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Annual Review 2002

Gastrointestinal Drugs

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Abstract

The *Annual Review* in this month's issue of **Drugs of the Future** is dedicated to updated information on gastrointestinal drugs. The following table lists 151 drugs under development in this area, some of which have been published in previous issues of the journal. Information on the following 21 products is updated here: **adefovir dipivoxil, alicaforsen sodium, alosetron hydrochloride, alvimopan, CDP-571, cilansetron, clevudine, deligoparin sodium, dexloxiglumide, entecavir, GM-611, IY-81149, loxiglumide, MKC-733, natalizumab, picroliv, prucalopride, renzapride hydrochloride, tegaserod maleate, vapreotide acetate** and **VX-497**.

Once again, we remind our readers that all of the information presented in this Review is available in electronic format in our drug discovery portal **Integrity**.

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Drug	Source	Indication/Action	Phase
1018-ISS	Dynavax	Hepatitis B	I/II
ACH-126443	Vion	Hepatitis B	II
Activax	Antex Biological	Diarrhea	I
Adalimumab[1]	Abbott	Inflammatory bowel disease	II
Adefovir Dipivoxil[1]	Gilead	Hepatitis B	III
AJG-049	Ajinomoto	Irritable bowel syndrome	I
Albuferon	Human Genome Sciences	Hepatitis C	I
Alicaforsen Sodium[1]	Isis Pharmaceuticals	Inflammatory bowel disease	III
Alosetron Hydrochloride[1]	GlaxoSmithKline	Irritable bowel syndrome	Prereg
Alvimopan[1]	Adolor	Constipation	III
	GlaxoSmithKline	Irritable bowel syndrome	II
ALX-0600	NPS Allelix	Short bowel syndrome	II
		Inflammatory bowel disease	I
AM-365	Amrad	Hepatitis B	II
Anti-Hepatitis N Hyperimmune	Cangene	Hepatitis B	Prereg
Anti-IL-6-Receptor MAb	Chugai	Inflammatory bowel disease	II
APC-2059	Celera/Bayer	Inflammatory bowel disease	II
AR-H047108	AstraZeneca	GERD	I
AU-224	Hokuriku	Prokinetic	I
Azathioprine	Santarus	Inflammatory bowel disease	II
AZD-3355	AstraZeneca	GERD	I/II
Beclometasone Dipropionate	Chiesi	Inflammatory bowel disease	Reg
	DOR Biopharm	Inflammatory bowel disease	II
Bile Salt-Stimulated Lipase	PPL	Pancreatic disorders	II
BNP-166	Ivax	Inflammatory bowel disease	I
BXT-51072	Oxis	Inflammatory bowel disease	II
Campylobacter jejuni Vaccine	Antex Biological	*Campylobacter pylori* diarrhea	II
CBP-1011	InKine	Inflammatory bowel disease	III
CC-1088	Celgene	Inflammatory bowel disease	I
CDC-801	Celgene	Inflammatory bowel disease	II
CDP-571[1]	Celltech	Inflammatory bowel disease	III
CDP-870	Celltech	Inflammatory bowel disease	II
CH-100	Cathay Herbal	Hepatitis C	II
Cilansetron[1]	Solvay	Irritable bowel syndrome	III
Clevudine[1]	Triangle Pharmaceuticals	Hepatitis B	I/II
CNI-1493	Axxima	Inflammatory bowel disease	II
CytoTab	Protherics	Inflammatory bowel disease	II
DA-9601	Dong-A	Cytoprotectant	II
		Gastritis	II
Deligoparin Sodium[1]	Incara/Elan	Inflammatory bowel disease	II/III
Dersalazine	Uriach/Indevus	Inflammatory bowel disease	I
Dexloxiglumide[1]	Rotta/Forest	Irritable bowel syndrome	III
DiffGAM	Immucell	Diarrhea	I/II
DPC-333	DuPont	Inflammatory bowel disease	II
Dronabinol/Cannabinol	GW Pharmaceuticals	Inflammatory bowel disease	III
E-3309	Eisai	*H. pylori* eradication	I
E-3620	Eisai	Gastritis	II
		Irritable bowel syndrome	II
EHC-18	Enzo	Hepatitis C	I
EHT-899	Enzo	Hepatitis B	II
Emtricitabine[1]	Triangle Pharmaceuticals	Hepatitis B	III
Entecavir[1]	Bristol-Myers Squibb	Hepatitis B	III
EpiBr	Hollis-Eden	Hepatitis B	I
Exisulind	Cell Pathways	Barret's esophagitis	II
Gastrimmune[1]	Aphton	GERD	II/III
GM-611[1]	Chugai	GERD	II
GT160-246	GelTex	*Clostridium difficilis* colitis	I
HCV E1 Therapeutic Vaccine	Innogenetics	Hepatitis C	II
Helicide	Axcan	*H. pylori* eradication	Prereg
Helicobacter pylori Vaccine	Chiron Behring	*H. pylori* eradication	I
Helivax	Antex Biological	*H. pylori* eradication	II
Hepagene	Celltech	Hepatitis B	Prereg
Hepatitis B Pharmaccine	Oxxon Pharmaccines	Hepatitis B	I
Hepatitis B Vaccines	GlaxoSmithKline	Hepatitis B	III

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Drug	Source	Indication/Action	Phase
Hepatitis C Immune Globulin (Human)	Nabi Biopharmaceuticals	Hepatitis C	I/II
Hepatitis E Vaccine	GlaxoSmithKline	Hepatitis E	II
Heptazyme	Ribozyme	Hepatitis C	II
Histamine Dihydrochloride	Maxim	Hepatitis C	III
IBStat	InKine	Antispasmodic	L-2002
Icatibant	Jerini/Aventis Pasteur	Liver cirrhosis	I
IDN-6556	Idun	Acute alcoholic hepatitis	I
Immunokine	Oxo-Chemie	Hepatitis C	II
Interferon Gamma-1b	InterMune	Liver fibrosis	II
Interferon Alfa	Viragen	Hepatitis C	II
Interferon Alfa-n1	Sumitomo Pharmaceuticals	Liver cirrhosis	II
Interferon Alfa-n3	Interferon Sciences	Hepatitis C	III
Interferon Beta-1a	Serono	Inflammatory bowel disease	II
		Hepatitis C	II
Interferon Omega	BioMedicines	Hepatitis C	II
Interleukin-10	Schering-Plough	Inflammatory bowel disease	I
Interleukin-11	Wyeth	Inflammatory bowel disease	III
IP-501	Indevus	Liver and biliary tract disorders	III
IPL-512602	InflaZyme/Aventis	Inflammatory bowel disease	I
IPL-550260	InflaZyme/Aventis	Inflammatory bowel disease	I
IS-741	Sumitomo Pharmaceuticals	Pancreatitis	II
ISIS-14803	Hepasense/Isis	Hepatitis C	I
ISIS-104838	Isis/Elan	Inflammatory bowel disease	II
Itriglumide[1]	Rotta	Gastric antisecretory	I
IY-81149[1]	Il-Yang	GERD	II
JTK-003	Japan Tobacco	Hepatitis C	I
KC-11458	Kali-Chemie/Solvay	Delayed gastric emptying	II
L-dT	Idenix	Hepatitis B	II
Levovirin	ICN/Roche	Hepatitis C	I
Loxiglumide[1]	Kaken	Pancreatitis	Prereg
LY-315920	Shionogi	Pancreatic disorders	II
LY-582563	Mitsubishi Pharma/Lilly	Hepatitis B	I
Methylnaltrexone Bromide	Progenics	Constipation	II
MIV-20	Medivir	Hepatitis C	I
Mivotilate	Yuhan	Hepatitis B	II
MKC-733[1]	Janssen	Non-ulcer dyspepsia	I
	Mitsubishi	GERD	II
		Constipation	II
MLN-02	Millennium/Genentech	Inflammatory bowel disease	II
Natalizumab[1]	Biogen	Inflammatory bowel disease	III
NBI-34041	Neurocrine Biosciences/GlaxoSmithKline	Irritable bowel syndrome	I
Nepadutant	Menarini	Irritable bowel syndrome	II
NO-Prednisolone	NicOx	Inflammatory bowel disease	I
ONYX-015	Onyx	Barret's esophagitis	III
OPC-6535	Otsuka	Inflammatory bowel disease	II
Opebacan	Baxter	Inflammatory bowel disease	II
P-54	Phytopharm	Inflammatory bowel disease	II
Pafase	Suntory	Pancreatic disorders	II
Peginterferon Alfa-2a	Roche	Hepatitis B	II
Piboserod Hydrochloride[1]	GlaxoSmithKline	GERD	II
Picroliv[1]	Central Drug Research Institute	Hepatoprotectant	II
Pirfeinidone[1]	Marnac	Liver fibrosis	III
PLD-116	Pilva	Inflammatory bowel disease	II
Polyethylene Glycol 3350	Dow Chemical	Constipation	II
Porcine fetal neuronal cells	Diacrin	Liver and biliary tract disorders	I
		Liver cirrohosis	I
PowderJect Hepatitis B DNA Vaccine	PowderJect/GlaxoSmithKline	Hepatitis B	I
Prednisolone Sodium Metasulfobenzoate	Alyzime	Inflammatory bowel disease	III
Prucalopride[1]	Janssen	Irritable bowel syndrome	III
		Constipation	III
RDP-58	SangStat	Inflammatory bowel disease	II
Recombinant TNF1	Serono	Inflammatory bowel disease	II
Recombinant Human Interleukin-18	Serono	Inflammatory bowel disease	I

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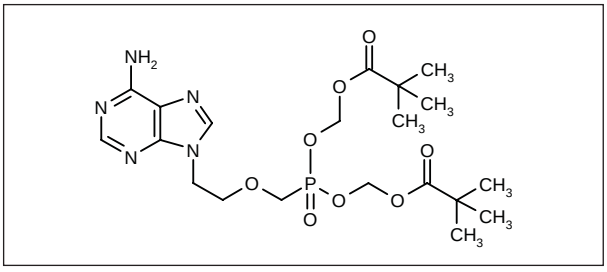
Drug	Source	Indication/Action	Phase
Renzapride Hydrochloride[1]	Alyzime	Irritable bowel syndrome	II
Repifermin	GlaxoSmithKline	Inflammatory bowel disease	II
	Human Genome Sciences	Inflammatory bowel disease	II
rhGH	Serono	Short bowel syndrome	III
Rofleponide	AstraZeneca	Inflammatory bowel disease	I
Rotavirus Vaccine	Merck & Co.	Diarrhea	II
RWJ-67657	R.W. Johnson	Inflammatory bowel disease	I
SB-281832	GlaxoSmithKline	Inflammatory bowel disease	I
SB-641257	GlaxoSmithKline	GERD	I
	Yuhan	Antiulcer	I
SB-683698	GlaxoSmithKline/Tanabe Seiyaku	Inflammatory bowel disease	I
SB-723620	GlaxoSmithKline	Irritable bowel syndrome	I
SB-M00026	GlaxoSmithKline	Hepatitis B	II
SMART Anti-Interferon Gamma	Protein Design Labs	Inflammatory bowel disease	II
Tacrolimus[1]	Fujisawa	Inflammatory bowel disease	III
Thalidomide[1]	Celgene	Inflammatory bowel disease	II
Talnetant	GlaxoSmithKline	Irritable bowel syndrome	I
Targit Budesonide[1]	West Pharmaceutical Services	Inflammatory bowel disease	I
Tegaserod Maleate[1]	Novartis	Irritable bowel syndrome	L-2001
Tenatoprazole[1]	Hokuruku	Gastric antisecretory	Prereg
TNX-100	Tanox	Inflammatory bowel disease	I/II
Torcitabine	Idenix	Hepatitis B	I/II
Transvax™ Hepatitis C Vaccine	Intercell	Hepatitis C	I/II
UR-906	Children's Hosp. Med. Center	Hepatobiliary disease in cystic fibrosis	II
Ursodeoxycholic Acid	Axcan	Nonalcoholic steatohepatitis	II
Ursodiol	Axcan	Nonalcoholic steatohepatitis	II
		Primary sclerosing cholangitis	II
Vapreotide Acetate[1]	Debiopharm	Gastrointestinal and pancreatic fistula	III
Viramidine Hydrochloride	ICN	Hepatitis C	I
Visicol	InKine	Prokinetic	L-2001
		Constipation	I
Visilizumab[1]	Protein Design Labs	Inflammatory bowel disease	I
VX-497[1]	Vertex	Hepatitis C	II
XTL-001	XTL Biopharmaceuticals	Hepatitis B	II
XTL-002	XTL Biopharmaceuticals	Hepatitis C	I
Z-203	Tanabe Seiyaku	Pancreatic disorders	I
Z-338	Zeria	Prokinetic	II
		Non-ulcer dyspepsia	II
Z-360	Zeria	Antiulcer	I

[1]Previously published in Drugs of the Future.

Adefovir Dipivoxil



Adefovir dipivoxil (GS-840, Hepsera™, formerly known as Preveon™; Gilead) is a nucleotide analog that blocks hepatitis B virus DNA polymerase. The drug is well tolerated and inhibits HBV replication, decreases HBV DNA levels and improves liver histology of patients infected with HBV resistant to other antivirals such as lamivudine. An NDA is currently under review by the FDA for the treatment of chronic HBV infection (1).

Preclinical studies have provided evidence of the antiviral properties of adefovir dipivoxil. An oral dose of 5 or 15 mg/kg/day was effective in woodchucks chronically infected with woodchuck hepatitis virus (WHV), decreasing mean virus DNA levels in plasma by more than 10- and 40-fold at 2 weeks and more than 45- and 300-fold at 12 weeks, respectively. In woodchucks, the mean maximum concentration in serum was 0.462 mcg/ml with an elimination half-life of 10.2 h. Adefovir was found to potently inhibit duck hepatitis B virus (DHBV) replication and viral covalently closed circular (CCC) DNA amplification, but it did not inhibit the formation of CCC DNA from incoming viral genomes. *In vitro* studies also showed that adefovir dipivoxil could be combined with nucleoside analogs. When combined with lamivudine or entecavir, the drug had additive antiviral effects on a cell line expressing high levels of wild-type HBV after 1 week of treatment (2-4).

No interaction was found between adefovir and either food or other drugs (*i.e.*, lamivudine, acetaminophen, ibuprofen or trimethoprim/sulfamethoxazole) in healthy volunteers and patients with HBV infection. However, adjustment of the adefovir dose was necessary when the patients also showed moderate or severe renal impairment (5-7).

The antiviral effects of adefovir have been assessed extensively in patients with chronic hepatitis B. Two randomized, placebo-controlled phase III studies evaluated the safety and efficacy of adefovir monotherapy in the treatment of HBV infection resistant to lamivudine. In one study, 515 patients with chronic HBV infection and HBe antigen-positive received either adefovir (10 or 30 mg once daily) or placebo for 48 weeks. Both adefovir doses led to significant improvements over placebo in liver histology (necroinflammation and fibrosis) (8). In some of these patients, HBV-specific T-cell responses were enhanced by adefovir treatment, depending on the decrease in HBV DNA levels (9). Compared to placebo, patients treated with adefovir showed a higher rate of seroconversion and a higher median decrease in HBV DNA levels in plasma compared to baseline. There were no differences between placebo-treated and adefovir-treated patients in the discontinuation rate, incidence of laboratory abnormalities and incidence of clinical adverse events after 48 weeks of treatment (10-16). Similar results were reported in a second study, which used the same design but was conducted in patients with precore mutant HBV infection (*i.e.*, HBe antigen-negative) (14-25). A daily dose of 10 mg of adefovir also effectively inhibited HBV replication when administered to liver transplant patients with HBV infection for 48 weeks. Clinical improvements in ALT, bilirubin and albumin levels were also reported in these patients (26-28). The results of these studies and some that follow are summarized in Table I.

Adefovir at a daily dose of 10 mg was also assessed in the treatment of lamivudine-resistant chronic HBV infection in 35 patients coinfected with HIV and HBV. Treatment with adefovir for 48 or 72 weeks decreased the serum HBV and ALT levels significantly and also induced histological improvement and, in some patients, HBeAg seroconversion (29-33). Addition of adefovir to lamivudine therapy had no effect on HIV-1 RNA or CD4 and CD8 cell counts (34-36). Other studies revealed that adefovir was not recommended for the treatment of advanced HIV infection. A daily dose of 120 mg of adefovir plus background antiretroviral therapy produced no benefits in terms of virological or immunological response, survival or cytomegalovirus prevention and was associated with nephrotoxicity via inhibition of mitochondrial DNA replication (37, 38).

A randomized, double-blind study determined that both adefovir alone (10 mg/day) and the combination of adefovir plus lamivudine (100 mg/day) induced greater reductions in serum HBV DNA and ALT levels than lamivudine alone in 59 patients suffering from lamivudine-resistant chronic hepatitis B (39). In another study, adefovir at 10 mg/day was added to the treatment regimen of 40 chronic hepatitis B patients with evidence of hepatic decompensation receiving lamivudine 100 mg. The combination was well tolerated and resulted in significant reductions in serum ALT and HBV DNA levels after 24 weeks (40).

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

Indication	Design	Treatments	n	Conclusions	Ref.
Hepatitis B	Randomized, double-blind, multicenter	Adefovir dipivoxil, 10 mg/d x 48 wk (n=172) Adefovir dipivoxil, 30 mg/d x 48 wk (n=173) Placebo (n=170)	515	Adefovir dipivoxil (10 mg) was well tolerated and effective against viral infection by HBV, with improvement in liver histology, increased HBeAg seroconversion rates and decreased levels of HBV DNA and ALT in HBeAg positive chronic hepatitis B patients	8, 10, 11
Hepatitis B	Randomized, multicenter	Adefovir dipivoxil (n=16) Placebo (n=6)	22	Adefovir dipivoxil was effective in significantly enhancing T-cell reactivity to HBV, favoring Th1 pattern, in patients with HBeAg+ hepatitis B. These changes were dependent on the magnitude of hepatits B virus DNA suppression	9
Hepatitis B	Randomized, double-blind	Study 437: (n=515) Adefovir, 10 mg od x 48 wk (n=172) Adefovir, 30 mg od x 48 wk (n=173) Placebo (n=170) Study 438: (n=185) Adefovir, 10 mg od x 48 wk (n=123) Placebo (n=62)	700	Adefovir was well tolerated and effective in improving liver histology and inducing seroconversion in patients with chronic precore mutant or lamivudine-resistant HBV infection. No adefovir resistance mutations were detected after the first 48 weeks of treatment in chronic hepatitis B patients	12
Hepatitis B	Randomized, double-blind, pooled/meta-analysis	Study 437: Adefovir, 10 mg od x 48 wk (n=172) Placebo (n=170) Study 438: Adefovir, 10 mg od x 48 wk (n=123) Placebo (n=62)	527	Adefovir demonstrated safety comparable to placebo and produced significant responses in patients with hepatitis B regardless of baseline patient or disease characteristics	14
Hepatitis B	Randomized, double-blind, multicenter	Adefovir, 10 mg x 48 wk Placebo	185	Adefovir dipivoxil had a safety profile similar to placebo and was significantly more effective in histological improvement and HBV DNA and ALT normalization in patients with chronic hepatitis B	17
Hepatitis B	Open	Adefovir dipivoxil, 10-30 mg/d x 2 y	39	Treatment with adefovir dipivoxil for approximately 2 years did not induce the appearance of HBV polymerase mutations that are associated with resistance to adefovir dipivoxil	19
Hepatitis B	Pooled/meta-analysis	Adefovir dipivoxil x 48 wk (n=467) Placebo (n=228)	695	Adefovir dipivoxil treatment was not associated with resistance mutations in chronic hepatitis B patients	21, 24
Hepatitis B	Open	Adefovir dipivoxil, 30 mg po od → 10 mg po od	39	Adefovir dipivoxil sustained antiviral activity and improved ALT in both wild-type and precore mutant chronic HBV patients with no evidence of adefovir-related resistance. Additionally, HBeAg+ patients showed HBeAg seroconversion	22
Hepatitis B, liver trans-plantation	Open	Adefovir dipivoxil, 10 mg od x 48 wk + Background lamivudine treatment	147	Adefovir dipivoxil was effective against all patterns of HBV mutations associated with resistance to lamivudine in liver transplant patients with hepatitis B infection resistant to lamivudine	23

Continued

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

Indication	Design	Treatments	n	Conclusions	Ref.
Hepatitis B, HIV infection	Open	Adefovir dipivoxil, 10 mg od + Lamivudine x 1 y	36	Long-term adefovir dipivoxil treatment did not show emergence of mutations in the polymerase gene in HIV-hepatitis B coinfected patients. Residual replication suggested a very slow clearance of the virus	25
Hepatitis B, liver transplantation		Adefovir dipivoxil, 10 mg/d x 11.1 [median] mo + Lamivudine or background antiviral therapy	9	Adefovir dipivoxil was well tolerated and highly effective in reducing hepatitis B virus replication after liver transplantation in patients with resistance or breakthrough under treatment with lamivudine	26
Hepatitis B, liver transplantation	Open, multicenter	Adefovir dipivoxil, 10 mg po + Immunosuppressive therapy + Background therapy for hepatitis B	131	Adefovir dipivoxil was well tolerated and effective in antiviral and clinical outcomes in postliver transplantation patients with lamivudine-resistant hepatitis B	27
Hepatitis B, liver transplantation	Open, Multicenter	Adefovir dipivoxil, 10 mg od x 11.5 [median] mo + Background medication	127	The addition of 10 mg od of adefovir dipivoxil increased the antiviral efficacy of the existing hepatitis B treatment and was not associated with treatment-limiting toxicity in most postliver transplant patients with chronic hepatitis B infection resistant to lamivudine	28
Hepatitis B, HIV infection	Open	Adefovir, 10 mg/d po + Lamivudine, 150 mg po bid + Previous anti-HIV therapy x 32 [median] wk	35	Adefovir 10 mg od added to lamivudine was well tolerated and showed significant activity against lamivudine-resistant hepatitis B virus and HIV coinfection	29, 31
Hepatitis B, HIV infection	Open	Adefovir dipivoxil, 10 mg od x 72 wk	35	Adefovir dipivoxil was well tolerated and effective in producing significant histological improvement, continued decline of serum HBV DNA and ALT and HBeAg seroconversion in HIV/HBV coinfected patients	32
Hepatitis B, HIV infection	Open	Adefovir dipivoxil, 10 mg od x 48 wk + Background lamivudine treatment	35	Adefovir dipivoxil (10 mg) was well tolerated and effective against lamivudine-resistant HBV in HIV-1/HBV coinfected patients	36
HIV infection	Randomized, double-blind, multicenter	Adefovir dipivoxil, 120 mg po od + Background medication (n=253) Placebo + Background medication (n=252)	505	The addition of 120 mg od of adefovir dipivoxil to background antiretroviral therapy in advanced HIV patients did not induce any virological or immunological benefits and was associated with significant nephrotoxicity	37
Hepatitis B	Double-blind, multicenter	Lamivudine, 100 mg od x 48 wk (n=19) Adefovir dipivoxil, 10 mg od + Lamivudine x 48 wk (n=20) Adefovir dipivoxil x 48 wk (n=20)	59	Adefovir dipivoxil alone or with lamivudine was effective in reducing hepatitis B DNA levels and ALT serum levels compared with lamivudine alone in lamivudine-resistant hepatitis B patients	39

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

Alicaforsen Sodium

Nonadecasodium salt of 20-mer phosphorothioate oligodeoxynucleotide whose sequence is 5'-GCCCAAGCTGGCATCCGTCA-3'

Alicaforsen (ISIS-2302; Isis Pharmaceuticals) is an antisense inhibitor of human ICAM-1 that is in development for the treatment of mild to moderate psoriasis, ulcerative colitis and active Crohn's disease. Phase III trials in Crohn's disease are currently under way (1).

In a double-blind, randomized, placebo-controlled, phase IIb clinical trial, 299 steroid-dependent patients with active Crohn's disease received either placebo or 2 mg/kg/day of alicaforsen i.v. 3 times weekly for 2 or 4 weeks. Patients with the highest drug exposure showed consistent disease improvement, with a median duration of remission of over 6 months and a clinical remission rate of 55.6% compared to 18.8% for placebo. This was reflected in an improved quality of life and a reduction in steroid use. The drug was well tolerated, with allergic reactions leading to withdrawal in only a small percentage of patients. The authors concluded that higher doses of alicaforsen might be effective in Crohn's disease (2).

In another randomized, placebo-controlled, dose-escalation phase II trial conducted at 11 European sites, 40 patients with active distal ulcerative colitis were randomized to receive 60-ml enemas containing placebo or alicaforsen 0.1, 0.5, 2 or 4 mg/ml every night for 1 month. Treatment with alicaforsen was associated with a higher median improvement in disease activity and clinical activity compared to placebo. These improvements were maintained at 3 and 6 months and no patients in the highest dose group required additional medication over 6 months, whereas half of the placebo patients did (3).

Two different studies conducted with stable and *de novo* renal transplant recipients reported that the following adverse events were associated with alicaforsen (0.05, 0.5, 1 or 2 mg/kg i.v. for 2 weeks): a dose-related, significant and transient increase in partial thromboplastin time, a trend for reduced platelet counts, mild headache, viral infections and gastrointestinal disturbances. In some cases, alicaforsen has been shown to induce intracranial bleeding leading to seizures, renal artery thrombosis and/or deep vein thrombophlebitis (4). The drug induced no changes in the rate of acute rejection after 3 months of treatment, and does not seem to induce genotoxicity (4, 5).

1. *New phase III trial initiated for alicaforsen in Crohn's disease*. DailyDrugNews.com (Daily Essentials) Dec 4, 2001.

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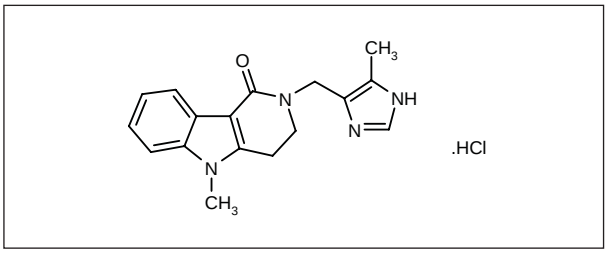
Original monograph - Drugs Fut 2002, 27(5): 439.

Alosetron Hydrochloride



Alosetron hydrochloride (Lotronex®; GlaxoSmithKline) was approved and launched in the U.S. in 2000, but withdrawn that same year after serious gastrointestinal events were reported with the use of the product in the treatment of irritable bowel syndrome (IBS). New data on the efficacy and safety of alosetron have prompted a joint FDA advisory panel recommendation that the FDA consider the possible reintroduction of alosetron hydrochloride for the treatment of women with diarrhea-predominant IBS, provided certain restrictions concerning risk prevention and management were introduced (1).

Pharmacokinetic studies conducted in healthy volunteers found no evidence of an interaction of an oral dose of 1 mg b.i.d. of alicaforsen with other drugs such as alprazolam (1 mg p.o.) or fluoxetine (20 mg p.o.) (2, 3). Comparison of the pharmacokinetics of alosetron 2 mg in 48 healthy young and elderly volunteers revealed a sex difference in clearance by metabolism, and also that serum concentrations tended to be higher in older subjects (4).

Several studies reported the effects of alosetron at a dose of 1 mg b.i.d. When administered for 4 days, this dose decreased the sensitivity of the colon to distention (5). After 1-2 weeks of treatment, alosetron improved rectal compliance and the threshold for the first sensation of stool and severe urgency (6). Treatment for 6 weeks significantly decreased small bowel and proximal and overall colonic transit in all IBS patients, but especially in women (7). In female IBS patients, treatment with alosetron for 12 weeks provided adequate relief of IBS pain, increased urgency and stool frequency and improved stool consistency (8, 9). These effects were reflected in significant improvements in the IBS Quality of Life Questionnaire (IBSQOL) for alosetron-treated patients (10). Treatment for 12 weeks was also associated with a decrease in the amount of time missed from work due to the disease (11). After 48 weeks of treatment, transient constipation was the most common adverse event (in 32% and 5% of patients treated with alosetron and placebo, respectively) (12). The results of these studies and those that follow are summarized in Table II.

Other doses and regimens were also tested in different studies. Treatment with alosetron for 12 weeks was effective in the relief of pain and discomfort associated with functional dyspepsia at the doses of 0.5, 1 and 2 mg b.i.d. (13). In 36 healthy volunteers, alosetron at 0.5 or 1 mg b.i.d. reduced aggregate symptoms, nausea and bloating after ingestion of the maximum tolerable volume of a liquid meal, without increasing gastric volume (14). A dose of 4 mg b.i.d. administered for 2.7 days increased motility and stool consistency and also decreased stool frequency (15).

1. *FDA advisory panel recommends reintroduction of Lotronex for irritable bowel syndrome*. DailyDrugNews.com (Daily Essentials) April 25, 2002.

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

Indication	Design	Treatments	n	Conclusions	Ref.
Healthy volunteers	Crossover	Alosetron, 1 mg bid x 4 d Loperamide, 2 mg bid x 4 d Placebo	10	Treatment with alosetron, but not loperamide, decreased sensitivity of the colon to distention in healthy volunteers	5
Healthy volunteers	Open	Alosetron, 1 mg bid po x 1-2 wk	5	Alosetron increased rectal compliance and the threshold for the first sensation of stool and severe urgency without affecting sphincter function in healthy volunteers	6
Diarrhea, irritable bowel syndrome	Open	Alosetron, 1 mg bid x 6 wk	37	Treatment with alosetron significantly decreased small intestine and colonic transit in patients with irritable bowel syndrome. The response to alosetron was greater among female patients than male patients	7
Diarrhea, irritable bowel syndrome	Randomized, double-blind	Alosetron, 1 mg po bid x 12 wk (n=309) Placebo (n=317)	626	Alosetron effectively relieved pain and rapidly improved some bowel function disturbances in female patients with diarrhea-predominant irritable bowel syndrome	8
Diarrhea, irritable bowel syndrome	Randomized, double-blind, multicenter	Alosetron, 1 mg bid x 12 wk (n=532) Placebo (n=269)	801	Alosetron significantly improved bowel urgency and led to global symptom improvement in female patients with irritable bowel syndrome	9
Diarrhea, irritable bowel syndrome	Randomized, double-blind	Alosetron, 1 mg bid x 12 wk Placebo	1275	Alosetron treatment resulted in significant improvements in health-related quality of life in female patients with diarrhea-predominant irritable bowel syndrome	10
Diarrhea, Irritable bowel syndrome	Randomized, double-blind	Alosetron, 1 mg bid x 12 wk Placebo	903	Alosetron was effective in relieving symptomatology and reduced days missed from work in diarrhea-predominant IBS patients who were employed full time. The effects began the first week of treatment and persisted until the end of treatment	11
Irritable bowel syndrome	Randomized, double-blind, multicenter	Alosetron, 1 mg bid x 48 wk (n=649) Placebo (n=210)	859	Alosetron treatment was well tolerated in patients with irritable bowel syndrome with transient constipation being the most common adverse event	12
Dyspepsia	Randomized, multicenter	Alosetron, 0.5 mg bid x 12 wk (n=77) Alosetron, 1 mg bid x 12 wk (n=79) Alosetron, 2 mg bid x 12 wk (n=83) Placebo (n=81)	320	Alosetron was more effective than placebo in relieving pain or discomfort in patients with functional dyspepsia, resulting in improvements in multiple functional dyspepsia symptoms	13
Healthy volunteers	Randomized, double-blind	Alosetron, 0.5 mg bid x 7 d Alosetron, 1 mg bid x 7 d Placebo	36	After a liquid meal, alosetron reduced aggregate symptoms, nausea and bloating without increasing gastric volume in healthy volunteers	14
Irritable bowel syndrome	Randomized, double-blind, crossover	Alosetron, 4 mg bid x 7 d Placebo	22	Left colonic preprandial phasic motility was slightly increased by alosetron, as were the number and propagation distance of high-amplitude propagated contractions, which paradoxically led to a decrease in stool frequency and a firming of stool consistency	15

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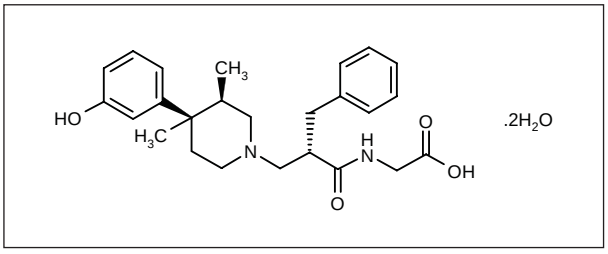
Original monograph - Drugs Fut 1992, 17(8): 660.

Alvimopan



The mu-opioid receptor antagonist alvimopan (ADL-8-2698, LY-246736 dihydrate) is being codeveloped by Adolor in collaboration with GlaxoSmithKline for the management of postoperative ileus and opioid bowel dysfunction. The companies expect to be able to submit an NDA with the FDA in the first half of 2003 (1).

Adolor is currently conducting four phase III trials in order to further determine the efficacy and safety of alvimopan in the treatment of postsurgical ileus and opioid bowel dysfunction. These studies are closely modeled on previous phase II studies; thus, doses of 6 and 12 mg are being administered twice daily to patients with postsurgical ileus included in any of the three current clinical trials. In another phase III clinical trial, patients aged 18 years or older and suffering from opioid bowel dysfunction are receiving either alvimopan or placebo as a single daily dose (2, 3).

In phase II clinical trials, improvement in the frequency and quality of bowel movements was reported by 80-100% of the patients with opioid bowel dysfunction who received 0.5-3.0 mg of alvimopan once daily; this percentage increased with the dose (3-5). Similar improvements were found in healthy volunteers, where alvimopan 4 mg prevented the increase in gastrointestinal transit time induced by morphine 0.5 mg/kg (6) (Table III).

Other phase II trials conducted in patients with postoperative ileus revealed that administration of alvimopan at doses of 3, 6 and 12 mg b.i.d. decreased postsurgical nausea and vomiting, allowed patients to eat solid food earlier, provided a quicker return to normal bowel function and decreased time to discharge from hospital after major abdominal surgery in a dose-dependent manner (7).

A randomized trial in 79 patients undergoing major abdominal surgery who received either placebo or alvimopan at doses of 1 and 6 mg in addition to opioids for postoperative pain relief found that the higher dose was associated with significantly more rapid recovery of gastrointestinal function than placebo, with a median time to the first passage of flatus of 49 h compared to 70 h on placebo, and a median time to first bowel movement of 70 h compared to 111 h on placebo. The time to hospital discharge was also significantly shorter on alvimopan 6 mg (68 h *vs*. 91 h on placebo). The effects of alvimopan 1 mg were not significantly different from placebo (8) (Table III).

In all these studies, no drug-related safety concerns were reported for alvimopan and none of the patients experienced a reduction in the desired analgesic effects of morphine or other opioid narcotic analgesics that they were receiving for chronic pain, regardless of the indication studied.

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

Indication	Design	Treatments	n	Conclusions	Ref.
Delayed gastric emptying	Randomized, double-blind, crossover, pooled/meta-analysis	Study I: Healthy subjects Alvimopan, 4 mg + Morphine, 0.05 mg/kg iv Placebo po + Morphine, 0.05 mg/kg iv Placebo po + Placebo iv Study II: Patients with dental extraction Alvimopan, 4 mg po + Morphine, 0.15 mg/kg po Placebo + Morphine, 0.15 mg/kg po Placebo po + Placebo iv	59	Alvimopan prevented the prolonged gastrointestinal transit time induced by morphine in healthy volunteers and did not affect morphine analgesia or pupil constriction in patients undergoing oral surgery	6
Constipation	Randomized, double-blind	Alvimopan, 1 mg po sd [2 h presurgery] → 1 mg po bid x 7 d Alvimopan, 6 mg po sd [2 h presurgery] → 6 mg po bid x 7 d Placebo	78	Alvimopan was effective in recovering bowel function and shortened the duration of hospitalization in patients who were taking opioids for postoperative pain in abdominal surgery	8

1. *Adolor's alvimopan will be codeveloped with GSK*. DailyDrugNews.com (Daily Essentials) April 17, 2002.

2. *Adolor conducts additional pivotal phase III trials of alvimopan in postoperative ileus*. DailyDrugNews.com (Daily Essentials) Feb 8, 2002.

3. *Adolor's ADL-8-2698 enters phase III for second indication*. DailyDrugNews.com (Daily Essentials) July 11, 2001.

4. *Adolor's opioid gastrointestinal drug enters late-stage clinical development*. DailyDrugNews.com (Daily Essentials) March 22, 2001.

5. *Phase II trials of ADL-8-2698 in opioid-induced bowel dysfunction successfully completed*. DailyDrugNews.com (Daily Essentials) Jan 19, 2001.

6. Liu, S.S., Hodgson, P.S., Carpenter, R.L., Fricke, J.R. *ADL 8-2698, a trans-3,4-dimethyl-4-(3-hydroxyphenyl)piperidine, prevents gastrointestinal effects of intravenous morphine without affecting analgesia*. Clin Pharmacol Ther 2001, 69(1): 66.

7. *Adolor's opioid narcotic antagonist completes phase II trials for two indications*. DailyDrugNews.com (Daily Essentials) July 2, 2001.

8. Taguchi, A., Sharma, N., Saleem, R.M., Sessler, D.I., Carpenter, R.L., Seedsadr, M., Kurz, A. *Selective postoperative inhibition of gastrointestinal opioid receptors*. New Engl J Med 2001, 345(13): 935.

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

CDP-571

CDP-571 (Humicade™) is a humanized anti-TNF-α antibody developed by Celltech Group that has proved effective in the treatment of active Crohn's disease. It is currently being developed by Celltech and Biogen. In the U.S., the drug has orphan drug status and fast track designation for steroid withdrawal in steroid-dependent Crohn's disease (1).

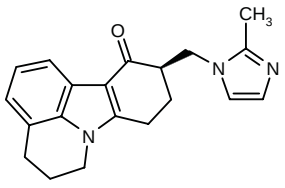
A randomized, double-blind, placebo-controlled trial examined the efficacy of CDP-571 in 169 Crohn's disease patients. After dose response assessment with single doses of either 10 or 20 mg/kg of CDP-571 or placebo, patients received 10 mg/kg CDP-571 or placebo every 8 or 12 weeks. Clinical response was defined as a decrease in the Crohn's Disease Activity Index score of at least 70 points. After 2 weeks of treatment, clinical response was found in 45% and 37% of patients treated with CDP-571 and placebo, respectively. The frequency of severe or serious adverse events was similar in all study groups (2).

1. *Celltech and Biogen collaborate on CDP-571*. DailyDrugNews.com (Daily Essentials) April 25, 2002.

2. Sandborn, W.J., Feagan, B.G., Hanauer, S.B. et al. *An engineered human antibody to TNF (CDP571) for active Crohn's disease: A randomized double-blind placebo-controlled trial*. Gastroenterology 2001, 120(6): 1330.

Original monograph - Drugs Fut 2000, 25(7): 669.

Cilansetron



Solvay's cilansetron is a 5-HT_3 antagonist in phase III clinical development for the treatment of IBS. Solvay intends to secure a marketing partner for cilansetron and foresees submitting a regulatory application for the drug in 2003 (1).

Two multicenter, randomized, double-blind, placebo-controlled, parallel-group phase III clinical trials confirmed the results of earlier phase II placebo-controlled trials, which had shown efficacy for cilansetron in the treatment of diarrhea-predominant IBS. Nonconstipated patients received cilansetron 1, 2, 8 or 16 mg t.i.d. in one study (n = 471) and 1, 2, 4 or 16 mg t.i.d. in the other study (n = 435). Among patients without adequate relief at baseline, the median adequate relief rate was 50-66% in the cilansetron groups compared to 25% on placebo. The agent was equally effective in patients meeting both Rome I and II criteria (2, 3). Cilansetron was well tolerated, with constipation and flatulence the most common adverse events. The frequency of constipation was dose-dependent up to 8 mg (4). The results of these studies are summarized in Table IV.

1. *Solvay advances cilansetron to phase III for IBS*. DailyDrugNews.com (Daily Essentials) July 19, 2001.

2. Caras, S., Carter, F., Algood, A., Driessen, S., Krause, G., Steinborn, C. *Cilansetron shows an increase in adequate relief rate in non-constipated IBS subjects who respond as having no adequate relief at baseline*. Dig Dis Week (May 19-22, San Francisco) 2002, Abst W1019.

3. Caras, S., Krause, G., Biesheuvel, E., Steinborn, C. *Cilansetron shows efficacy in non-constipated irritable bowel syndrome patients independent of the definition of the patient population by Rome I or Rome II*. Dig Dis Week (May 20-23, Atlanta) 2001, Abst 1138.

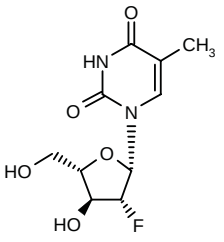
4. Caras, S., Krause, G., Biesheuvel, E., Steinborn, C. *Cilansetron shows efficacy in male and female non-constipated patients with irritable bowel syndrome in a United States study*. Dig Dis Week (May 20-23, Atlanta) 2001, Abst 1139.

Original monograph - Drugs Fut 1999, 24(5): 475.

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

Indication	Design	Treatments	n	Conclusions	Ref.
Irritable bowel syndrome	Randomized, double-blind, multicenter, pooled/meta-analysis	Cilansetron, 1, 2, 4, 8 or 16 mg tid x 12 wk Placebo	896	Cilansetron resulted in higher rates of adequate relief of symptoms than placebo in patients with nonconstipated irritable bowel syndrome who showed no response at baseline	2
Irritable bowel syndrome	Double-blind, multicenter, pooled/meta-analysis	Cilansetron, 1 mg po tid x 12 wk Cilansetron, 2 mg po tid x 12 wk Cilansetron, 4 mg po tid x 12 wk Cilansetron, 8 mg po tid x 12 wk Cilansetron, 16 mg po tid x 12 wk Placebo	906	Cilansetron was effective in relieving the symptoms of nonconstipated irritable bowel syndrome	3
Irritable bowel syndrome	Randomized, double-blind, multicenter	Cilansetron, 1 mg po tid x 12 wk Cilansetron, 2 mg po tid x 12 wk Cilansetron, 8 mg po tid x 12 wk Cilansetron, 16 mg po tid x 12 wk Placebo	454	Cilansetron was safe, well tolerated and effective in achieving adequate relief of symptoms in patients with nonconstipated irritable bowel syndrome	4

Clevudine



The purine analog clevudine (L-FMAU) exerts strong antiviral effects against HBV through preferential inhibition of specific stages of the viral replication cycle. Triangle Pharmaceuticals holds worldwide rights (except Korea) from Bukwang. An ongoing phase I/II clinical trial is assessing its tolerability, safety and efficacy in patients with chronic hepatitis B infection.

A new synthesis of clevudine has been described:

Peracetylation of L-arabinose (I) with acetic anhydride and pyridine provides acetylated arabinose (II), which is then brominated by means of HBr in $AcOH/Ac_2O$ to furnish the bromo-sugar (III). Treatment of the sugar (III) with Zn dust, $CuSO_4$ and NaOAc in $AcOH/H_2O$, followed by chromatographic separation, gives L-arabinal (IV), which is then converted to the fluoro derivative (V) by reaction with Selectfluor® (F-TEDA-BF_4) in refluxing nitromethane/H_2O. Deacetylation of compound (V) with NaOMe in MeOH yields compound (VI), which is then converted into the methyl furanoside (VII) by treatment with H_2SO_4 in MeOH. Benzoylation of the furanoside (VII) with benzoyl chloride in pyridine affords a mixture of isomers, from which (VIII) is separated by chromatography and then brominated with HBr/AcOH in CH_2Cl_2 to provide the bromo-sugar (IX). Condensation of the sugar (IX) with the silylated pyrimidine derivative (X) in refluxing chloroform affords 3,5-di-*O*-benzoylclevudine (XI), which is finally deprotected by treatment with *n*-butylamine in refluxing methanol. Compound (X) is obtained by treatment of thymine (XII) with HMDS (1,1,1,3,3,3-hexamethyldisilazane) and ammonium sulfate in refluxing chloroform (1). Scheme 1.

The antiviral properties of clevudine were assessed in several preclinical studies. When the drug was administered orally once daily for 4 weeks to woodchucks with chronic hepatitis B infection, it induced a dose-dependent and significant decrease in viremia, antigenemia, intrahepatic viral replication and intrahepatic expression of woodchuck hepatitis virus (WHV) core proteins (2). When treatment was prolonged to 12 weeks, the levels of WHV covalently closed circular DNA were below the limit of detection and remained low for up to 68 weeks in 3 out of 4 woodchucks included in the study (3). Researchers also found that mutant virus strains that conferred resistance to lamivudine in woodchucks chronically infected with WHV also showed cross-resistance to clevudine and that the mutations were primarily in the B region (4, 5).

Higher antiviral efficacy was reported for clevudine when combined with other drugs, such as DAPD and emtricitabine (6). In the woodchuck hepatitis B virus infection model, greater benefits, including a broad immune response and delays in disease progression, were found in animals treated with clevudine 10 mg/kg/day for 32 weeks followed by WHsAg vaccine 50 μg s.c. at weeks 32, 36, 40 and 48 (7).

Preclinical studies in rats and monkeys demonstrated that clevudine lacks the toxicity found with the nucleoside analogs D-FIAU and D-FMAU (8).

An ongoing open-label phase I/II trial is being conducted to determine the antiviral activity, safety and tolerability of escalating once-daily doses of clevudine in treatment-naive chronic HBV-infected subjects. Data have been reported from 4 subjects on 10 mg, 10 subjects on 50 mg and 10 subjects on 100 mg who had completed the 28-day dosing period. The median viral load at baseline was 7.13, 7.96 and 8.76 $\log_{10}$ copies/ml in the 10-, 50- and 100-mg cohorts, respectively, and was reduced at the end of the dosing period by a median of 2.48, 2.74 and 2.95 $\log_{10}$ copies/ml, respectively. At 5 months, a median decrease in HBV DNA of 1.9 $\log_{10}$ copies/ml was seen in patients treated at the lowest dose. The median decrease after 24-week follow-up in 7 patients on the intermediate dose was 2.07 $\log_{10}$ copies/ml, and 5 patients on the highest dose had a mean decrease of 3 $\log_{10}$ copies/ml at 1 month posttreatment (9).

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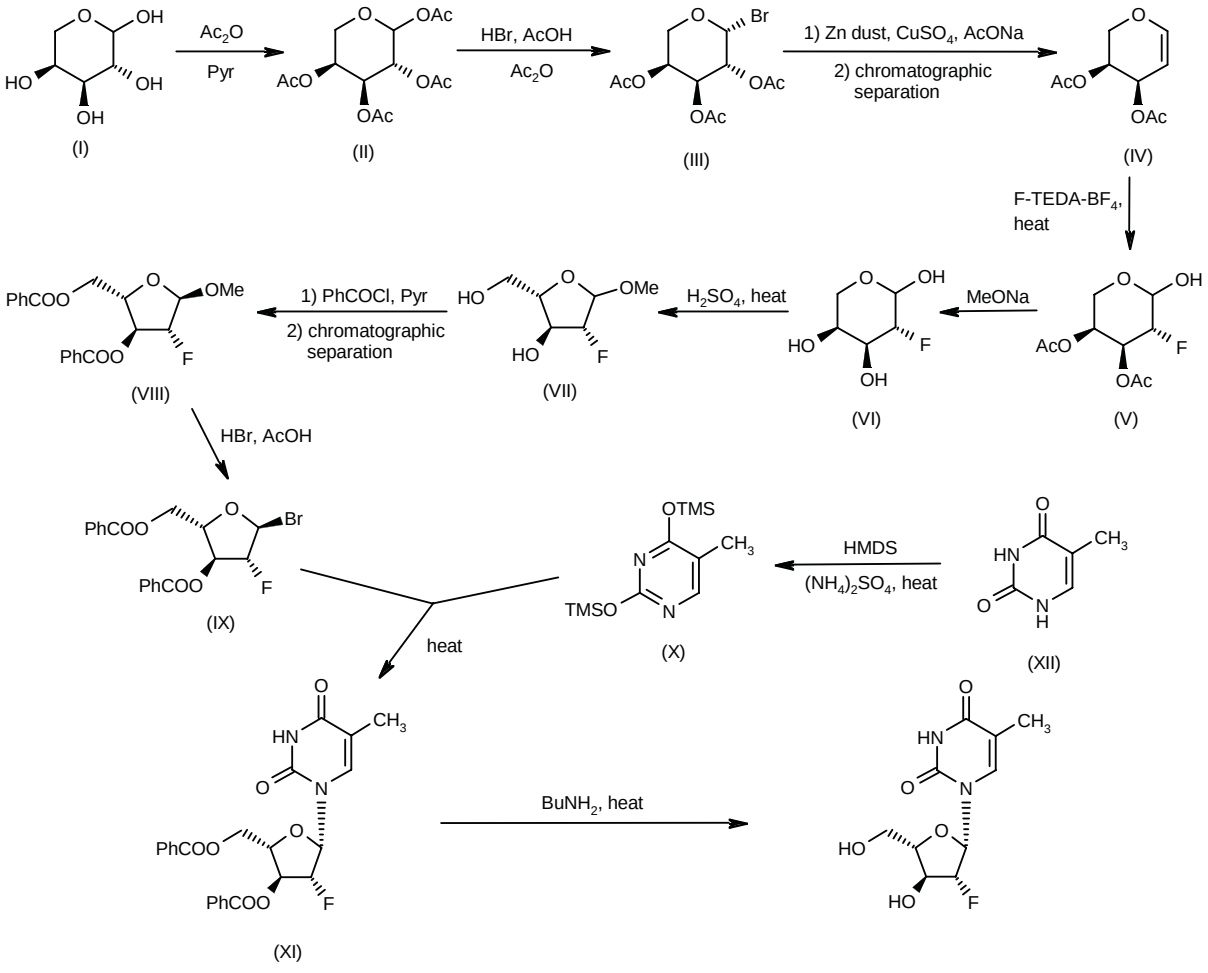
Scheme 1: Synthesis of Clevudine



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Original monograph - Drugs Fut 1998, 23(8): 821.

Deligoparin Sodium

Deligoparin sodium (OP-2000) is an ultra-low-molecular-weight heparin discovered by Opocrin and jointly developed by Incara and Elan. Its antithrombotic and antiinflammatory properties, together with data from earlier studies conducted with unfractionated heparin in patients with inflammatory bowel disease (IBD), appear to justify its use in the treatment of active ulcerative colitis.

The mechanism of action of OP-2000 in IBD was explored in a randomized, open-label study in which 38 healthy volunteers were given once-daily doses of 100 or 150 mg/kg s.c. for 8 days. Administration of OP-2000 at both doses resulted in sustained release of tissue factor pathway inhibitor and anti-factor Xa (1).

In January 2001, patient enrollment began in a pivotal phase II/III trial of OP-2000 for the treatment of patients receiving standard treatment with aminosalicylates who had developed symptoms of active ulcerative colitis. The study, sponsored by both Elan and Incara, intends to evaluate complete remission or a significant improvement in the signs and symptoms of the disease in approximately 270 patients treated with either drug or placebo once daily for 6 weeks. In studies in over 230 healthy subjects and patients with cardiovascular disease, OP-2000 was shown to be safe and well tolerated (2, 3).

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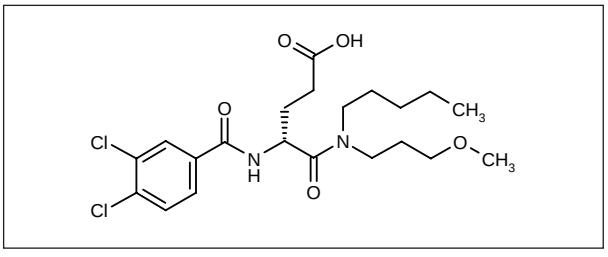
Dexloxiglumide



The cholecystokinin CCK-A (CCK-1) receptor antagonist dexloxiglumide (CR-2017) is being developed by Rotta and Forest primarily for the treatment of irritable bowel syndrome. The drug has also shown efficacy against gastric distention in patients suffering from functional dyspepsia.

Using rats with electrodes on the proximal colon and on the striated muscle of the abdomen, researchers found that while rectal distension inhibited the occurrence of colonic spike bursts and increased abdominal contractions, dexloxiglumide 20 mg/kg significantly reduced the inhibition of colonic spike bursts without affecting abdominal contractions. Dexloxiglumide also inhibited the hyperalgesia and allodynia induced by inflammation in this model (1).

Scientists investigating the ability of dexloxiglumide to inhibit human cytochrome P-450 concluded that although the drug interacts with CYP2C9, no clinically relevant metabolic interactions with other CYP2C9 substrates were likely (2).

The tolerability, safety and pharmacokinetics of dexloxiglumide (100-400 mg o.d. followed by t.i.d. for 7 days) were evaluated in a randomized, double-blind, crossover study in 20 healthy male volunteers. Treatment was well tolerated, with no serious adverse events reported. Dexloxiglumide presented a dose-independent pharmacokinetic profile following single doses of 100-400 mg and multiple doses of 100-200 mg. The elimination half-life was around 3 h and the recommended dose for treatment of constipation-predominant IBS was 200 mg t.i.d (3, 4).

A multicenter, randomized, placebo-controlled, 12-week trial in 405 IBS patients established that the 200 mg t.i.d. dose of dexloxiglumide was more effective than placebo, but significantly superior in female patients with constipation-predominant IBS (5). The risk of gallstone formation did not increase with dexloxiglumide, even when it was administered to 262 of these patients for another 12 months (5, 6) (Table V).

An initial study on functional dyspepsia and lipid ingestion showed that duodenal infusion of 10% or 20% lipid increased gastric volume compared to saline and plasma CCK levels in both healthy controls and patients with functional dyspepsia. During gastric distention and infusion of 20% lipid, dyspeptic patients had higher symptom scores than healthy subjects, whereas healthy subjects had a greater increase in gastric compliance than the patients. In a second study, 12 patients with function-

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

Indication	Design	Treatments	n	Conclusions	Ref.
Irritable bowel syndrome	Randomized, double-blind, multicenter	Study 1: (n=405) Dexloxiglumide, 200 mg tid x 12 wk Placebo Study 2: (n=262) Dexloxiglumide, 200 mg tid x 12 mo	667	A dose of 200 mg tid dexloxiglumide did not increase the risk of gallstones and was effective in the treatment of patients with irritable bowel syndrome	5, 6
Dyspepsia	Randomized, double-blind	Study 1: 10% lipid solution i.d. over 1 ml/min sd 20% lipid solution i.d. over 1 ml/min sd Placebo Study 2: Dexloxiglumide, 15 mg/kg/h iv over 10 min → 5 mg/kg/h iv over 10 min → 20% lipid solution i.d. over 1 ml/min sd Placebo	18	Dexloxiglumide was effective in reducing the increase in gastric volume and dyspepsia symptoms induced by duodenal lipid infusion	7

al dyspepsia were given dexloxiglumide (5 mg/kg/h) during duodenal infusion of 20% lipid with or without gastric distention. The CCK-A antagonist completely prevented the increase in gastric volume and dyspeptic symptoms during lipid infusion, decreased gastric compliance and symptom scores during gastric distention, and appeared to reduce the patients' sensitivity to distention (7) (Table V).

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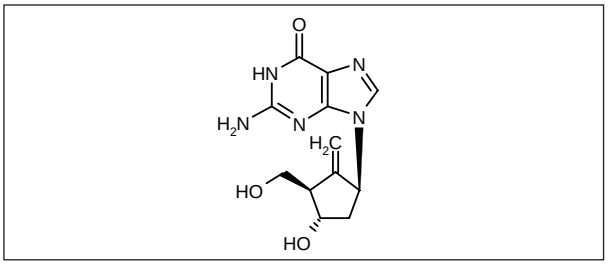
Original monograph - Drugs Fut 1999, 24(7): 725.

Entecavir



Bristol-Myers Squibb's entecavir (BMS-200475) is a potent deoxyguanosine nucleoside analog developed for the treatment of hepatitis B and presently undergoing phase III testing.

New preclinical data on the efficacy and safety of entecavir have been reported. In woodchucks chronically infected with WHV, treatment with oral entecavir (0.5 mg/kg/day for 8 weeks followed by 0.5 mg/kg/week for 12-22 months) significantly decreased the levels of viral antigens and covalently closed circular DNA. Entecavir was well tolerated and no signs of viral resistance were found during the study. Several animals showed sustained responses and survived more than 3 years, thus suggesting that entecavir delayed the onset of hepatocellular carcinoma and prolonged life expectancy in this model (1). Another study conducted in transgenic mice expressing HBV established that 0.1 mg/kg/day administered orally once daily for 10 days was the minimal effective dose (2). Entecavir was also found to be a well

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

Indication	Design	Treatments	n	Conclusions	Ref.
Hepatitis B	Randomized	Entecavir, 0.1mg od x 24 wk Entecavir, 0.5 mg od x 24 wk Entecavir, 1.0 mg od x 24 wk Lamivudine, 100 mg od x 24 wk	181	Entecavir significantly decreased hepatitis B viremia in patients failing lamivudine therapy	6
Hepatitis B	Randomized, double-blind	Entecavir, 0.01 mg po od x 24 wk (n=45) Entecavir, 0.1 mg po od x 24 wk (n=45) Entecavir, 0.5 mg po od x 24 wk (n=45) Lamivudine, 100 mg po od x 24 wk (n=45)	180	Treatment with entecavir at daily doses of 0.1 mg and 0.5 mg was well tolerated and more effective than lamivudine in the treatment of chronic hepatitis B	7
Hepatitis B	Randomized, double-blind	Entecavir, 0.05 mg po od x 28 d (n=8) Entecavir, 0.1 mg po od x 28 d (n=9) Entecavir, 0.5 mg po od x 28 d (n=9) Entecavir, 1 mg po od x 28 d (n=8) Placebo (n=8)	42	Entecavir induced a significant decrease in HBV DNA levels and was as well tolerated as placebo when given as short-term therapy in patients with chronic hepatitis B	8, 9
Hepatitis B, liver transplantation	Open	Entecavir, 1 mg od x 42 wk (range 20-67)	9	Entecavir monotherapy was well tolerated and highly effective in reducing hepatitis B viral load and the biochemical markers of the disease in liver transplant recipients	10

tolerated, highly potent inhibitor of duck hepatitis B virus infection in duck hepatocytes and ducklings (3).

The efficacy of entecavir against wild-type and lamivudine-resistant HBV is based on the results of *in vitro* studies and randomized clinical trials. The analysis of mutations in the HBV polymerase gene revealed that entecavir was effective against wild-type HBV and also against some, but not all, mutations resistant to lamivudine (4). Enzyme inhibition studies revealed that both entecavir and its active form entecavir-triphosphate were more potent than lamivudine against clinically relevant mutations in the nucleotide binding site of HBV DNA polymerase and in HepG2 cultures (5).

Daily doses of 0.1, 0.5 or 1 mg of entecavir were reported to be more effective than a dose of 100 mg lamivudine in decreasing HBV viral load and replication among patients with chronic hepatitis B infection previously treated or not with other antiviral therapies. In one study, 25% of the patients treated with entecavir showed HBV viral levels below the limit of detection. A dose of 1 mg/day of entecavir was also safe and effective in patients with liver transplants and infected with HBV. Overall, treatment with entecavir was safe and well tolerated. One study reported more frequent mild to moderate nervous system adverse events in patients treated with 0.5 mg/day entecavir than in the lamivudine-treated group, and also that 1 subject receiving entecavir 0.1 mg discontinued therapy after 18 weeks due to lethargy and photosensitivity. Slow return of HBV DNA to baseline was found in patients treated with entecavir doses of 0.5 and 1 mg/day (6-10). The results of these studies are summarized in Table VI.

Entecavir has been included in antiviral combinations claimed by GlaxoSmithKline in the treatment of HBV infections, including those caused by HBV mutants resistant to nucleoside and non-nucleoside inhibitors of HBV viral replication (11).

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9. de Man, R.A., Wolters, L.M.M., Nevens, F., Chua, D., Sherman, M., Lai, C.L., Gadano, A., Lee, Y., Mazzotta, F.,

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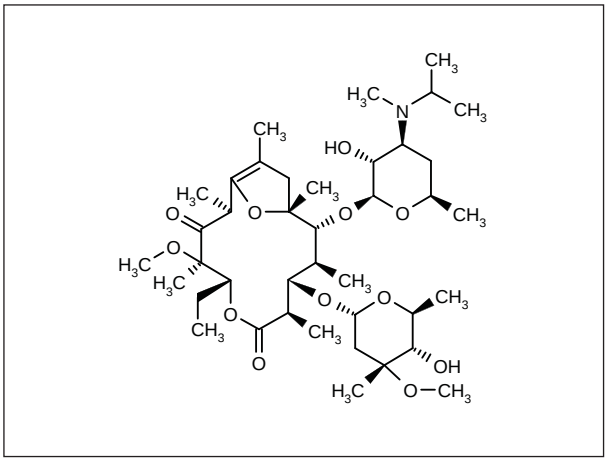
GM-611



The motilin receptor agonist GM-611 (Chugai) is a derivative of erythromycin A that has gastroprokinetic effects and is potentially useful for the treatment of gastroparesis and similar gastric motility disorders.

GM-611 is currently under phase II clinical development. In February 2002, Chugai received authorization by the FDA to resume a U.S. trial that had been temporarily suspended due to possible serious adverse events in long-term carcinogenicity studies in rats (1, 2).

A double-blind, randomized trial conducted in the U.S. compared four different doses of GM-611 (10, 20 and 30 mg b.i.d. and 20 mg t.i.d.) to placebo in 104 patients suffering from symptomatic gastroparesis. After 28 days of treatment, 10 and 30 mg b.i.d. were the doses that had the greatest gastric emptying-accelerating effect compared to placebo (3).

1. *Clinical hold placed on GM-611 pending analysis of animal toxicity studies*. DailyDrugNews.com (Daily Essentials) June 20, 2001.

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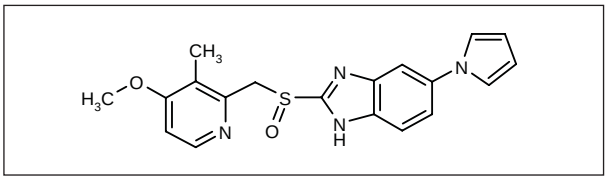
IY-81149



The new proton pump inhibitor IY-81149 (Ilaprazole), developed by Il-Yang, has demonstrated promising results in preclinical studies in preventing reflux esophagitis and inhibiting gastric acid secretion, which prompted Axcan to acquire an option to license the compound in phase II clinical trials.

Comparison of the two proton pump inhibitors IY-81149 and omeprazole revealed significant differences between the compounds. In a rabbit parietal cell preparation, IY-81149 inhibited H^+/K^+-ATPase about 17 times more potently than omeprazole at a pH of 7.4. Similarly, in histamine-stimulated rabbit and human parietal cells, IY-81149 inhibited the accumulation of [^{14}C]-aminopyrine more potently than omeprazole. *In vivo* studies in pylorus-ligated rats, anesthetized rats, fistular rats and Heidenhain pouch dogs demonstrated that oral IY-81149 had inhibitory effects on acid output that were 2-3 times more potent than those of oral omeprazole. Inhibitory activity was found for IY-81149 under conditions of both normal and increased gastric acid secretion. Compared to omeprazole, IY-81149 had a shorter duration of action and it was thus suggested that it might induce fewer adverse events (1, 2).

IY-81149 was administered orally at doses ranging from 0.3-1000 mg/kg in general pharmacology studies to assess the potential toxic effects of this drug on the central nervous, cardiovascular, respiratory and other organ systems in mice, rats, guinea pigs and dogs. Oral doses

of 1-3 mg/kg significantly decreased gastric secretion in pylorus-ligated rats, and no notable effects were found on the other body systems at doses below 100 mg/kg. Adverse effects in mice consisted of reduced locomotor activity, impaired motor function, prolongation of phenobarbital sleeping time, a dose-dependent hypothermic effect and an analgesic effect; all these effects appeared at doses at least 20 times higher than the estimated clinically effective dose. No anticonvulsant activity (mice), no cardiovascular or respiratory effects (rats, dogs) and no effect on smooth muscle contraction (guinea pigs), intestinal transport (mice) or renal function (mice) were seen (3).

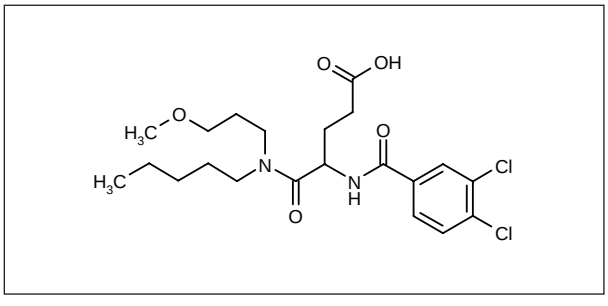
1. Kil, B.J., Kim, I.W., Shin, C.Y., Jeong, J.H., Jun, C.H., Lee, S.M., Kim, D.Y., Huh, I.H., Sohn, U.D. *Comparison of IY81149 with omeprazole in rat reflux oesophagitis*. J Auton Pharmacol 2000, 20(5-6): 291.

2. Kwon, D., Chae, J.B., Park, C.W., Kim, Y.S., Lee, S.M., Kim, E.J., Huh, I.H., Kim, D.Y., Cho, K.D. *Effects of IY-81149, a newly developed proton pump inhibitor, on gastric acid secretion in vitro and in vivo*. Arzneim-Forsch Drug Res 2001, 51(3): 204.

3. Kim, E.J., Lee, R.K., Lee, S.M., Kim, D.Y. *General pharmacology of IY-81149, a new proton pump inhibitor*. Arzneim-Forsch Drug Res 2001, 51(1): 51.

Original monograph - Drugs Fut 1999, 24(6): 618.

Loxiglumide



Loxiglumide (CR-1505, Loxizin®) is a cholecystokinin antagonist discovered at Rotta and developed by Kaken and Mitsubishi Pharma for acute and chronic pancreatitis. Its possible use in the treatment of other disorders, such as IBD and gastroesophageal reflux disease, is also currently being evaluated.

Loxiglumide inhibits the effects induced by cholecystokinin octapeptide (CCK-8) both *in vivo* and *in vitro*. Muscle contractions induced by CCK-8 in colonic muscle strips *in vitro* were inhibited by loxiglumide. The finding that CCK-8 increased the colon motility index and peak amplitude after a meal in patients with irritable bowel syndrome but not in controls suggests a role for loxiglumide in the treatment of this disease. The increase in pancreatic blood flow and protein secretion induced in dogs by CCK-8 was also inhibited. In hamsters, loxiglumide inhibited the carcinogenic effects induced by *N*-nitrosobis-(2-oxopropyl)amine in the gallbladder and extrahepatic bile duct, but not in the intrahepatic bile ducts or pancreas (1-3).

A study in duodenal ulcer patients found that infection by *Helicobacter pylori* was associated with enhanced gastric emptying and unresponsiveness to treatment with loxiglumide. Eradication of the infection decreased the

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

Indication	Design	Treatments	n	Conclusions	Ref.
Duodenal ulcer	Randomized, pooled/meta-analysis	Loxiglumide, 10 mg/kg iv Placebo	20	Loxiglumide did not affect the gastric emptying rate in *H. pylori*-infected patients, in whom gastric emptying was enhanced. In *H. pylori*-eradicated patients, the gastric empyting rate was prolonged and was significantly enhanced by loxiglumide	4
Gastro-esophageal reflux disease	Randomized, double-blind, crossover	Loxiglumide, 30 mg/kg/h iv x 10 min → 10 mg/kg/h x 2 h Placebo	19	Loxiglumide attenuated the postprandial drop in lower esophageal sphincter pressure and increased transient lower esophageal sphincter relaxations in both healthy subjects and patients with GERD. Nevertheless, the effect on acid reflux was modest	5

gastric emptying rate but restored the enhancement of gastric emptying induced by loxiglumide (4) (Table VII).

In a randomized, double-blind study, 10 healthy volunteers and 9 patients with symptomatic gastroesophageal reflux disease received an infusion of loxiglumide or placebo followed by a liquid meal. Loxiglumide attenuated the postprandial drop in lower esophageal sphincter pressure and increased transient lower esophageal sphincter relaxation in both healthy subjects and those with reflux disease, although the effect on acid reflux was modest (5) (Table VII).

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2. Nakajima, M., Naruse, S., Kitagawa, M., Ishiguro, H., Jin, C., Ito, O., Hayakawa, T. *Role of cholecystokinin in the intestinal phase of pancreatic circulation in dogs*. Am J Physiol - Gastrointest Liver Physiol 2001, 280(4): G614.

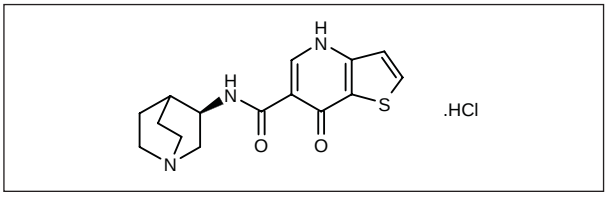
3. Ogura, Y., Matsuda, S., Itho, M., Sasaki, H., Tanigawa, K., Shimomura, M. *Inhibitory effect of loxiglumide (CR 1505), a cholecystokinin receptor antagonist, on N-nitrosobis(2-oxopropyl)amine-induced biliary carcinogenesis in Syrian hamsters*. World J Surg 2002, 26(3): 359.

4. Konturek, J.W., Stoll, R., Menzel, J., Konturek, M., Konturek, S.J., Domschke, W. *Eradication of Helicobacter pylori restores the inhibitory effect of cholecystokinin on gastric motility in duodenal ulcer patients*. Scand J Gastroenterol 2001, 36(3): 241.

5. Trudgill, N.J., Hussain, F.N., Moustafa, M., Ajjan, R., D'Amato, M., Riley, S.A. *The effect of cholecystokinin antagonism on postprandial lower oesophageal sphincter function in asymptomatic volunteers and patients with reflux disease*. Aliment Pharmacol Ther 2002, 15(9): 1357.

Original monograph - Drugs Fut 1990, 15(1): 32.

MKC-733



MKC-733 is a 5-HT_3 agonist with gastrointestinal motility-enhancing properties that is currently under phase II evaluation by Mitsubishi Pharma and Janssen for the treatment of several digestive disorders, including constipation, gastroesophageal reflux disease and nonulcer dyspepsia.

Two randomized, double-blind, placebo-controlled, crossover studies were performed to evaluate the effects of MKC-733 on small bowel transit time, gastric fundal relaxation and antral motility. Single oral doses of MKC-733 (0.2, 1 or 4 mg) or placebo were administered to fasting healthy male volunteers. After 30 min, subjects consumed either a radiolabeled pancake and milkshake meal or a viscous drink. The results revealed that 5-HT_3 agonists relax the gastric fundus but do not inhibit antral motility and may have a stimulatory effect on small bowel secretion and motility, resulting in faster intestinal transit (1).

The effects of MKC-733 were further analyzed in a study that followed a similar design to administer single doses of either the 5-HT_3 agonist or placebo to 12 healthy male subjects under fasting and fed conditions. MKC-733 was found to increase the number of antral contractions in fasting subjects, but not after these same subjects had been fed a mixed nutrient meal (2).

The results of these two studies are summarized in Table VIII.

Table VIII: Clinical studies of MKC-733 (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Healthy volunteers	Randomized, double-blind, crossover, pooled/meta-analysis	MKC-733, 0.2 mg sd MKC-733, 1.0 mg sd MKC-733, 4.0 mg sd Placebo	12	MKC-733 relaxed the gastric fundus but did not change antral contraction speed or frequency in healthy volunteers. The drug may be useful in the treatment of constipation and functional dyspepsia with impaired gastric accommodation	1
Healthy volunteers	Randomized, double-blind, crossover	MKC-733, 0.2 mg sd → MKC-733, 0.2 mg sd + mixed nutrient meal MKC-733, 1.0 mg sd → MKC-733, 1.0 mg sd + mixed nutrient meal MKC-733, 4.0 mg sd → MKC-733, 4.0 mg sd + mixed nutrient meal Placebo → Placebo + mixed nutrient meal	12	MKC-733 increased the frequency of antral migrating myoelectric complex and the number of antral phase II contractions in fasting, but had no significant effect on fed antral motility in healthy volunteers	2

1. Coleman, N.S., Marciani, L., Blackshaw, P.E., Gowland, P.A., Perkins, A.C., Spiller, R.C. *MKC-733, a selective 5-HT$_3$ receptor agonist, stimulates small bowel transit and relaxes the gastric fundus in man*. Dig Dis Week (May 20-23, Atlanta) 2001, Abst 376.

2. Coleman, N.S., Wright, J., Parker, M., Spiller, R.C. *MKC-733, a selective 5-HT$_3$ receptor agonist, stimulates fasting human antral motility*. Dig Dis Week (May 20-23, Atlanta) 2001, Abst 2343.

Original monograph - Drugs Fut 1999, 24(9): 966.

Natalizumab

Natalizumab (Antegren®) is a humanized monoclonal antibody that inhibits α_4 integrin, thereby blocking immune cell adhesion to blood vessel walls and subsequent migration of lymphocytes into tissue. Elan and Biogen have an agreement to develop, manufacture and commercialize natalizumab for the treatment of Crohn's disease and multiple sclerosis.

Phase II studies conducted to date have yielded promising results for natalizumab in the treatment of Crohn's disease and prompted the initiation of an ongoing phase III clinical trial (1, 2).

A double-blind, placebo-controlled phase II trial conducted at 38 sites in 8 European countries included 240 patients with moderate to severe Crohn's disease. Patients receiving natalizumab showed statistically positive results on multiple endpoints, including induction of remission as measured by the Crohn's Disease Activity Index (1).

A single dose of natalizumab (3 mg/kg i.v.) administered to 30 patients with mild to moderate active Crohn's disease for 2 weeks induced remission in 7 of 18 patients. Rescue medication was required in 4 natalizumab-treated patients compared to 2 placebo-treated patients. Natalizumab was well tolerated and significantly increased the circulating levels of B-cells, T-cells, eosinophils and monocytes, but not neutrophils, basophils and natural killer cells. When the same dose was administered to 10 patients with ulcerative colitis by i.v. infusion over 25-45 min, it significantly improved the patients' quality of life at 2 and 4 weeks after treatment (3-5) (Table IX).

Linear pharmacokinetics were found for natalizumab when administered to patients with active Crohn's disease as a single 3 mg/kg infusion, two 3 mg/kg infusions with a 4-week interval or two 6 mg/kg infusions with a 4-week interval (6).

1. *Promising phase II results reported for Antegren in both MS and Crohn's disease*. DailyDrugNews.com (Daily Essentials) Jan 23, 2001.

2. *Initiation of phase III trials of Antegren in multiple sclerosis and Crohn's disease.* DailyDrugNews.com (Daily Essentials) Dec 21, 2001.

3. Gordon, F.H., Lay C.W.Y., Hamilton, M.I. et al. *A randomized, placebo-controlled trial of a humanized monoclonal antibody to alpha$_4$ integrin in active Crohn's disease.* Gastroenterology 2001, 121(2): 268.

4. Gordon, F.H., Pounder, R.E., Amlot, P.L., Donghue, S. *The effect of natalizumab, a humanized monoclonal antibody to α_4 integrin on circulating activated leukocytes in active inflammatory bowel disease (IBD)*. Dig Dis Week (May 19-22, San Francisco) 2002, Abst T1213.

5. Gordon, F.H., Hamilton, M.I., Donoghue, S., Greenless, C., Palmer, T., Rowley-Jones, D., Dhillon, A.P., Amlot, P.L., Pounder, R.E. *A pilot study of treatment of active ulcerative colitis with natalizumab, a humanized monoclonal antibody to α-4 integrin*. Aliment Pharmacol Ther 2002, 16(4): 699.

6. Van Deventer, S., Rutgeerts, P., Rask-Madsen, J., Shah, J., Palmer, T., Godlblum, R. *Pharmacokinetics (PK) and pharmacodynamics (PD) of natalizumab in active Crohn's disease patients*. Dig Dis Week (May 19-22, San Francisco) 2002, Abst T1212.

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

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

Indication	Design	Treatments	n	Conclusions	Ref.
Crohn's disease	Randomized, double-blind	Natalizumab, 3 mg/kg iv over 30-75 min sd (n=18) Placebo (n=12)	30	Treatment with 3 mg/kg sd of natalizumab was well tolerated but not significantly more effective than placebo in the treatment of Crohn's disease, suggesting that the dose used was probably suboptimal	3
Ulcerative colitis	Open	Natalizumab, 3 mg/kg iv over 25-45 min	10	A single infusion of natalizumab was well tolerated and showed efficacy, thus warranting future randomized clinical trials in patients with ulcerative colitis	5

Picroliv

The immunomodulator picroliv, discovered by the Central Drug Research Institute, is a standardized iridoid glycoside fraction obtained from roots and rhizomes of *Picrorhiza kurroa* that contains kutkin (picroside I and kutkoside in a 1:1.5 ratio). The product is under phase II clinical development as a hepatoprotectant.

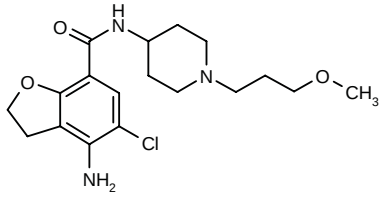
New preclinical data has been published on the protective effects of picroliv in the liver after administration of aflatoxin B_1 in rats. Treatment with picroliv or silymarin normalized aflatoxin B_1-induced increases in lipid peroxide levels and decreases in enzymatic antioxidant levels in the liver and kidney. At the enzymatic level, an oral dose of 25 mg/kg/day of picroliv significantly inhibited the increases in γ-glutamyltranspeptidase, 5'-nucleotidase, acid phosphatase and acid ribonuclease activities and the decreases in succinate dehydrogenase, glucose-6-phosphatase, catalase, superoxide dismutase, glutathione-S-transferase, glutathione peroxidase and glutathione reductase in liver after aflatoxin B_1 administration (2 mg/kg i.p.) (1, 2).

1. Rastogi, R., Srivastava, A.K., Rastogi, A.K. *Long term effect of aflatoxin B_1 on lipid peroxidation in rat liver and kidney: Effect of picroliv and silymarin*. Phytother Res 2001, 15(4): 307.

2. Rastogi, R., Srivastava, A.K., Rastogi, A.K. *Biochemical changes induced in liver and serum of aflatoxin B_1-treated male Wistar rats: Preventive effect of picroliv*. Pharmacol Toxicol 2001, 88(2): 53.

Original monograph - Drugs Fut 2001, 26(9): 25.

Prucalopride



Janssen's prucalopride (R-93877, Resolor®) is a 5-HT_4 receptor agonist that stimulates colonic motility. It is effective in the treatment of constipation caused by different disorders, and is currently under phase III evaluation in Europe and the U.S. for the treatment of constipation in children and constipation-predominant IBS.

Confirmation of the involvement of cholinergic transduction in colonic motility was provided by a study in beagle dogs that found that prucalopride decreased the time to the first giant migrating contraction, inhibited motility in the distal colon and stimulated it in the ileal and proximal colon. These effects were dose-dependent and were not influenced by the mode of administration (*i.e.*, oral or intravenous). Pharmacological research found no anticholinergic, anticholinesterase or nonspecific inhibitory activity for this drug (1-3).

In healthy subjects, administration of 4 mg/day prucalopride increased high-amplitude propagated contractions, segmental pressure waves and bowel movements and no serious adverse events were reported (4).

Two randomized, double-blind, placebo-controlled studies assessed the effects of prucalopride at daily doses of 1, 2 or 4 mg in patients with constipation. Compared to placebo, prucalopride dose-dependently accelerated overall gastric emptying and small intestine transit, and no changes in anorectal function were reported. Similar effects were found in patients suffering from constipation due to spinal cord injury. Prucalopride was generally well tolerated; adverse events were mild to moderate and consisted of headache, diarrhea, flatulence, nausea and abdominal pain. The percentage of patients who withdrew from the studies due to adverse events ranged from 5-21.7%, depending on the study (5-7). The results of these studies are summarized in Table X.

Two female patients with scleroderma were successfully treated with prucalopride (2 mg/day) for gastrointestinal dysmotility. Temporarily withdrawing treatment resulted in symptoms returning in both patients, which were reversed following resumption of prucalopride (8).

1. Prins, N.H., ver Donck, L., Eelen, J., Ghoos, E.C.R., Schuurkes, J.A.J. *M_3 cholinoceptor blockade inhibits dog colonic motility and antagonises 5-HT_4 receptor agonist-induced giant migrating contractions*. Dig Dis Week (May 20-23, Atlanta) 2001, Abst 4047.

2. Briejer, M.R., Prins, N.H., Schuurkes, J.A.J. *Effects of the enterokinetic prucalopride (R-093877) on colonic motility in fasted dogs*. Neurogastroenterol Motil 2001, 13(5): 465.

3. Briejer, M.R., Bosmans, J.P., Van Daele, P., Jurzak, M., Heylen, J.E., Prins, N.H., Schuurkes, J.A.J. *The in vitro pharmacological profile of prucalopride, a novel enterokinetic compound*. Eur J Pharmacol 2001, 423(1): 71.

4. De Schryver, A.M.P., Amdriesse, G.I., Samsom, M., Smout,

A.J.P.M., Gooszen, H.G., Akkermans, L.M.A. *The effects of the specific 5-HT$_4$ receptor agonist, prucalopride, on colonic motility in healthy volunteers*. Aliment Pharmacol Ther 2002, 16(3): 603.

5. Bouras, E.P., Camilleri, M., Burton, D.D., Thomforde, G., McKinzie, S., Zinsmeister, A.R. *Prucalopride accelerates gastrointestinal and colonic transit in patients with constipation without a rectal evacuation disorder*. Gastroenterology 2001, 120(2): 354.

6. Sloots, C.E.J., Poen, A.C., Kerstens, R., Stevens, M., De Pauw, M., van Oene, J.C., Meuwissen, S.G.M., Felt-Bersma, R.J.F. *Effects of prucalopride on colonic transit, anorectal function and bowel habits in patients with chronic constipation*. Aliment Pharmacol Ther 2002, 16(4): 759.

7. Krogh, K., Jensen, M.B., Gandrup, P., Laurberg, S., Nilsson, J., Kerstens, R., De Pauw, M. *Efficacy and tolerability of prucalopride in patients with constipation due to spinal cord injury*. Scand J Gastroenterol 2002, 37(4): 431.

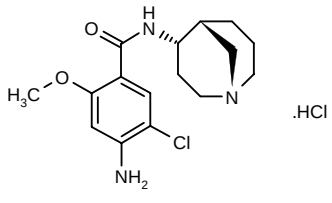
8. Boeckxstaens, G.E., Bartelsman, J.F.W.M., Lauwers, L., Tytgat, G.N.J. *Treatment of GI dysmotlity in scleroderma with the new enterokinetic agent prucalopride*. Am J Gastroenterol 2002, 97(1): 194.

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

Table X: Clinical studies of prucalopride (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Constipation	Randomized, double-blind	Prucalopride, 2 mg od x 7 Prucalopride, 4 mg od x 7 d Placebo	40	Transit through the stomach, small intestine and colon was accelerated after treatment with prucalopride in patients with constipation unassociated with a rectal evacuation disorder	5
Constipation	Randomized, double-blind, crossover	Prucalopride, 1 mg x 2 wk Prucalopride, 2 mg x 2 wk Placebo	28	Prucalopride was safe and effective in improving stool frequency and consistency and the urge to defecate, and may decrease colonic transit in patients with chronic functional constipation	6
Constipation, spinal cord injury	Randomized, double-blind	Prucalopride, 1 mg od x 4 wk Prucalopride, 2 mg od x 4 wk Placebo	23	Prucalopride decreased the severity of constipation and the median colonic transit time, and also increased the average weekly frequency of all bowel movements in patients with chronic constipation due to spinal cord injury	7

Renzapride Hydrochloride



Renzapride hydrochloride (AZM-112, ATL-1251, BRL-24924) acts as a potent 5-HT$_4$ receptor agonist and 5-HT$_3$ receptor antagonist and is being developed by Alizyme for the treatment of IBS. This dual mechanism of action makes this drug a potentially useful therapeutic option for the treatment of both diarrhea and constipation.

Regulatory authorities in the U.S. and the U.K. have authorized Alizyme to conduct double-blind, randomized phase IIb clinical trials aimed at evaluating the efficacy of renzapride in IBS. Patients with constipation-predominant syndrome and patients with the form of the disease characterized by mixed symptoms of constipation and diarrhea will be included in separate studies. The company expects that the results obtained from these studies will allow a phase III trial to begin in the second half of 2003. Alizyme gained full ownership of ATL-1251 from SmithKline Beecham prior to its merger with Glaxo Wellcome to form GlaxoSmithKline (1–3).

A preliminary study in healthy volunteers revealed that the use of COLAL™, Alizyme's proprietary colonic delivery system, increased the delivery of renzapride to the lower gastrointestinal tract. The study also confirmed that renzapride stimulates GI motility (4).

1. *Pharmacodynamic and pharmacokinetic effects of renzapride examined in IBS*. DailyDrugNews.com (Daily Essentials) April 15, 2002.

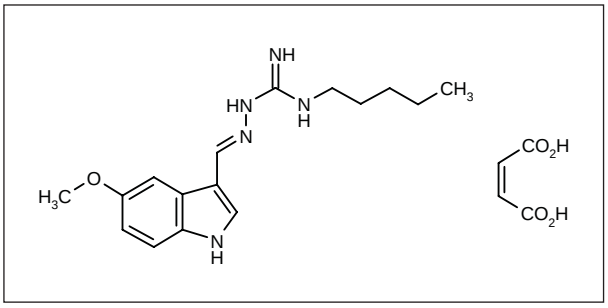
2. *Phase IIb trial of ATL-1251 in mixed-symptom IBS cleared by U.K. authorities*. DailyDrugNews.com (Daily Essentials) Feb 1, 2002.

3. *Phase IIb clinical trial of ATL-1251 to begin in U.K. in IBS patients*. DailyDrugNews.com (Daily Essentials) Sept 18, 2001.

4. *Alizyme highlights product development efforts*. DailyDrugNews.com (Daily Essentials) Oct 18, 2001.

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

Tegaserod Maleate



The first of the 5-HT_4 agonist class of drugs developed to target the gastrointestinal tract, tegaserod maleate (Zelnorm®, Zelmac®). is being codeveloped by Novartis and Bristol-Myers Squibb and was recently approved in several countries for the treatment of IBS, including Switzerland, Canada, Brazil and the U.S., following its first launch in Mexico in July 2001. It is also currently being evaluated in chronic constipation and functional dyspepsia (1-5).

Human liver and small intestinal slices were used to identify the metabolic pathways and enzymes involved in tegaserod metabolism. The main metabolite in human plasma showed no inhibitory potential toward cytochrome P-450 enzymes *in vitro*, suggesting that tegaserod is unlikely to interact with compounds such as HMG-CoA reductase inhibitors (6). In *in vitro* experiments, intraarterial injection of tegaserod increased the basal activity of polymodal inferior splanchnic afferents (PISAs) and blocked the responsiveness of high-threshold PISAs to colorectal distension (7).

Administration of a single dose of 12 mg tegaserod to healthy young and elderly volunteers of both sexes revealed that no dose adjustments for age or gender were needed. Systemic exposure was significantly higher in elderly female compared to elderly male subjects, but the difference was not deemed clinically relevant. Tegaserod did not accumulate in the plasma of healthy volunteers who received doses of 2, 6 or 12 mg b.i.d. for 5 days. The pharmacokinetics of the agent were found to be proportional to dose after multiple doses. No dose adjustments were found to be necessary when tegaserod was coadministered with theophylline or digoxin (8-11).

Several double-blind, randomized, placebo-controlled trials were conducted in healthy volunteers to further characterize the effects of tegaserod on the digestive system. The compound was found to increase intragastric volumes before and after a meal, increase gastric emptying rate and colonic filling (thus reducing colonic and small intestinal transit) (13) and reduce sensitivity to rectal distention (12-14). The results of these studies and those that follow are summarized in Table XI.

A multicenter, open-label, 12-month, dose-titration study evaluated tegaserod treatment in 579 IBS patients. Treatment was begun at 4 mg/day and titrated up (80.3% achieving a dose of 12 mg/day), and considerable relief was experienced by 62.2% of patients after 1 year of treatment (15).

Multicenter, double-blind, placebo-controlled studies conducted in women with irritable bowel syndrome revealed that patients treated with varying doses (2 mg b.i.d., 6 mg b.i.d.) of tegaserod showed significantly greater relief of abdominal pain, bloating and constipation compared to patients treated with placebo. Most patients experienced relief within the first week of treatment, and a high percentage of the patients responding to tegaserod within the first month continued to respond up to the end of the treatment period (16-19).

Looking for what might be a new indication for tegaserod, a multicenter, randomized, double-blind, placebo-controlled, phase II study evaluated the efficacy of 8 weeks of oral tegaserod 1, 4 and 12 mg b.i.d. in 271 patients with functional dyspepsia and normal gastric emptying. Female patients receiving a dose of 12 mg b.i.d. showed a trend towards improvement of symptom relief over placebo (20).

In patients with IBS and associated diarrhea, tegaserod at 4 and 12 mg/day induced no serious adverse events, although 5 patients withdrew due to diarrhea and/or abdominal pain. The ECG analysis of the data from 3 clinical studies including 2400 patients showed that the cardiac safety profile of tegaserod was similar to that of placebo and superior to available gastric prokinetic agents. The most common adverse events found in these large-scale multicenter studies were mild and transient diarrhea and headache, and 6.4% and 4.7% of tegaserod and placebo patients, respectively, withdrew due to adverse events (21-24).

Utilizing a disease state model, cost-of-treatment data, patient preference data and the results of a European double-blind, randomized phase II trial, researchers found that tegaserod treatment of IBS in Switzerland was highly cost-effective when compared to current standards (25).

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

Indication	Design	Treatments	n	Conclusions	Ref.
Healthy volunteers	Randomized, double-blind, crossover	Tegaserod, 2 mg bid x 7 d Tegaserod, 6 mg bid x 7 d Placebo	19	Tegaserod improved impaired meal accommodation and enhanced gastric emptying more effectively than placebo, and allowed larger intragastric volume	12
Healthy volunteers	Randomized, double-blind, crossover	Tegaserod, 6 mg po bid x 3 d → 6 mg po od x 1 d Tegaserod, 0.6 mg iv over 2 h x 3 d → 0.6 mg iv x 2 h od x 1 d Placebo	12	Tegaserod significantly increased the gastric emptying rate, accelerated colonic filling and decreased small intestine transit time in healthy volunteers	13
Healthy volunteers	Randomized, double-blind	Tegaserod, 6 mg bid x 7 d Placebo	20	Measurement of the nociceptive RIII reflex during slow ramp and rapid phasic rectal distension in healthy volunteers indicated that tegaserod reduced sensitivity to rectal distention	14
Constipation, irritable bowel syndrome	Open, multicenter	Tegaserod, 2 mg bid → 6 mg/d x 12 mo	579	Tegaserod was well tolerated and effective in relieving gastrointestinal symptoms, abdominal pain/discomfort and constipation in patients with constipation-predominant irritable bowel syndrome	15
Constipation, irritable bowel syndrome	Double-blind, pooled/meta-analysis	Tegaserod, 12 mg/d x 12 wk Placebo	3199	Treatment with tegaserod was effective in relieving IBS symptoms in a consistent and reproducible manner. Early response to tegaserod therapy (at 1 month) was predictive of continued response to treatment in patients enrolled in 3 placebo-controlled trials	16
Constipation, irritable bowel syndrome	Double-blind, multicenter, retrospective	Tegaserod, 2 mg bid x 12 wk (n=299) Tegaserod, 6 mg bid x 12 wk (n=294) Placebo (n=288)	881	Tegaserod was well tolerated and effective in producing rapid relief of abdominal pain and constipation in patients with irritable bowel syndrome	18
Constipation, irritable bowel syndrome	Randomized, double-blind, multicenter, pooled/meta-analysis	Studies B301 and B351 (n=579 and n=534): Tegaserod, 2 mg bid x 12 wk Tegaserod, 6 mg bid x 12 wk Placebo Study O358 (n=1519) Tegaserod, 6 mg bid Placebo	2632	Tegaserod 6 mg bid was well tolerated and effective in improving abdominal pain/discomfort, bloating and constipation in patients with irritable bowel syndrome and constipation	19
Dyspepsia	Randomized, double-blind, multicenter	Tegaserod, 1 mg po bid x 8 wk Tegaserod, 4 mg po bid x 8 wk Tegaserod, 12 mg po bid x 8 wk Placebo	271	Tegaserod was safe and well tolerated and a trend towards improvement of symptom relief over placebo was observed in female patients with functional dyspepsia and normal gastric emptying with the 12 mg dose	20
Diarrhea, irritable bowel syndrome	Randomized, double-blind, multicenter	Tegaserod, 4 mg/d x 8 wk (n=35) Tegaserod, 12 mg/d x 8 wk (n=34) Placebo (n=17)	86	Tegaserod was safe and well tolerated and was not associated with adverse events or complications of diarrhea in patients with irritable bowel syndrome and constipation with occasional periods of diarrhea	21

Continued

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

Indication	Design	Treatments	n	Conclusions	Ref.
Constipation, irritable bowel syndrome	Randomized, pooled/meta-analysis	Tegaserod Placebo		Treatment with tegaserod led to global symptom relief more often than placebo in patients with irritable bowel syndrome and constipation. Adverse events were not signficantly different between placebo and tegaserod	22
Irritable bowel syndrome	Pooled/meta-analysis	Tegaserod, 4-12 mg/d x 12 wk (n=1679) Placebo (n=837)	2516	Tegaserod showed an incidence of QTc prolongation and ECG abnormalities similar to placebo when administered to patients with irritable bowel syndrome, indicating a favorable cardiac safety profile compared with older gastroprokinetic agents	23
Constipation, irritable bowel syndrome	Randomized, double-blind, multicenter	Tegaserod, 6 mg bid x 12 wk Placebo	1519	Tegaserod was well tolerated and effective in quickly and significantly improving abdominal discomfort, bloating and bowel-related symptoms in female patients with irritable bowel syndrome	24
Irritable bowel syndrome	Randomized, double-blind	Tegaserod x 12 wk Placebo		Tegaserod was a cost-effective drug in irritable blowel syndrome	25

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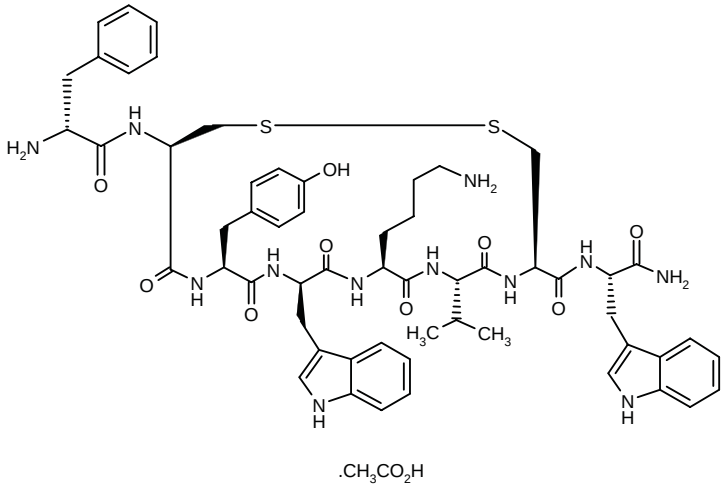
Vapreotide Acetate



Vapreotide (RC-160, Sanvar®, Octastatin®) a somatostatin analog, is currently being evaluated in phase III clinical trials sponsored by Debiopharm for the treatment of esophageal variceal hemorrhage in patients with portal hypertension, as well as gastrointestinal and pancreatic fistulas.

An open, randomized, crossover study analyzed the pharmacokinetics of s.c. doses of 300, 600 and 1200 μg of vapreotide in 8 healthy male volunteers. Plasma vapreotide C_{max} and $AUC_{0-\infty}$ were linear and the absolute bioavailability was calculated at 57.7 ± 21.9%. Less than 0.1% of the dose was eliminated in the urine (1).

A total of 227 patients with cirrhosis who had been hospitalized with variceal bleeding were randomized to receive placebo or vapreotide (50 μg by i.v. bolus followed by 50 μg/h by i.v. infusion for 5 days) prior to endoscopic treatment in a double-blind, multicenter trial. Survival and control of bleeding were achieved in 66% and 50% of patients in the vapreotide and placebo treatment groups, respectively. The overall survival rates of both groups of patients at 42 days were similar (2).

A meta-analysis of 8 randomized trials in 939 patients with acute variceal bleeding was undertaken to compare treatment with endoscopic therapy to endoscopic therapy combined with drug therapy. It was found that the addition of octeotride, somatostatin or vapreotide to endoscopic therapy improved the initial control of bleeding and 5-day hemostasis, but did not significantly decrease mortality (3).

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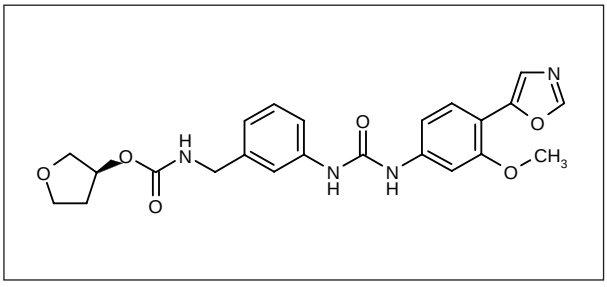
VX-497



VX-497 (merimempodib) is a potent, selective and reversible oral inhibitor of IMP (inosine monophosphate) dehydrogenase (IMPDH). Vertex is currently sponsoring a phase II trial in Europe to determine its efficacy against hepatitis C infection when combined with pegylated interferon and ribavirin (1).

Preliminary *in vitro* studies conducted using a hepatitis C virus (HCV) subgenomic replicon model in hepatoma cells suggested that inhibition of IMPDH might be an effective treatment for HCV infection. Compounds such as ribavirin (IC_{50} = 15 μM), merimempodib (IC_{50} = 0.3 μM), mycophenolic acid (IC_{50} =0.3 μM), interferon (IC_{50} = 1 IU/ml) and pegylated interferon (IC_{50} = 1 IU/ml) inhibited the replication of the HCV replicon in the cells when administered alone (2). *In vivo* research in HCV-infected patients found that merimempodib and ribavirin reduced serum ALT levels but did not affect HCV RNA levels.

Based on the observation that combination therapy with ribavirin and interferon alfa induced an improved and sustained antiviral response in patients compared to either compound alone, a 4-week, double-blind, randomized, placebo-controlled safety study of merimempodib and interferon alfa was conducted in 53 treatment-naive HCV patients. Patients were randomized to receive interferon alfa-2b for 3 weeks plus either placebo or merimempodib at doses of 100 or 300 mg p.o. t.i.d. for 28 days, after which they were switched to interferon alfa-2b plus ribavirin for 11 months. The combination therapy was well tolerated, did not increase hematological toxicity compared with interferon alfa alone and showed a trend for enhanced antiviral efficacy compared to interferon alone (3, 4).

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