Drugs Fut 2007, 32(2): 187-200

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Update 2006/2007 – Treatment of Hepatitis

(Source: Prous Science Integrity®)

Treatment of Hepatitis by Condition

Condition	Phase	Drug	Source
Hepatitis B	L-2006	Hepatitis B immune globulin (human)	Cangene/Apotex
	L-2006	SuperVax	Rhein Biotech/Dynavax
	L-2006	Telbivudine[2]	Indenix/Novartis
	R-2006 (KR)	Clevudine[2]	Bukwang
	III (US, EU, Asia)	Clevudine[2]	Eisai/Pharmasset
	III	Heplisav™	Dynavax
	III	Tenofovir disoproxil fumarate[1,2]	Gilead
	II	ANA-380 (LB-80380)	Anadys/LG Life Sciences
	II	EHT-899	Enzo
	II	Hepatitis B vaccine	Emergent BioSolutions
	II	Hepatitis B vaccine	Oxxon Therapeutics
	II	MIV-210	Tibotec/Medivir
	II	Pradefovir mesilate	Metabasis Therapeutics/Valeant/ Schering-Plough
	II	Valtorcitabine dihydrochloride	Idenix/Novartis
	I/II	Hepatitis B vaccine	Vaxine
	I/II	Resiquimod[2]	University of British Columbia
	I	HBV-DNA vaccine	Institut Pasteur
	I	Hepatitis B vaccine	Vaxine
	I	Hepatitis B vaccine	CellDex Therapeutics
	I	Hepatitis B vaccine	Cent. Ingenieria Genetica Biotecnologia
	I	HepaVaxx B	ViRexx
	I	INNO-102	Innogenetics/Genencor/Pharmexa-Epimmune
	I	pdpSC18	PowderMed (Pfizer)
Hepatitis C	III	Albumin interferon alfa	Human Genome Sciences/Novartis
	III	Human leukocyte interferon alfa[1]	Hemispherx Biopharma/Guangdong
	III	Taribavirin hydrochloride[2]	Valeant
	II	ACH-0137171	Achillion
	II (Prereg. EG)	BIVN-401	Bioenvision
	II	Celgosivir[2]	Migenix
	II	DEBIO-025	Debiopharm
	II	HCV-796	Wyeth Pharmaceuticals/ViroPharma
	II	Hepatitis C immune globulin (human)	Nabi Biopharmaceuticals/Kedrion/NIAID
	II	Hepatitis C vaccine	CSL/Chiron (Novartis)
	II	IC-41	Intercell
	II	INNO-101	Innogenetics
	II	Interferon omega	Intarcia Therapeutics
	II	ME-3738	Meiji Seika
	II	Nitazoxanide[1]	Romark
	II	NM-811	Novartis
	II	R-1626	Roche
	II	Sch-503034	Schering-Plough
	II	Telaprevir	Vertex/Janssen/Tibotec
	II	UT-231B	United Therapeutics
	II	Valopicitabine[2]	Idenix/Novartis
	II	VGX-410C[1]	VGX Pharmaceuticals

Continuation

Treatment of Hepatitis by Condition

Condition	Phase	Drug	Source
Hepatitis C	I/II	AVI-4065	AVI BioPharma
	I/II	EHC-18	Enzo
	I/II	HCV-I.E.T.	Transition Therapeutics
	I/II	Interferon alfa-2b XL	Flamel Technologies
	I/II	VCH-759	ViroChem Pharma
	I	A-831	Arrow Therapeutics
	I	Bavituximab	Peregrine Pharmaceuticals
	I	GI-5005	GlobeImmune
	I	HCV E1E2/MF59C.1 vaccine	Chiron (Novartis)/St. Louis University
	I	Hepatitis C vaccine	Pevion Biotech
	I	ITMN-191 (R-7227)	InterMune/Roche
	I	PF-868554	Pfizer
	I	R-7025	Roche/Maxygen
	I	R-7128	Roche/Pharmasset
	I	XTL-2125	XTL Biopharmaceuticals
	I	XTL-6865	XTL Biopharmaceuticals
	IND filed	GS-9190	Gilead
	Discontinued	GS-9132 (ACH-806)	Gilead/Achillion
Hepatitis D	II	Peginterferon alfa-2a	NIDDK
Hepatitis E	II	Hepatitis E vaccine	GlaxoSmithKline/Genelabs
Hepatitis, viral	II	DDB-S	Daewoo Pharmaceuticals

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

Treatment of Hepatitis by Source

Source	Condition	Drug	Phase
Achillion	Hepatitis C	ACH-0137171	II
		GS-9132 (ACH-806)	Discontinued
Anadys	Hepatitis B	ANA-380 (LB-80380)	II
Apotex	Hepatitis B	Hepatitis B immune globulin (human)	L-2006
Arrow Therapeutics	Hepatitis C	A-831	I
AVI BioPharma	Hepatitis C	AVI-4065	I/II
Bioenvision	Hepatitis C	BIVN-401	II (Prereg. EG)
Bukwang	Hepatitis B	Clevudine[2]	R-2006 (KR)
Cangene	Hepatitis B	Hepatitis B immune globulin (human)	L-2006
CellDex Therapeutics	Hepatitis B	Hepatitis B vaccine	I
Cent. Ingenieria Genetica Biotecnologia	Hepatitis B	Hepatitis B vaccine	I
Chiron (Novartis)	Hepatitis C	HCV E1E2/MF59C.1 vaccine	I
		Hepatitis C vaccine	II
CSL	Hepatitis C	Hepatitis C vaccine	II
Daewoo Pharmaceuticals	Hepatitis, viral	DDB-S	II
Debiopharm	Hepatitis C	DEBIO-025	II
Dynavax	Hepatitis B	Heplisav™	III
		SuperVax	L-2006
Eisai	Hepatitis B	Clevudine[2]	III (US, EU, Asia)
Emergent BioSolutions	Hepatitis B	Hepatitis B vaccine	II
Enzo	Hepatitis B	EHT-899	II
	Hepatitis C	EHC-18	I/II
Flamel Technologies	Hepatitis C	Interferon alfa-2b XL	I/II
Genelabs	Hepatitis E	Hepatitis E vaccine	II
Genencor	Hepatitis B	INNO-102	I
Gilead	Hepatitis B	Tenofovir disoproxil fumarate[1,2]	III
	Hepatitis C	GS-9132 (ACH-806)	Discontinued
		GS-9190	IND filed
GlaxoSmithKline	Hepatitis E	Hepatitis E vaccine	II
GlobeImmune	Hepatitis C	GI-5005	I
Guangdong	Hepatitis C	Human leukocyte interferon alfa[1]	III
Hemispherx Biopharma	Hepatitis C	Human leukocyte interferon alfa[1]	III
Human Genome Sciences	Hepatitis C	Albumin interferon alfa	III
Indenix	Hepatitis B	Telbivudine[2]	L-2006
		Valtorcitabine dihydrochloride	II
	Hepatitis C	Valopicitabine[2]	II
Innogenetics	Hepatitis B	INNO-102	I
	Hepatitis C	INNO-101	II
Institut Pasteur	Hepatitis B	HBV-DNA vaccine	I
Intarcia Therapeutics	Hepatitis C	Interferon omega	II
Intercell	Hepatitis C	IC-41	II
InterMune	Hepatitis C	ITMN-191 (R-7227)	I
Janssen	Hepatitis C	Telaprevir	II
Kedrion	Hepatitis C	Hepatitis C immune globulin (human)	II
LG Life Sciences	Hepatitis B	ANA-380 (LB-80380)	II
Maxygen	Hepatitis C	R-7025	I
Medivir	Hepatitis B	MIV-210	II
Meiji Seika	Hepatitis C	ME-3738	II
Metabasis Therapeutics	Hepatitis B	Pradefovir mesilate	II
Migenix	Hepatitis C	Celgosivir[2]	II
Nabi Biopharmaceuticals	Hepatitis C	Hepatitis C immune globulin (human)	II
NIAID	Hepatitis C	Hepatitis C immune globulin (human)	II
NIDDK	Hepatitis D	Peginterferon alfa-2a	II
Novartis	Hepatitis B	Telbivudine[2]	L-2006
		Valtorcitabine dihydrochloride	II
	Hepatitis C	Albumin interferon alfa	III
		NM-811	II
		Valopicitabine[2]	II
Oxxon Therapeutics	Hepatitis B	Hepatitis B vaccine	II
Peregrine Pharmaceuticals	Hepatitis C	Bavituximab	I
Pevion Biotech	Hepatitis C	Hepatitis C vaccine	I
Pfizer	Hepatitis C	PF-868554	I
Pharmasset	Hepatitis B	Clevudine[2]	III (US, EU, Asia)
	Hepatitis C	R-7128	I

Continuation

Treatment of Hepatitis by Source

Source	Condition	Drug	Phase
Pharmexa-Epimmune	Hepatitis B	INNO-102	I
PowderMed (Pfizer)	Hepatitis B	pdpSC18	I
Rhein Biotech	Hepatitis B	SuperVax	L-2006
Roche	Hepatitis C	ITMN-191 (R-7227)	I
		R-1626	II
		R-7025	I
		R-7128	I
Romark	Hepatitis C	Nitazoxanide[1]	II
Schering-Plough	Hepatitis B	Pradefovir mesilate	II
	Hepatitis C	Sch-503034	II
St. Louis University	Hepatitis C	HCV E1E2/MF59C.1 vaccine	I
Tibotec	Hepatitis B	MIV-210	II
	Hepatitis C	Telaprevir	II
Transition Therapeutics	Hepatitis C	HCV-I.E.T.	I/II
United Therapeutics	Hepatitis C	UT-231B	II
University of British Columbia	Hepatitis B	Resiquimod[2]	I/II
Valeant	Hepatitis B	Pradefovir mesilate	II
	Hepatitis C	Taribavirin hydrochloride[2]	III
Vaxine	Hepatitis B	Hepatitis B vaccine	I/II
		Hepatitis B vaccine	I
Vertex	Hepatitis C	Telaprevir	II
VGX Pharmaceuticals	Hepatitis C	VGX-410C[1]	II
ViRexx	Hepatitis B	HepaVaxx B	I
ViroChem Pharma	Hepatitis C	VCH-759	I/II
ViroPharma	Hepatitis C	HCV-796	II
Wyeth Pharmaceuticals	Hepatitis C	HCV-796	II
XTL Biopharmaceuticals	Hepatitis C	XTL-2125	I
		XTL-6865	I

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

Drugs Under Development for the Treatment of Hepatitis

N.E. Mealy, B. Lupone, M. Tell
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A-831

A-831 is a hepatitis C virus (HCV) NS5A inhibitor in early clinical trials at Arrow Therapeutics for the treatment of hepatitis C. NS5A is a virus-encoded protein that is essential for viral RNA production, has no homologous protein in the human genome and is well conserved across HCV genotypes. A-831 has shown potent activity in the replicon assay. AstraZeneca recently announced an agreement to acquire Arrow.

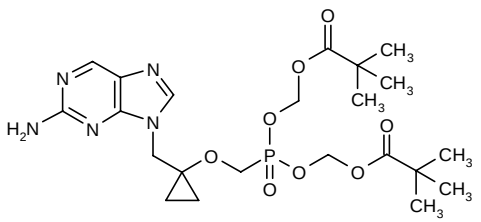
ACH-0137171

ACH-0137171 is currently in phase II clinical trials at Achillion for the oral treatment of chronic hepatitis C infection.

Albumin Interferon Alfa

A novel, long-acting formulation of interferon alfa, albumin interferon alfa (Albuferon®, albinterferon alfa-2b), is in phase III clinical trials at Human Genome Sciences for the treatment of hepatitis C. Specifically, the drug candidate is being evaluated in combination with ribavirin in patients with chronic HCV genotype 1 who fail to respond to interferon alfa-based treatment regimens and in patients who are naïve to interferon alfa-based treatment regimens. Recombinant interferon alfa is approved for the treatment of hepatitis C, hepatitis B and a broad range of cancers. Human Genome Sciences modified interferon alfa to improve its pharmacological properties by using the company's proprietary albumin fusion technology. In mid-2006, albumin interferon alfa was licensed on a worldwide basis to Novartis for the treatment of chronic hepatitis C.

ANA-380 (LB-80380)



ANA-380 (LB-80380) is in phase II trials at Anadys and LG Life Sciences for the oral, once-daily treatment of chronic and acute lamivudine-resistant hepatitis B virus (HBV) infection. The drug is a guanosine phosphonate nucleoside analogue and an orally active double prodrug of LB-80317. The prodrug was developed to correct the low cell permeability and poor oral bioavailability of the parent drug, and produces LB-80317 intracellularly as a result of a series of metabolic events. In April 2004, Anaydys acquired an exclusive license from LG Life Sciences for the commercialization of ANA-380 worldwide excluding China, Korea, India and Southeast Asia.

AVI-4065

The phosphorodiamidate morpholino oligomer AVI-4065 is in phase I/II clinical trials at AVI BioPharma for the treatment of chronic HCV infection. The drug candidate is designed to hybridize to a highly conserved region including the AUG translation start site of HCV. In addition to results from *in vitro* and *in vivo* animal models, the conservation of AVI-4065's target site has led researchers to identify the compound as being likely to inhibit all 5 genotypes of HCV. AVI-4065, one of AVI BioPharma's NeuGene® antisense compounds, does not activate,

complement or bind to α-adrenoceptors like the phosphorothioate antisense compounds.

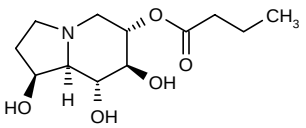
Bavituximab

Bavituximab (Tarvacin™), a chimeric monoclonal antibody, is currently in early clinical evaluation at Peregrine Pharmaceuticals for antiviral and anticancer indications, including HCV infection and advanced refractory tumors. Preclinical studies are also under way at the company to explore the potential of bavituximab as a therapy for influenza, HIV and cytomegalovirus infections. The first investigational agent in a new class of anti-phosphotidylserine immunotherapeutics, bavituximab targets and binds to phospholipids which are exposed on the cell surface when cells are infected with certain viruses or malignant cells, while leaving healthy cells untouched. The antibody then stimulates the body's immune defenses to destroy both the virus particles and the infected or malignant cells. In terms of its antiviral action, bavituximab binds to the host (human) cell and not the virus, suggesting that the antibody may not be susceptible to viral drug resistance. The company also believes that in addition to treating active illness, bavituximab may also confer long-term immunity.

BIVN-401

BIVN-401 (methylene blue, Suvus™) is in phase II clinical trials at Bioenvision for the treatment of chronic HCV infection. The company has filed for marketing authorization in Egypt. The drug acts by preventing the replication of nucleic acid (RNA and DNA) in pathogens, especially when photosensitized by light. Bioenvision obtained global license rights from the Oklahoma Medical Research Foundation (OMRF) to develop and market the product for antiviral indications. It has also shown evidence of activity against West Nile virus and avian flu virus.

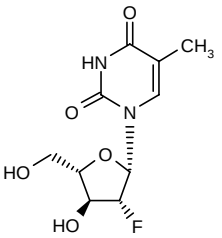
Celgosivir



A potent α-glucosidase I inhibitor, celgosivir (MX-3253) is currently in phase II clinical development at Migenix as monotherapy in treatment-naïve and interferon-intolerant genotype 1 HCV patients (in Canada) and in combination with peginterferon alfa-2b with or without ribavirin for the treatment of chronic HCV genotype 1 infections (in Canada and the U.S.). Celgosivir is an oral prodrug of castanospermine, a natural product derived from the Australian black bean chestnut tree *Castanospermum australe*. Because it inhibits a mammalian enzyme rather than a viral target, celgosivir is less likely to lead to drug-resistant viral mutations. Celgosivir is the only oral drug in development that acts through host-directed glycosylation. Migenix acquired worldwide rights to celgosivir from Virogen in February 2004. Virogen had acquired rights from the former Aventis Pharma (sanofi-aventis).

Original monograph – Drugs Fut 2005, 30(6): 545.

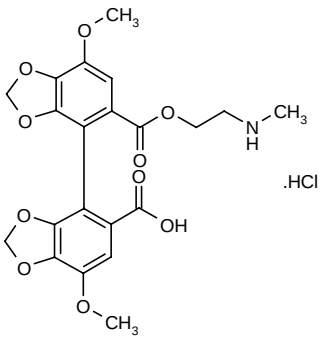
Clevudine



Bukwang obtained South Korean approval in 2006 for clevudine (Levovir®), an oral, once-daily pyrimidine nucleoside analogue, for the treatment of hepatitis B. It is also being evaluated in phase III trials in Asia by Eisai and phase III trials are planned for this year in the U.S. and Europe by Pharmasset. The drug functions by inhibiting DNA polymerase. Originally developed at the University of Georgia and Yale University, rights to clevudine were subsequently acquired by Bukwang. In November 2004, Eisai obtained exclusive rights to develop, manufacture and market clevudine in 10 Asian contries, excluding South Korea, and Pharmasset licensed rights for North, Central and South America, Europe, the Caribbean and Israel in July 2005.

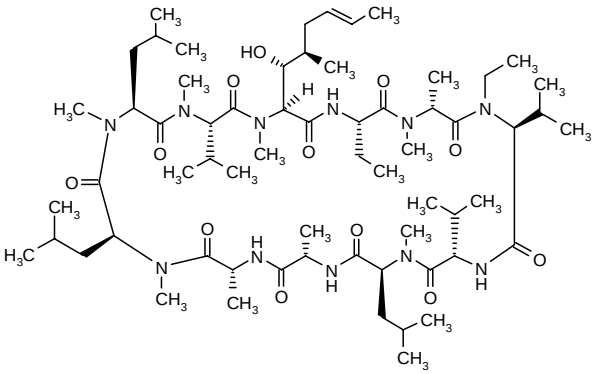
Original monograph – Drugs Fut 1998, 23(8): 821.

DDB-S



DDB-S (Lebecel) is in phase II trials at Daewoo Pharmaceuticals for the treatment of acute and chronic hepatitis. The drug was jointly developed by Daewoo and Pusan National University.

DEBIO-025



DEBIO-025 is a nonimmunosuppressive ciclosporin analogue, a synthetic, first-in-class compound that displays high binding affinity for cyclophilins, host cell proteins thought to confer a replication advantage to HCV. It is currently in phase II for the treatment of HCV infection.

EHC-18

The immunomodulator EHC-18 has been tested in phase I trials at Enzo for the treatment of hepatitis C.

EHT-899

EHT-899 is an immunoregulating product in phase II clinical trials at Enzo for the oral treatment of HBV infection. EHT-899 is a proprietary formulation of an HBV viral protein designed to eliminate the undesirable immune response provoked by HBV infection. The product also apparently enhances a secondary immune response to clear the viral infection, resulting in a reduction in liver damage and a decrease in viral load.

GI-5005

GI-5005 is a whole, heat-inactivated recombinant *Saccharomyces cerevisiae* yeast genetically modified to express an HCV fusion protein comprised of NS3 protease and core protein sequences. The vaccine candidate is currently undergoing phase I clinical trials at GlobeImmune for the treatment of chronic HCV infection. It is a member of GlobeImmune's Tarmogen™ class of products which are taken up by antigen-presenting cells (APCs) that in turn activate the immune system by inducing $CD4^+$ and $CD8^+$ cell-mediated responses against the desired target. Preclinical studies have demonstrated the efficacy of GI-5005 in inducing T-cell responses. The compound was originally developed at the University of Colorado and was later licensed to GlobeImmune.

GS-9132 (ACH-806)

The development of GS-9132 (ACH-806), a small-molecule inhibitor of HCV replication discovered at Achillion and licensed to Gilead, was recently discontinued based on preliminary data from a phase Ib/II trial. Preliminary data from the first cohort of the trial indicated that the compound demonstrated antiviral activity, validating the novel anti-HCV mechanism that involves inhibition of a viral protein called NS4A, which binds to a portion of HCV protease. However, based on small elevations in serum creatinine, which were reversible after completion of dosing, Gilead and Achillion have elected to shift their focus to the evaluation of other NS4A antagonists developed by Achillion to identify a lead candidate for development.

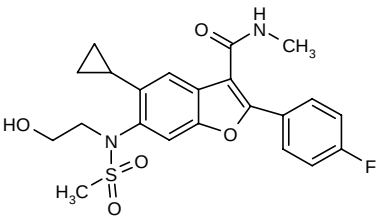
GS-9190

An RNA-directed RNA polymerase (NS5B) inhibitor, GS-9190 is the subject of an IND filed by Gilead in 2006 seeking FDA approval to commence clinical evaluation for the treatment of hepatitis C.

HBV-DNA Vaccine

The Institut Pasteur is developing an HBV-DNA vaccine in early clinical trials for the treatment of chronic HBV infection. The vaccine expresses the HBV small (S) and middle (preS2) enveloped proteins.

HCV-796



HCV-796 is a non-nucleoside RNA polymerase (NS5B) inhibitor in phase II clinical development at ViroPharma and Wyeth Pharmaceuticals for the treatment of HCV in combination with pegylated interferon alfa-2b and ribavirin. In 1999, ViroPharma entered into a collaboration and license agreement with Wyeth to co-develop products for the treatment of HCV. Preclinical studies have shown that HCV-796 may be more potent than other anti-HCV compounds developed to date under the collaboration.

HCV E1E2/MF59C.1 Vaccine

Novartis (formerly Chiron), in collaboration with St. Louis University, is conducting early clinical trials with an HCV vaccine, referred to as HCV E1E2/MF59C.1.

HCV-I.E.T.

Transition Therapeutics' HCV-Interferon Enhancing Therapy, or HCV-I.E.T., is a combination therapy in phase I/II clinical trials for the treatment of HCV infection in patients who have not responded to standard pegylated interferon and ribavirin combination therapy. HCV-I.E.T. combines Transition's interferon enhancer EMZ-702 (hydroxycobalamin), pegylated interferon alfa and ribavirin, and has demonstrated a 2-3-fold increase in antiviral activity over standard therapy alone.

Hepatitis B Vaccines

Early clinical trials are under way at CellDex Therapeutics for a vaccine for the treatment of chronic HBV infection. The vaccine candidate features CDX-2101, a virus-like particle (VLP) comprising 240 modified HBV core protein subunits, formulated with RC-529-SE, a lipid A-mimetic adjuvant. It has been designed to induce an appropriate immune response to HBV, similar to that occurring naturally in patients with spontaneous resolution of HBV infection.

The Centro de Ingenieria Genetica y Biotecnologia is developing a nasally administered HBV vaccine composed of recombinant hepatitis B surface and core antigens combined in a new aggregated structure. The vaccine candidate is currently in early clinical trials for the prevention and treatment of HBV infection.

Emergent BioSolutions (formerly Microscience) has developed an oral vaccine that is in phase II clinical development for the treatment of chronic hepatitis B. The vaccine incorporates the company's spi-VEC technology, which in the case of the hepatitis B vaccine consists of harmless *Salmonella* bacteria that have been modified to carry a hepatitis B antigen and deliver it directly to cells of the immune system, resulting in antigen presentation and strong immune responses. These responses are primarily characterized by the production of interferon gamma, important in promoting the clearance of HBV.

Vaxine is developing a prophylactic hepatitis B vaccine which has successfully completed phase I clinical trials and is entering phase II clinical evaluation for the prevention of HBV infection. The vaccine candidate consists of a hepatitis B antigen with the ADVAX Super D adjuvant and has shown a substantially enhanced cell-mediated response to HBV in preclinical studies. The company has also developed a therapeutic HBV vaccine, currently in phase I clinical trials.

Oxxon Therapeutics is conducting phase II trials with an HBV therapeutic vaccine, Hi-8™, for the treatment of HBV. The vaccine is based on the company's PrimeBoost™ platform, which consists of a two-stage treatment regimen: a priming component containing an HBV surface antigen(s) to stimulate the immune system to produce disease-specific T-cells, followed by a boosting component containing the same antigen(s) delivered in a nonreplicating vector.

Hepatitis B Immune Globulin (Human)

HepaGam B™, a human hepatitis B immune globulin, is a highly purified gammaglobulin fraction of human plasma containing antibodies to hepatitis B surface antigen (HBsAg), which was approved in the U.S. in 2006 for the treatment of acute exposure to blood containing HBsAg, perinatal exposure of infants born to HBsAg-positive mothers, sexual exposure to HBsAg-positive persons and household exposure to persons with acute HBV infection. In 2007, Cangene received approval for HepaGam B™ in Canada for the prevention of hepatitis B recurrence following liver transplantation in adult patients with hepatitis B who have no or low levels of HBV replication. Apotex distributes the product in the U.S.

Hepatitis C Immune Globulin (Human)

Hepatitis C immune globulin (human) is an investigational human polyclonal antibody product that contains antibodies to HCV. Also known as Civacir®, the drug candidate is being co-developed by Nabi Biopharmaceuticals and Kedrion and is in phase II trials for the prevention of the recurrence of hepatitis C-related liver disease in HCV-positive liver transplant recipients or in patients who receive an HCV-positive liver. The National Institute of Allergy and Infectious Diseases (NIAID) is conducting phase I/II clinical trials for the same indication. The drug candidate received orphan drug designation from the FDA in 2002 for the prevention of HCV infection in liver transplant recipients, and the EMEA granted orphan drug designation for the same indication in June 2005. In June 2006, Nabi signed an agreement with Kedrion for the development and commercialization of hepatitis C immune globulin in the U.S. and Europe. Specifically, Kedrion was granted an exclusive license to commercialize the product in Europe. Kedrion will also assume costs for the product candidate in both Europe and the U.S. through to at least phase II clinical development. Upon positive results from the phase II trials, both Nabi and Kedrion will collaborate on the development of a phase III trial. Nabi and Kedrion will jointly oversee registration of the potential product in Europe.

Hepatitis C Vaccines

Early clinical trials are being conducted by Pevion Biotech with a synthetic carrier-based vaccine for the treatment of chronic HCV infection. The vaccine candidate utilizes Pevion's PeviTER™/PeviPRO™ technology, which incorporates virosomes that are used to deliver cellular immune response-eliciting antigens. The vaccine candidate induces both specific cytotoxic T-lymphocyte (CTL) responses (PeviTER™) and a helper T-cell response (PeviPRO™).

An HCV vaccine is also being co-developed by Chiron, now a subsidiary of Novartis, and CSL, where it is currently in phase II clinical trials for the treatment of HCV infection. This collaboration was established in 2004 with the aim of combining Chiron's recombinant HCV proteins with CSL's Iscomatrix® adjuvant to produce an immunotherapeutic vaccine. The vaccine is designed to boost the immune system to initiate a strong $CD4^+$ and $CD8^+$ T-cell response, which is believed to play a pivotal role in the clearance of virus during both acute and chronic infection.

Hepatitis E Vaccine

GlaxoSmithKline has developed a prophylactic hepatitis E virus (HEV) vaccine that is currently being tested in phase II clinical trials. The company obtained an exclusive worldwide license to develop and commercialize HEV vaccines from Genelabs, the first to clone and characterize HEV.

HepaVaxx B

HepaVaxx B is a recombinant chimeric vaccine in phase I clinical trials at ViRexx for the treatment of chronic HBV infection. The vaccine candidate is based on ViRexx's proprietary Chimigen™ technology, which is aimed at developing recombinant variants of selected antigens that have been rendered more immunogenic through an enhancement of function and delivery. The technology enables the body to mount a humoral as well as a cellular response to effectively clear the virus responsible for chronic infection. HepaVaxx B contains the elements of both an HBV antigen and a xenotypic antibody. It is expressed in insect cells which produce the desired product in large quantities under appropriate culture conditions. In April 2005, ViRexx announced the completion of a collaborative development agreement with Protein Sciences Corporation for the manufacture of the vaccine candidate.

Heplisav™

Heplisav™ (HBV-ISS) is a prophylactic HBV vaccine candidate in phase III clinical trials at Dynavax. Early clinical studies are also under way in patients with end-stage renal failure (predialysis). Unlike conventional vaccines, Heplisav™ is composed of HBV surface antigen (HBsAg) and a phosphorothioate oligonucleotide immunostimulatory sequence (ISS) (1018-ISS) that specifically targets toll-like receptor 9 (TLR9), and it appears to require only 2 immunizations over 2 months to achieve protective antibody responses. The vaccine stimulates a Th1 immune response while suppressing the Th2 immune response. Dynavax had an agreement with Berna Biotech for supply of HBsAg for use with Heplisav™, but this agreement, as well as Berna's option to market the vaccine, were terminated following Dynavax's acquisition of Rhein Biotech (93%-owned by Berna) last year.

Human Leukocyte Interferon Alfa

Human leukocyte interferon alfa, an injectable formulation of natural interferon alfa, was initially launched by Hemispherx Biopharma in 1989 as Alferon N Injection® for the intralesional treatment of refractory or recurring external genital and perianal exophytic warts caused by human papillomavirus (HPV) in patients 18 years of age or older. Alferon N® is a highly purified, natural-source, glycosylated, multispecies interferon alfa product that does not induce antibody formation, a problem associated with recombinant forms of nonglycosylated interferon alfa. Development of the compound in other indications is progressing, including phase III clinical trials for the treatment of HCV infection. Phase II/III trials are evaluating a low-dose oral formulation and an injection formulation for the treatment of HIV infection, and phase II trials are ongoing with human leukocyte interferon alfa injection for the treatment of West Nile virus infection and multiple sclerosis (MS). An oral formulation of interferon alfa is being developed for severe acute respiratory syndrome (SARS). Phase I/II trials are under way for the treatment of subacute panencephalitis. Hemispherx has a partnership with Guangdong for the compound's clinical development, sales and distribution in China for infectious disease indications.

IC-41

Intercell's IC-41 hepatitis C vaccine is in phase II clinical trials for the treatment of HCV infection. The vaccine consists of 5 synthetic peptides (IPEP 83, 84, 87, 89 and 1426) formulated with poly-L-arginine as adjuvant.

INNO-101

The HCV E1 therapeutic vaccine INNO-101, based on the purified viral envelope E1 protein from HCV genotype 1b, is currently in phase II development at Innogenetics for the treatment of HCV infection as an intramuscular injection formulation.

INNO-102

INNO-102 (EP-2210, HBV EpiGene) is a polyepitope recombinant plasmid DNA vaccine in early clinical trials at Innogenetics for the prevention of hepatitis B infection. It was originally developed under a collaboration between Pharmexa-Epimmune and Genencor. The drug candidate utilizes the former Epimmune's PADRE® technology, a process by which antigen-specific epitopes are identified from the genetic information of the infectious agents.

Interferon Alfa-2b XL

A long-acting sustained-release formulation of a native interferon, interferon alfa-2b XL, is in phase I/II trials at Flamel Technologies for the treatment of HCV infection. The product is based on the company's Medusa® nanotechnology.

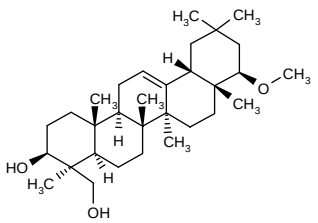
Interferon Omega

Interferon omega is in phase II trials at Intarcia Therapeutics for the treatment of chronic hepatitis C infection. It is a naturally occurring human type 1 interferon manufactured using a novel genetic engineering process for which Intarcia acquired rights from Boehringer Ingelheim in 1998. Intarcia has also acquired rights from Alza to a delivery system called DUROS® that allows the continuous delivery of interferon omega for 3 or more months with a single administration via a subcutaneous implant. Omega DUROS® is currently in preclinical testing.

ITMN-191 (R-7227)

ITMN-191 (R-7227; also previously referred to as ITMN-B), an orally available HCV NS3/4A protease inhibitor being developed under a collaboration between InterMune and Roche, recently entered phase I clinical testing in Europe. This compound is the result of a collaboration between InterMune and Array BioPharma formed in 2002 to discover novel small-molecule inhibitors of HCV NS3/4 protease. Roche obtained exclusive worldwide development and marketing rights from InterMune in 2006.

ME-3738

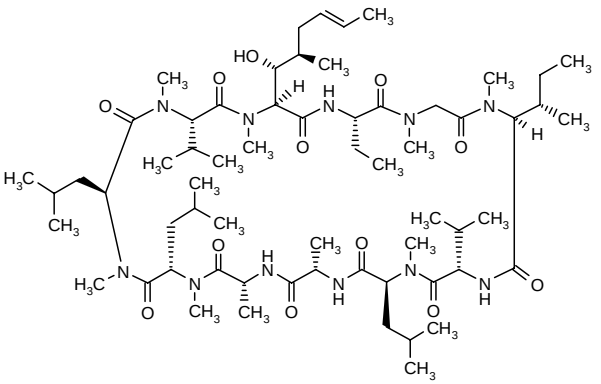


The IL-6 agonist ME-3738 is undergoing phase II clinical testing at Meiji Seika for the oral treatment of chronic HCV.

MIV-210

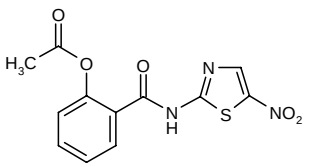
MIV-210 is a nucleoside reverse transcriptase inhibitor (NRTI) with potential for the treatment of both hepatitis B and HIV infection that had reached phase II clinical evaluation at Medivir for the oral treatment of HIV. In 2006, it was licensed to Tibotec.

NIM-811



NIM-811 is a ciclosporin derivative from Novartis that binds to cyclophilins with greater affinity than ciclosporin but is devoid of the immunosuppressive activity of the latter. *In vitro*, NIM-811 has demonstrated activity against HCV alone and enhanced activity when combined with non-nucleoside inhibitors of HCV polymerase. NIM-811 is in phase I clinical investigation for HCV infection.

Nitazoxanide



Nitazoxanide is an antiprotozoal agent that was launched in 1996 by Romark for the oral treatment of diarrhea caused by *Cryptosporidium parvum* or *Giardia lamblia* in children aged 12 months to 11 years. The drug's indication was later extended to include patients 12 years of age and older. Romark is seeking FDA approval for use in treating diarrhea in patients with AIDS. Phase III and phase II clinical studies are also being conducted at the company for the oral treatment of *Clostridium difficile*-associated diarrhea (CDAD) and HCV infection, respectively.

pdpSC18

A therapeutic DNA vaccine known as pdpSC18 is in phase I clinical trials at PowderMed, now a wholly owned

subsidiary of Pfizer, for the treatment of chronic HBV infection as monotherapy or in combination with lamivudine. The vaccine candidate contains a combination of two plasmids, HBsAg and HBcAg, providing a potential mechanism to both clear the virus via the $CD8^+$ response and overcome unresponsiveness in chronically infected patients via the $CD4^+$ response. pdpSC18 is administered using PowderMed's proprietary Particle Mediated Epidermal Delivery (PMED™) device, a needle-free delivery technology. The plasmids are precipitated onto microscopic gold particles, which are propelled by a pressurized helium cartridge at high velocity to be deposited in the epidermal cells of the skin.

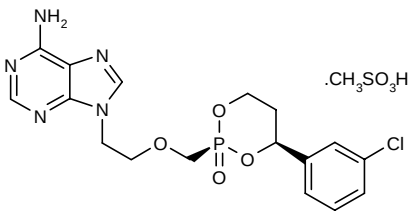
Peginterferon Alfa-2a

Roche first launched peginterferon alfa-2a (Pegasys®) in 2001 for the treatment of chronic hepatitis C infection and in 2003 for the treatment of chronic hepatitis B infection. The drug is currently in phase III clinical trials at Universitätsklinikums Tuebingen for the treatment of malignant melanoma. Chugai is conducting phase III clinical trials for the treatment of compensated liver cirrhosis caused by HCV in combination with ribavirin. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) is conducting phase II trials in patients with chronic hepatitis D. Peginterferon alfa-2a is a covalent conjugate of recombinant interferon alfa-2a with a single branched bis-monomethoxy polyethylene glycol (PEG) chain.

PF-868554

The anti-HCV drug candidate PF-868554 is in early clinical trials at Pfizer.

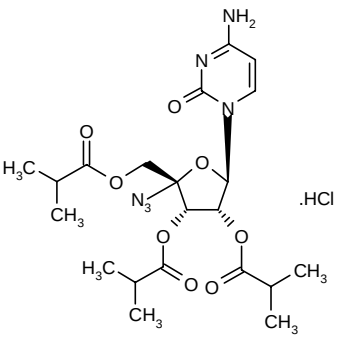
Pradefovir Mesilate



Pradefovir mesilate (MB-06866, formerly remofovir, Hepavir B) is in phase II clinical development for the oral treatment of chronic hepatitis B. A prodrug of adefovir dipivoxil, pradefovir mesilate was developed at Metabasis Therapeutics using its HepDirect™ prodrug technology. In October 2000, Valeant entered into an exclusive worldwide development and license agreement with Metabasis, pursuant to which Valeant was primarily responsible for the clinical development and registration of pradefovir. However, in December 2006, the compound was licensed to Schering-Plough by Metabasis and Valeant for worldwide development and marketing for hepatitis B. Unlike adefovir dipivoxil, an approved chronic HBV drug which is converted to its active form mainly in the plasma, pradefovir mesilate is activated by cytochrome P-450 3A4, which is found primarily in the liver. Activation in the liver allows more direct contact with the hepatitis B virus, as well as reduced exposure outside the liver. This is potentially important because while adefovir is associated with significant decreases in HBV DNA levels, it also appears to be associated with treatment-limiting renal toxicity.

See monograph this issue.

R-1626



The HCV polymerase inhibitor R-1626 is in phase II trials at Roche for the treatment of hepatitis C. Fast track designation was received in the U.S. for this indication in 2006.

R-7025

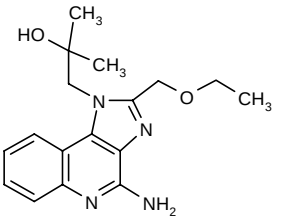
Roche is conducting a phase Ia trial in New Zealand to evaluate the safety, tolerability, pharmacokinetic and pharmacodynamic profile of R-7025 (Maxy-alpha), a next-generation interferon alfa for the treatment of HCV infection. The double-blind, dose-escalation, controlled study will evaluate a single s.c. administration of R-7025 in healthy volunteers, with both placebo and Pegasys® (peginterferon alfa-2a) control groups. R-7025 is a novel PEGylated interferon alfa variant created through the use of Maxygen's proprietary MolecularBreeding™ directed molecular evolution technologies. It has been designed to have enhanced antiviral activity against HCV and to be more effective in stimulating immune responses to help combat the infection.

R-7128

R-7128 is an RNA-directed RNA polymerase (NS5B) inhibitor in phase I clinical trials at Pharmasset and Roche for the oral treatment of chronic HCV genotype 1 infec-

tion. RNA polymerase is essential for the hepatitis C virion to make RNA from DNA or RNA templates, which allows the production of proteins necessary for viral reproduction. R-7128 was developed as an oral prodrug of Pharmasset's nucleoside polymerase inhibitor PSI-6130. Pursuant to an agreement signed between Roche and Pharmasset in October 2004, Roche gained worldwide rights, excluding Latin America and Korea, to PSI-6130 and its prodrugs.

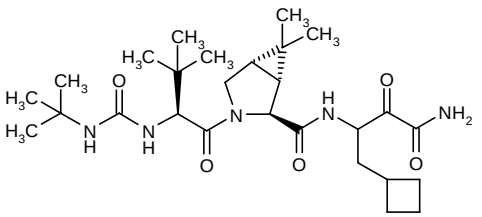
Resiquimod



Resiquimod is an immunomodulating gel in early clinical trials at the University of British Columbia for enhancing the protective response to a hepatitis B vaccine. Resiquimod is an analogue of 3M Pharmaceuticals' first-generation immune response modifier (IRM) drug imiquimod, with 100-fold greater potency for inducing cytokine production in dermal cells. Results from previous studies show that the imidazoloquinoline compound acts directly on dendritic cells to induce Th1 cytokine secretion, and may therefore be useful for increasing Th1 immunity.

Original monograph – Drugs Fut 1999, 24(6): 622.

Sch-503034

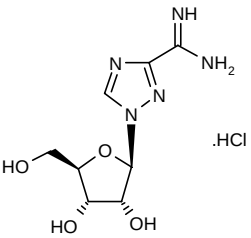


Sch-503034 is an HCV NS3 protease inhibitor in phase II clinical trials at Schering-Plough for the treatment of chronic hepatitis C genotype 1 infection in combination with pegylated interferon with and without ribavirin in patients who do not respond to pegylated interferon and ribavirin combination therapy. In February 2006, Sch-503034 received fast track designation from the FDA for this indication.

SuperVax

A recombinant DNA hepatitis B vaccine known as SuperVax was approved and launched in Argentina in 2003 and 2006, respectively, for the prevention of HBV infection. The vaccine is produced using proprietary *Hansenula polymorpha* technology and is combined with the fully synthetic adjuvant RC-529 developed by the former Corixa (subsequently acquired by GlaxoSmithKline). SuperVax was developed by Rhein Biotech, a company which was 93%-owned by Berna Biotech. In early 2006, Crucell acquired Berna Biotech, and in mid-2006, Dynavax acquired a Rhein Biotech subsidiary (Rhein Biotech GmbH).

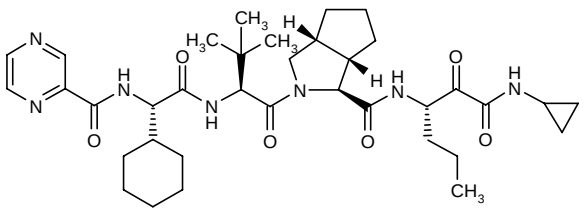
Taribavirin Hydrochloride



Phase III clinical trials are under way for taribavirin hydrochloride (Viramidine®), a liver-targeted prodrug of ribavirin, a synthetic nucleoside analogue IMP dehydrogenase inhibitor. Valeant is developing taribavirin for use in combination with pegylated interferon as oral therapy for treatment-naïve patients with chronic HCV. Following oral administration, taribavirin is rapidly absorbed and subsequently taken up extensively by the liver and converted to its active metabolite ribavirin. Due to the compound's rapid assimilation and conversion, exposure to red blood cells is minimized, reducing the severity of anemia, a dose-limiting side effect associated with standard HCV treatment, and increasing exposure to the liver, the site of HCV replication.

Original monograph – Drugs Fut 2004, 29(7): 687.

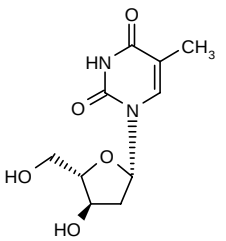
Telaprevir



Telaprevir (VX-950) is an investigational oral HCV protease inhibitor in phase II evaluation in combination with pegylated interferon for the treatment of hepatitis C. Additional phase II trials involve treatment-naïve HCV patients. Originally developed at Lilly, Vertex obtained rights to the drug as a result of a collaborative agreement. The compound has been granted fast track designation in the U.S. for the treatment of hepatitis C. Vertex and Janssen (Johnson & Johnson) recently signed a develop-

ment and commercialization agreement whereby Janssen gains exclusive rights to the product in Europe, South America, the Middle East, Africa and Australia, while Vertex retains rights for North America. Tibotec, another J&J company, will lead the development and commercialization for Janssen.

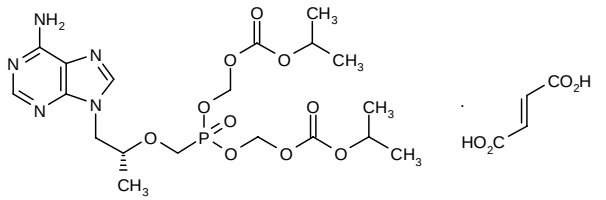
Telbivudine



An HBV-specific nucleoside analogue, telbivudine is a DNA polymerase inhibitor that was approved and launched in 2006 in Switzerland as Sebivo® for the oral treatment of chronic hepatitis B in compensated patients with evidence of viral replication and active liver inflammation. FDA approval under the name Tyzeka™ was also obtained in 2006, and the product has been filed for approval in the E.U., China and several countries worldwide by Idenix and development partner Novartis. Telbivudine's high specificity for HBV allows the treatment of subjects co-infected with other viruses, such as HIV, without an increased risk of resistance to these viruses. Idenix believes that this specificity, along with the favorable safety profile, will allow telbivudine to be used to manage different categories of patients with hepatitis B.

Original monograph – Drugs Fut 2003, 28(9): 870.

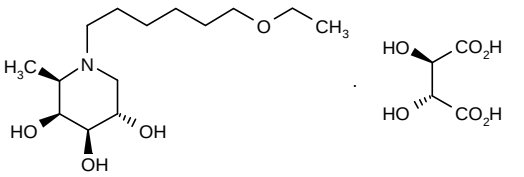
Tenofovir Disoproxil Fumarate



Gilead's tenofovir disoproxil fumarate (Viread®), a prodrug of the nucleotide reverse transcriptase inhibitor (NtRTI) tenofovir, was launched in 2001 as a combination therapy with other antiretroviral agents for the oral treatment of HIV infection in adults. Phase III clinical trials are also being conducted at Gilead for the treatment of chronic hepatitis B. The NIAID and Gilead are collaborating on phase II trials of a 1% topical gel formulation of the compound for the prevention of HIV via sexual transmission in patients at high risk of contracting the virus.

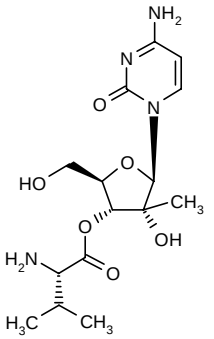
Original monograph – Drugs Fut 1998, 23(12): 1279.

UT-231B



UT-231B, a therapeutic iminosugar, is currently undergoing phase II clinical trials at United Therapeutics for the treatment of HCV. Research suggests that UT-231B alters the assembly of the virus, thereby preventing it from replicating and infecting cells.

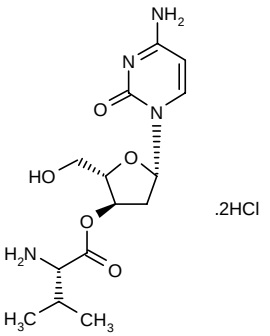
Valopicitabine



A first-in-class RNA polymerase inhibitor, valopicitabine (NM-283) is in phase II clinical trials at Idenix and Novartis for the once-daily oral treatment of HCV in combination with pegylated interferon in treatment-naïve patients and treatment-refractory patients. Valopicitabine was co-discovered by Idenix and the University of Cagliari. Pursuant to a development and commercialization agreement, Novartis and Idenix will co-promote valopicitabine in the U.S., the U.K., Spain, France, Italy and Germany, while Novartis will have exclusive marketing rights in the rest of the world.

Original monograph – Drugs Fut 2006, 31(4): 320.

Valtorcitabine Dihydrochloride



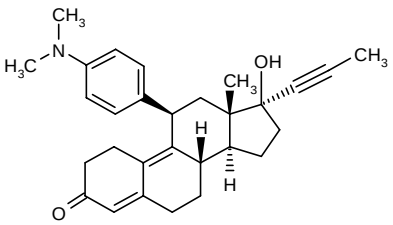
The DNA polymerase inhibitor valtorcitabine dihydrochloride is in phase II trials at Idenix and Novartis for

the treatment of hepatitis B in combination with telbivudine. The drug is an orally bioavailable prodrug of NM-107, a nucleoside analogue that directly inhibits HBV DNA polymerase. Valtorcitabine has been shown to dose-dependently decrease plasma HBV DNA levels.

VCH-759

VCH-759 (BCH-27759) is an HCV NS5B RNA polymerase inhibitor in phase I/II clinical trials at ViroChem Pharma for the oral treatment of HCV infection. HCV NS5B RNA polymerase is crucial for viral replication. VCH-759 has shown promising results in the cellular replicon model.

VGX-410C



VGX Pharmaceuticals' candidate for the treatment of chronic HCV infection VGX-410C (mifepristone) is currently in phase II clinical trials at the University of Connecticut, St. Louis University and the University of Pennsylvania. VGX-410C, an orally active small molecule, is the first drug in a novel class of HCV internal ribosomal entry site (IRES) inhibitors. It prevents HCV replication by suppressing HCV translation. Mifepristone was first launched in 1989 by the former Aventis Pharma (sanofi-aventis) for the termination of pregnancy. VGX is also evaluating the compound in phase II trials for HIV-infected patients. Other companies are studying the potential of mifepristone in a number of other conditions.

XTL-2125

XTL Biopharmaceuticals is conducting early clinical trials with XTL-2125 (formerly BC-2125), a non-nucleoside RNA-directed RNA polymerase (NS5B) inhibitor for the oral treatment of chronic HCV infection. The drug candidate is the lead compound in XTL's HCV-SM small-molecule program. BC-2125 was originally developed at B&C Biopharm and subsequently licensed to XTL.

XTL-6865

XTL-6865 (formerly HepeX-C) is a combination of two fully human monoclonal antibodies (Ab68 and Ab65) against the HCV E2 envelope protein. The antibodies are expected to trap the virus in the serum and prevent the infection of healthy liver cells. Phase I trials of the product candidate are under way at XTL Biopharmaceuticals for the prevention of HCV re-infection following liver transplantation and for the treatment of chronic HCV disease. The FDA has granted fast track designation to XTL-6865 for the treatment of patients with recurrent HCV following liver transplant.