounds have not yet been fully clarified, but it appears that these drugs affect nearly all points of the inflammatory cascade in IBD to one extent or another. It has been hypothesized that mesalamine (5-ASA), the active component of aminosalicylates, inhibits the production of cyclooxygenase, thromboxane synthase, PAF synthase and interleukin-1 by macrophages and that they may reduce the production of immunoglobulin by plasma cells. Mesalamine has also been suggested to act as a superoxide-free radical scavenger. Sulfasalazine tablets are generally used in the first-line treatment and maintenance of remission of mild to moderate ulcerative colitis and Crohn's disease affecting the colon. Although they are not approved for the treatment of Crohn's disease, some studies indicate that 5-ASA drugs are also effective in some patients with this condition. Drugs in this class are safe for long-term use.

Other new sulfasalzine compounds, including new formulations and new molecular entities, in development for the treatment of IBD are listed in Table III.

Corticosteroids

Oral corticosteroids were first used to treat ulcerative colitis in the early 1950s. Topical corticosteroids were introduced soon thereafter. Corticosteroids, used to control acute attacks of ulcerative colitis or Crohn's disease, can rapidly improve symptoms. Due to their well-known side effects, however, use of corticosteroids should be limited to the short-term treatment of exacerbations.

The exact mechanism of action of corticosteroids is not known, but they are believed to affect both

Table III: Sulfasalazine drugs in development for the treatment of IBD.

Drug Name	Source	Description	Status (indication)
Canasa™	Axcan	New rectal gel formulation of mesalamine	Phase III (Crohn's disease, ulcerative colitis)
SPD-476	Shire	New formulation (high-dose tablets) of mesalamine	Phase II (ulcerative colitis)
SPD-480	Shire	New rectal foam formulation of mesalamine	Phase II (ulcerative colitis)
NAA-004	Nobex	5-ASA-containing prodrug	IND filed (IBD)

Table IV: Corticosteroids in development for the treatment of IBD.

Drug Name	Source	Description	Status (indication)
Hydrocortisone acetate*	Schwarz	New formulation (aerosol, foam suspension for rectal administration)	L-2002 (ulcerative colitis)
Beclometasone dipropionate*	Chiesi	Gastroresistant tablet and enema formulations	Phase III (ulcerative colitis)
Prednisolone sodium metasulfobenzoate	Alizyme	Novel formulation using proprietary colonic drug delivery system	Phase III (ulcerative colitis, maintenance of remission)
Etiprednol dicloacetate	Ivax	"Soft" corticosteroid	Phase II (Crohn's disease, ulcerative colitis)
Budesonide*	West Pharmaceutical Services	New oral formulation based on Targit™ drug delivery system	Phase I (Crohn's disease, ulcerative colitis)
NCX-1015	NicOx	Nitric oxide-releasing steroid derivative	Phase I (IBD)

*Marketed for other indication(s).

immunologic and inflammatory responses. Thus, corticosteroids have been reported to diminish the production of proinflammatory cytokines including IL-1 and IL-6, the chemokine IL-8, the Th1 cytokines IL-2 and IFN-γ, and the Th2 cytokines IL-4 and IL-5.

The status of new corticosteroids and new formulations of marketed corticosteroids in development for the treatment of IBD are summarized in Table IV.

Cytokine-targeted therapy

Although the causes of IBD have not been fully elucidated, increasing evidence suggests that $CD4^+$ lymphocytes and certain proinflammatory cytokines are key factors in its development. The administration of anti-inflammatory cytokines or of drugs to inhibit proinflammatory cytokines, especially tumor necrosis factor α (TNF-α), represents one of the most promising new approaches to the treatment of IBD and is being actively pursued in the pharmaceutical industry.

One of the leading compounds in this class is Centocor's **infliximab** (Remicade®), a monoclonal antibody to TNF-α that has been marketed since 1998 for the treatment of Crohn's disease. Development and marketing partner Schering-Plough is now conducting phase III trials evaluating infliximab in the treatment of ulcerative colitis, the other major form of IBD.

Table V describes cytokine-targeted therapeutics in development for the treatment of IBD.

Agents targeting adhesion molecules

Cellular adhesion molecules (CAMs) are a class of cell surface proteins belonging to the Ig supergene family that are involved in the binding together of cells in tissues. In IBD, CAMs facilitate inflammation by helping circulating leukocytes to migrate toward areas of inflammation in the intestinal mucosa. Several drugs targeting adhesion molecules are in development for IBD, as indicated in Table VI.

Drugs acting on other inflammatory mediators

Proinflammatory cytokines and chemokines activate endothelial cells and macrophages to produce reactive oxygen species, nitric oxide, leukotrienes and proteases, all of which mediate intestinal inflammation and injury. New approaches to antagonize the effects of these and other inflammatory mediators are also being developed for the treatment of IBD.

Various antiinflammatory mechanisms are being explored in the search for effective new drugs to treat IBD, as reflected in Table VII.

Immunosuppressive agents

Immunosuppressive agents commonly used in the treatment of IBD include mercaptopurine (6-MP), the

Table V: Cytokine-targeted therapeutics in development for the treatment of IBD.

Drug Name	Source	Mechanism of Action	Status (indication)
CBP-1011	InKine	TNF-α antagonist/IL-6 antagonist	Phase III (Crohn's disease)
Infliximab*	Centocor/Schering-Plough	Anti-TNF-α MAb	Phase III (ulcerative colitis)
Adalimumab	Abbott	Anti-TNF-α MAb	Phase II/III (Crohn's disease)
ABT-874	Abbott	Anti-IL-12 MAb	Phase II (Crohn's disease)
Atlizumab	Chugai/Roche	Anti-IL-6 MAb	Phase II (Crohn's disease)
CC-1088	Celgene	TNF-α production inhibitor	Phase II (Crohn's disease)
CDP-870	Celltech/Pharmacia	Pegylated recombinant human anti-TNF-α antibody fragment	Phase II (Crohn's disease)
CNI-1493	Cytokine PharmaSciences	TNF-α production inhibitor/IL-1 production inhibitor/ MAP kinase inhibitor	Phase II (Crohn's disease)
DPC-333	Bristol-Myers Squibb	TNF-α converting enzyme inhibitor	Phase II (IBD)
Daclizumab*	Protein Design Labs	Anti-IL-2 receptor MAb	Phase II (ulcerative colitis)
Doramapimod	Boehringer Ingelheim	TNF-α production inhibitor/p38 MAP kinase inhibitor	Phase II (Crohn's disease)
Fontolizumab	Protein Design Labs	SMART anti-IFN-γ antibody	Phase II (Crohn's disease)
Onercept	Serono	Recombinant TNF binding protein-1	Phase II (Crohn's disease)
RDP-58	SangStat	Inhibitor of production of IL-2, IL-12 and TNF-α	Phase II (Crohn's disease, ulcerative colitis)
5D12	Tanox	Anti-CD40, chimeric MAb	Phase I/II (Crohn's disease)
CC-7085	Celgene	TNF-α production inhibitor	Phase I (IBD)
STA-5326	Synta Pharmaceuticals	IL-12 production inhibitor	Phase I (Crohn's disease)
T-487	Tularik	Chemokine CXCR3 antagonist	Phase I (IBD)
rhIL-18-bp	Serono	Recombinant human IL-18 binding protein	Phase I (Crohn's disease)

*Marketed for other indication(s).

Table VI: Drugs targeting adhesion molecules in development for IBD.

Drug Name	Source	Mechanism of Action	Status (indication)
Alicaforsen sodium	Isis Pharmaceuticals	Antisense oligonucleotide directed to ICAM-1	Phase III (Crohn's disease)
Natalizumab	Biogen/Elan	Humanized MAb directed against α_4 integrin	Phase III (Crohn's disease)
LDP-02	Genentech/Millennium	Humanized MAb targeting $\alpha_4\beta_7$ integrin	Phase II (Crohn's disease, ulcerative colitis)
683699	GlaxoSmithKline	Integrin $\alpha_4\beta_1$ (VLA-4) antagonist	Phase I (IBD)
TR-14035	Tanabe Seiyaku/ GlaxoSmithKline	Integrin $\alpha_4\beta_1$ (VLA-4) and $\alpha_4\beta_7$ (LPAM-1) antagonist	Phase I (IBD)
Vapaliximab	BioTie Therapies	Chimeric anti-VAP-1 MAb	Phase I (Crohn's disease, ulcerative colitis)

Table VII: Other antiinflammatory agents in development for IBD.

Drug Name	Source	Mechanism of Action	Status (indication)
OPC-6535	Otsuka	Antioxidant/PDE4 inhibitor	Phase III (ulcerative colitis)
BTX-51072	Oxis	Catalytic antioxidant	Phase II (IBD)
CP-461	Cell Pathways	PDE2A and PDE5 inhibitor	Phase II (Crohn's disease)
P-54	Phytopharm	Plant extract, COX-2 inhibitor	Phase II (Crohn's disease, ulcerative colitis)
S-3013	Shionogi	Phospholipase A_2 inhibitor	Phase II (IBD)
ONO-4817	Ono	Matrix metalloproteinase inhibitor	Phase I (IBD)
VX-702	Vertex	p38 protein kinase inhibitor	Phase I (Crohn's disease)

6-MP prodrug azathioprine and methotrexate. Steroid dosage can often be reduced by the addition of immunosuppressive therapy. These drugs are most frequently used to treat Crohn's disease, which has fewer treatment options than ulcerative colitis. Intravenous ciclosporin has been shown in clinical trials to relieve the symptoms of ulcerative colitis and Crohn's disease, but its potential side effects are so serious that use is recommended only in the most severely affected patients.

Fujisawa is evaluating its flagship immunosuppressant **tacrolimus** (marketed as Prograf®) in phase III trials for the new indication of ulcerative colitis. Tacrolimus has been marketed since 1993 for the treatment of transplant rejection, and since 1999 for the treatment of atopic dermatitis.

Table VIII: Miscellaneous drugs in development for the treatment of IBD.

Drug Name	Source	Mechanism of Action	Status (indication)
Body protection compound-15	Pliva	Cytoprotective pentadecapeptide	Phase II (ulcerative colitis)
Interferon β-1a*	Serono	Interferon	Phase II (Crohn's disease, ulcerative colitis)
Nolpitantium besilate	Sanofi-Synthélabo	Tachykinin NK_1 antagonist	Phase II (IBD)
Opebacan	Xoma	Recombinant bactericidal/permeability-increasing protein	Phase II (Crohn's disease)
Repifermin	GlaxoSmithKline	Keratocyte growth factor	Phase II (ulcerative colitis)
Dronabinol/cannabidiol	GW Pharmaceuticals	Cannabinoid agonist combination	Phase I (IBD)
LTβR-Ig	Biogen	Lymphotoxin-β receptor fusion protein	Phase I (IBD)

*Marketed for other indication(s).

Protein Design Labs is developing **visilizumab** (Nuvion®), a humanized IgG_2 antibody targeting the CD3 antigen on T-cells, as an immunosuppressive agent for the treatment of ulcerative colitis. The company has completed a phase I, dose-escalating pilot study in patients with severe, corticosteroid-refractory ulcerative colitis.

Nicotine and nicotine receptor agonists

Nicotine has come to the attention of investigators following the observation that individuals who quit smoking were at greater risk of developing ulcerative colitis. Nicotine may act by blocking the production of IL-2 and TNF as well as promoting the production of mucus. Targacept and development partner Dr. Falk Pharma have conducted preliminary phase I trials evaluating the neuronal nicotine receptor agonist **metanicotine** (TC-2403-12), designed as a potential new treatment for ulcerative colitis. These studies indicated that metanicotine, administered as an enema formulation to healthy volunteers, did not cause any significant safety or tolerability concerns. A delayed-release oral formulation of the drug is also in active development.

Miscellaneous drugs

In addition to the major drug classes presented above, several other products are known to be in active development at this time for the indication of IBD. In some cases the mechanism of action falls outside the scope of the classification scheme above, while in others the mechanism of action has not yet been revealed or remains unknown. See Table VIII for more information.

Irritable bowel syndrome

IBS is a common, chronic, relapsing gastrointestinal syndrome in which abnormal contractions of the lower bowel muscles produce characteristic symptoms of abdominal pain, alterations in gastrointestinal function and frequency (*e.g.*, diarrhea or constipation), gas and/or symptoms of bloatedness and distention. Abdominal pain/discomfort with a change in the consistency or frequency of stools, with relief of symptoms upon defecation, is the hallmark of disease. IBS may be diarrhea-predominant or constipation-predominant, or may vary between the two extremes. Abdominal pain may also be variable in both location and intensity.

IBS is one of the most frequently encountered conditions in gastroenterology clinics, affecting 10-25% of the population in Western countries at any one time. It has often been reported to affect 2-3 times as many women as men, although population studies suggest that both genders may be equally affected. Patients with IBS make 2.4-3.5 million physician visits each year and account for 2.2 million of the prescriptions written each year.

Data on the cost of IBS as reported from several sources are conflicting. However, one study has calculated that the median annual cost of health services for patients with IBS is USD 742, while that for asymptomatic persons is USD 429 (in 1992 U.S. dollars). If these figures are extrapolated to the entire U.S. population, the annual direct cost of IBS is in excess of USD 8 billion. Indirect costs, especially those incurred by work absenteeism, are believed to be much greater. In fact, IBS is second only to the common cold as a cause of worker absenteeism.

As the underlying pathology of IBS is unclear at this time, treatment must be directed to the relief of symptoms rather than resolution of the syndrome. Choice of treatment strategy is initially based on symptom severity. In patients with mild symptoms, who represent the vast majority of those presenting to primary care physicians, simple techniques like lifestyle modification, reassurance, education and elimination of offending dietary or medical substances is generally sufficient. In addition to the above, patients with moderate symptoms may also require pharmacotherapy, which can target specific symptoms of pain, constipation or diarrhea. Only a very small proportion of IBS patients experience severe symptoms. These patients may require antidepressants or anxiolytics in addition to drugs for pain and motility disturbances, and often require psychosocial support and/or psychotherapy.

Table IX: Serotonergic agents recently launched or in development for the treatment of IBS.

Drug Name	Source	Mechanism of Action	Status
Tegaserod maleate	Novartis/Bristol-Myers Squibb	5-HT_4 partial agonist	L-2001
Alosetron hydrochloride	GlaxoSmithKline	5-HT_3 antagonist	L-2002
Cilansetron	Solvay	5-HT_3 antagonist	Phase III
Prucalopride	Janssen	5-HT_4 agonist	Phase III
E-3620	Eisai	5-HT_3 antagonist/5-HT_4 agonist	Phase II
Ramosetron hydrochloride*	Yamanouchi	5-HT_3 antagonist	Phase II
Renzapride hydrochloride	Alizyme	5-HT_3 antagonist/5-HT_4 agonist	Phase II

*Marketed for other indication(s).

Serotonergic agents

Serotonin (5-HT) receptors are widely distributed throughout the body. At least 14 different 5-HT receptors and multiple receptor subtypes have been identified. 5-HT_3 in the central and peripheral nervous systems and 5-HT_4 receptors in the gut have been identified as targets for drugs to treat IBS. Through its interaction with both 5-HT_3 and 5-HT_4 receptors, serotonin enhances the sensitivity of visceral neurons projecting between the gut and the CNS. The sensitizing and physiological actions of 5-HT on gastrointestinal motor and sensory functions are mediated via 5-HT_4 and 5-HT_3 receptors, respectively. Furthermore, through its interactions with 5-HT_4 receptors, serotonin also increases the sensitivity of enteric neurons that react to luminal stimuli.

GlaxoSmithKline's Lotronex® (**alosetron hydrochloride**) was reintroduced in the U.S. in 2002 under restricted conditions of use. Alosetron is indicated for use in women with severe diarrhea-predominant IBS who have failed to respond to conventional therapy, whose IBS symptoms are chronic and who have had other gastrointestinal medical conditions ruled out. Severe diarrhea-predominant IBS is defined as frequent and serious abdominal pain, fecal incontinence or the uncontrolled urge to have a bowel movement, or restricted daily activities because of IBS. Alosetron was originally approved in the U.S. in February and launched in March 2000, but was voluntarily withdrawn by the manufacturer in November 2000 after serious gastrointestinal events, some fatal, were reported in association with the use of the product. These events included ischemic colitis and serious complications of constipation that resulted in hospitalization, blood transfusion and/or surgery. A risk management plan presented by GSK in conjunction with the product reintroduction includes enhanced warnings in product labeling, restricted eligibility for prescribers and patients, mandatory counseling of patients on benefits and risks, directions for active follow-up and management of patients, and appropriate measures to document and evaluate plan compliance as well as to educate those involved about the requirements of the plan.

Last summer the U.S. FDA approved Novartis's Zelnorm™ (**tegaserod maleate**) for the short-term treatment of women with IBS whose primary bowel symptom is constipation. Tegaserod is the first of the 5-HT_4 agonist class of drugs developed to target the gastrointestinal tract. It stimulates the peristaltic reflex and normalizes impaired motility in the gastrointestinal tract. Marketed internationally as Zelmac® by Bristol-Myers Squibb, tegaserod was first launched in Mexico in 2001 and has been approved in more than 30 countries. Novartis is also evaluating the drug in other gastrointestinal disorders such as chronic constipation, functional dyspepsia and GERD.

Table IX contains further information on the development of these and other serotonergic agents for the treatment of IBS.

Cholecystokinin CCK_A antagonists

Cholecystokinin (CCK) is a peptide hormone widely distributed in the small intestine (duodenal cells and enteric nerves). It is secreted in response to meals, especially fatty meals, and plays an important role in regulating gallbladder contraction and pancreatic enzyme secretion. The peptide delays gastric emptying rate in both humans and animals, decreases small bowel and increases colonic transit time and causes lower esophageal sphincter relaxation. The biological action of CCK on exocrine pancreas, gallbladder and gastrointestinal smooth muscle is mediated by CCK_A subtype receptors located on the target organs.

Rotta's **dexloxiglumide** (CR-2017) is a potent and specific CCK_A antagonist. The company is currently conducting large-scale phase III trials in both the U.S. and Europe, evaluating the efficacy of dexloxiglumide in the treatment of constipation-predominant IBS. U.S. development and marketing rights have been licensed to Forest.

Tachykinin antagonists

The tachykinins – substance P (SP), neurokinin A (NK_A) and neurokinin B (NK_B) – are a family of structurally related peptides that are synthesized and stored in neurons of the central and peripheral nervous systems. They produce their biological effects by binding to G-protein-coupled tachykinin receptors. SP is the preferred

Table X: Tachykinin receptor antagonists in development for the treatment of IBS.

Drug Name	Source	Mechanism of Action	Status
Nepadutant	Menarini	Tachykinin NK_2 antagonist	Phase II
Saredutant	Sanofi-Synthélabo	Tachykinin NK_2 antagonist	Phase II
Talnetant	GlaxoSmithKline	Tachykinin NK_3 antagonist	Phase II

ligand for the NK_1 receptor, while NK_A and NK_B are the preferred ligands for NK_2 and NK_3 receptors, respectively. Tachykinins are expressed abundantly throughout the gastrointestinal tract. They are found on intrinsic excitatory motor neurons, interneurons, sensory neurons and extrinsic sensory neurons, and their role in the regulation of enteric secretomotor functions – especially following pathophysiological stimuli – is well established. As NK receptors are expressed throughout the central nervous system as well as the gastrointestinal tract, they are considered an attractive target for the treatment of IBS, a functional gastrointestinal disorder involving both peripheral and central mechanisms. Preclinical data indicate the efficacy of NK antagonists in regulating motor disturbances (both diarrhea and constipation) as well as in reducing visceral pain associated with the disorder.

Several drugs targeting tachykinin receptors are known to be in development for the treatment of IBS at this time, as indicated in Table X.

Opioid receptor targets

The effects of the endogenous opioid peptides – enkephalins, beta-endorphin and dynorphins – at the gut level are the balanced net result of their binding to mu, delta and kappa opioid receptor subtypes located along the brain-gut axis. Kappa opioid receptors, in particular, appear to modify and counteract the adverse effects of stress on gastrointestinal function by blocking the hypothalamic release of corticotropin-releasing factor (CRF) as well as through direct effects on receptors located in the gastrointestinal tract.

Opioid agonists of the mu, delta and kappa receptors all have antinociceptive effects. Mu opioid receptor agonists like morphine have both peripherally and vagally mediated actions as well as central actions. At least two compounds in this class are known to be in development for the treatment of IBS at this time.

Positive results were obtained in a pilot clinical trial evaluating **PTI-901**, a low-dose version of naltrexone hydrochloride in development by Pain Therapeutics, in patients with IBS. In the open-label pilot study, 50 patients received daily treatment with PTI-901 for a 4-week period. The primary efficacy endpoint was the patients' observations of Global Assessment of Adequacy of Treatment. At the conclusion of the 4-week study, both male and female patients reported a response rate of 76.2%, a response far greater than the study was designed to demonstrate. The study also met the secondary endpoints of improving daily abdominal pain, bowel habits and stool consistency. The improvements were observed in patients whose baseline symptoms were either diarrhea or constipation, or both. The male and female response rates were 76.5% and 75.0%, respectively. Patients on PTI-901 reported a 193% increase in number of pain-free days at week 4 compared to baseline. Significant clinical improvements in bowel urgency, stool consistency and number of stools per day were also reported at week 4 in men and women. Pain Therapeutics plans to follow this pilot study with a 600-patient pivotal phase III trial in the U.S.

Merck KGaA's **asimadoline** (EMR-63320) is a peripherally acting kappa agonist in clinical development for functional gastrointestinal disorders and visceral pain. Asimadoline is being studied in phase II trials for the treatment of IBS. Additional investigational areas include irritable bladder, dyspepsia and dysmenorrhea.

CRF_1 antagonists

Numerous studies have shown a close relationship between stress resulting from life events or psychiatric disturbance and altered perception of colonic stimuli in IBS patients. Recent studies have suggested that corticotropin releasing factor (CRF), which is believed to be a primary mediator of stress, plays an important role in the control or modulation of the gastrointestinal system. These data suggest that CRF_1 receptor antagonism may represent a new therapeutic strategy for the treatment of IBS. **SB-723620**, a CRF_1 antagonist from GlaxoSmithKline, is being evaluated in phase I trials for this indication, as well as for the treatment of anxiety and depression.

Miscellaneous drugs

Various other mechanisms of action have been explored in preclinical and clinical testing in an effort to identify more effective drugs to treat IBS. As shown in Table XI, no clear consensus regarding the most effective approach has yet been reached.

Postoperative ileus

Postoperative ileus is a transient impairment of bowel motility that occurs following surgical procedures,

Table XI: Miscellaneous drugs in development for the treatment of IBS.

Drug Name	Source	Mechanism of Action	Status
IBStat	InKine	Antispasmodic, oral spray formulation of hysocyamine sulfate	L-2002
Artofisopam	Vela Pharmaceuticals	(*R*)-Enantiomer of a marketed anxiolytic	Phase II
Lubiprostone	Sucampo	Chloride channel activator	Phase II
AJM-300	Ajinomoto	Undisclosed	Phase I
SLV-317	Solvay	Undisclosed	Phase I

particularly those that involve the colon. The condition causes pain, abdominal distention or bloating, nausea, decreased motility, increased risk of complications, delayed enteral feeding, diminished healing and prolonged hospitalization. The ultimate consequence of the condition is an increased cost of surgical recovery, estimated at USD 1.1 billion annually in the U.S. There are currently no FDA-approved therapies for postoperative ileus.

Opioid antagonists

Alvimopan hydrate, a mu opioid antagonist from Adolor, is in phase III testing for the treatment of postoperative ileus and opioid-induced bowel dysfunction in collaboration with GlaxoSmithKline. The company announced in June 2003 that enrollment of 500 patients in a double-blind, placebo-controlled trial in postoperative ileus had been completed. Patients in the study, who are scheduled to undergo surgery for partial small/large bowel resection or radical hysterectomy, will be treated with alvimopan or placebo beginning 2 h prior to surgery and continuing until discharge or for a maximum of 7 days. Top-line results from the trial will be announced later in the year.

Progenics is evaluating another opioid antagonist, **methylnaltrexone bromide**, for the same indication. Phase II trials were initiated earlier this year.

Chloride channel activators

In May 2003, Sucampo announced that an IND had been filed in the U.S. to begin clinical testing of the novel chloride channel activator **lubiprostone** (SPI-0211) for the treatment of postoperative ileus. The protocol covers a placebo-controlled, double-blind, phase II efficacy trial which is now under way.

Hemorrhoids

Hemorrhoids are among the most common of health ailments, affecting approximately 8 out of 10 peopleat some time in their lives. Hemorrhoids are enlarged or varicosed veins of the anus and rectum. There are two types of hemorrhoids, internal and external, that can occur separately or in combination. Hemorrhoids may have a genetic component, but they are most likely caused, and remedied by, such things as diet and toilet habits.

Mild symptoms can be relieved frequently by increasing the amount of fiber and fluids in the diet. Eliminating excessive straining reduces the pressure on hemorrhoids and helps prevent them from protruding. A sitz bath can also provide some relief. With these measures, the pain and swelling of most symptomatic hemorrhoids will decrease in 2-7 days, and the firm lump should recede within 4-6 weeks. In cases of severe, persistent pain, a physician may elect to remove the hemorrhoid containing the clot with a small incision. Performed under local anesthesia as an outpatient, this procedure generally provides relief.

Miscellaneous therapies

Mitsubishi Pharma has filed in Japan for manufacturing approval of **OC-108** (Zione®), a novel treatment for internal hemorrhoids.

Under license from SamAmer, Tsumura is developing **TJN-219** (MPEC) as a salve for the treatment of internal hemorrhoids in phase II clinical trials. Based on a single active ingredient, TJN-219 shows potent affinity for inflamed veins in the hemorrhoidal tissue, and promises to be an effective alternative to surgery.

Cellegy is developing **Cellegesic™**, a topical formulation of nitroglycerin, as a treatment for hemorrhoids. Phase II studies have been reported for this indication. The product is also being developed for the treatment of pain associated with anal fissures, as discussed below.

Anal fissures

An anal fissure is a small tear or cut in the skin lining the anus which can cause pain and/or bleeding. The typical symptoms of an anal fissure are extreme pain during defecation and red blood streaking the stool. Fissures may be acute or chronic. An acute fissure is usually due to altered bowel habits, while a chronic fissure may be either due to poor bowel habits, overly tight or spastic anal sphincter muscles, scarring or an underlying medical problem.

An acute fissure is managed with nonsurgical treatments and over 90% will heal without surgery. Bowel habits are improved with a high fiber diet, bulking agents, stool softeners and plenty of fluids to avoid constipation and promote the passage of soft stools. Warm baths are soothing and promote relaxation of the anal muscles. Occasionally, special medicated creams may be recommended. In the severest of cases, surgery may be required.

Miscellaneous therapies

In August 2003, Cellegy reported good progress in an ongoing 150-patient phase III trial evaluating **Cellegesic™** (topical nitroglycerin) for the treatment of pain associated with chronic anal fissures. The study is designed to confirm the statistically significant pain reduction recorded in the previous two phase III studies. The FDA has agreed to a Special Protocol Assessment, allowing for NDA approval if prespecified trial results are achieved. The protocol includes agreement on the statistical methodology to be used for the analysis of results, a point of contention in the earlier trial. Since the pivotal study commenced in June 2003, 40 clinical sites have been recruited in the U.S. and Europe. To date, 25 of 150 patients have been enrolled at seven sites. The study will compare an active dose with placebo and will evaluate the reduction in pain over a 21-day period as the primary endpoint.

SLA-324 (**Anoheal®**) is a cream formulation of the calcium channel blocker diltiazem that is being codeveloped by SLA Pharma and Solvay for the treatment of anal fissures. SLA Pharma is conducting III trials of the product, while Solvay is conducting phase II studies.

Pancreatic insufficiency

The pancreas provides a variety of functions required for proper digestion and absorption of nutrients. Pancreatic enzymes regulate the digestion of fats, proteins and starches. When the pancreas is unable to produce sufficient quantities of active digestive enzymes, the result may be malabsorption of nutrients, abdominal pain and bloating, cramping, diarrhea and weight loss. This condition, known as exocrine pancreatic insufficiency, is often related to an underlying disease state. For example, as many as 90% of patients suffering from cystic fibrosis are also afflicted with pancreatic insufficiency. The condition is also frequent in patients with chronic pancreatitis or pancreatic cancer. These individuals often have poor growth and may be at increased risk for infections.

Current treatment consists of oral enzyme replacement therapy, which requires patients to take up to 50 pills per day. This therapy is associated with poor patient compliance as well as severe tolerability issues.

TheraCLEC, the lead product in development by Altus Biologics, is intended to treat malabsorption as a result of pancreatic insufficiency. The product is being developed as an orally delivered protein to replace missing digestive enzymes in people with malabsorption, namely, lipase to digest fats, protease to digest proteins and amylase to digest starches and carbohydrates. Positive results from phase I safety and efficacy studies were reported by the company in May 2003, and a clinical trial is under way at several cystic fibrosis centers in the U.S. TheraCLEC is being developed in collaboration with the Cystic Fibrosis Foundation and in Europe with Dr. Falk Pharma. Dr. Falk Pharma has licensed the commercial rights to TheraCLEC for Europe, and Altus retains exclusive commercial rights in all other territories.

PPL Therapeutics is developing **recombinant bile salt-stimulated lipase** (BSSL) in phase II studies for the same indication. The availability of a pure recombinant source of human BSSL should mean a much-reduced dose and fewer side effects, greatly increasing patient acceptability and compliance. The product is being developed under license from AstraZeneca; the latter retains an option, exercisable upon completion of phase II trials, to comarketing rights.

Hepatitis

Viral hepatitis (inflammation of the liver) is a serious liver disease caused by one of the hepatitis viruses (hepatitis A, B, C, D or E) or by chronic excessive use of alcohol. Hepatitis has been recognized as a serious viral illness since the 1880s, although the viral agents responsible for the disease were not identified until much later. The hepatitis B virus (HBV) was identified in the 1960s and the hepatitis A virus (HAV) was isolated in 1973. The hepatitis C virus (HCV) was cloned and sequenced in 1989.

The different viruses differ in their common methods of transmission, virulence and fatality, although even among patients infected by the same hepatitis virus strain, symptoms and severity may differ widely. The most common symptom of hepatitis is fatigue. Other symptoms typically encountered in hepatitis patients include flu-like symptoms (stomach pain, loss of appetite, tiredness, vomiting) and, in the later stages of disease, jaundice or darkening of the urine. Chronic hepatitis can lead to cirrhosis, liver cancer and even liver failure. In fact, hepatitis C is now the leading cause of liver transplants in the U.S.

Hepatitis is an extremely prevalent disease. Worldwide, approximately 350 million individuals are infected with hepatitis B. In addition, 3% of the world's population (approximately 170 million people) is infected with the hepatitis C virus. Hepatitis A infects approximately 180,000 people per year in the U.S. alone.

Prevention of hepatitis viral infection is considered an important goal, as the prevention of acute infection is highly preferable to treatment of chronic disease. At the present time no effective hepatitis C vaccine has yet reached the market, although several hepatitis B

Table XII: New hepatitis vaccines in development.

Product Name	Source	Description	Status (indication)
HBvaxPRO	Aventis Pasteur MSD	Recombinant hepatitis B vaccine	L-2002 (hepatitis B prophylaxis)
Ambirix	GlaxoSmithKline	Combined two-dose hepatitis A and B vaccine	R-2002 (prevention of hepatitis A and B in children aged 6-15 years)
Fendrix	GlaxoSmithKline	Hepatitis B vaccine (HBsAg) formulated with the adjuvant SBAS4	Prereg. (hepatitis B prophylaxis in high-risk patients)
Hepatitis B vaccine	GlaxoSmithKline	Recombinant extra-strength hepatitis B vaccine formulated with MPL adjuvant	Phase III (hepatitis B prophylaxis in poor/nonresponders)
Hepatitis B pharmaccine	Oxxon Pharmaccines	Hepatitis B vaccine that utilizes prime-boost technique (sequential immunization with two vectors carrying the gene for the same antigen)	Phase II (hepatitis B prophylaxis)
Hepatitis E vaccine	GlaxoSmithKline/ Walter Reed Army Institute	Recombinant baculovirus-expressed hepatitis E vaccine	Phase II (hepatitis E prophylaxis)
InnoVax C	Innogenetics/Rhein Biotech	Therapeutic hepatitis C vaccine based on the purified viral envelope E1 protein subtype 1b	Phase II (treatment of hepatitis C)
Therapeutic hepatitis C vaccine	Intercell	Synthetic vaccine based on five peptides and poly-L-arginine that specifically targets the T-cell immune system	Phase II (treatment of chronic hepatitis C infection)
PowderJect hepatitis B DNA vaccine	GlaxoSmithKline/ Chiron Vaccines (formerly PowderJect)	DNA vaccine for hepatitis B using PowderJect® delivery system	Phase I (hepatitis B prophylaxis)

vaccines are currently available. A variety of single and combination vaccines are progressing through the pipeline, as indicated in Table XII. At least two of these vaccines are indicated for treatment rather than prevention of hepatitis, as indicated in the table.

Acutely infected patients do not typically receive antiviral therapy. For example, virtually all hepatitis A and E infections and up to 90% of hepatitis B infections are acute and resolve without medical intervention. Antiviral therapy is initiated when infection becomes chronic (*i.e.*, lasting more than 6 months). Approximately 85% of hepatitis C infections become chronic, requiring drug therapy.

Vaccine adjuvants

Dynavax's immunostimulatory sequences (ISS) can be linked to antigens used in vaccines to increase the visibility of the antigen to the immune system. The result is a highly specific and enhanced Th1 immune response to the linked antigen. In cases in which complex antigens may not be directly linked to ISS, Dynavax is developing alternative ISS formulations that can be used in combination with antigens to produce similar results. In September 2002, Dynavax initiated a phase II study to compare the protective immune response of patients after immunization with either Engerix-B®, a commercially available hepatitis B vaccine, or recombinant hepatitis B surface antigen (rHBsAg) co-administered with Dynavax's proprietary immunostimulatory DNA sequences (**1018-ISS**).

Coley Pharmaceuticals' **CpG-7909** is a CpG oligonucleotide that improves the immune response to active immunization. The company is currently conducting a phase I/II trial evaluating the product as an adjuvant to Engerix-B® in the prevention of hepatitis B.

Immunoglobulins

Cangene is pursuing U.S. marketing approval for its **antihepatitis B hyperimmune**. Hyperimmunes are highly purified antibodies made from specialty human plasma used for therapeutic purposes and differ from vaccines in that they do not require the patient's own immune system to produce immunity, allowing them to act immediately.

Nabi is developing Civacir™ (**hepatitis C immune globulin [human]**), an investigational hyperimmune globulin containing a mixture of HCV-neutralizing antibodies, for the prevention of HCV reinfection in liver transplant recipients and individuals who are frequently exposed to the virus. The product, which has been granted Orphan Drug status, is currently being evaluated in a phase I/II trial sponsored by the National Institute of Allergy & Infectious Diseases.

Interferons

Interferons (IFNs) have antiviral, antiproliferative and immunomodulatory effects. IFN-α and IFN-β show predominantly antiviral effects that are nonspecific and are

Table XIII: New interferons in development for the treatment of chronic hepatitis infection.

Drug Name	Source	Status (indication)
Interferon β-1a*	Serono	Phase III (hepatitis C)
Peginterferon alfa-2a*	Roche	Phase III (hepatitis B)
Interferon alfa-n3*	HemispheRx Biopharma	Phase II/III (hepatitis C)
Omega interferon	BioMedicines (licensed from Boehringer Ingelheim)	Phase II (hepatitis C)
Albumin interferon alfa	Human Genome Sciences	Phase I (hepatitis C)
Interferon alfa* (intranasal formulation)	Nastech	Phase I (hepatitis B and C)
Pegylated interferon alfacon-1	InterMune	Phase I (hepatitis C)

*Marketed for other indication(s).

Table XIV: Immunomodulating agents in development for the treatment of hepatitis.

Drug Name	Source	Description	Status (indication)
Atvogen	HemispheRx	Nucleic acid compound	Phase II (hepatitis B)
EHT-899	Enzo Biochem	Proprietary formulation of an HBV viral protein designed to eliminate the undesirable immune response elicited by the HBV infection	Phase II (hepatitis B)
Histamine dihydrochloride	Maxim	Inhibitor of the production and release of oxygen free radicals	Phase II (hepatitis C)
XTL-001	XTL Biopharmaceuticals	Combination therapy consisting of two fully human MAbs targeting different sites on the HBV surface	Phase II (hepatitis B)
XTL-002	XTL Biopharmaceuticals	High-affinity full human MAb	Phase II (hepatitis C)
EHC-18	Enzo Biochem	Broad-spectrum immune regulation drug	Phase I/II (hepatitis C)
ANA-245	Anadys	Cytokine inducer	Phase I (hepatitis C)

held to be due to blockade of the viral life cycle at several stages. Several interferons are marketed for the treatment of chronic HBV or HCV infection. New interferons in development for hepatitis are presented in Table XIII.

Among the new treatment approaches being studied, perhaps the most anxiously awaited have been the long-acting, pegylated interferons. Pegylation consists in attaching one or more hair-like strands of polyethylene glycol (PEG), an inert, synthetic polymer, to a therapeutically active molecule so as to prolong the half-life of the same. Pegylation provides rapid and sustained delivery of interferon and other proteins, increasing their solubility and tolerability, prolonging their circulation lifetime and eliminating the large peak-to-trough fluctuations experienced with standard interferon. Roche's **peginterferon alfa-2a** (Pegasys®) has been marketed since 2001 for the treatment of chronic hepatitis C, and is in late-stage clinical testing for treatment of chronic hepatitis B.

Immunomodulators

Immunomodulating agents constitute another component of hepatitis therapy. Immunomodulators are administered in an attempt to boost the immune response. Several new immunomodulating agents are in development for the treatment of hepatitis B and C, as shown in Table XIV.

XTL Biopharmaceuticals is developing two novel products for the prevention of hepatitis reinfection in liver transplant recipients. HepeX-B (**XTL-001**) for hepatitis B and HepeX-C (**XTL-002**) for hepatitis C are both in phase II clinical trials. The company is seeking licensing partners for both products.

Anadys Pharmaceuticals announced earlier this year the initiation of phase Ib clinical testing of **ANA-245**. ANA-245 induces the innate immune response, including multiple cytokines. The ongoing phase Ib study will assess safety, tolerability, pharmacokinetics and pharmacodynamics of ANA-245 following multidose intravenous administration to patients chronically infected with hepatitis C virus. Administration of ANA-245 to mice showed dose-dependent induction of multiple immune response genes in the liver and circulating levels of interferon-alfa. ANA-245 demonstrated dose-related, immune-mediated protection against multiple lethal virus infections in mice, and also showed significant antimetastatic activity in tumor models. Studies in other species are consistent with the immune pharmacology of ANA-245. Anadys is developing the agent under license from ICN.

Antiviral agents

Antiviral agents such as ribavirin block viral replication within cells. Most investigational antiviral agents act as inhibitors of virus-specific enzymes such as protease,

Table XV: Antiviral agents recently marketed and in active development for the treatment of chronic viral hepatitis.

Drug Name	Source	Mechanism of Action	Status (indication)
Adefovir dipivoxil	Gilead	DNA polymerase inhibitor	L-2002 (hepatitis B)
Emtricitabine*	Gilead	Reverse transcriptase inhibitor	Phase III (hepatitis B)
Entecavir	Bristol-Myers Squibb	Nucleoside analogue	Phase III (hepatitis B)
Telbivudine	Idenix	Nucleoside analogue	Phase III (hepatitis B)
Elvucitabine	Achillion	DNA polymerase/reverse transcriptase inhibitor	Phase II (hepatitis B)
ISIS-14803	Isis Pharmaceuticals	Antisense compound directed to the IRES/ translation region of HCV, inhibitor of viral protein translation and inducer of viral RNA	Phase II (hepatitis C)
JTK-003	Japan Tobacco	RNA polymerase inhibitor	Phase II (hepatitis C)
Merimepodib	Vertex	Inosine monophosphate dehydrogenase (IMPDH) inhibitor	Phase II (hepatitis C)
Viramidine hydrochloride	Ribapharm	Nucleoside analogue	Phase II (hepatitis C)
MCC-478	Lilly (licensed from Mitsubishi Pharma)	DNA polymerase inhibitor	Phase I/II (hepatitis B)
NM-283	Idenix	Nucleoside analogue	Phase I/II (hepatitis C)
Valtorcitabine dihydrochloride	Idenix	Nucleoside analoguePhase I/II (hepatitis B, in combination with telbivudine)	Phase I (hepatitis B)
Hepavir B	Ribapharm	Liver-specific prodrug of adefovir	
LB-80380	LG Chem	Nucleoside analogue	Phase I (hepatitis B)
Levovirin	Ribapharm/Roche	Cytokine production promoter	Phase I (hepatitis C)
JTK-109	Japan Tobacco	RNA polymerase inhibitor	Phase I (hepatitis C)
MIV-210	Medivir/GlaxoSmithKline	Reverse transcriptase inhibitor	Phase I (hepatitis B)
R-1479	Roche	Polymerase inhibitor	Phase I (hepatitis C)
R-1518	Roche (licensed from ICN)	Levovirin prodrug	Phase I (hepatitis C)

reverse transcriptase, helicase and polymerase. Due to the essential role they play in the viral life cycle, these unique, virally encoded proteins constitute promising drug targets. Table XV summarizes the development of antiviral agents for the treatment of hepatitis.

In September 2002, **adefovir dipivoxil** (Gilead's Hepsera™) became the first nucleoside analogue to gain FDA approval and be launched for the treatment of chronic hepatitis B infection. The specific approved indication for the drug is the oral treatment of chronic HBV in adults with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease. In clinical studies the drug provided significant improvement in liver histology and fibrosis, reductions in serum HBV DNA levels, increased rates of seroconversion and normalization of ALT levels as compared to placebo in both treatment-naive patients and those previously treated with interferon. Adefovir is the first drug with demonstrated efficacy in hepatitis "e" antigen-negative, or precore mutant, patients and has also proved effective in patients resistant to the only other marketed viral enzyme inhibitor, lamivudine. Mutations associated with resistance to the new drug have not been detected following up to 48 weeks of therapy.

Hepatoprotectants

Iden Pharmaceuticals's **IDN-6556** is a broad-spectrum caspase inhibitor and apoptosis modulator with potential in the treatment of hepatitis, especially acute alcoholic hepatitis. This condition is largely mediated by apoptosis, which may be reversed by IDN-6556, preserving the structure and function of hepatic cells under stress. Phase I trials in healthy adults and in patients with mild liver failure have confirmed that IDN-6556 is safe and well tolerated. Patients with hepatitis C and hepatic impairment are currently being enrolled in an efficacy trial at Duke University.

Daewoo Pharmaceuticals is developing a novel hepatoprotective agent designated **DDB-S** (Lebecel®) for the treatment of hepatitis. This agent is being evaluated in phase II clinical trials.

Another hepatoprotective agent in phase II trials is Meiji Seika's **ME-3738**. This compound appears to work via an IL-6-dependent mechanism of action.

Mivotilate, a hepatoprotective (hepatotropic) agent from Yuhan, is in phase II clinical testing for the treatment of hepatitis B infection. This product is outlicensed to Grelan.

Picroliv, a standardized iridoid glycoside fraction prepared from the roots and rhizome of the plant *Picrorhiza kurrooa*, is in clinical development at India's Central Drug Research Institute. Picroliv demonstrates hepatoprotective and anticholestatic activities in animal studies and is being evaluated for the treatment of acute viral hepatitis. Four phase II trials have been completed, and the institute has requested permission to proceed to phase III.

Miscellaneous drugs

Ursodeoxycholic acid (UDCA) is a hydrophilic bile acid with cytoprotective effects, especially in patients with chronic cholestatic disorders. Mitsubishi Pharma, which has marketed the drug for many years as a treatment for gallstones and for primary biliary cirrhosis, is conducting phase III trials in Japan for the indication of hepatitis C.

Cathay Herbal is evaluating the Chinese herbal medicine preparation **CH-100** for the treatment of chronic hepatitis C. Clinical trials have been conducted in Australia at the University of Newcastle.

Liver fibrosis

Liver fibrosis is a life-threatening disease characterized by excessive scarring of the liver, typically caused by chronic hepatitis C infection or alcoholism. Excessive scarring of the liver results in compromised liver function and can lead to death.

Treatment of patients with hepatitis C, a common cause of liver fibrosis, is typically directed only to treatment of the viral infection and not to the fibrosis it causes. Several preclinical studies have demonstrated that **interferon gamma-1b** may prevent and even reverse the fibrosis that forms in the liver as a result of infections or liver toxins. On the basis of these findings, InterMune, which markets the interferon (as Actimmune®) for other indications, has initiated a phase II clinical trial of interferon gamma-1b for the treatment of liver fibrosis in patients with chronic hepatitis C infections who have failed prior antiviral treatment.

Cirrhosis

When excessive alcohol use, hepatitis or another chronic disease causes the liver to become permanently injured and scarred, the condition is called cirrhosis. The scar tissue that forms in cirrhosis harms the structure of the liver, blocking the flow of blood through the organ. The loss of normal liver tissue slows the processing of nutrients, hormones, drugs and toxins by the liver. This also slows the production of proteins and other substances made by the liver. Cirrhosis is the eleventh leading cause of death by disease in the U.S. Almost one-half of these are alcohol-related. About 25,000 people die from cirrhosis each year.

The primary objective of cirrhosis therapy is to stop the development of scar tissue in the liver and prevent complications. When cirrhosis is due to an identifiable cause, treatment programs may be specific, such as for management of hepatitis B and C, or steroids and immunosuppressive agents for autoimmune chronic active hepatitis. Another important component of cirrhosis therapy is the treatment of complications such as edema, ascites and bleeding esophageal varices.

Diuretics

Diuretics are often administered to treat edema, ascites (retention of fluid in the abdomen) and other vascular complications of advanced cirrhosis. Sanofi-Synthélabo is developing the diuretic compound and vasopressin V_2 receptor antagonist **SR-121463A** for several indications, including the treatment of cirrhotic ascites. SR-121463A is in phase IIa clinical trials.

Bradykinin antagonists

Many cirrhosis patients are at great risk of death not directly because of their liver problems, but because of resulting disturbances in their vasculature and kidneys. The activation of bradykinin is thought to be a key step along the way to both of these complications. A drug that inhibits excessive bradykinin in late-stage liver cirrhosis would prevent these life-threatening events in a targeted and specific way.

Icatibant (JE-049), a highly potent and selective peptidomimetic bradykinin B_2 receptor antagonist, is being developed by Jerini for the treatment of decompensated liver cirrhosis with resistant ascites, a complication affecting approximately 10% of all patients with cirrhosis. Phase I trials have provided excellent results, confirming the drug's safety and full antagonism of elevated bradykinin levels. A multicenter phase IIa efficacy trial was initiated in Europe in August 2002 and will continue through the fourth quarter of 2003. Jerini inlicensed icatibant from Aventis in 2001.

Interferons

Treatment of underlying hepatitis is a vital component of cirrhosis therapy. Interferons are used widely in the treatment of viral hepatitis. Sumitomi is conducting phase II trials to evaluate its marketed interferon product Sumiferon® (**interferon alfa-n1**) for the new indication of liver cirrhosis. Daiichi Pharmaceutical, in collaboration with Toray, is also investigating this potential new indication for its own marketed interferon, Feron® (**interferon β**). Phase II/III trials are under way in Japan.

Treatment of bleeding esophageal varices

Bleeding esophageal varices are a consequence of cirrhosis of the liver following alcohol abuse or viral hepatitis. **Vapreotide** (Sanvar™) is a synthetic analogue of somatostatin with much greater metabolic stability as compared to the parent hormone. It is being developed by Debiopharm for several indications including bleeding esophageal varices. Vapreotide is able to produce specific splanchnic vasoconstriction, which is useful in controlling acute hemorrhage of the upper gastrointestinal tract after the rupture of esophageal varices. Phase III studies

to date have confirmed the ability of vapreotide to control bleeding and improve survival in patients with bleeding esophageal varices. The drug was administered as a lyophilized formulation in early association with endoscopic therapy. This product was recently licensed to H3 Pharma for worldwide development and marketing.

Nonalcoholic steatohepatitis

Nonalcoholic steatohepatitis (also known as nonalcoholic fatty liver disease) is a chronic liver disease of unknown cause that involves the accumulation of fat and fibrous tissue in the liver, leading to liver cirrhosis in 10-15% of patients and significant liver scarring in another 30%. Although similar to a condition that affects people who drink excessive amounts of alcohol (alcoholic steatohepatitis), nonalcoholic steatohepatitis occurs in people who drink only minimal or no alcohol. It is most often seen in patients with insulin resistance, although fatty liver can also occur as a result of poor diet and certain illnesses, such as tuberculosis, intestinal bypass surgery for obesity and certain drugs such as corticosteroids.

Nonalcoholic steatohepatitis is a common problem worldwide, with an estimated prevalence of 14%-21% in Europe and Asia. The true prevalence of the condition in the U.S. is not known, but a recent study estimated that 23.5% of adults have some form of the disorder. It is more common in men than women, and is also more common in African Americans than Caucasians. As the prevalence of obesity increases in the U.S. and other populations, nonalcoholic steatohepatitis has the potential to become one of the most common types of liver disease.

Presently, there are no existing medications capable of reversing or reducing liver damage, and thus there is no specific treatment that is universally agreed upon. However, patients who are obese, diabetic and have high lipids in their blood are advised to lose weight and control their diabetes and elevated lipids. Usually, a low fat, low calorie diet is recommended along with insulin or medications to lower blood sugar for diabetes. For patients with the condition who are not overweight and not diabetic, a low fat diet is recommended.

Ursodeoxycholic acid (URSO 250) is a naturally occurring bile acid produced by the liver in very small amounts. A preliminary study showed that people with nonalcoholic steatohepatitis who were treated with URSO 250 for 1 year had improved liver function tests and decreased fat accumulation in the liver. Axcan has completed phase II testing of URSO 250 in patients with nonalcoholic steatohepatitis, but does not plan to pursue phase III studies for this indication using the current formulation.

In September 2002, Sucampo initiated the first U.S. phase II trials evaluating the functional fatty acid compound **RU-8811** in a small group of patients with nonalcoholic steatohepatitis. In preclinical models the compound was shown to protect against liver disease. Clinical studies had previously been conducted in Japan and Germany.

The National Institute of Diabetes and Digestive and Kidney Diseases is sponsoring a phase II trial to evaluate the effectiveness of the marketed antidiabetic agent **pioglitazone hydrochloride** in the treatment of nonalcoholic steatohepatitis. Pioglitazone, a PPARγ agonist discovered by Takeda and marketed since 1999 for the treatment of type 2 diabetes mellitus, decreases insulin resistance and improves blood lipid levels, effects that support its potential utility in this indication.

Primary sclerosing cholangitis

Primary sclerosing cholangitis is a biliary tract disorder in which the bile ducts inside and outside the liver become inflamed and scarred. As the scarring increases, the ducts become blocked. If the ducts are blocked, bile builds up in the liver and damages liver cells. Eventually, the condition can cause liver failure. The cause remains unknown, although the possible roles of bacteria, viruses and immune system disorders have been explored. There does appear to be a positive association between primary sclerosing cholangitis and ulcerative colitis.

Primary sclerosing cholangitis usually begins between the of ages 30 and 60 years, but can also arise during childhood. The disorder is more common in men than women. It progresses slowly, such that a person may be affected for years before symptoms develop. The main symptoms are itching, fatigue and jaundice. An infection in the bile ducts can cause chills and fever.

Ursodeoxycholic acid has cytoprotective effects, especially in patients with chronic cholestatic disorders. Axcan is conducting NIH-sponsored multicenter phase III trials in the U.S. for the indication of primary sclerosing cholangitis. Ursodeoxycholic acid has been marketed for many years as a treatment for gallstones and for primary biliary cirrhosis.

Hyperbilirubinemia

The body normally breaks down used red blood cells (heme) and replaces them with new cells. When hemoglobin and other hemoproteins are broken down, a substance called bilirubin is released. However, before the body can dispose of bilirubin, the liver must change it into a form than can be eliminated from the body in the feces. When babies are born prematurely, their liver isn't fully developed, so it may be difficult for them to break down the bilirubin into the correct form. When this occurs, bilirubin levels in the blood may rise (hyperbilirubinemia), causing jaundice. Hyperbilirubinemia in newborns with glucose-6-phosphate dehydrogenase (G6PD) deficiency is a serious clinical problem because of the severity and unpredictability of its course. Extreme hyperbilirubinemia can lead to kernicterus, a condition that can lead to devastating neurologic injury. Hyperbilirubinemia may also develop in otherwise healthy, full-term infants, or may be a complication of some other medical condition

(hemolysis, Gilbert syndrome, malaria and other parasitic diseases) or occur as a congenital disorder.

The heme oxygenase inhibitor **stannsoporfin** is a synthetic heme analogue that can inhibit the catabolism of heme and, therefore, bilirubin in a wide variety of naturally occurring forms of jaundice in humans. It is especially useful in reducing plasma bilirubin in newborns shortly after birth. A single, small dose of stannsoporfin administered shortly after birth has been shown to substantially decrease plasma bilirubin levels and thus the requirement for phototherapy in preterm infants. Also, when administered at a somewhat later time after birth, it can entirely eliminate the need for phototherapy in jaundiced infants. WellSpring is currently progressing to phase III trials to study stannsoporfin in this indication. The company hopes to file an NDA by first quarter of 2004.

Information sources on the internet

American Association for the Study of Liver Diseases
http://www.aasld.org

American College of Gastroenterology
http://www.acg.gi.org

American Gastroenterological Association
http://www.gastro.org

Centers for Disease Control and Prevention (CDC)
National Center for Infectious Diseases. Viral Hepatitis
http://www.cdc.gov/ncidod/diseases/hepatitis/index.htm

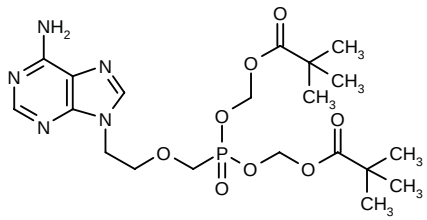
Crohn's and Colitis Foundation of America
http://www.ccfa.org

National Digestive Diseases Information Clearinghouse
http://digestive.niddk.nih.gov/index.htm

Monograph Updates of Gastrointestinal Drugs

N.E. Mealy, M. Bayés
Prous Science, P.O. Box 540, 08080 Barcelona, Spain

Adefovir Dipivoxil



Following European Commission approval to market adefovir dipivoxil (Hepsera®), Gilead's orally active antiviral agent for chronic hepatitis B virus (HBV) infection, in the 15 member states of the E.U., the product was introduced this spring in the U.K. for use in adults with compensated liver disease and evidence of active viral replication, persistently elevated serum alanine aminotransferase (ALT) levels and histological evidence of active liver inflammation and fibrosis, and for the treatment of decompensated liver disease. This follows its first approval and launch in the U.S. last year. It has also been submitted for approval in Australia, Switzerland, Turkey and Canada. Gilead has retained the rights to the product in the U.S., Canada, Europe, Australia and New Zealand and has granted GlaxoSmithKline a license to rights in Asia, Latin America and selected other territories (1-7).

Adefovir dipivoxil, which works by blocking HBV DNA polymerase, is the first nucleotide available for the treatment of chronic hepatitis B. In clinical studies, adefovir produced a sustained antiviral effect in treatment-experienced and treatment-naive patients, as well as in those with virus resistant to lamivudine or with a mutant strain of hepatitis B – hepatitis B "e" antigen (HbeAg)-negative, or precore mutant. To date, no adefovir dipivoxil-associated resistance mutations have been identified in patients treated for up to 136 weeks.

At the 11th International Symposium on Viral Hepatitis and Liver Diseases (ISVHLD) held earlier this year in Sydney, Gilead reported 96-week results from a study of adefovir dipivoxil in patients with HBeAg-negative, or precore mutant, chronic HBV infection. More than 70% of patients treated with the drug showed persistent suppression of HBV DNA viral replication, continued histological improvements and sustained improvements in liver function through 96 weeks of treatment. The randomized, double-blind, placebo-controlled trial in 184 patients with HBeAg-negative chronic hepatitis B and compensated liver function is designed to evaluate the long-term safety and efficacy of adefovir. It is being conducted in Australia, Canada, France, Greece, Israel, Italy and Southeast Asia. Patients in the study will continue to receive adefovir for an additional 3 years. At study entry, patients were randomized to receive once-daily adefovir or placebo for 48 weeks. The 48-week results demonstrated that therapy with adefovir was associated with significant histological, virological and biochemical improvements compared to placebo. Following the first 48 weeks of treatment, patients who had received adefovir for the first year of the study were rerandomized to receive either adefovir or placebo for a second year. Patients who received placebo for the initial 48 weeks of the study received adefovir for the second 48 weeks of the study. Among patients who received continuous adefovir treatment over 96 weeks, 71% achieved undetectable levels of serum HBV DNA. The median reduction in serum HBV DNA levels among adefovir-treated patients was 3.47 $\log_{10}$ copies/ml at week 96, representing a decrease of around 99.97% in viral load from a median baseline level of 7.07 $\log_{10}$ copies/ml. Adefovir also provided sustained improvement in liver function through 96 weeks, as measured by blood levels of ALT. Of patients with abnormal baseline ALT levels, 73% experienced a return to normal of ALT levels at 96 weeks. Among patients who had an

Table I: Clinical studies of adefovir dipivoxil (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Hepatitis B	Randomized, double-blind, multicenter	Adefovir, 10 mg po od x 48 wk (n=123) Placebo (n=61)	184	Adefovir 10 mg daily was safe and effective in the treatment of HBeAg-negative patients with chronic hepatitis B	9
Hepatitis B	Open	Adefovir x 96 wk	79	The emergence of resistance to adefovir after long-term treatment was infrequent in HBeAg-negative chronic hepatitis B patients	10
Hepatitis B	Randomized, double-blind	Adefovir, 10 mg Placebo		Long-term adefovir demonstrated sustained efficacy and safety in chronic hepatitis B patients	11
Hepatitis B	Randomized, double-blind, multicenter	Adefovir, 10 mg po od x 48 wk (n=171) Adefovir, 30 mg po od x 48 wk (n=173) Placebo (n=167)	515	A daily dose of adefovir dipivoxil 10 mg was effective in improving histology, necroinflammation and fibrosis and reducing the Knodell score and safer than a dose of 30 mg or placebo in the treatment of HBeAg-positive patients with chronic hepatitis B	12
Hepatitis B	Pooled/meta-analysis	Adefovir, 10 mg od x 48 wk (n=228) Placebo (n=294)	514	Adefovir was safe in patients with chronic hepatitis B	13
Hepatitis B	Pooled/meta-analysis	Adefovir, 10 mg od Placebo	492	Adefovir demonstrated long-term tolerability in patients with chronic hepatitis B	14
Hepatitis B	Open	Lamivudine + Adefovir, 10 mg od x 6 [median] mo	14	Adefovir was safe and effective as rescue therapy in patients with lamivudine-resistant hepatitis B infection	15
Hepatitis B	Pooled/meta-analysis	Adefovir, 10 mg od x 48 wk Adefovir, 30 mg od x 48 wk Placebo	700	Regardless of patient baseline characteristics, adefovir produced histological improvements in patients with chronic hepatitis B virus infection	16
Hepatitis B	Open	Adefovir, 10 mg/d x 48 wk	129	Viral kinetics were predictive of HBeAg loss in HBeAg-positive chronic hepatitis patients treated with adefovir	17
Hepatitis B	Open	Adefovir, 10 mg x 5.25 [median] mo	473	Adefovir was well tolerated and effective in lamivudine-resistant chronic hepatitis B patients	18
Hepatitis B	Open	Adefovir, 10 mg/d x 48 wk	269	Adefovir treatment in patients with diverse chronic hepatitis B did not result in the emergence of adefovir resistance mutations	19
Hepatitis B	Pooled/meta-analysis	Adefovir, 10 mg od x 48 wk	692	Adefovir was effective in diverse populations of chronic hepatitis B patients	20
Hepatitis B	Randomized	Lamivudine, 100 mg od + Adefovir, 10 mg od x 1 y (n=46) Lamivudine, 100 mg od + Placebo x 1 y (n=49)	95	The addition of adefovir to lamivudine treatment in chronic hepatitis B patients was well tolerated and increased the efficacy of therapy	21

optional liver biopsy after 96 weeks of continuous adefovir treatment, 79% showed improvement in liver histology. In previous clinical studies, including pivotal studies of the drug, no adefovir-related resistance mutations were identified through 48 weeks of treatment. To evaluate the incidence of resistance with extended treatment, viral resistance was monitored in 124 patients who completed 96 weeks of treatment in various studies. At 96 weeks, a novel resistance mutation (rtN236T) in the HBV polymerase was detected in 2 of the 124 patients. The mutation reduced susceptibility to adefovir by 5- to 23-fold *in vitro*, but did not confer cross-resistance to lamivudine. A total of 9 (5%) patients discontinued the treatment. The safety profile of the drug showed no significant differences after the two treatment periods, and the most frequent adverse events were headache, pharyngitis, abdominal pain, asthenia and flu. Evaluation continues for up to 5 years in long-term clinical efficacy and safety studies (8-11). The results from these studies and those that follow are summarized in Table I.

A double-blind clinical trial randomized 515 patients with chronic HBeAg-positive hepatitis B to receive placebo or adefovir dipivoxil (10 or 30 mg once daily). Greater improvements in the necroinflammatory scores, fibrosis scores, serum HBV DNA levels and median reductions in serum ALT levels were reported with the 30-mg dose of the drug than with the 10-mg dose or placebo after 48 weeks of treatment. Neither dose induced the appearance of resistance mutations in the sequence of the HBV polymerase gene. Patients treated with placebo or the 10-mg dose showed similar safety profiles, whereas those treated with the 30-mg dose reported a slightly higher incidence of adverse events and an increase in the serum creatinine levels that disappeared with dose reduction or interruption of treatment. These results favored the use of a daily dose of 10 mg in the long-term treatment of HBeAg-positive hepatitis B (12).

In 2 randomized, double-blind, placebo-controlled phase III trials, adefovir 10 mg/day was investigated in patients with chronic hepatitis B. Safety analyses revealed that, through 48 weeks of treatment, the adverse event profile of adefovir was similar to that of placebo and it was well tolerated for up to 109 weeks. Elevations in ALT were observed in 25% of patients switching from adefovir to placebo after 48 weeks (13, 14).

Patients with lamivudine-resistant hepatitis B infection (n=14), both before and after liver transplantation, were treated with adefovir 10 mg once daily for a median of 6 months. Significant reductions in HBV DNA were seen by month 3 in most patients, although viremia was detectable in 2 patients who received over 1 year of continuous adefovir treatment (15).

In 2 clinical trials, 700 chronic hepatitis B patients were treated with adefovir 10 or 30 mg/day or placebo for 48 weeks. Significant histological improvement was seen with adefovir 10 mg compared to placebo, and improvements were seen in HBeAg-positive and HBeAg-negative patients and in patients with other differences in baseline characteristics and disease parameters (16).

In order to determine the relationship between viral kinetics and the loss of HBeAg, the levels of HBV DNA were monitored every 4 weeks in 129 patients with HBeAg-positive chronic hepatitis B who received adefovir 10 mg/day for 48 weeks. All but 1 patient had a steep viral decline in the first week, after which they entered either a flat second phase (< 0.05 log/week; 35%) or a slow second-phase decline (0.15 log/week; 65%). The latter was followed by one of three possible third-phase patterns: undetectable HBV DNA levels (28%), a flat third phase (35%) or a staircase pattern (28%). Loss of HBeAg was found in 77%, 28% and 43% of the patients, respectively, whereas no patient entering a flat second phase lost HBeAg (17).

The efficacy of adefovir (10 mg) was evaluated in 473 lamivudine-resistant chronic hepatitis B patients in an open study. The drug significantly reduced serum HBV DNA levels and normalized ALT levels in 46% and 61% of patients after 3 and 6 months of treatment, respectively. In patients over 65 years of age, these percentages increased to 57% and 80%, respectively. The effects of adefovir were considered to be independent of age or baseline fibrosis scores. The treatment was well tolerated, with 3.6% of patients experiencing adverse events, mostly gastrointestinal (18).

A surveillance study showed that the emergence of resistance to adefovir after long-term treatment is uncommon. No resistance mutations were found in genotypic analyses of the HBV reverse transcriptase domain in isolates from 269 chronic hepatitis B patients treated with adefovir 10 mg/day for 48 weeks. This result was not affected by the HBeAg status of the patients, resistance to lamivudine, HIV coinfection or having received a liver transplant (19).

The effects of a daily dose of adefovir administered for 48 weeks to 692 patients with chronic hepatitis B, including HBeAg-positive and HBeAg-negative patients, lamivudine-resistant subjects, HIV-infected patients, liver transplant recipients and patients with compensated and decompensated liver function, have been reported. The overall results revealed that adefovir was effective regardless of the characteristics of the patients (20).

The addition of adefovir 10 mg/day to lamivudine 100 mg/day therapy was assessed in 95 patients with compensated chronic hepatitis B with YMDD variant HBV. In patients receiving lamivudine and adefovir, serum HBV DNA and ALT were significantly lower after 1 year compared to levels measured in patients administered lamivudine and placebo. HBeAg seroconversion occurred in 8% and 2% of patients in these groups, respectively (21).

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4. *Gilead's Hepsera approved for marketing in E.U. countries*. DailyDrugNews.com (Daily Essentials) March 12, 2003.

5. *First nucleotide analogue for HBV approved by FDA*. DailyDrugNews.com (Daily Essentials) Sept 25, 2002.

6. *Positive opinion issued in E.U. for Hepsera*. DailyDrugNews.com (Daily Essentials) Nov 26, 2002.

7. *Gilead to acquire Triangle Pharmaceuticals*. DailyDrugNews.com (Daily Essentials) Dec 9, 2002.

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Original monograph - Drugs Fut 1997, 22(8): 825.

Alicaforsen Sodium

Isis Pharmaceuticals has initiated a phase II trial of alicaforsen sodium (ISIS-2302), an antisense inhibitor of intercellular adhesion molecule-1 (ICAM-1), in patients with active ulcerative colitis.

The randomized, double-masked, placebo-controlled study will compare the safety and efficacy of different dosing regimens of the enema formulation of alicaforsen to placebo. The trial will enroll 100 patients in the U.S. and Europe. The primary endpoint is improvement in the Disease Activity Index (DAI) upon completion of the 6-week dosing period. Patients with an improvement in DAI will be followed for up to a year. This phase II study is being conducted in parallel with a 170-patient phase II study comparing alicaforsen enema to mesalamine enema. In an earlier phase II study of alicaforsen enema in ulcerative colitis, patients demonstrated improvement in DAI and Clinical Activity Index (CAI) scores (73% and 58%, respectively) after 1 month of nightly alicaforsen enemas (240 mg). The improvements in DAI and CAI were maintained at 3 and 6 months. An i.v. formulation of alicaforsen is also being evaluated in a phase III program in Crohn's disease (1, 2).

The efficacy, safety and pharmacokinetics of high doses (250-350 mg i.v. over 2 h, 3 times weekly for 4 weeks) of alicaforsen were determined in an open-label, randomized, uncontrolled phase II clinical trial conducted in 22 patients with a Crohn's Disease Activity Index (CDAI) score of at least 220. These doses were about 2.5 times greater than those previously studied. Patients were allowed background aminosalicylates, antibiotics, immunosuppressants and corticosteroids, but not TNF-α inhibitors. The primary endpoint was clinical remission (CDAI = 150 or less). The results of the study revealed that alicaforsen administered for 12 weeks induced clinical remission in 41% of the total (9 of 22) and 53% of evaluable (9 of 17) patients, and a clinical response was seen in 59% of the total (13 of 22) and 76% of the evaluable (13 of 17) patients. A clinical response was defined as a 70-point reduction in the CDAI score and a clinical remission as a CDAI score of 150 or less, with no increase in the use of corticosteroids or immunosuppressants, or need for surgery. Infusion-related symptoms (*e.g.*, fever, chills, nausea, arthralgia, headache and diarrhea) responded well to treatment with acetaminophen or hydrocortisone, and 5 patients discontinued due to these adverse events. Although phosphorothioate oligonucleotides are associated with prolongation of the partial thromboplastin time (aPTT), the prolongation observed with alicaforsen (18, 21 and 23 s for 250, 300 and 350 mg, respectively) was transient and resolved within 4 h postinfusion. There was overlap in the C_{max} and AUC values for all dose groups and the $t_{1/2}$ was approximately 1 h regardless of dose (3, 4).

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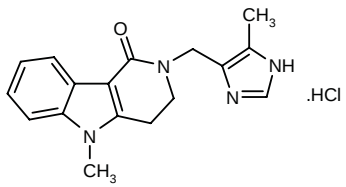
Alosetron Hydrochloride



GlaxoSmithKline's selective 5-HT_3 antagonist, alosetron hydrochloride (Lotronex®), is now available under restricted conditions of use, including a narrower indication for specific use in female patients with severe diarrhea-predominant irritable bowel syndrome (IBS), an extensive risk management program involving physicians, patients and pharmacists, and additional safety and efficacy studies.

Alosetron is for use in women with severe diarrhea-predominant IBS who have failed to respond to conventional therapy, whose IBS symptoms are chronic and who have had other gastrointestinal medical conditions ruled out. Severe diarrhea-predominant IBS is defined as frequent and serious abdominal pain, fecal incontinence or the uncontrolled urge to have a bowel movement, or restricted daily activities because of IBS. Serious gastrointestinal events such as ischemic colitis and complications of constipation have been associated with alosetron, resulting in hospitalization, blood transfusion and/or surgery, and some fatalities. Three women in 1,000 developed ischemic colitis over 6 months in clinical trials. Alosetron was voluntarily withdrawn by GlaxoSmithKline in November 2000 when the company and the FDA could not agree on a suitable risk management plan for the drug. Discussions were resumed in January 2001, eventually leading to the submission of a supplemental NDA which was approved in June 2002 (1).

The long homozygous polymorphism for the L/S (long/short, 5-HTTLPR) polymorphism in the promoter of the 5-HT transporter was found to be associated with a slower transit colonic and greater response to alosetron treatment in patients with diarrhea-predominant IBS (2).

Alosetron was compared with placebo in the treatment of IBS and severe bowel urgency symptoms in a 12-week, multicenter, randomized, double-blind trial. Among the 492 patients enrolled, significantly more of those given alosetron had global improvement at weeks 4, 8 and 12 than those given placebo. Alosetron increased days with control of urgency significantly over placebo. Adverse events were largely similar in both treatment groups, although a greater incidence of constipation was recorded in alosetron-treated patients (3).

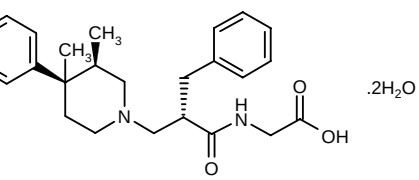
1. *Lotronex available under restricted use for women with diarrhea-predominant IBS*. DailyDrugNews.com (Daily Essentials) Nov 25, 2002.

2. Camilleri, M., Atanasova, E., Carlson, P.J., Ahmad, U., Kim, H.J., Viramontes, B.E., McKinzie, S., Urrutia, R. *Serotonin-transporter polymorphism pharmacogenetics in diarrhea-predominant irritable bowel syndrome*. Gastroenterology 2002, 123(2): 425.

3. Ameen, V., Gordon, S., Carter, E. *Global improvement and satisfactory control of bowel urgency in irritable bowel syndrome (IBS) patients treated with alosetron hydrochloride (Lotronex(R))*. Dig Dis Week (May 17-22, Orlando) 2003, Abst M1680.

Original monograph - Drugs Fut 1992, 17(8): 660.

Alvimopan Hydrate



Alvimopan hydrate (ADL-8-2698) is a peripherally selective mu opioid receptor antagonist currently being developed by Adolor in collaboration with GlaxoSmithKline for the management of opioid-induced bowel dysfunction and postoperative ileus. It is presently in phase III trials. Adolor originally acquired rights to the compound under Lilly patent applications through an agreement with Roberts, which had acquired the rights from Lilly in 1996 (1).

Adolor has completed enrollment in its phase III trial (14CL313) of alvimopan in the management of postoperative ileus. The double-blind, placebo-controlled study enrolled 500 patients who were scheduled to undergo surgery for partial small/large bowel resection or radical hysterectomy. Patients were randomized to receive either 6 or 12 mg of alvimopan or placebo 2 h prior to surgery, then twice daily until hospital discharge or for a maximum of 7 days. Topline results are expected in the third quarter of 2003. The phase III program for alvimopan in postoperative ileus comprises 3 additional studies: 14CL302, from which topline results were previously reported; 14CL308, which is enrolling patients; and the fully enrolled 14CL306 (2).

The multicenter, double-blind, placebo-controlled 14CL302 study enrolled 450 patients who were scheduled to undergo partial colectomies, simple or radial hysterectomies and to receive opioid analgesics. Patients

were randomized to receive 6 or 12 mg alvimopan or placebo at least 2 h prior to surgery and then twice daily beginning on the first postoperative day until hospital discharge, or for a maximum of 7 days. A statistically significant difference was achieved in the primary endpoint of the study, defined as the time to first flatus or first bowel movement and the time to tolerability of solid foods, whichever occurred last, in patients receiving 6 mg alvimopan as compared with placebo. There was a positive trend in the primary endpoint for the alvimopan 12 mg cohort, although the difference was not significant compared to the placebo group. A difference in favor of all secondary endpoints, including time to hospital discharge, was observed in the 6 mg cohort as compared with the placebo group. Alvimopan was generally well tolerated, the most common adverse events occurring in both the placebo and treatment groups being nausea, vomiting and hypotension (3, 4).

In an open-label study, 6 patients with opioid-induced bowel dysfunction received alvimopan in ascending doses of 0.125, 0.25, 1 and 3 mg. While it did not inhibit opioid-induced analgesia, alvimopan dose-proportionately improved constipation in these patients. Gastrointestinal side effects were seen in 1 patient after taking the highest dose (5).

Adolor has announced the results of a phase III study with alvimopan in 168 outpatients with opioid-induced bowel dysfunction. Patients received alvimopan (0.5 or 1 mg) every day for 21 days or placebo, with the primary endpoint being the proportion of patients with at least 1 bowel movement within 8 h of dosing. The agent was well tolerated, the most frequent adverse events observed being diarrhea, abdominal cramps, nausea and vomiting. The proportion of patients achieving the primary endpoint following administration of 0.5 or 1 mg alvimopan or placebo was 43%, 55% and 29%, respectively (6, 7).

1. *Adolor enters opioid antagonist license agreement with Lilly*. DailyDrugNews.com (Daily Essentials) Aug 20, 2002.

2. *Enrollment completed in phase III alvimopan study in postoperative ileus*. DailyDrugNews.com (Daily Essentials) June 10, 2003.

3. *Topline results for alvimopan phase III study*. DailyDrugNews.com (Daily Essentials) April 4, 2003.

4. *First phase III alvimopan trial in postoperative ileus completes enrollment*. DailyDrugNews.com (Daily Essentials) Dec 10, 2002.

5. Rauck, R.E., Southern, J.P., Carpenter, R.L. *Use of alvimopan, a peripheral selective mu-opioid antagonist, to speed gastrointestinal transit in patients with opioid-induced bowel dysfunction*. 10th World Congr Pain (Aug 17-22, San Diego) 2002, Abst 1669-P217.

6. *Top-line results of phase III study of alvimopan in opioid bowel dysfunction*. DailyDrugNews.com (Daily Essentials) Nov 12, 2002.

7. *Phase III alvimopan trial in opioid-induced bowel dysfunction completes enrollment*. DailyDrugNews.com (Daily Essentials) Sept 12, 2002.

Original monograph - Drugs Fut 1994, 19(12): 1078.

Atlizumab

Atlizumab (MRA, R-1569) is a humanized anti-human IL-6 receptor monoclonal antibody which was developed by Chugai, now a member of the Roche group, in collaboration with Osaka University.

Under a codevelopment and copromotion agreement between Chugai and Roche covering all countries except Japan, South Korea and Taiwan, the parties will copromote atlizumab in the U.K., France and Germany and Chugai reserves the option to copromote it in the U.S., Italy and Spain. It has completed phase II evaluation and is being prepared for phase III trials for the treatment of rheumatoid arthritis. Its use in other indications, including Castleman's disease, juvenile idiopathic arthritis, Crohn's disease and multiple myeloma, is also being investigated clinically (1).

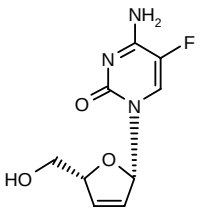
A multicenter, double-blind clinical trial randomized 36 patients with active Crohn's disease refractory to conventional therapies to supplement their baseline treatments with placebo or atlizumab (8 mg/kg once every 2 or 4 weeks) for 12 weeks. Clinical response, which was defined as a reduction of at least 70 points in the baseline CDAI of the patients, was achieved in 80% of patients who received atlizumab every 2 weeks, in 42% of those treated with atlizumab every 4 weeks, and in 31% of placebo-treated patients. The administration of atlizumab every 2 weeks was also associated with clinical remission in 20% of the patients, an increase in the mean Inflammatory Bowel Disease Questionnaire score from 129 to 161, and normalization of erythrocyte sedimentation rates and serum levels of C-reactive protein, amyloid A protein and fibrinogen. The drug was well tolerated, and no significant differences were found among the safety profiles of the study groups (2).

1. *First Chugai product licensed by Roche for codevelopment/copromotion*. DailyDrugNews.com (Daily Essentials) Feb 25, 2003.

2. Ito, H., Takazoe, M., Fukuda, Y. et al. *Effective treatment of active Crohn's disease with humanized monoclonal antibody MRA to interleukin-6 receptor: A randomized placebo-controlled trial*. Dig Dis Week (May 17-22, Orlando) 2003, Abst 176.

Original monograph - Drugs Fut 2003, 28(4): 315.

Elvucitabine



The L-nucleoside cytosine analog elvucitabine (β-L-Fd4C, L-D4FC, ACH-126443) is Achillion's lead product candidate for hepatitis B virus (HBV) infection. Achillion is currently evaluating elvucitabine in phase II trials including lamivudine-resistant HBV and HIV patients.

A placebo-controlled phase I/II trial evaluated treatment with elvucitabine in 40 patients with chronic HBV infection. The patients were randomized to receive placebo or oral doses of elvucitabine of 1-100 mg/day for 14 days. Whereas mean plasma HBV DNA levels showed no change from baseline in the placebo group, a reduction of 0.5 $\log_{10}$ was obtained on the lowest dose of the active drug and reductions of 1.5-2.5 $\log_{10}$ on higher doses. These levels returned to baseline during the 2 weeks following treatment, but no disease flares were observed. The treatment was well tolerated, with no drug-related adverse events reported (1). The results of this study and those that follow are summarized in Table II.

A phase I/II trial in 36 treatment-naive chronic HBV-infected patients evaluated elvucitabine as single daily doses of 1-100 mg. Mean declines of up to 3.0 $\log_{10}$ in plasma HBV DNA levels were achieved after only 14 days of dosing, indicating potent suppression of viral replication at doses of 5-100 mg/day. In this dose range, peak plasma levels exceeded the concentration required to inhibit *in vitro* the replication of both wild-type and lamivudine-resistant HBV (2).

A multicenter, double-blind, randomized clinical trial assessed the efficacy and safety of elvucitabine in 87 previously untreated patients with chronic HBV infection. The patients received oral doses of placebo, lamivudine (100 mg) or elvucitabine (5, 20 or 50 mg) once daily for 12 weeks. At the end of the treatment period, blinded pooled data for all patients showed a mean reduction of 3.15 $\log_{10}$ in plasma HBV DNA levels compared to baseline. All elvucitabine doses were well tolerated, and no grade 3-4 drug-related adverse events or laboratory abnormalities were reported (3).

1. Afdhal, N., O'Brien, C., Oshana, S., Dunkle, L. *Rapid, potent anti-HBV activity of ACH-126,443 in a phase 1/2 trial in chronic hepatitis B infection*. 42nd Intersci Conf Antimicrob Agents Chemother (Sept 27-30, San Diego) 2002, Abst V-690.

2. Afdhal, N.H., O'Brien, C.B., Oshana, S.C., Dunkle, L.M. *Potent anti-HBV activity of ACH-126,443 correlated with 14-day pharmacokinetics and safety: Predictions for activity against YMDD mutant strains*. 53rd Annu Meet Am Assoc Study Liver Dis (Nov 1-5, Boston) 2002, Abst 837.

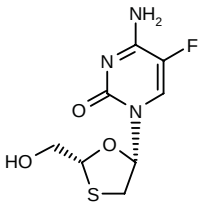
3. Pottage, J.C. Jr., Oshana, S.C., Yen, P.T. et al. *Antiviral activity and safety of 12 weeks of oral treatment with ACH-126,443 (beta-L-Fd4C) in treatment-naive patients with chronic HBV infection*. J Hepatol 2003, 38(Suppl. 2): Abst 468.

Original monograph - Drugs Fut 2002, 27(12): 1131.

Table II: Clinical studies of elvucitabine (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Hepatitis B	Randomized, double-blind, multicenter	Elvucitabine, 1 mg po od x 14 d Elvucitabine, 5 mg po od x 14 d Elvucitabine, 10 mg po od x 14 d Elvucitabine, 20 mg po od x 14 d Elvucitabine, 50 mg po od x 14 d Elvucitabine, 100 mg po od x 14 d Placebo	40	Elvucitabine was well-tolerated, without clear dose- or drug-related adverse events, and exhibited rapid and potent anti-hepatitis B virus activity comparable or superior to that seen with other agents	1, 2
Hepatitis B	Randomized, double-blind, multicenter	Elvucitabine, 5 mg po od x 12 wk Elvucitabine, 20 mg po od x 12 wk Elvucitabine, 50 mg po od x 12 wk Lamivudine, 100 mg po od x 12 wk Placebo	87	Elvucitabine administered at doses of 5, 20 or 50 mg once daily for 12 weeks was well tolerated and reduced HBV DNA levels in patients with chronic hepatitis B	3

Emtricitabine



Gilead's emtricitabine (Emtriva™), a new, once-daily nucleoside reverse transcriptase inhibitor (NRTI), was approved by the FDA and launched this summer for the treatment of HIV infection in adults in combination with other antiretroviral medications (1, 2).

The European Union's Committee for Proprietary Medicinal Products (CPMP) subsequently recommended granting marketing approval for this indication of the drug, with a final decision expected later this year. The company recently entered into a licensing agreement with Japan Tobacco under which the latter will commercialize Gilead's HIV portfolio, including emtricitabine, tenofovir disoproxil fumarate (Viread®) and a future coformulation of the two products, in Japan. Emtricitabine, licensed by the former Triangle Pharmaceuticals from Emory University in 1996, is also in phase III evaluation for hepatitis B virus (HBV) infection, and Gilead is developing a fixed-dose coformulation of emtricitabine and tenofovir disoproxil fumarate for the treatment of HIV, which could be available by early 2005 (3-6).

Patients (n=98) with chronic HBV infection enrolled in a randomized, double-blind trial received emtricitabine 25, 100 or 200 mg/day for 1 year and 200 mg/day during the following year. After 2 years, 42% of patients had undetectable viremia, 51% lost hepatitis B e antigen (HbeAg) and 29% seroconverted to HBeAb. In patients receiving emtricitabine for 2 years, the rate of resistance-associated mutations was 19% (7). The results of this study and the one that follows are summarized in Table III.

A meta-analysis of 3 multicenter clinical trials assessed the antiviral efficacy of emtricitabine against HBV in patients coinfected with both HIV and HBV. A total sample of 1,603 HIV-infected patients was included in these trials and randomized to receive different triple-drug regimens (most of which contained emtricitabine) for up to 48 weeks. Fifty-two patients treated with emtricitabine were positive for HBV antigen at baseline, and the analysis of the variation in their median HBV DNA levels revealed that emtricitabine administered in the context of a HAART regimen strongly suppressed HBV replication (8).

1. *Emtriva approved by FDA for treatment of HIV*. DailyDrugNews.com (Daily Essentials) July 7, 2003.

2. *Coviracil NDA accepted for filing by FDA*. DailyDrugNews.com (Daily Essentials) Nov 6, 2002.

3. *European approval recommended for Emtriva*. DailyDrugNews.com (Daily Essentials) July 29, 2003.

4. *Japan Tobacco to commercialize Gilead HIV products in Japan*. DailyDrugNews.com (Daily Essentials) Aug 5, 2003.

5. *Gilead to acquire Triangle Pharmaceuticals*. DailyDrugNews.com (Daily Essentials) Dec 9, 2002.

6. *Triangle files MAA for emtricitabine*. DailyDrugNews.com (Daily Essentials) Jan 13, 2003.

7. Marin, H.M., Leung, N., Gish, R., Corey, L., Sacks, S., Fried, M., Wright, T., Mondou, E., Snow, A., Wakeford, C., Fousseau, F. *Antiviral activity and incidence of resistance after treatment for two years with emtricitabine in patients with chronic hepatitis B*. 42nd Intersci Conf Antimicrob Agents Chemother (Sept 27-30, San Diego) 2002, Abst V-239.

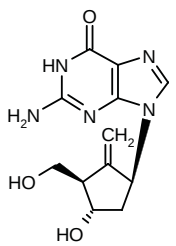
8. Raffi, F., Snow, A., Borroto-Esoda, K. et al. *Anti-HBV activity of emtricitabine (FTC) in patients co-infected with HIV and hepatitis B virus*. Antivir Ther 2003, 8(Suppl. 1): Abst 215.

Original monograph - Drugs Fut 1995, 20(8): 761.

Table III: Clinical studies of emtricitabine (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Hepatitis B	Randomized, double-blind	Emtricitabine, 25 mg od x 1 y → 200 mg qd x 1 y Emtricitabine, 100 mg od x 1 y → 200 mg qd x 1 y Emtricitabine, 200 mg od x 2 y	98	Emtricitabine produced sustained hepatitis B virus suppression with a low rate of mutations	7
Hepatitis B	Randomized, pooled/meta-analysis	Emtricitabine + Didanosine + Efavirenz x 48 wk Emtricitabine + Stavudine + Efavirenz x 48 wk Emtricitabine + Stavudine + Nevirapine x 48 wk Emtricitabine + Stavudine + Emivirine x 48 wk Emtricitabine + Stavudine + Abacavir x 48 wk	52	Emtricitabine administered in the context of a highly active antiretroviral therapy regimen was well tolerated and effectively suppressed hepatitis B replication	8

Entecavir



Entecavir (BMS-200475) is a potent deoxyguanosine nucleoside analogue developed for the treatment of hepatitis B and currently in phase III evaluation at Bristol-Myers Squibb.

Entecavir was 17-fold more potent than lamivudine in inhibiting DNA synthesis by wild-type HBV-pol in recombinant baculovirus-derived HBV nucleocapsids. Furthermore, entecavir yielded IC_{50}/[dNTP] values of 46 and 59 nM for inhibition of chimeric nucleocapsids carrying the clinically relevant mutations M550V/L526M and M550I, respectively, revealing an intrinsic potency of this agent 2 orders of magnitude greater than lamivudine. EC_{50} values for HBV viral replication inhibition in HepG2 cells by entecavir and lamivudine were 3 and 196 nM, respectively. These results demonstrate potent antiviral activity for entecavir against wild-type HBV and clinically relevant mutants (1).

Data from a phase II study which randomized 66 treatment-naive patients to receive 0.01, 0.1 or 0.5 mg/day of entecavir for 24 weeks revealed that the maximum log decrease in HBV viral load was obtained for AUC_{0-24} values that fell between the mean AUC values for the 0.1- and 0.5-mg dose groups. This supported the selection of a daily entecavir dose of 0.5 mg for further study in phase III clinical trials (2).

A total of 181 HBV-infected patients who did not respond to previous antiviral treatment with lamivudine were randomized to receive lamivudine 100 mg/day or entecavir 0.1, 0.5 or 1.0 mg/day for 24 weeks (increased to 52 weeks if there was a complete response to the drug). Compared to lamivudine, entecavir administered for 48 weeks provided a higher mean $\log_{10}$ decrease in HBV DNA levels, a higher percentage of patients with normalized ALT levels and a higher percentage of patients with undetectable HBV DNA levels. No novel mutations conferring resistance to entecavir were detected during the study, and the drugs showed very similar safety profiles. These results supported the use of a daily dose of 1.0 mg of entecavir in HBV-infected patients not responding to lamivudine (3). The results of this study and those that follow are summarized in Table IV.

The safety results from 6 phase II clinical trials conducted with entecavir have been reported. A total of 409 patients with HBV infection received entecavir alone, lamivudine alone, entecavir combined with lamivudine or placebo in these studies. Most adverse events were mild or moderate, and the most common were headache, rhinitis, fatigue and abdominal pain. No significant differences among treatments were found in the frequency of serious adverse events (7% with entecavir, 9% with lamivudine and 4% with the combination therapy) or in the percentage of patients who discontinued the treatment due to adverse events (3% with entecavir and 5% with lamivudine) (4, 5).

A phase II trial in 177 treatment-naive patients revealed that the viral load reduction induced by entecavir was not affected by the baseline ALT levels of the patients. A daily dose of 0.5 mg for 22 weeks reduced HBV DNA levels by 4.7-4.8 $\log_{10}$ and increased the percentage of patients with undetectable HBV DNA levels to 80-86%, independent of ALT status. In contrast, lamivudine was affected by the baseline ALT levels of the patients. It reduced HBV DNA levels by 4.6 $\log_{10}$ in patients with ALT levels > 2.5 times the upper limit of normality, but by only 2.9 $\log_{10}$ in patients with ALT levels < 1.25 times the upper limit of normality. A similar trend was found for lamivudine and the percentage of patients with undetectable HBV DNA levels (75% with ALT levels > 2.5 times the upper limit of normality and 39% with ALT levels < 1.25 times the upper limit of normality) (6).

1. Levine, S., Hernandez, D., Yamanaka, G., Zhang, S., Rose, R., Weinheimer, S., Colonno, R.J. *Efficacies of entecavir against lamivudine-resistant hepatitis B virus replication and recombinant polymerases in vitro*. Antimicrob Agents Chemother 2002, 46(8): 2525.

2. Fiske, W., Olse, S., Yan, J.-H., Grasela, D., Phillips, L., Owen, J. *Pharmacokinetic-pharmacodynamic (PK-PD) modeling of entecavir: Prediction of log decrease in hepatitis B viral load*. 53rd Annu Meet Am Assoc Study Liver Dis (Nov 1-5, Boston) 2002, Abst 1872.

3. Chang, T.-T., Hadziyannis, S., Cianciara, J. et al. *Sustained viral load and ALT reduction following 48 weeks of entecavir treatment in subjects with chronic hepatitis B who have failed lamivudine*. 53rd Annu Meet Am Assoc Study Liver Dis (Nov 1-5, Boston) 2002, Abst 550.

4. Schiff, E.R., Hindes, R., O'Donnell, A., DeHertogh, D., Kreter, B. *Summary of phase II clinical and laboratory safety experience with entecavir*. J Hepatol 2003, 38(Suppl. 2): Abst 585.

5. Schiff, E., Hindes, R., O'Donnell, A., DeHertogh, D., Kreter, B. *Summary of phase II clinical and laboratory safety experience with entecavir*. 53rd Annu Meet Am Assoc Study Liver Dis (Nov 1-5, Boston) 2002, Abst 1919.

6. Rosmawati, M., Lai, C.L., Lao-Tan, J., Sherman, M., Thomas, N., DeHertogh, D.A. *Entecavir is highly effective in reducing viral load regardless of baseline ALT status*. 53rd Annu Meet Am Assoc Study Liver Dis (Nov 1-5, Boston) 2002, Abst 1842.

Original monograph - Drugs Fut 1999, 24(11): 1173.

Table IV: Clinical studies of entecavir (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Hepatitis B	Randomized, double-blind	Entecavir, 0.1 mg od x 24 wk [prolonged 52 wk if complete response] Entecavir, 0.5 mg od x 24 wk [prolonged to 52 wk if complete response] Entecavir, 1.0 mg od x 24 wk [prolonged to 52 wk if complete response] Lamivudine, 100 mg od x 24 wk [prolonged to 52 wk if complete response]	181	Entecavir administered for 48 weeks was safe and effectively reduced viral load and normalized ALT levels in hepatitis B patients who had failed previous treatment with lamivudine	3
Hepatitis B	Randomized, double-blind, pooled/meta-analysis	Entecavir (n=315) Lamivudine (n=86) Entecavir + Lamivudine (n=75) Placebo (n=8)	409	Entecavir was well tolerated and had a safety profile very similar to that of lamivudine in patients with hepatitis B. Most adverse events were mild or moderate, the most frequent being headache, rhinitis, fatigue and abdominal pain	4, 5
Hepatitis B	Randomized	Entecavir, 0.01 mg od x 24 wk Entecavir, 0.1 mg od x 24 wk Entecavir, 0.5 mg od x 24 wk Lamivudine, 100 mg od x 24 wk	177	Entecavir was highly effective in reducing HBV viral load and, compared with lamivudine, was not affected by patients' baseline ALT levels	6

Natalizumab

Elan and Biogen are collaborating on the development, manufacturing and marketing of natalizumab (Antegren®), a humanized monoclonal antibody with a novel mechanism of action, being the first α_4 antagonist in the new SAM (selective adhesion molecule) inhibitor class.

Natalizumab was designed to selectively inhibit immune cells from leaving the bloodstream and to prevent these cells from migrating into tissue where they may cause or maintain inflammation. Elan and Biogen are conducting phase III trials for the treatment of both Crohn's disease and multiple sclerosis. Biogen has signed a definitive merger agreement with Idec Pharmaceuticals to create a global biotechnology company called Biogen Idec, with natalizumab as one of its major products in clinical development. The transaction is expected to close by the end of the third quarter or early in the fourth quarter of this year. As part of its restructuring plans, Elan purchased royalty rights to natalizumab from Autoimmune Disease Research & Development (1, 2).

As recently reported, the phase III induction trial of natalizumab failed to meet the primary endpoint of response as defined by a 70-point decrease in the Crohn's Disease Activity Index (CDAI) at week 10, apparently due to a larger than expected placebo response rate. However, data indicated that the biological activity of natalizumab was similar to that seen in a phase II study. In the phase II study, a significant effect was seen on multiple markers of inflammation, including C-reactive protein and platelets, in natalizumab-treated patients compared to placebo-treated patients. An analysis of a subset of patients comprising 72% of the total population enrolled in the trial, known as ENACT-1 (Evaluation of Natalizumab in Active Crohn's Disease Therapy-1), demonstrated evidence of active inflammation. The subset had statistically significant clinical response and remission rates at week 10 and multiple other time points compared to placebo. A double-blind, placebo-controlled trial, ENACT-1 randomized patients to receive 300 mg natalizumab or placebo dosed at weeks 0, 4 and 8. The study evaluated 905 patients. The week 12 response and remission endpoints were significant compared to placebo, as was a secondary endpoint of IBDQ (Inflammatory Bowel Disease Questionnaire) at week 10. Throughout the study, the time to remission and, at weeks 6 through 12, mean changes in CDAI were also significant in natalizumab-treated patients compared to those treated with placebo. The natalizumab maintenance trial known as ENACT-2, for Evaluation of Natalizumab as Continuous Therapy-2, in Crohn's disease is also ongoing. In addition, two phase III studies in multiple sclerosis (MS) are under way. AFFIRM (natalizumab safety and efficacy in relapsing-remitting MS) will evaluate the ability of natalizumab to slow the rate of disability in MS and reduce the rate of clinical relapses. SENTINEL (safety and efficacy of natalizumab in combination with Avonex® [Interferon

Table V: Clinical studies of natalizumab (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Crohn's disease	Randomized	Natalizumab, 3 mg/kg sd iv Natalizumab, 3 mg/kg iv x 2 Natalizumab, 6 mg/kg iv x 2 Placebo	59	Natalizumab effectively reduced inflammation in patients with Crohn's disease	5
Crohn's disease	Randomized, double-blind	Natalizumab, 3 mg/kg iv Natalizumab, 3 mg/kg iv 1x/4 wk x 2 Natalizumab, 6 mg/kg iv 1x/4 wk x 2 Placebo	248	Natalizumab treatment showed significant improvements in the Inflammatory Bowel Disease Questionnaire score in patients with active Crohn's disease. These improvements involved the bowel, social, emotional and systemic domains of the questionnaire, and confirmed that natalizumab was effective in improving the quality of life in patients with moderate to severe active Crohn's disease	6
Crohn's disease	Randomized, double-blind, multicenter	Natalizumab, 3 mg/kg iv → Placebo iv (n=68) Natalizumab, 3 mg/kg iv → 3 mg/kg iv (n=66) Natalizumab, 6 mg/kg iv → 6 mg/kg iv (n=51) Placebo (n=63)	248	Natalizumab was effective and well tolerated in patients with Crohn's disease	7

β-1a] in patients with relapsing-remitting MS) will determine if the combination of natalizumab and Avonex® is more effective than treatment with Avonex® alone in slowing the rate of disability and reducing the rate of clinical relapses (3).

The binding specificity and activity of natalizumab were compared with AN100226m, the murine version of natalizumab, in lymphocytes, monocytes and neutrophils *in vitro*. Both natalizumab and AN100226m were equally effective in binding to guinea pig and human lymphocytes and inhibiting the adhesion of human lymphocytes to VCAM-1, an adhesion molecule that is upregulated on the vascular endothelium of sites with chronic inflammation. A weak interaction was found for natalizumab with human neutrophils. These results suggest that natalizumab might be effective in modulating the function of leukocytes and reducing chronic inflammation (4).

Placebo or natalizumab was assigned to 248 patients with moderate to severe Crohn's disease in a randomized, double-blind, placebo-controlled trial. Placebo or natalizumab (3 or 6 mg/kg) was given in 2 infusions 4 weeks apart. Response and remission rates were superior with natalizumab. C-reactive protein (CRP) levels were significantly reduced in patients with Crohn's disease and elevated CRP levels who were treated with natalizumab. The reductions in CRP were maintained for 12 weeks in patients given 2 infusions of the 3 mg/kg dose. The study also determined the changes in the quality of life induced by natalizumab. The quality of life of the patients, which was evaluated using the IBDQ, improved significantly with natalizumab compared to placebo. The drug improved all the IBDQ domains (*i.e.*, bowel, social, emotional and systemic) (5-7). These results are summarized in Table V.

1. *Idec and Biogen to merge*. DailyDrugNews.com (Daily Essentials) June 30, 2003.

2. *Elan repositions business for long-term growth*. DailyDrugNews.com (Daily Essentials) Sept 10, 2002.

3. *Phase III induction trial of Antegren fails to meet primary endpoint*. DailyDrugNews.com (Daily Essentials) July 29, 2003.

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6. Rutgeerts, P., Donoghue, S., Palmer, T. *Quality of life improvements in a phase 2 study of natalizumab for active Crohn's disease*. Dig Dis Week (May 17-22, Orlando) 2003, Abst M1585.

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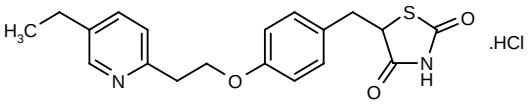
Original monograph - Drugs Fut 2000, 25(9): 917.

Pioglitazone Hydrochloride



Pioglitazone hydrochloride is a thiazolidinedione insulin sensitizer which has been available for several years as Actos® from Takeda and Lilly for the treatment of type 2 diabetes as monotherapy or in combination with sulfonylureas or α-glucosidase inhibitors (1, 2).

A study randomized 4-week-old rats to receive a liquid diet with or without ethanol for 10 weeks, supplemented or not with 10 mg/kg pioglitazone once daily. Rats receiving the liquid diet with ethanol showed a moderate degree of fatty liver that was markedly attenuated when the animals were fed an ethanol-containing diet supplemented with pioglitazone. The results suggested that pioglitazone increased the expression of hepatic apolipoprotein B, which in turn would mobilize VLDL from hepatocytes. It was also suggested that the proto-oncogene c-Met played a crucial role in the effects induced by pioglitazone in alcoholic fatty liver (3).

In a model of acid acetic-induced ulcera in rats, pioglitazone (5-40 mg/kg) reduced the ulcerated area by down-regulating the mucosal gene and protein expression of Il1b, Tnf, Nos2 (iNos) and Ptgs2 (Cox-2), and up-regulating the mRNA and protein expression of Hspa1a (Hsp70) (4).

The benefits of pioglitazone in nonalcoholic steatohepatitis were demonstrated in a study that included 12 patients with evidence of the condition (fatty infiltration, inflammation and various degrees of fibrosis), ALT levels higher than normal, and glucose intolerance but normal HbA1c levels. Administration of 15 mg/day of pioglitazone over 3 months normalized ALT levels and increased those of serum insulin and LDL cholesterol, but had no effect on the levels of triglycerides and HDL cholesterol (5). These results and those from the following study are summarized in Table VI.

A prospective, randomized, controlled pilot study compared the efficacy of pioglitazone (30 mg p.o. once daily) combined with vitamin E (400 IU p.o. once daily) with that of vitamin E alone in 21 patients with biopsy-proven nonalcoholic steatohepatitis. After 6 months of treatment, the combination therapy was found to be significantly more effective than vitamin E alone in improving steatosis, Mallory hyaline levels and cytologic ballooning. Both treatments were well tolerated; neither of them affected fibrosis scores and only 1 patient receiving pioglitazone showed ALT increases leading to discontinuation from the study (6).

The clinical and histological outcome of a patient with recurrence of nonalcoholic steatohepatitis following liver transplantation has been reported. Treatment for 2 years with pioglitazone improved glycemic control, decreased insulin requirements from > 2 U/kg to < 0.3 U/kg, decreased steatosis from 80% to 15% and resolved inflammation, although symptoms of chronic ductopenia also appeared. Pioglitazone may therefore be useful in the treatment of liver inflammation and steatosis, but severe hepatotoxicity has been reported to be associated with this type of drug and caution is therefore recommended (7).

1. *CPMP grants positive opinion on new indication for Actos*. DailyDrugNews.com (Daily Essentials) June 6, 2003.

Table VI: Clinical studies of pioglitazone (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Hepatic steatosis	Open	Pioglitazone, 15 mg od x 3 mo (n=7) Increased physical activity (n=5)	12	Pioglitazone was well tolerated in nonalcoholic steatohepatitis patients with normal HbA1c levels. The improvement in ALT levels found with pioglitazone supported its use as a therapeutic option for nonalcoholic steatohepatitis	5
Hepatic steatosis	Randomized, double-blind	Pioglitazone, 30 mg po od + Vitamin E, 400 IU po od x 6 mo (n=10) Vitamin E, 400 IU po od x 6 mo (n=11)	21	The combination therapy of vitamin E plus pioglitazone was better than vitamin E alone in improving steatosis, ballooning and Mallory hyaline levels in patients with nonalcoholic steatohepatitis	6

2. *European approval obtained for Actos*. DailyDrugNews.com (Daily Essentials) Sept 3, 2003.

3. Tomita, K., Azuma, T., Kitamura, N., Nishimura, T., Inokuchi, S., Kato, S., Ishii, H. *Pioglitazone prevents alcohol-induced fatty liver in rats, through the upregulation of c-Met*. 53rd Annu Meet Am Assoc Study Liver Dis (Nov 1-5, Boston) 2002, Abst 949.

4. Konturek, P. et al. *Pioglitazone, a specific PPAR-gamma ligand, accelerates ulcer healing, importance of proinflammatory cytokines, cyclooxygenase-2, inducible NO-synthase and heat shock protein 70 expression*. Dig Dis Week (May 17-22, Orlando) 2003, Abst 861.

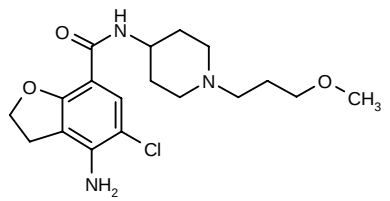
5. Azuma, T., Tomita, K., Kato, S., Adachi, M., Inokuchi, S., Kitamura, N., Nishimura, T., Ishii, H. *A pilot study of the thiazolidinedione, pioglitazone, in nonalcoholic steatohepatitis*. 53rd Annu Meet Am Assoc Study Liver Dis (Nov 1-5, Boston) 2002, Abst 972.

6. Sanyal, A.J., Contos, M.J., Sargeant, C., Stravitz, R.T., Luketic, V.A., Sterling, R.K., Shiffman, M.L., Mills, S. *A randomized controlled pilot study of pioglitazone and vitamin E versus vitamin E for nonalcoholic steatohepatitis*. 53rd Annu Meet Am Assoc Study Liver Dis (Nov 1-5, Boston) 2002, Abst 875.

7. Gilroy, R.K., Cauble, M., Larsen, J., Sanjevi, A., Sorrell, M.F., Mukherjee, S. *Severe recurrent nonalcoholic steatohepatitis following transplantation successfully treated with pioglitazone*. Am J Gastroenterol 2002, 97(9, Suppl.): Abst 633.

Original monograph - Drugs Fut 1990, 15(11): 1080.

Prucalopride



Prucalopride (R-93877, Resolor®), a 5-HT_4 receptor agonist that stimulates colonic motility, is in phase III clinical development at Janssen for the treatment of constipation in children and constipation-predominant irritable bowel syndrome (IBS).

Treatment of constipation with prucalopride was studied in 74 female patients in a randomized, double-blind, placebo-controlled trial. Placebo or prucalopride 1 mg daily was assigned for 4 weeks. Prucalopride was well tolerated and significantly increased stool frequency and improved stool consistency. Upper gut transit was accelerated in all patients and colonic transit was accelerated in patients with slow colonic transit. Visceral sensitivity was also improved by prucalopride (1).

Prucalopride was compared to placebo in a randomized, double-blind pilot study in 53 patients with chronic constipation who were not relieved by laxatives. Prucalopride 4 mg once daily was given for 4 weeks and the dose could be reduced after 2 weeks in patients with excessive responses. The drug was well tolerated and effective, significantly softening stools, decreasing straining and reducing the time to first stool compared to placebo (2).

1. Emmanuel, A.V., Roy, A.J., Nicholls, T.J., Kamm, M.A. *Prucalopride, a systemic enterokinetic, for the treatment of constipation*. Aliment Pharmacol Ther 2002, 16(7): 1347.

2. Coremans, G., Kerstens, R., DePauw, M., Stevens, M. *Prucalopride is effective in patients with severe chronic constipation in whom laxatives fail to provide adequate relief - Results of a double-blind, placebo-controlled clinical trial*. Digestion 2003, 67(1-2): 82.

Original monograph - Drugs Fut 1999, 24(7): 729.

Ramoplanin

Genome Therapeutics is conducting a clinical development program for the novel glycolipodepsipeptide antibiotic ramoplanin to investigate its role in controlling the spread of important antibiotic-resistant pathogens in the hospital setting, including phase III trials for the prevention of bloodstream infections caused by vancomycin-resistant enterococci and phase II trials for treatment of *Clostridium difficile*-associated diarrhea (CDAD).

Genome Therapeutics acquired development and commercialization rights to ramoplanin for North America from Vicuron Pharmaceuticals. The glycolipodepsipeptide has potent *in vitro* bactericidal activity targeted against Gram-positive bacteria, including many antibiotic-resistant strains such as VRE, MRSA (methicillin-resistant *Staphylococcus aureus*) and VRSA (vancomycin-resistant *S. aureus*). It is also bactericidal *in vitro* against *C. difficile*. It is not absorbed systemically from the gastrointestinal tract following oral dosing and exerts bactericidal activity in the GI tract (1).

Genome Therapeutics has begun a phase II trial of ramoplanin for the treatment of CDAD. A total of 87 patients will be enrolled in the multicenter, open-label trial. Two doses of ramoplanin (200 and 400 mg) given twice daily will be compared over a treatment period of 10 days to vancomycin given at 125 mg 4 times daily. Data analysis is expected to occur later this year and the

results will help in the design of a phase III trial of ramoplanin for the same indication (2).

The *in vivo* efficacy of ramoplanin was recently studied using a hamster model of CDAD. The animals received a single dose of 100 mg/kg s.c. of clindamycin with or without an oral bacterial suspension of *C. difficile*, and 24 h later were treated with oral ramoplanin (25-100 mg/kg once daily), vancomycin (25-100 mg/kg once daily) or metronidazole (100-400 mg/kg once daily) for 5 days. The hamsters that received no antibiotics after induction of colitis with clindamycin developed a fatal enterocolitis with a 100% mortality rate within 4 days. Both ramoplanin and vancomycin protected against mortality, with 80% survival in ramoplanin-treated animals and 20% survival in vancomycin-treated animals. In the more severe form of colitis induced by clindamycin and *C. difficile*, only ramoplanin was able to prevent mortality (20% survival) (3).

1. *Genome Therapeutics expands ramoplanin development program*. DailyDrugNews.com (Daily Essentials) Aug 7, 2003.

2. *Initiation of phase II for ramoplanin in Clostridium difficile-associated diarrhea*. DailyDrugNews.com (Daily Essentials) Feb 24, 2003.

3. Candiani, G., Jabes, D. *Efficacy of ramoplanin in the hamster model of C. difficile associated colitis*. Clin Microbiol Infect 2003, 9(Suppl. 1): Abst P1626.

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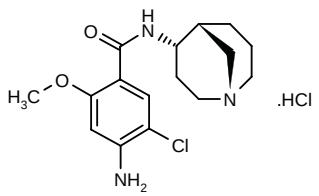
Renzapride Hydrochloride



The potent 5-HT_4 receptor agonist/5-HT_3 receptor antagonist renzapride hydrochloride (AZM-113, ATL-1251, BRL-24924) is a potential new therapy for both diarrhea and constipation in IBS. It was acquired by Alizyme from the former SmithKline Beecham (GlaxoSmithKline).

Alizyme has completed patient recruitment in a phase IIb trial of renzapride in patients with alternating or mixed-symptom IBS. The multicenter, randomized, double-blind, parallel-group trial involves over 170 patients in Europe. Three doses of renzapride and placebo are compared over an 8-week treatment period for efficacy in providing symptom relief. Preliminary results are expected later this year in October. The drug is also being studied in a pharmacokinetic/pharmacodynamic study at the Mayo Clinic in up to 48 constipation-predominant IBS patients in order to determine the relationship between the effects of different doses on gastrointestinal motility and levels of drug absorbed. This study is expected to report in the fourth quarter of 2004. Alizyme plans to prepare for phase III development and initiate discussions with potential licensing partners (1).

Alizyme has reported preliminary results from a phase IIb trial of renzapride in patients with constipation-predominant IBS. The randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study evaluated the efficacy and safety of renzapride (1, 2 and 4 mg/day) and placebo administered once daily over a 12-week treatment period. The U.K.-based trial involved 510 evaluable patients with constipation-predominant IBS. The primary endpoint was the patient's weekly assessment of adequate relief of abdominal pain and discomfort during weeks 5-12 of treatment. A patient was classified as a responder if he/she recorded adequate relief in 75% of the weeks of treatment. Renzapride increased the responder rate for adequate relief of abdominal pain and discomfort by up to 9% over placebo. Treatment with renzapride also increased both the frequency of bowel movements and improved stool consistency, the latter with dose-related effect. Statistical significance was recorded in frequency of bowel movements at 2 and 4 mg/day, and on stool consistency at 4 mg/day. The data obtained for renzapride were similar to the level of overall benefit reported for tegaserod in phase III trials: approximately 8% improvement over placebo in patients with alternating or mixed-symptom IBS (2, 3).

A total of 17 patients with constipation-predominant IBS were given placebo for 28 days followed by renzapride 2 mg once daily for 28 days and then 2 mg twice daily for another 28 days. The results demonstrated dose-dependent decreases in overall gastrointestinal transit times on renzapride and increased segmental colonic motility. Furthermore, 30-64% of patients showed improvement in symptoms (pain) following treatment with renzapride. Renzapride was well tolerated, with a similar incidence and type of adverse events on placebo and renzapride (4).

Two scintigraphic studies in fasted healthy subjects investigated the effects of single oral doses of renzapride (2 mg) on gastric emptying, small intestinal transit and colonic motility. Renzapride had no significant effect on gastric emptying time, while it reduced small intestinal transit time and enhanced colonic motility. The drug was well tolerated and, in particular, no effect was seen on Q-Tc interval (5).

1. *Alizyme completes enrollment of phase IIb trial of renzapride*. DailyDrugNews.com (Daily Essentials) April 15, 2003.

2. *Preliminary results from phase IIb trial of renzapride in c-IBS*. DailyDrugNews.com (Daily Essentials) May 14, 2003.

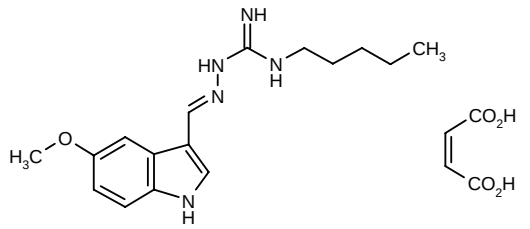
3. *Patient enrollment completed in phase IIb renzapride trial in IBS*. DailyDrugNews.com (Daily Essentials) Sept 26, 2002.

4. Meyers, N.L., Tack, J., Middleton, S., Horne, M., Piessevaux, H., Bloor, J., Palmer, R. *Efficacy and safety of renzapride in patients with constipation-predominant irritable bowel syndrome*. Gut 2002, 51(Suppl. 3): Abst OP-G-033.

5. Meyers, N.L., Palmer, R.M., Wray, H.A., Bloor, J.R., Wilding, I.R. *Effects of single oral doses of renzapride on gastrointestinal motility in fasted, healthy subjects*. Gut 2002, 51(Suppl. 3): Abst MON-G-510.

Original monograph - Drugs Fut 1987, 12(11): 1009.

Tegaserod Maleate



Following its first introduction in 2001 in Mexico for the treatment of IBS, the 5-HT_4 receptor partial agonist tegaserod maleate (Zelmac®, Zelnorm®; Novartis, Bristol-Myers Squibb) is now available in more than 30 countries, including Australia, Switzerland, Canada, the U.S. and Brazil. Novartis and Bristol-Myers Squibb are also evaluating the drug in chronic consipation and functional dyspepsia.

Novartis has initiated the ZENSAA study to evaluate repeated treatment with tegaserod in female patients with IBS with constipation who experience a positive response to initial treatment but whose symptoms recur after treatment is stopped. The prospective, multicenter, randomized, double-blind, parallel-group study will enroll 2,500 women aged 18-65 who suffer from IBS with constipation. It will be conducted at 262 centers in 24 countries, including the U.S., the U.K., Canada, Mexico, Germany, France, Italy, Spain, South Africa and New Zealand. Patients will receive either tegaserod at 6 mg twice daily or placebo. Primary efficacy variables are overall relief of IBS symptoms and overall relief of abdominal pain/discomfort. Efficacy will be measured by patient responses to several assessment questionnaires, with abdominal pain/discomfort, bloating, constipation and bowel habits to be recorded on a daily and weekly basis. Secondary variables include the individual gastrointestinal symptoms of IBS, such as pain/discomfort and bloating (daily) and constipation (weekly) and the time of onset of GI symptom relief. Quality of life will also be assessed. Patients will complete the Hospital Anxiety and Depression Scale (HADS), an Overall Satisfaction with Treatment questionnaire, and Work-Productivity Activity Impairment IBS questionnaire (1).

The pharmacokinetics of a single 12-mg oral dose of tegaserod in patients with severe renal insufficiency requiring hemodialysis were evaluated in an open-label, parallel-group study and compared with data from healthy controls matched for age, weight, height and gender. The pharmacokinetics of tegaserod were similar in patients with and without severe renal insufficiency; respective values were: AUC = 14.6 ± 8.5 ng.h/ml *vs*. 14.3 ± 7.1 ng·h/ml; C_{max} = 4.6 ± 2.3 ng/ml *vs*. 5.1 ± 2.2 ng/ml; t_{max} = 1.0 h for both. It was concluded that no dose adjustments are required for tegaserod in patients with severe renal insufficiency (2).

A randomized, double-blind, multicenter, phase II trial compared placebo to tegaserod 1.5, 6 and 18 mg/day in patients with functional dyspepsia but normal gastric emptying. Treatment with tegaserod for 8 weeks was well tolerated, and while not providing substantial relief of overall functional dyspepsia symptoms over placebo, early satiety and postprandial fullness were improved in female patients taking the 6 mg/day dose (3). These results and those from some of the following studies are summarized in Table VII.

A multicenter, open, 8-week trial was undertaken to assess the safety of tegaserod 6 mg b.i.d. in 837 patients with non-diarrhea-predominant IBS. Data from 219 evaluable patients showed that most adverse events were mild. Diarrhea occurred in 28% of 186 patients evaluable for that event, and was mild in 26% of episodes, moderate in 49% and severe in 24% (4).

A randomized, double-bind, crossover trial assessed gastrointestinal motility in 9 healthy volunteers after administration of tegaserod 6 mg b.i.d or placebo. Manometry assessments revealed that tegaserod increased interdigestive jejunal motility and postprandial antral and intestinal motility compared to placebo (5).

Tegaserod was evaluated in 647 Nordic patients with IBS in a trial in which patients were given placebo or tegaserod 6 mg b.i.d. during a 12-week double-blind treatment period followed by a 4-week withdrawal period. Subjective assessments indicated that significantly more tegaserod-treated patients had satisfactory relief of symptoms at weeks 2, 3 and 5-12 than placebo-treated patients. The adverse event incidence was similar between treatments, and serious adverse events were

Table VII: Clinical studies of tegaserod maleate (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Dyspepsia	Randomized, double-blind, multicenter	Tegaserod, 1.5 mg/d po x 8 wk (n=63) Tegaserod, 6 mg/d po x 8 wk (n=62) Tegaserod, 18 mg/d po x 8 wk (n=59) Placebo (n=63)	247	Tegaserod was well tolerated in patients with functional dyspepsia and improved some upper gastrointestinal symptoms, primarily in women	3
IBS	Open, multicenter	Tegaserod, 6 mg bid x 8 wk	837	Tegaserod was well tolerated and did not cause serious diarrhea in patients with irritable bowel syndrome	4
Healthy Volunteers	Randomized, double-blind, crossover	Tegaserod, 6 mg bid x 3 d Placebo	9	Tegaserod increased interdigestive jejunal motility and postprandial antral and intestinal motility in healthy volunteers	5
IBS	Randomized, double-blind	Tegaserod, 6 mg bid x 12 wk (n=259) Placebo (n=261)	520	Tegaserod showed safety, good tolerability and efficacy in patients with irritable bowel syndrome without diarrhea as the predominant symptom	6
Constipation, IBS	Open	Tegaserod, 6 mg bid x 6 wk	117	Tegaserod was well tolerated and effective in males and females with irritable bowel syndrome and constipation	7
Constipation, IBS	Open	Tegaserod x 12 wk → [Responders] no treatment x 8 wk → [Relapse patients] tegaserod x 4 wk	513	Initial and retreatment of patients with irritable bowel syndrome with constipation with tegaserod was well tolerated and effective	8
Constipation, IBS	Open, multicenter	Tegaserod, 6 mg bid x 1 mo → [Responders] no treatment Tegaserod, 6 mg bid x 1 mo → [Responders] tegaserod x 2 mo	718	Tegaserod was effective in patients with irritable bowel syndrome and constipation; withdrawal of treatment was associated with relapse	9
Delayed gastric emptying, dyspepsia, gastroparesis	Randomized, double-blind	Tegaserod, 6 mg bid x 8 wk Tegaserod, 6 mg tid x 8 wk Tegaserod, 12 mg bid x 8 wk Placebo	163	Tegaserod improved gastric emptying in patients with delayed gastric emptying and dyspeptic symptoms	10
Constipation	Randomized, double-blind, multicenter	Tegaserod, 2 mg bid x 12 wk (n=450) Tegaserod, 6 mg bid x 12 wk (n=451) Placebo (n=447)	1,348	Tegaserod was effective and well tolerated in patients with chronic constipation	11, 12
Constipation, IBS	Randomized, double-blind	Tegaserod, 6 mg bid x 6 wk Placebo	510	Tegaserod was effective and well tolerated in Chinese patients with irritable bowel syndrome and constipation	13

reported for 5 and 6 tegaserod- and placebo-treated patients, respectively (6).

An open-label study in 117 patients investigated tegaserod 6 mg b.i.d. for 6 weeks for the treatment of IBS with constipation. Tegaserod was well tolerated and significantly improved the number of bowel movements, straining at defecation, sense of incomplete evacuation and abdominal pain. Tegaserod was effective in males as well as females, with equal efficacy in improving the symptoms of abdominal pain and straining at defecation, and greater efficacy in males in increasing the number of bowel movements per week (7).

In an open-label study, 513 patients with IBS with constipation were treated with tegaserod for 12 weeks, after which responders were followed up for 8 weeks. Those relapsing during that time were retreated for 4 weeks. An initial response was seen in 85% of patients, and 84% of these had symptom recurrence at a mean of

38 days. The response rate among retreated patients was 88%. Adverse events were also similar between treatment periods (8).

In an open study at multiple centers, 718 patients with IBS with constipation were treated with tegaserod 6 mg b.i.d. After treatment for 1 month, responders (those with satisfactory relief during 2 weeks of treatment) were randomly assigned to withdrawal or further tegaserod treatment for 2 months. Of 678 evaluable patients, 82% responded and 544 were randomized again. Of 268 assigned withdrawal, 67% relapsed at a median of 21 days. Relapse was 18 times less likely in patients continuing tegaserod therapy (9).

Patients with dyspeptic symptoms and delayed gastric emptying (n=163) were randomized to tegaserod 6 mg b.i.d., tegaserod 6 mg t.i.d., tegaserod 12 mg b.i.d. or placebo in an 8-week, double-blind trial. A [^{99m}Tc]-labeled test meal was given at baseline and after 8 weeks, and scintigraphy showed that gastric retention was reduced with tegaserod. The tegaserod 6 mg t.i.d. and 12 mg b.i.d. regimens were particularly effective, with normal gastric emptying seen in 80% of patients given tegaserod 6 mg t.i.d. verus 50% of patients given placebo (10).

In a multicenter, randomized, double-blind, placebo-controlled trial, tegaserod 2 or 6 mg b.i.d. was evaluated in 1,348 patients with chronic constipation. Treatment with tegaserod for 12 weeks was well tolerated and significantly increased complete spontaneous bowel movements per week compared with placebo. The drug also reduced abdominal discomfort/pain, bloating/distension, straining and stool consistency compared with placebo. Responses were sustained throughout the treatment period (11, 12).

Tegaserod 6 mg b.i.d. was evaluated in 510 Chinese patients with IBS with constipation in a randomized, double-blind, placebo-controlled trial. Treatment lasted 6 weeks, including a 2-week withdrawal phase. Subjects' global assessments indicated that symptoms were reduced significantly more by tegaserod than placebo. Adverse events occurred in 10% of tegaserod and 6% of placebo patients and included diarrhea, abdominal pain and dizziness (13).

Solid pharmaceutical formulations suitable for oral administration and comprising the 5-HT$_4$ receptor partial agonist tegaserod, or a pharmaceutically acceptable salt thereof (*e.g.*, maleate), have been claimed for the prevention and treatment of disorders related to gastrointestinal motility, including IBS, gastroesophageal reflux disease (GERD), functional dyspepsia, postoperative ileus, diabetic gastroporesis and chronic constipation. The claim embodies compositions comprising tegaserod at as much as 10% by weight, a disintegrant such as crospovidone at less than 15% by weight and a diluent such as lactose at 70-90% by weight of composition, as well as a glidant and a lubricant (14).

1. *Novartis initiates ZENSAA study of Zelmac in IBS*. DailyDrugNews.com (Daily Essentials) Dec 3, 2002.

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3. Talley, N.J., Tack, J., D'Elia, T., Ligozio, G., Lefkowitz, M., Shah, D., Vanderplassche, G. *Tegaserod (T), a partial 5-HT$_4$ agonist, in functional dyspepsia (FD) patients with normal gastric emptying (NGE): A randomized, double blind, placebo controlled trial*. Gut 2002, 51(Suppl. 3): Abst TUE-G-408.

4. Plebani, G. et al. *Safety of tegaserod in patients with irritable bowel syndrome: The Swiss experience*. Gut 2002, 51(Suppl. 3): Abst WED-G-323.

5. Di Stefano, M., Vos, R., Janssens, J., Tack, J.F. *Effect of tegaserod, a 5-HT$_4$ receptor partial agonist, on interdigestive and postprandial gastrointestinal motility in healthy volunteers*. Dig Dis Week (May 17-22, Orlando) 2003, Abst S1148.

6. Nyhlin, H., Bang, C., Elsborg, L. et al. *Tegaserod is an effective and safe therapy for irritable bowel syndrome in a Nordic population*. Dig Dis Week (May 17-22, Orlando) 2003, Abst M1645.

7. Shah, H.A., Jafri, W., Butt, J.A., Mohsin, A., Khan, I. *An open label study to determine the efficacy and tolerability of tegaserod in the treatment of constipation dominant irritable bowel syndrome (IBS-C)*. Dig Dis Week (May 17-22, Orlando) 2003, Abst T1435.

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12. Johansen, J.F., Tougas, G., Chey, W.D., Novick, J.S., Lembo, A., Fordham, F., Guella, M.P., Nault, B. *Tegaserod provides rapid and sustained relief of constipation, abdominal bloating/distension, and abdominal discomfort/pain in patients with chronic constipation*. Dig Dis Week (May 17-22, Orlando) 2003, Abst 371.

13. Lin, S., Zhou, L., Liu, X. et al. *Tegaserod provides rapid, effective relief of abdominal pain/discomfort, bloating and constipation in Chinese patients with irritable bowel syndrome with constipation (IBS-C)*. Dig Dis Week (May 17-22, Orlando) 2003, Abst S1017.

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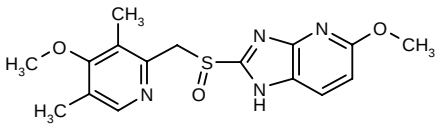
Original monograph - Drugs Fut 1999, 24(1): 38.

Tenatoprazole



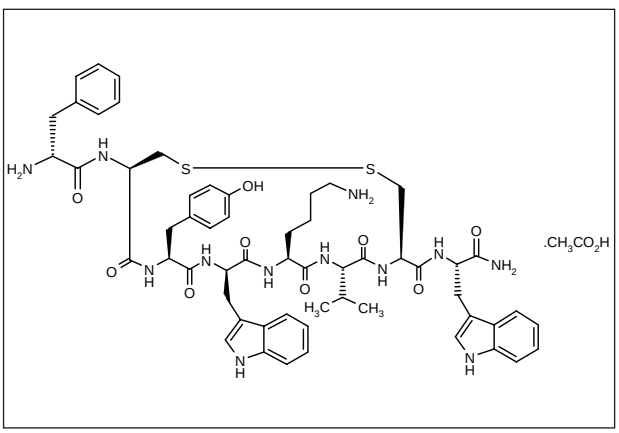
Tenatoprazole (TU-199) is a proton pump inhibitor discovered at Mitsubishi Pharma and licensed to Negma. Clinical trials are under way to evaluate its potential in the treatment of peptic ulcer.

A double-blind, randomized, placebo-controlled clinical trial assessed the pharmacokinetics of tenatoprazole in healthy male volunteers. Each subject received a single oral dose of tenatoprazole (10, 20, 40 or 80 mg) or placebo, followed 14 days later by 7 additional daily doses of the same treatment. The administration of single doses resulted in a plasma half-life of 4.3 h and peak plasma concentrations were reached at 2.5-4.3 h post-dose. Both the mean peak plasma concentration (891-8248 ng/ml) and the mean AUC value (7429-97,169 ng·h/ml) increased dose-dependently when single doses were administered. The repeated oral doses further increased these parameters, with mean peak concentrations of 1284-11,819 ng/ml and mean AUC at steady state of 12,675-218,372 ng·h/ml (1).

1. Domagala, F., Ficheux, H. *Pharmacokinetics of tenatoprazole, a novel proton pump inhibitor, in healthy male Caucasian volunteers*. Dig Dis Week (May 17-22, Orlando) 2003, Abst S1608.

Original monograph - Drugs Fut 1994, 19(11): 1018.

Vapreotide Acetate



Debiopharm has granted H3 Pharma worldwide research, development and commercialization rights to vapreotide acetate (Sanvar®).

According to a well-conducted clinical study, early use of vapreotide was beneficial in the treatment of acute esophageal variceal bleeding, in stopping acute hemorrhage prior to endoscopic intervention and in the prevention of recurring bleeding during the critical 5 days following treatment. Esophageal variceal bleeding is a complex medical emergency with a high mortality rate that accounts for about 7% of gastrointestinal bleeding in North America. An immediate-release formulation of vapreotide has successfully completed a phase III clinical trial in Europe and has been awarded orphan drug status in the U.S. H3 Pharma also recently received written confirmation from the FDA that the dossier for the somatostatin analog is acceptable for filing for the treatment of esophageal variceal bleeding and the immediate-release formulation is expected to be available in the U.S. by late 2004. Phase III clinical trials of a sustained-release formulation in acromegaly and neuroendocrine tumors are also planned for this fall. The drug may have additional potential in Crohn's disease and a clinical phase III program may commence for this indication during 2004. H3 Pharma plans to license out the commercialization rights to the sustained-release formulation at the same time as immediate-release vapreotide (1, 2).

1. *H3 Pharma acquires rights to vapreotide from Debiopharm*. DailyDrugNews.com (Daily Essentials) July 17, 2003.

2. *Sanvar registration dossier accepted for filing by FDA*. DailyDrugNews.com (Daily Essentials) July 29, 2003.

Original monograph - Drugs Fut 1989, 14(11): 1052.

Visilizumab

Protein Design Labs (PDL) recently decided to concentrate on the development of visilizumab (Nuvion®), the company's SMART™ anti-CD3 antibody, as a potential therapy for patients with steroid-refractory ulcerative colitis, whereas it will discontinue its development for the treatment of steroid-refractory graft-*versus*-host disease (GvHD) following bone marrow transplantation.

Previously reported partial data from a phase I dose-ranging study of visilizumab in patients with severe ulcerative colitis refractory to treatment with steroids revealed that all 8 patients in the initial dose cohort responded and 7 of 8 achieved remission. A second phase I/II dose-ranging study is expected to begin this year to explore lower doses of visilizumab for this indication (1).

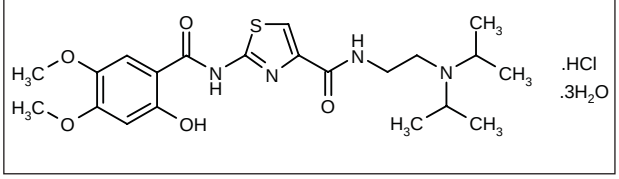
A multicenter, dose-escalating phase I clinical trial evaluated the benefits of visilizumab in the management of severe steroid-refractory ulcerative colitis. Five patients with a median modified Truelove and Witts (MTWSI) score of 13, an endoscopy score of 3 (indicative of severe disease) and > 60 cm of colon involvement at baseline received an i.v. infusion of 15 μg/kg of visilizumab on study days 1 and 2. At 30 days after drug administration, all patients showed clinical and endoscopic remission (MTWSI score < 3) and an endoscopy score of 0-1; these benefits were maintained for months and resulted in the reduction of concomitant medication doses. The only complications associated with the treatment were transient reduction in peripheral T-cell counts, moderate cytokine release symptoms (*e.g.*, nausea, vomiting, arthralgia and chills), severe dehydration (in 1 patient) and low Epstein-Barr titers in whole blood (in 2 patients) (2).

1. *Nuvion development targeted for ulcerative colitis*. DailyDrugNews.com (Daily Essentials) June 5, 2003.

2. Plevy, S.E., Salzberg, B.A., Regueiro, M., Sandborn, W., Hanauer, S.B., Targan, S.R., Mayer, L., Walters, I.B. *A humanized anti-CD3 monoclonal antibody, visilizumab, for treatment of severe steroid-refractory ulcerative colitis: Preliminary results of a phase I study*. Dig Dis Week (May 17-22, Orlando) 2003, Abst 62.

Original monograph - Drugs Fut 2002, 27(5): 469.

Z-338



Zeria's prokinetic agent Z-338 is in phase II clinical trials for the treatment of nonulcer dyspepsia. Z-338 has been shown to improve gastrointestinal disorders and increases gastrointestinal motility by promoting the release of acetylcholine. Yamanouchi has been granted the exclusive development and marketing rights for the product (YM-443) in the U.S. and Canada, as well as first right of refusal for licensing in the E.U. and Japan.

The major action of Z-338 on guinea pig gastric myocytes appears to be enhancement of L-type voltage-gated calcium currents I_{Ca} via M_5-like muscarinic receptor activation. Z-338 potentiated I_{Ca} in a concentration-dependent manner, with an EC_{50} of 0.12 μM, an effect that was blocked by pretreatment with atropine or GDPβS. The effects of Z-338 on I_{Ca} were blocked by intracellular PKC inhibitor peptide and potentiated by extracellular application of phorbol-12,13-dibutyrate. The results cannot exclude the involvement of M_3 receptors (1).

A multicenter, double-blind, randomized, placebo-controlled pilot study has been conducted to assess the efficacy and safety of Z-338 in the treatment of functional dyspepsia, a syndrome with limited therapeutic options. The drug was administered at doses of 50, 100 or 300 mg t.i.d. for 3 weeks. The treatment was well tolerated, the major adverse event being headache. The highest dose of Z-338 significantly improved meal accommodation compared to placebo, whereas no significant effect was seen on gastric sensitivity or gastric emptying at any dose. Symptomatic improvement was obtained on the dose of 100 mg at 2 and 3 weeks, and this dose was also associated with significant improvement in several aspects of quality of life. It was concluded that improvement in gastric accommodation may underlie the beneficial effects of Z-338 in functional dyspepsia (2).

1. Morita, H., Abe, K., Ito, Y., Inoue, R. *Possible involvement of M_5 muscarinic receptor in the enhancing actions of the novel gastroprokinetic agent Z-338 on nifedipine-sensitive voltage-dependent Ca^{2+} currents in guinea pig stomach*. Jpn J Pharmacol 2002, 89(4): 356.

2. Tack, J., Masclee, A., Heading, R., Berstad, A., Piessevaux H., Popiela, T., Vandenberghe, A., Kobayashi, S. *A phase II randomised multicentric double-blind placebo controlled parallel group pilot study with Z-338 in functional dyspepsia (FD) patients*. Gut 2002, 51(Suppl. 3): Abst OP-G-143.

Original monograph - Drugs Fut 2003, 28(1): 26.