

Viramidine Ribapharm Dale Barnard

Address

Institute for Antiviral Research
Utah State University
5600 Old Main Hill
Logan
UT 84322-5600
USA
Email: honery@cc.usu.edu

Current Opinlon in Investigational Drugs 2002 3(11):1585-1589
© PharmaPress ISSN 1472-4472

Viramidine, an analog of ribavirin is a broad-spectrum antiviral under development by Ribapharm (previously the R&D division of ICN Pharmaceuticals) for the potential treatment of viral infections [378507]. In September 2000, phase I trials began in Europe. In December 2001, the company filed a US IND for the clinical development of viramidine as part of a combination therapy with interferon- α for the treatment of chronic hepatitis C virus (HCV) infection [435007], [441613]; a phase I trial was initiated in the US in late March 2002 [435598]. In November 2002, Ribapharm reported that it would start phase II trials of viramidine in the treatment of chronic HCV by the end of 2002 [469062].

Introduction

Viramidine an ammoniated derivative of ribavirin [465745], is a broad-spectrum antiviral nucleoside analog under clinical investigation by Ribapharm (formerly the R&D division of ICN Pharmaceuticals) primarily for the treatment of viral infections, including chronic hepatitis C virus (HCV) infection. Initially synthesized as part of a program targeting purine inosine 5'-monophosphate (IMP) dehydrogenase, viramidine was found to inhibit nucleoside phosphorylase [465739] and to have immunomodulation properties [456725]; the compound was later shown to exhibit antitumor activity [465740]. Subsequently, viramidine was found to inhibit a broad-spectrum of viruses similar to that of the parent compound ribavirin [119906], [218908], [435598], [465741], [465744]. Viramidine acts as a prodrug of ribavirin as it is taken up by liver cells and converted by adenosine deaminase to the parent compound [435598], [442408], [456720], [456723]. Encouraging results indicating liver targeting, and preclinical models of viral liver disease, have led to the current interest in the development of viramidine for the potential treatment of HCV infection.

Synthesis and SAR

Viramidine is a 3-carboxamidine analog of ribavirin [465739]. Initially, synthesis involved the glycosylation of a 3-cyano-1,2,4-triazole with 1,2,3,5-tetra-O-acetyl-D-ribofuranose, followed by separation of the isomers by chromatography. However, this produced a low overall yield of the final product [465739]. An easier method of synthesis resulting in greater yields was developed by treating an imidate derivative of ribavirin with methanolic ammonia in the presence of ammonium chloride [465740].

Studies have demonstrated that altering the carboxamidine group of ribavirin by making imidate derivatives (eg, OCH_3 and OCH_2CH_3), instead of an amidine derivative (viramidine), resulted in the loss of *in vitro* antiviral activity,

Originator ICN Pharmaceuticals Inc

Licensee Ribapharm Inc

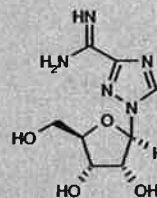
Status Phase I Clinical

Indication Viral infection

Action Antiviral

Synonyms & Analogs ICN-3142, ribamidine, ribavirin amidine, ribavirin analog

CAS 1H-1,2,4-Triazole-3-carboximidamide, 1- β -D-ribofuranosyl-
Registry No: 119567-79-2



although antitumor activity was detected [465740]. The importance of the carboxamidine group for antiviral activity was verified when substitutions of the amidine nitrogen with alkyl, cyano, or various amino acids were made. These substitutions eliminated any antiviral activity previously demonstrated with viramidine against a variety of bunyaviruses [465744]. In general, viramidine was less toxic *in vitro*, although a less potent antiviral inhibitor, when compared with ribavirin [119906], [218908], [465741], [465744].

Pharmacology

Pharmacological studies in rats have indicated that radioactive viramidine is targeted to the liver better than ribavirin [218908], [444003], [447635]; thus, viramidine has been pursued as a treatment for chronic HCV infections. The compound has been undergoing preclinical research on its mechanism of action in various animal models and safety and efficacy studies for the treatment of bunyavirus infections [378507], [381453], [451762].

In rhesus monkey kidney (LLC-MK2 derivative) cells, Adames and Balliet strains of Punta Toro virus (PTV) were inhibited by viramidine (ED_{50} values of 8 and 12 $\mu\text{g}/\text{ml}$, respectively; CD_{50} value of 320 $\mu\text{g}/\text{ml}$) [465741]. PTV-infected C57BL/6 mice were used as a model for the efficacy of viramidine against bunyavirus infection. Viramidine (administered sc bid for 5 days, commencing 4 h prior to inoculation with 10^5 plaque-forming units of virus) showed a significant level of inhibition, with increased survivor numbers (therapeutic index = 65) and acted in a direct antiviral, rather than immunomodulatory manner [218908].

In an Adames PTV-induced murine model of liver disease, sc and oral treatments were equally effective, with a 100% survival rate. A single dose of viramidine, administered either sc 48 h post-infection (minimum effective dose = 125 mg/kg, maximum tolerated dose = 1000 mg/kg) or tid as late as 72 h post-infection (minimum effective dose = 31.3 to 62.5 mg/kg/day, maximum tolerated dose = 1000 mg/kg/day) normalized liver functions, as evidenced by reduced hepatic icterus, serum oxalic acid transaminase and serum glutamic pyruvic acid transaminase. In the bunyavirus model, a single dose administered ip 48 h post-infection was sufficient to reduce virus titer up to 4 logs. More importantly, liver functions were normalized compared with untreated, virus infected animals [465741].

Viramidine shows efficacy against a variety of viruses, such as HCV, bovine diarrhea virus, respiratory syncytial virus, influenza virus and HIV, with IC_{50} values of between 1 and 100 μ M. For yellow fever virus, Dengue virus, poliovirus, Japanese encephalitis virus and lymphocyte choriomeningitis virus, however, higher concentrations than this are required in order to demonstrate efficacy [435598]. Moreover, in an HCV replicon system, viramidine had an IC_{50} value of approximately 100 μ M for inhibition of virus transcript expression, compared with ribavirin, which had an IC_{50} value of approximately 30 μ M [435598]. Viramidine has demonstrated efficacy against influenza A infections in mice and in a murine bunyavirus-induced liver disease model; a single-dose (ip or po) 48 h after infection prevented animal death and cleared the virus infection. It also showed efficacy against an arenavirus infection in hamsters [442408].

Viramidine and ribavirin were tested in 3-week-old, random-bred Golden Syrian hamsters (LVG/Lak strain) that had been inoculated ip with Pichinde virus. Mortality occurred in untreated animals 6 to 9 days post-infection; high virus titers were present in visceral organs, serum, brain and salivary glands near the time of death. Treatment with ribavirin (10 and 32 mg/kg ip) and viramidine (32, 100 and 320 mg/kg ip) for 10 days, starting 24 h post virus challenge, decreased mortality and virus titers (100- to > 10,000-fold) in the liver, spleen, serum and brain. Levels of serum alanine aminotransferase, an indicator of liver damage, were also reduced in treated animals [119906].

Toxicity

Preclinical toxicological studies in cynomolgus monkeys demonstrated that viramidine was non-toxic at a dose of 600 mg/kg/day for 10 days. In contrast, ribavirin, given at 300 mg/kg/day for 10 days caused hematological changes in both male and female animals. In the same study, viramidine was absorbed at significantly lower levels by monkey red blood cells compared with ribavirin [429125]. This supports *in vitro* findings that viramidine is less cytotoxic than ribavirin [465748]. In another study in cynomolgus monkeys, animals received several oral doses of viramidine or ribavirin. When equal doses of the two compounds were compared, viramidine was better tolerated [444003].

Also of great significance is the finding that no significant teratogenic effects due to viramidine have been detected in contrast to ribavirin, although viramidine was considered to be weakly positive in a mouse lymphoma assay for genotoxicity [442408].

Metabolism

Viramidine is a prodrug of ribavirin that is taken up by liver cells and converted by adenosine deaminase to ribavirin [218908], [456720], [456723]. It is converted by bovine adenosine deaminase with a K_m value of 10 mM, k_{cat} value of 1.9/s and k_{cat}/K_m value of 0.19 mM/s [451762].

Clinical Development

Phase I

Data from clinical trials is sparse, because the drug has only recently entered clinical development. A phase I clinical trial to test the safety of viramidine has been completed. In a randomized, blinded, rising single-dose study to evaluate the safety, tolerability and PK profiles of viramidine, oral doses of 200, 600 and 1200 mg were given to adult healthy male individuals. Ten fasting, healthy volunteers were given 200 mg of viramidine ($n = 8$) or placebo ($n = 2$) and monitored for 1 week [451762]. The drug was well tolerated and no serious adverse effects were noted; 20 fasting or fed, healthy volunteers were given 600 or 1200 mg of viramidine or placebo ($n = 8$ and 2, respectively for both fasting and fed groups) and followed for 1 week. No serious adverse effects were observed. For the doses tested in each study, T_{max} occurred at 2.5 h and there was a linear relationship between dose and C_{max} . AUC values were 557, 1680 and 4698 ng.h/ml, and $t_{1/2}$ values were 3.9, 11 and 35.6 h for the 200, 600 and 1200 mg doses, respectively [451762].

Viramidine is currently in further phase I clinical trials for possible treatment of chronic HCV infections [448191], [465749] and phase II clinical trials are expected to begin in the first quarter of 2003 for this indication [465750]. To this end, Ribapharm has filed a US IND for clinical development of viramidine as part of a combination therapy that would include an interferon- α product [435007].

Side Effects and Contraindications

Since the majority of viramidine seems to be metabolized to ribavirin in the liver, one would not expect to detect the red blood cell toxicity that is associated with ribavirin [447635]. Plasma levels of ribavirin at a dose of 1200 mg of viramidine never exceeded 4000 ng/ml and were as low as 3000 ng/ml at 21 days, while plasma levels of ribavirin at an equivalent dose never went lower than 5000 ng/ml and were as high as 11,000 ng/ml [442408]. This suggests that the great majority of viramidine is metabolized to ribavirin in the liver. This conclusion is strengthened by the finding that viramidine had a 3- to 6-fold longer residence time in the liver [469187].

In clinical trials, no hematological abnormalities were detected [429125]. Headache was the only adverse effect noted and there were no significant changes in blood chemistry or heart function attributable to the drug [451762].

Current Opinion

Viramidine, although a less potent antiviral agent on a molar basis than ribavirin, has the same broad spectrum of antiviral activity that is sensitive to inhibitory effects. Because of its predisposition for metabolism in the liver, however, viramidine appears to be a viable, less toxic

alternative to ribavirin for the treatment of certain viral infections, especially chronic infections of the liver such as those caused by HCV.

Since the compound concentrates in the liver as a prodrug, the use of viramidine may be restricted to the treatment of virus infections causing liver disease. Further pharmacological data is needed to determine if adequate concentrations of viramidine can be achieved in the circulatory system to treat other systemic viral diseases and whether such amounts will lead to the development of anemia. Significantly, because viramidine concentrates in the liver and is then metabolized to ribavirin, there should be much less anemia detected with the use of viramidine than is associated with continuous ribavirin therapy for HCV infections. This bodes well for patients with chronic diseases of the liver who may require prolonged

chemotherapy to manage the disease. In addition, in the one genotoxic test for which data are currently available, the compound was only weakly positive. Ribavirin performs well in many genotoxic assays, again suggesting that viramidine might do well in a prolonged treatment scenario.

Until further clinical data become available, it is impossible to predict the future usage of viramidine. If the drug performs well in additional genotoxicity assays and no severe adverse effects are observed in long-term chemotherapy trials, this compound promises to be a worthy addition to the treatment options available for chronic HCV infections. For other virus infections, especially lower respiratory tract infections for which the use of ribavirin has been indicated, there is currently no way of knowing whether viramidine will prove to be a less toxic, yet satisfactorily potent replacement for ribavirin.

Licensing

Ribapharm Inc

Ribapharm (previously the R&D division of ICN Pharmaceuticals) has been developing viramidine. The company was officially spun off from ICN on April 17, 2002 [456045].

Development history

Developer	Country	Status	Indication	Date	Reference
Ribapharm Inc	US	Phase I	Viral infection	28-MAY-02	456045
Ribapharm Inc	Western Europe	Phase I	Viral infection	28-MAY-02	456045

Literature classifications

Chemistry

Study Type	Results	Reference
Synthesis.	3-Cyano-1,2,4-triazole was glycosylated with 1,2,3,5-tetra- <i>O</i> -acetyl-D-ribofuranose, followed by separation of the isomers by chromatography. This produces a low overall yield of viramidine.	465739
Synthesis.	An imidate derivative of ribavirin was treated with methanolic ammonia in the presence of ammonium chloride. This route results in greater yields of viramidine.	465740
SAR.	3-Carboxamide substitutions are critical for antiviral but not antitumor activity.	465744

Biology

Study Type	Effect Studied	Experimental Model	Results	Reference
<i>In vitro</i>	Efficacy against PTV.	LLC-MK2 cell line.	Viramidine was inhibitory against Adames and Balliet strains of PTV with ED ₅₀ values of 8 to 12 µg/ml.	465741
<i>In vitro</i>	Efficacy against a panel of viruses.	Cell culture.	Viramidine demonstrates a similar antiviral inhibitory spectrum to that of ribavirin. Many viruses were inhibited with IC ₅₀ values of 1 to 100 µM, however, some required higher concentrations.	435598
<i>In vivo</i>	Antiviral efficacy.	Pichinde virus infection of Golden Syrian Hamsters.	Viramidine significantly decreased mortality and reduced virus titers in liver, spleen, brain and serum.	119906
<i>In vivo</i>	Antiviral efficacy.	PTV-infected C57BL/6 mice.	Significant inhibition of infection and increased survival was observed.	218908
<i>In vivo</i>	Antiviral efficacy.	Bunyavirus-induced liver disease mouse model.	Viramidine reduced virus titers up to 4 logs, but showed no immunomodulatory properties in this disease model.	442408

Biology (continued)

Study Type	Effect Studied	Experimental Model	Results	Reference
<i>In vivo</i>	Toxicity.	Cynomolgus monkey.	Viramidine (600 mg/kg/day for 10 days) was not toxic compared with ribavirin (300 mg/kg/day for 10 days) which caused hematological changes in both male and female animals. Viramidine was not appreciably absorbed by red blood cells.	429125
<i>In vivo</i>	Antiviral efficacy.	Bunyavirus-induced liver disease mouse model.	Oral or sc treatment with viramidine resulted in 100% survival. A single dose given 48 h post-infection or tid as late as 72 h post-infection normalized liver functions.	465741

Metabolism

Study Type	Effect Studied	Model Used	Results	Reference
<i>In vitro</i>	Pharmacokinetics.	Conversion by bovine adenosine deaminase.	Converted with a K_m of 10 mM, k_{cat} of 1.9/s and a k_{cat}/K_m of 0.19 mM/s.	451762
<i>In vivo</i>	Distribution and metabolism.	Rats.	Targeted to liver and converted to ribavirin by adenosine deaminase.	456723

Clinical

Effect Studied	Model Used	Results	Reference
Safety and pharmacokinetics.	Phase I, escalating single-dose study of fasting human volunteers (n = 30) administered viramidine (200, 600 or 1200 mg po) or placebo.	All doses were well tolerated after 1 week. There were no serious adverse effects noted, with headache the only adverse effect at the highest dose. T_{max} was 2.5 h and there was a linear relationship between dose and C_{max} .	451762

Associated patent

Title Nucleoside analogs with carboxamidine modified monocyclic base.

Assignee ICN Pharmaceuticals Inc

Publication WO-00160379 23-AUG-01

Priority US-00182676 15-FEB-00

Inventors Tam R, Ramasamy K, Hong Z, Lau J.

Associated references

119906 **Treatment of lethal Pichinde virus infections in weaning LVG/Lak hamsters with ribavirin, ribamidine, selenazofurin, and ampliten.** Smee DF, Gilbert J, Leonhardt JA, Barnett BB, Huggins JH, Sidwell RW *ANTIVIRAL RES* 1993 20 1 57-70

• This paper describes the spectrum of viruses inhibited by viramidine *in vitro*.

218908 **Antiviral and immunomodulating inhibitors of experimentally-induced Punta Toro virus infections.** Sidwell RW, Huffman JH, Bamard DL, Smee DF, Warren RP, Chirigos MA, Kende M, Huggins J *ANTIVIRAL RES* 1994 25 2 105-122

• This report describes the first study of the efficacy of viramidine in a bunyavirus-induced liver disease model in mice, and its very weak genotoxicity.

378507 **Annual report - ICN Pharmaceuticals.** ICN Pharmaceuticals Inc *ANNUAL REPORT* 1999 December 31

381453 **ICN spin-off Ribapharm expects tiazole phase III results by 2002.** *FDC REPORTS PINK SHEET* 2000 62 36 21

389982 **Schering-Plough and ICN Pharmaceuticals announce strategic licensing agreement.** Schering-Plough Corp *PRESS RELEASE* 2000 November 15

414330 **Annual Report 2000 - ICN Pharmaceuticals Inc.** ICN Pharmaceuticals Inc *ANNUAL REPORT* 2001 March 15

429125 **ICN presents new data on viramidine and levovirin at the AASLD Annual Meeting.** ICN Pharmaceuticals Inc *PRESS RELEASE* 2001 November 12

435007 **ICN Pharmaceuticals files Viramidine IND.** ICN Pharmaceuticals Inc *PRESS RELEASE* 2002 January 07

435598 **HEP DART 2001 (Part II), Frontiers in Drug Development for Viral Hepatitis, Maui, HI, USA.** Bartenschlager R *IDDB MEETING REPORT* 2001 December 16-20

441613 **ICN Pharmaceuticals reports record fourth quarter and record year.** ICN Pharmaceuticals Inc *PRESS RELEASE* 2002 February 27

442408 **Antiviral development of viramidine: A safer and liver-targeting prodrug of ribavirin for treatment of hepatitis C.** Hong Z, Lin CC, Fang J, Sidwell R, Lau JYN *ANTIVIRAL RES* 2002 53 3 Abs 10

444003 **Antiviral Research - 15th International Conference (Part I) - OVERNIGHT REPORT, Prague, Czech Republic.** Paterson D *IDDB MEETING REPORT* 2002 March 17-21

447635 **Antiviral Research - 15th International Conference (Part VIII), Anti-HCV Agents, Prague, Czech Republic.** Smee DF *IDDB MEETING REPORT* 2002 March 17-21

448191 **Antiviral Research - 15th International Conference (Part IX), Prague, Czech Republic.** Bamard DL *IDDB MEETING REPORT* 2002 March 17-21

451762 **Preclinical and clinical characterization of viramidine - A liver-targeting ribavirin.** Fang JWS, Lin CC, Wu J, Edalatpour N, Hong Z, Lau JYN *GASTROENTEROLOGY* 2002 122 4 Suppl 1 Abs T1376

• This abstract details the results from a phase I clinical safety trial.

456045 **Form 10-Q.** Ribapharm Inc *FORM 10-Q* 2002 May 28

456720 **Viramidine, a prodrug of ribavirin, demonstrated superior liver-targeting properties and a much improved toxicity profile in cynomolgus monkey studies.** Lin CC, Luu K, Loureno D, Corritori S, Hong Z, Lau JY *HEPATOLOGY* 2001 34 4 Part 2 453A

• This paper describes the targeting of viramidine to the liver and its metabolic fate.

456723 **Comparative absorption, metabolism and excretion studies of ribavirin versus viramidine, a liver-targeted ribavirin prodrug.** Lin CC, Luu K, Loureno D, Huang J, Fang JW, Lau JY *HEPATOLOGY* 2001 34 4 Part 2 219A

456725 **Immunomodulatory activities of viramidine, a liver-targeting ribavirin prodrug, *in vitro* and *in vivo*.** Tam R, Lim C, Bard J, Bagha P, Lau JY, Hong Z *HEPATOLOGY* 2001 34 4 Part 2 351A

465739 **An *in vivo* and *in vitro* evaluation of 1-β-D-ribofuranosyl-1,2,4-triazole-3-carboxamidine: An inhibitor of human lymphoblast purine nucleoside phosphorylase.** Willis RC, Robins RK, Seegmiller JE *MOL PHARMACOL* 1980 18 2 287-295

• This paper describes the first synthesis of viramidine.

465740 Synthesis and antitumor activity of ribavirin imidates. A new facile synthesis of ribavirin amidine (1- β -D-ribofuranosyl-1,2,4-triazole-3-carboxamidine hydrochloride). Kini GD, Robins RK, Avery T *J MED CHEM* 1989 32 1447-1449

• This paper describes an alternative, more facile way of synthesizing viramidine, compared with that outlined in other publications.

465741 Effects of ribamidine, a 3-carboxamidine derivative of ribavirin, on experimentally induced Phlebovirus infections. Sidwell RW, Huffman JH, Bamard DL, Pifat DY *ANTIVIRAL RES* 1988 10 4-5 193-207

• This paper reports the efficacy of viramidine against an arenavirus in a guinea pig model.

465744 Synthesis and antiviral evaluation of N-carboxamidine-substituted analogues of 1- β -D-ribofuranosyl-1,2,4-triazole-3-carboxamidine hydrochloride. Gabrielsen B, Phelan MJ, Barthel-Rosa L, See C, Huggins JW, Kefauver DF, Monath TP, Ussery MA, Chmumy GN, Schubert EM *et al J MED CHEM* 1992 35 17 3231-3238

• This paper describes the spectrum of viruses inhibited by viramidine *in vitro*.

465745 Design, synthesis and broad spectrum antiviral activity of the nucleoside, 1- β -D-ribofuranosyl-1,2,4-triazole-3-carboxamide and related nucleosides. Witkowski JT, Robins RK, Sidwell RW, Simon LN *J MED CHEM* 1972 15 11 1150-1154

465748 ICN presents new data on viramidine™ and levovirin™ at the AASLD annual meeting. Focus: On hepatitis C International: HCV News *INTERNET SITE* 2002 September 23 1-4

• The lack of cytotoxicity of viramidine *in vitro* is described.

465749 The NIH consensus conference on the management of hepatitis C: 2002. Part 4. Thomas DL *INTERNET SITE* 2002 1-18

• A summary of the potential of viramidine for treating chronic hepatitis C infections is provided.

465750 Viramidine being investigated for chronic hepatitis C. USB Warburg Conference Ribapharm *INTERNET SITE* 2002 1-24

• Ribapharm's estimate of when phase II studies with viramidine may begin.

469062 Viramidine to advance to phase II clinical trials in hepatitis C. Ribapharm Inc *PRESS RELEASE* 2002 November 04

469187 NIH Consensus Development Conference on Management of Hepatitis C 2002: Alternative ribavirin-like drugs. Medical Advocates for Justice *INTERNET SITE* 2002 June 10