# Hepatitis C

## New developments in the pharmacotherapy of chronic infection

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Over the past five years, the treatment of chronic hepatitis C virus (HCV) infection has changed dramatically with the development of direct-acting antiviral (DAA) agents that target various phases of the HCV life cycle. Cure rates for chronic HCV genotype 1, the most common type of HCV infection in Canada, are now above 90% as a result of the all-oral, interferon-free DAA regimens.[1-11] DAA treatment response rates in the setting of human immunodeficiency virus (HIV) and HCV genotype 1 co-infection are also comparable to those experienced by HCV mono-infected patients.[12-14]

Standard HCV treatment in 2015 involves the concurrent use of at least two or three drugs from different pharmacological classes, with the treatment duration lasting eight to 24 weeks.[15,16] Prior HCV treatment experience, the presence of cirrhosis, the HCV genotype and HCV ribonucleic acid (RNA) level are elements to be considered when determining treatment duration.[15,16] The novel DAA pharmacological classes include the following: nonstructural gene 5B (NS5B) nucleotide and non-nucleoside inhibitors, NS5A inhibitors and second-generation NS3/4A protease inhibitors.

The significantly improved efficacy and tolerability profile of all oral DAA regimens has prompted a desire to avoid interferon- and/or ribavirin-containing regimens. The first-generation NS3/4A protease inhibitors (telaprevir and boceprevir) are no longer recommended for HCV treatment and have been discontinued by their manufacturers.[15,17,18]

This article outlines the current pharmacological management of HCV infection, with a focus on first-line genotype 1 treatment options. It is intended as an update to a hepatitis C article published in *Pharmacy Practice* in 2012.[19] Tables 1 and 2 depict the currently recommended treatment options for HCV genotype 1.[16] The mechanisms of metabolism for the most recently approved DAA regimens, as well as administration and renal/hepatic dysfunction dosing details, are summarized in Tables 3[20,25,26,28,33,34] and 4,[20,25,26,28] respectively.

## Sofosbuvir/ledipasvir

Harvoni, a once-daily, fixed-dose oral tablet containing sofosbuvir 400 mg and ledipasvir 90 mg, was the first product approved in Canada for the treatment of chronic HCV genotype 1 in a regimen that does not include pegylated interferon and ribavirin.[20] Sofosbuvir is also commercially available as a 400 mg tablet (brand name Sovaldi).[21]

**Mechanism of action** Sofosbuvir is a pan-genotypic NS5B inhibitor with a high barrier to resistance.[20] NS5B is a viral protein that possesses RNA-dependent RNA polymerase activity and plays an essential role in the HCV replication process. Sofosbuvir is a nucleotide prodrug that rapidly undergoes conversion in the liver to form the active triphosphorylated metabolite GS-461203. This metabolite competes with natural nucleotides for incorporation into HCV RNA via NS5B's polymerase activity. Incorporation of GS-461203 into the HCV RNA chain causes premature termination of RNA synthesis and subsequent halting of viral replication. A rapid decline in HCV RNA ensues.

Ledipasvir is an NS5A inhibitor with high potency and a low barrier to resistance.[23] NS5A inhibitors have been postulated to cause rapid HCV RNA decline by efficiently blocking both RNA replication and virion assembly.[20]

**Drug interactions** The majority of clinically significant drug interactions with sofosbuvir involve potent P-glycoprotein (P-gp) inducers (e.g., rifampin, St. John's wort), which may decrease sofosbuvir concentrations and potentially compromise efficacy.[20] In April 2015, Health Canada issued a warning, based on nine postmarketing reports, about the development of serious symptomatic bradycardia in patients treated concurrently with amiodarone and sofosbuvir-containing DAA regimens.[22] The mechanism of this potential drug interaction is currently unclear. Health Canada recommends against co-administration of amiodarone with either Harvoni or Sovaldi in combination with another DAA. In cases where concomitant administration of amiodarone and a sofosbuvir-containing regimen is considered unavoidable, Health Canada recommends inpatient heart monitoring for the first 48 hours followed by daily self-monitoring of heart rate for the first two weeks of treatment. Due to amiodarone's long half-life, cardiac monitoring is also recommended for individuals who stopped amiodarone within the three months preceding initiation of a sofosbuvir-containing regimen.

The most clinically relevant drug interactions involving ledipasvir occur via gastric pH or transporter-mediated mechanisms.[20] Ledipasvir solubility decreases with increasing gastric pH. Antacids should be administered four hours apart from ledipasvir, while $H_2$-receptor antagonists should be administered with, or 12 hours apart from, ledipasvir. Doses equivalent to famotidine 40 mg twice daily should not be exceeded. Proton pump inhibitor doses equivalent to omeprazole 20 mg can be administered at the same time as ledipasvir, but should not be administered in advance of ledipasvir. Potent P-gp-inducing drugs may also interact with ledipasvir and reduce its efficacy. As a weak inhibitor of P-gp and breast cancer resistance protein (BCRP), ledipasvir may increase intestinal absorption of concurrently administered drugs that are substrates for these transporters (e.g., digoxin, tenofovir, rosuvastatin). Management options for such interactions include avoiding the use of ledipasvir with such drugs, if possible, or monitoring closely for toxicity.

**Adverse reactions** (all grades) reported in ≥ 5% of subjects receiving sofosbuvir/ledipasvir during clinical trials included fatigue (16%–18%), headache (11%–17%), nausea (6%–9%), diarrhea, (3%–7%) and insomnia (3%–6%).[24] The majority of these adverse reactions were mild in severity.

## Ombitasvir, paritaprevir/ritonavir and dasabuvir

Another all-oral regimen approved for the treatment of chronic HCV genotype 1 is the combination of ombitasvir, paritaprevir with ritonavir, and dasabuvir (marketed as Holkira Pak in Canada). This combination is also known as the 3D regimen because it is comprised of agents from three different pharmacological classes.[25]

**Mechanism of action** Ombitasvir is a pan-genotypic NS5A inhibitor, paritaprevir is an NS3/4A second-generation protease inhibitor and dasabuvir is a NS5B non-nucleoside inhibitor.[25] These three drugs target multiple steps in the viral lifecycle by focusing on proteins that play an essential role in HCV RNA replication. Ritonavir is a pharmacokinetic enhancer used specifically to boost paritaprevir exposure via CYP3A4 enzyme inhibition; it does not possess anti-HCV activity. Dosing of the 3D regimen consists of two ombitasvir 12.5 mg/paritaprevir 75 mg/ritonavir 50 mg tablets taken once daily and one dasabuvir 250 mg tablet taken twice daily. In certain patient populations, the 3D regimen is used in combination with ribavirin (Tables 1 and 2[16]).

**Drug interactions** Due to the involvement of multiple metabolic enzymes and transport proteins, the 3D regimen has the potential for many drug interactions.[25] Contraindicated medications include sensitive CYP3A

substrate drugs associated with serious adverse reactions at elevated plasma concentrations, moderate-strong CYP3A inducers, and strong CYP2C8 inhibitors and inducers. Drugs that are substrates of UGT 1A1, BCRP, OATP1B1, OATP1B3 or OATP2B1 may have significantly increased plasma concentrations when co-administered with the 3D regimen. Caution should be exercised if the 3D regimen is co-administered with drugs that are both moderate inhibitors of CYP3A4 and inhibitors of multiple transporters because of potential for clinically relevant increases in paritaprevir exposure.

**Adverse reactions** Side effects from the 3D regimen are usually mild or moderate in severity.[25] When used with ribavirin, adverse effects reported in ≥ 10% of subjects included fatigue, headache, nausea, pruritus and insomnia. When used without ribavirin, fatigue and headache were reported in ≥ 10% of subjects. Transient asymptomatic elevations of alanine transaminase (ALT) ≥ 5 times the upper limit of normal occurred in approximately 1% of all clinical trial subjects receiving the 3D regimen. Efavirenz or ethinyl estradiol-containing products are contraindicated with the 3D regimen because of increased ALT elevation risk. Ethinyl estradiol-containing medications can be restarted approximately two weeks after completion of the 3D regimen. Progestin-only or nonhormonal contraceptives may be used during treatment with the 3D regimen.

Transient bilirubin elevations (predominantly indirect bilirubin) may also occur in patients taking the 3D regimen with ribavirin as a result of inhibition of bilirubin transporters OATP1B1/1B3 and ribavirin-induced hemolysis. The 3D regimen is also associated with concentration-dependent QTc prolongation. Caution is required if co-administered with medications that prolong the QTc interval. Concurrent use of rilpivirine, an antiretroviral drug with a dose-related QT effect, is not recommended because rilpivirine exposure is increased by 243% in the presence of the 3D regimen. Salmeterol is contraindicated with the 3D regimen due to the potential for increased cardiovascular adverse effects associated with salmeterol (e.g., QT prolongation, palpitations, sinus tachycardia).

## Simeprevir

Simeprevir (Galexos), a second-generation NS3/4A protease inhibitor, can also be combined with sofosbuvir to create an all-oral option for the treatment of HCV genotype 1.[16,26] Simeprevir should not be used in HCV genotype 1a patients with cirrhosis and the Q80K mutation because of lower response rates.[16] Simeprevir is dosed as 150 mg once daily when combined with sofosbuvir 400 mg once daily.[16,26]

**Drug interactions** Simeprevir is primarily metabolized by CYP3A.[26] Co-administration of simeprevir with drugs that moderately or strongly induce or inhibit CYP3A is not recommended because this may lead to significantly lower or higher simeprevir exposure, respectively. Inducers of P-gp may decrease the exposure of simeprevir and reduce its therapeutic effect. Co-administration of simeprevir with OATP1B1 substrates (e.g., rosuvastatin) and P-gp substrates (e.g., digoxin) may result in increased plasma concentrations of such drugs.

**Adverse reactions** When simeprevir is combined with sofosbuvir (without ribavirin) for 12 weeks, the most common side effects are fatigue (25%), headache (21%), nausea (17%), insomnia (14%) and pruritus (11%).[26]

## Daclatasvir

Daclatasvir (Daklinza), a pan-genotypic NS5A inhibitor with a low barrier to resistance, was approved by Health Canada in August 2015 for the treatment of genotypes 1–3 chronic HCV infection, when combined with sofosbuvir.[27,28] For genotype 1 or 3 treatment-naïve or experienced patients without cirrhosis, 12 weeks of daclatasvir and sofosbuvir is indicated.[27] For genotype 1 or 3 patients with compensated cirrhosis, as well as all genotype 2 patients, 24 weeks of daclatasvir and sofosbuvir is indicated.[27] The standard dose of daclatasvir is 60 mg orally once daily.[27]

**Drug interactions** Daclatasvir, a CYP3A4 substrate, requires dose reduction to 30 mg orally once daily when combined with strong CYP3A4 inhibitors (e.g., clarithromycin, itraconazole, ketoconazole, certain ritonavir-boosted HIV protease inhibitors) and dose increase to 90 mg orally once daily when co-administered with moderate CYP3A4 inducers (e.g., efavirenz, etravirine, nevirapine, bosentan, modafinil).[27] Daclatasvir is contraindicated with the concurrent use of drugs that strongly induce CYP3A4 and P-gp (e.g., phenytoin, carbamazepine, rifampin, dexamethasone, St. John's wort) as these drugs may lead to lower daclatasvir exposure and loss of efficacy.[27]

**Adverse reactions** Daclatasvir has been well tolerated in clinical studies to date. When taken in combination with sofosbuvir, the most common adverse events observed in clinical studies were fatigue, headache and nausea.[11,14,29]

## Financial considerations

A 12-week supply of Harvoni and Holkira Pak costs $67,000 and $55,860, respectively.[30] Both regimens are currently covered by many provincial/territorial governments in Canada for eligible patients.[31] A 12-week supply of simeprevir with sofosbuvir costs $91,560.[30] When this article was written, daclatasvir was still undergoing review by the Canadian Agency for Drugs and Technologies in Health (CADTH) and no provincial/territorial drug plans in Canada had yet approved daclatasvir coverage. Pharmacists are encouraged to visit http://ctac.ca/home for up-to-date HCV drug coverage details based on the individual provincial/territorial government plans.

**TABLE 1**

**TREATMENT RECOMMENDATIONS FOR CHRONIC HCV GENOTYPE 1, NONCIRRHOTIC, TREATMENT-NAÏVE PATIENTS AND PATIENTS WHO FAILED ON PEGYLATED INTERFERON–RIBAVIRIN TREATMENT[16]**

| Genotype | Sofosbuvir/ ledipasvir | Paritaprevir/ ritonavir/ombitasvir/ dasabuvir | Sofosbuvir/ simeprevir | Sofosbuvir/ daclatasvir |
|---|---|---|---|---|
| **GENOTYPE 1A** | 12 weeks* | 12 weeks with ribavirin** | 12 weeks | 12 weeks |
| **GENOTYPE 1B** | 12 weeks* | 12 weeks | 12 weeks | 12 weeks |

HCV–hepatitis C virus
*The 2015 Canadian HCV guidelines state that in noncirrhotic, treatment-naive patients with HCV genotype 1a or 1b, treatment with sofosbuvir/ledipasvir can be considered for eight weeks if baseline HCV RNA ≤ 6 million IU/mL.[15]
** Ribavirin weight-based dosing: 1000 mg daily if < 75 kg; 1200 mg daily if ≥ 75 kg.

**TABLE 2**

**TREATMENT RECOMMENDATIONS FOR CHRONIC HCV GENOTYPE 1, COMPENSATED CIRRHOTIC, TREATMENT-NAÏVE PATIENTS AND PATIENTS WHO FAILED ON PEGYLATED INTERFERON–RIBAVIRIN TREATMENT[16]**

| Genotype | Sofosbuvir/ ledipasvir | Paritaprevir/ ritonavir/ombitasvir/ dasabuvir | Sofosbuvir/ simeprevir | Sofosbuvir/ daclatasvir |
|---|---|---|---|---|
| **GENOTYPE 1A** | 12 weeks (treatment-naïve or when combined with ribavirin for treatment-experienced) or 24 weeks (if treatment-experienced) | 24 weeks with ribavirin | 24 weeks with or without ribavirin (for patients without the Q80K polymorphism) | 24 weeks with or without ribavirin |
| **GENOTYPE 1B** | 12 weeks (treatment-naïve or if treatment-experienced and combined with ribavirin) or 24 weeks (if treatment-experienced) | 12 weeks | 24 weeks with or without ribavirin | 24 weeks with or without ribavirin |

HCV–hepatitis C virus. Ribavirin weight-based dosing is 1000 mg daily if < 75 kg; 1200 mg daily if ≥ 75 kg

**TABLE 3**

**DIRECT-ACTING ANTIVIRAL METABOLISM CHARACTERISTICS[20,25,26,28,33,34,35]**

| Drug | Pharmacological class | Substrate | Inhibition effects | Induction effects |
|---|---|---|---|---|
| Sofosbuvir | NS5B inhibitor | P-gp, BCRP | --- | --- |
| Ledipasvir | NS5A inhibitor | P-gp, BCRP | P-gp (weak), BCRP (weak) | --- |
| Ombitasvir | NS5A inhibitor | CYP3A4, P-gp | BCRP, UGT1A1 | --- |
| Paritaprevir | NS3/4A protease inhibitor | CYP3A, P-gp, OATP1B1/3, BCRP | OATP1B1/3, OATP2B1, BCRP, UGT1A1, P-gp (in vitro) | --- |
| Ritonavir | Pharmacokinetic enhancer | CYP3A4, 2D6, P-gp | Primarily CYP3A4, 2C19, 2C8, 2C9, 2D6, 2E1, OATP2B1, BCRP, P-gp (in vitro) | CYP1A2, 2B6, 2C9, 2C19, 3A, and UGT enzymes |
| Dasabuvir | NS5B non-nucleoside inhibitor | Primarily CYP2C8, minimal CYP3A4, P-gp, BCRP | BCRP, UGT1A1, P-gp (in vitro) | --- |
| Simeprevir | NS3/4A protease inhibitor | CYP3A4, P-gp, OATP1B1 | CYP1A2 (weak), CYP3A4 (intestinal but not hepatic), P-gp, OATP1B1 | --- |
| Daclatasvir | NS5A inhibitor | CYP3A4, P-gp, OCT 1 | P-gp (weak to moderate), OATP1B1/3 (weak), BCRP (weak) | --- |

BCRP–breast cancer resistance protein; CYP–cytochrome P450; NS–nonstructural gene; OATP–organic anion transporting polypeptide; OCT–organic cation transporter; P-gp–P-glycoprotein; UGT–UDP-glucuronosyltransferases.

The Momentum Support Program (Gilead) and the AbbVie Care Program were developed to help with drug insurance-related needs or enrollment in a co-pay assistance program to help eligible patients with the out-of-pocket costs of Harvoni/Sovaldi and Holkira Pak, respectively.[32] If needed, ribavirin is provided free of charge with Holkira Pak. Patients prescribed Galexos who require assistance securing financial coverage for treatment can be enrolled in Janssen's Galexos Bioadvance Program.[32] Bristol-Myers Squibb has created the Claire patient support program to help patients with reimbursement assistance for Daklinza.[33]

## Pharmacist's role

Pharmacists can be particularly helpful when it comes to predicting/managing drug interactions with the novel DAAs and supporting HCV medication adherence. Given the relatively short course of DAA treatment, consideration may be given to discontinuing nonessential medications during this time in order to minimize drug interactions and simplify therapy. Pharmacists are encouraged to consult the continuously updated HCV drug information resources listed in Box 1.

## Conclusion

The demand for HCV treatment is predicted to increase with the approval of novel DAAs that achieve excellent cure rates and demonstrate enhanced tolerability over prior HCV treatment options. Pharmacists are well positioned to play an instrumental role in the care of patients with chronic HCV infection.

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### BOX 1

**HEPATITIS C: USEFUL ONLINE RESOURCES**

**www.hcvdruginfo.ca**
This website, maintained by the Toronto General Hospital, focuses on the safe prescribing of direct-acting antiviral therapy for hepatitis C infection and features continuously updated information about drug interactions.

**www.hep-druginteractions.org**
This website, designed by The University of Liverpool, offers comprehensive drug-drug interaction checking for hepatitis treatments.

**www.hcvguidelines.org**
This online resource was developed by the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) in collaboration with the International Antiviral Society–USA (IAS–USA). It features continuously updated evidence-based, expert-developed recommendations for the management of hepatitis C infection.

**www.hepatitisc.uw.edu/**
This comprehensive educational website from the University of Washington addresses the diagnosis, monitoring and management of hepatitis C virus infection.


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**TABLE 4**

**HCV DRUG ADMINISTRATION AND DOSING IN RENAL/HEPATIC DYSFUNCTION[20,25,26,28]**

| Drug therapy | Administration requirements | Dose adjustment needed in renal impairment | | | | Dose adjustment needed in hepatic impairment | | |
|---|---|---|---|---|---|---|---|---|
| | | Mild | Moderate | Severe (eGFR < 30 mL/min/1.73 m²) | ESRD requiring hemodialysis | Mild (Child Pugh A) | Moderate (Child Pugh B) | Severe (Child Pugh C) |
| **SOFOSBUVIR/LEDIPASVIR (HARVONI)** | With or without food | No | | Safety and efficacy not established | | No | | |
| **3D REGIMEN (HOLKIRA PAK)** | With food | No | | No | Not studied | No | Not recommended due to lack of safety and efficacy data | |
| **SIMEPREVIR (GALEXOS)** | With food | No | | No | Not studied; unlikely to be removed by hemodialysis | No | | No dose recommendation can be given |
| **DACLATASVIR (DAKLINZA)** | With or without food | No | | No | No | No | | |

eGFR–estimated glomerular filtration rate; ESRD–end-stage renal disease; HCV–hepatitis C virus

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