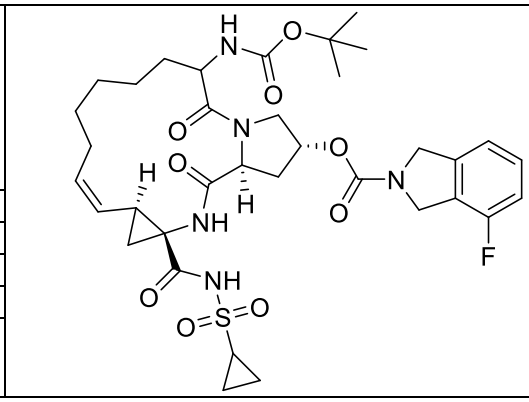
Product data sheet

MedKoo Cat#: 315123 Name: Danoprevir CAS#: 850876-88-9 (free base) Chemical Formula: $C_{35}H_{46}FN_5O_9S$ Exact Mass: 731.30003 Molecular Weight: 731.83	

Product supplied as:	Powder
Purity (by HPLC):	≥ 98%
Shipping conditions	Ambient temperature
Storage conditions:	Powder: -20°C 3 years; 4°C 2 years.
	In solvent: -80°C 3 months; -20°C 2 weeks.

1. Product description:

Danoprevir, also known as ITMN-191 and RG-7227, is under development by InterMune Inc and Roche Holding AG, is a promising, potent NS3/4A protease inhibitor for the oral treatment of HCV infection. Preclinical data demonstrated that danoprevir binds with high affinity and dissociates slowly from the HCV NS3 protease, allowing high liver drug exposure with only modest plasma drug exposure. A phase Ib, 'IFN-free' clinical trial demonstrated that danoprevir, combined with the HCV polymerase inhibitor RG-7128 (Pharmasset Inc/Roche Holding AG), was effective in reducing HCV-RNA levels in a large proportion of treatment-naÃ¯ve patients with HCV infection and in approximately half of previously non-responsive patients with HCV-1 infection, without resistance or safety concerns.

2. CoA, QC data, SDS, and handling instruction

SDS and handling instruction, CoA with copies of QC data (NMR, HPLC and MS analytical spectra) can be downloaded from the product web page under “QC And Documents” section. Note: copies of analytical spectra may not be available if the product is being supplied by MedKoo partners. Whether the product was made by MedKoo or provided by its partners, the quality is 100% guaranteed.

3. Solubility data

Solvent	Max Conc. mg/mL	Max Conc. mM
DMSO	90.0	122.98
Ethanol	80.0	109.32

4. Stock solution preparation table:

Concentration / Solvent Volume / Mass	**1 mg**	**5 mg**	**10 mg**
1 mM	1.37 mL	6.83 mL	13.66 mL
5 mM	0.27 mL	1.37 mL	2.73 mL
10 mM	0.14 mL	0.68 mL	1.37 mL
50 mM	0.03 mL	0.14 mL	0.27 mL

5. Molarity Calculator, Reconstitution Calculator, Dilution Calculator

Please refer the product web page under section of “Calculator”

6. Recommended literature which reported protocols for in vitro and in vivo study

In vitro study

1. Seiwert SD, Andrews SW, Jiang Y, Serebryany V, Tan H, Kossen K, Rajagopalan PT, Misialek S, Stevens SK, Stoycheva A, Hong J, Lim SR, Qin X, Rieger R, Condroski KR, Zhang H, Do MG, Lemieux C, Hingorani GP, Hartley DP, Josey JA, Pan L, Beigelman L, Blatt LM. Preclinical characteristics of the hepatitis C virus NS3/4A protease inhibitor ITMN-191 (R7227). Antimicrob Agents Chemother. 2008 Dec;52(12):4432-41. doi: 10.1128/AAC.00699-08. Epub 2008 Sep 29. PMID: 18824605; PMCID: PMC2592891.

In vivo study

1. Seiwert SD, Andrews SW, Jiang Y, Serebryany V, Tan H, Kossen K, Rajagopalan PT, Misialek S, Stevens SK, Stoycheva A, Hong J, Lim SR, Qin X, Rieger R, Condroski KR, Zhang H, Do MG, Lemieux C, Hingorani GP, Hartley DP, Josey JA, Pan L, Beigelman L, Blatt LM. Preclinical characteristics of the hepatitis C virus NS3/4A protease inhibitor ITMN-191 (R7227). Antimicrob Agents Chemother. 2008 Dec;52(12):4432-41. doi: 10.1128/AAC.00699-08. Epub 2008 Sep 29. PMID: 18824605; PMCID: PMC2592891.

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7. Bioactivity

Biological target:

Danoprevir (ITMN-191) is a NS3/4A protease inhibitor for hepatitis C virus (HCV) with an IC50 of 0.29 nM and is selective for NS3/4A over a panel of 53 proteases (IC50 higher than 10 μM).

In vitro activity

In peptide cleavage assays, ITMN-191 reduced genotype 1b NS3/4A (K2040) protease activity in a concentration-dependent fashion (Fig.2). In support of a slow/tight binding mechanism, suggested by Fig.2, NS3/4A activity was substantially lower in samples subjected to preincubation with 20 nM ITMN-191 than in samples with the same final enzyme and inhibitor concentrations that were not preincubated (Fig.3). Thus, ITMN-191 disassociated from genotype 1b NS3/4A with a half-life on the order of several hours, as evidenced by the persistence of inhibition over the same time scale. Dose-dependent reductions of a patient-derived HCV genotype 1b replicon harbored in hepatocyte-derived Huh7 cells were observed following 2-day incubation with ITMN-191 (Fig.4A). TMN-191 was a highly potent inhibitor of HCV replication in a cell-based system, as well as a highly potent inhibitor in biochemical assays. Treatment with 45 nM ITMN-191 (~3 times its EC90) reduced HCV replicon RNA levels below the RT-PCR detection limit in a sustained fashion (Fig.4B) and completely cleared replicon RNA, as judged by the inability to select for replicon-containing cells in a 4-week follow-up period (Fig.4C).

Reference: Antimicrob Agents Chemother. 2008 Dec; 52(12): 4432–4441. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2592891/

In vivo activity

Doses of 30 mg/kg were administered to rats and monkeys via oral gavage, which corresponded to a human equivalent dose of 290 mg or 580 mg, respectively. Importantly, the concentrations of ITMN-191 observed in the livers of both species were significantly above the compound's EC50, although concentrations in rats were higher than in monkeys (Table 44 and Fig.6). In monkey liver tissue, the Cmax and C12 h were sufficient to reduce HCV replicon RNA by 3.1 log10 and 2.0 log10 units, respectively, and also resulted in HCV replicon clearance from cells in 14-day antiviral assays (Table4). While HCV is thought to replicate exclusively or nearly exclusively in the liver, significant reduction in HCV replicon RNA would also be supported by plasma concentrations (Table4). Thus, although the exposure of ITMN-191 in monkeys is lower than that observed in rats, concentrations achieved in the livers and plasma of both species would be predicted to significantly impair viral replication. These preclinical characteristics compare favorably to those of other inhibitors of NS3/4A in clinical development and therefore support the clinical investigation of ITMN-191 for the treatment of chronic hepatitis C.

Reference: Antimicrob Agents Chemother. 2008 Dec; 52(12): 4432–4441. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2592891/