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TIMELY, INDEPENDENT INFORMATION ABOUT NEW DRUGS

RADAR

EDITORIAL

Outmanoeuvring hepatitis C

New PBS listings and changes for hepatitis C medicines

Cover image: New PBS listed anti-hepatitis-C combinations outmanoeuvre chronic hepatitis C infection to effectively comprise a cure for most patients.

From 1 March 2016 several new antiviral agents became available on the PBS for use in patients with chronic hepatitis C. They include daclatasvir (Daklinza), sofosbuvir (Sovaldi), ribavirin (Ibavyr) and the fixed-dose combination ledipasvir with sofosbuvir (Harvoni).[1]

Read more about the PBS listing for ledispasvir with sofosbuvir on page 4.

Read more about the PBS listing for daclatasvir on page 10.

Read more about the PBS listing for sofosbuvir on page 17.

Read more about the PBS listing for ribavirin on page 26.

Hepatitis C medicines now available on the PBS General Schedule

This listing of these medicines is a significant change from previous listings for hepatitis C virus (HCV) treatments, which were under the Section 100 (S100) highly specialised drugs program (HSD) only.

The new listings are now included in both the PBS General Schedule ('Section 85') and the S100 HSD Program. The S100 listing provides prisoner access through arrangements under the HSD Program.[1]

Who can prescribe these medicines?

PBS patient and prescriber eligibility will be the same whether the medicine is prescribed on the PBS General Schedule or the HSD program.

The listing on the general schedule removes the requirement for GPs to be accredited to meet prescriber eligibility. Under the new listing, gastroenterologists, hepatologists, or infectious-disease physicians experienced in treating chronic hepatitis C infection will be eligible to prescribe.

All other medical professionals, including GPs, will also be eligible to prescribe under the PBS provided that it is done in consultation with a specialist. 'In consultation with' means that the prescribing GP must consult with a specified specialist by phone, mail, email or videoconference before authority is given.[1]

Prescribers will require a PBS *Authority* before prescribing these medicines, using either written or telephone channels to seek approval.[1]

No change to dispensing rules for new hepatitis C listings

These medicines will not be available under the new S100 HSD Community Access arrangements introduced on 1 July 2015. Approved pharmacists in the community will be able to dispense when a prescription is issued under the General Schedule. However, if the prescription has been written under S100 HSD arrangements in a public hospital, approved pharmacists in the community will not be able to dispense.[2]

Continued ...

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Find additional information by going to the link provided

Medicine Update articles are available where indicated

NPS RADAR **articles may be updated when there is new evidence about safety or efficacy, or in case of regulatory or PBS listing changes.**

Please refer to **www.npsradar.org.au** for the most recent version as well as any supplementary information.

Find out more about new hepatitis C treatments listed on the PBS website.

Read more about the July 2015 S100 supply arrangements in the September 2015 *NPS RADAR* brief item 'New supply arrangements for some S100 medicines'.

Introduction of direct-acting antivirals a major advance

The introduction of new direct-acting antiviral (DAA) treatment regimens has been described as a major advance for HCV therapy.[2] Most people will now be suitable for treatment and most people who start treatment will be cured, which is defined as HCV RNA below the level of detection at least 12 weeks after the end of treatment.[3]

Eradicating the virus reduces the risk of liver fibrosis or progression of existing liver disease in patients with HCV.[4] All patients with HCV should be considered for antiviral therapy.

The DAA agents are now the treatment of choice for HCV in Australia, and the agent used will depend on the presence or absence of liver cirrhosis, the HCV genotype and whether the person has had therapy previously.[3]

The new S85 provision for community dispensing of DAA therapy by GPs is intended to increase capacity for treatment and reduce the burden of HCV and secondary liver disease.[3]

At the same time these advancements necessitate the development of new models of care for HCV treatment, which have been outlined in the newly released *Australian recommendations for the management of hepatitis C virus infection: a consensus statement 2016.*

Treatment in primary care is appropriate for most people with HCV. However, people with complications arising from infection, such as severe fibrosis, cirrhosis, complex comorbidities or other types of liver disease, or those who have failed previous DAA treatment, should be referred for specialist care.[3]

Follow the prescribing matrix outlined by the PBAC

The Pharmaceutical Benefits Advisory Committee has outlined a prescribing matrix based on treatment history and HCV genotype for antiviral treatment regimens that are supported by evidence and available for PBS rebate.

See the prescribing matrix in the *General Statement for Drugs for the Treatment of Hepatitis C* for information on how these new PBS listed medicines fit into management of patients with chronic hepatitis C.

More information

For more information regarding diagnosis and management of HCV in primary care see the CPD-accredited online learning module *Managing hepatitis C in primary care.* This is a collaboration between NPS MedicineWise and the Gastroenterological Society of Australia.

ADDITIONAL INFORMATION

New hepatitis C treatments listed on the PBS: www.pbs.gov.au/info/news/2016/03/new-hepatitis-c-treatments-listed-on-the-pbs

New supply arrangements for some S100 medicines: www.nps.org.au/radar/articles/new-supply-arrangements-for-some-s100-medicines

Australian recommendations for the management of hepatitis C virus infection: a consensus statement 2016: www.asid.net.au/documents/item/1208

ADDITIONAL INFORMATION

PBS General Statement for Drugs for the Treatment of Hepatitis C: www.pbs.gov.au/info/healthpro/explanatory-notes/general-statement-hep-c

Managing hepatitis C in primary care: www.nps.org.au/health-professionals/cpd/activities/online-courses/managing-hepatitis-c-in-primary-care

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FULL REVIEW

Ledipasvir with sofosbuvir (Harvoni)

fixed-dose combination for chronic hepatitis C
(le-DI-pas-veer with soe-FOS-bue-veer)

Now PBS listed as a first-line interferon-free treatment option for chronic HCV genotype 1

KEY POINTS

Ledipasvir with sofosbuvir inhibits replication of the hepatitis C virus
Ledipasvir selectively inhibits HCV viral replication by targeting the NS5A protein, and is used in combination with sofosbuvir, which targets the HCV NS5B RNA polymerase.[1]

PBS listed as a first-line treatment option for patients with chronic genotype 1 HCV infection
Patients are eligible for PBS subsidy irrespective of treatment experience and cirrhotic status; however, these factors influence treatment duration.[2]

High rates of sustained viral response in patients with chronic genotype 1 HCV infection
Ledipasvir with sofosbuvir fixed-dose combination is highly effective for treatment-naïve or treatment-experienced patients, with or without cirrhosis.[3-5]

Community pharmacists can only dispense under the General Schedule
If the prescription is written under S100 Highly Specialised Drug arrangements, approved community pharmacists will not be able to dispense.[6]

PBS listing

Authority required

The FDC product ledipasvir with sofosbuvir (Harvoni) is now listed on the PBS for treatment of chronic hepatitis C, under both the General Schedule (S85) and Section 100 Highly Specialised Drugs (HSD) program for patients 18 years or older with chronic genotype 1 infection.[2]

Treatment duration is influenced by cirrhotic status and whether the patient has received prior treatment for hepatitis C.[2]

For patients without cirrhosis

The duration of treatment in treatment-naïve patients is guided by pre-treatment HCV RNA level. If less than 6 million IU/mL consider a treatment duration of 8 weeks, otherwise 12 weeks is subsidised on the PBS.[2]

For patients who are treatment-experienced and for whom prior treatment with peginterferon alfa/ribavirin with or without an HCV protease inhibitor has failed, a 12-week treatment duration is PBS subsidised.[2]

Patients with cirrhosis

Treatment-naive patients can receive PBS-subsidised treatment with ledipasvir/sofosbuvir for 12 weeks, and treatment-experienced patients for whom prior treatment with peginterferon alfa/ribavirin with or without an HCV protease inhibitor has failed are eligible for 24 weeks of treatment on the PBS.[2]

May be prescribed by specialists or GPs

Gastroenterologists, hepatologists or infectious-disease physicians experienced in the treatment of chronic hepatitis C infection are eligible to prescribe this medicine under S85 or S100 arrangements.[6]

EVIDENCE SNAPSHOT

WHAT IS KNOWN ABOUT THESE DRUGS?

The fixed-dose combination (FDC) product ledipasvir with sofosbuvir has been shown to produce high rates of sustained viral response (SVR) in patients with chronic genotype 1 HCV infection, with similar efficacy to that of ledipasvir/sofosbuvir FDC plus ribavirin.[3-5] It was also effective for patients with genotype 1 or 4 infection who were co-infected with HIV-1 and undergoing treatment with anti-retrovirals.[7]

The FDC product was well tolerated across key trials; common adverse events included fatigue, headache, insomnia and nausea.[3-5] The incidence of these adverse events was lower in patients treated with the FDC product alone compared with those receiving the FDC with ribavirin.[3-5]

AREAS OF UNCERTAINTY

No head-to-head trials have compared ledipasvir/sofosbuvir against other treatments for chronic genotype 1 hepatitis C infection, and in this instance the Pharmaceutical Benefits Advisory Committee considered 'no treatment' to be the most appropriate comparator, in view of the broader context of infected individuals whose treatment preference is interferon-free therapies.[8]

WHAT DOES NPS SAY?

Ledipasvir/sofosbuvir is an oral, interferon-free first-line treatment option for patients with chronic genotype 1 hepatitis C infection,[9] which is well tolerated and produces high rates of response.

Other health professionals, including general practitioners, are also eligible to prescribe under the general schedule of the PBS, provided that it is done in consultation with one of these specialists, via phone, mail, email or videoconference.[6]

Community pharmacists can only dispense under the General Schedule

Ledipasvir/sofosbuvir FDC will not be available under the new S100 HSD Community Access arrangements introduced on 1 July 2015. Approved pharmacists in the community will be able to dispense when a prescription is issued under the General Schedule.[6]

However, if the prescription has been written under S100 HSD arrangements in a public hospital, approved pharmacists in the community will not be able to dispense.[6]

What is it?

Ledipasvir is an inhibitor of the NS5A protein, which regulates replication of the hepatitis C virus (HCV), and has shown in vitro antiviral activity against genotypes 1–6.[1] Sofosbuvir is an inhibitor of NS5B RNA polymerase, which is also essential for replication of the HCV virus, and has activity against all HCV genotypes.[1]

In combination, sofosbuvir and ledipasvir have complementary antiviral activity, particularly regarding activity against resistance-associated sequence variants.[1]

Who is it for?

Ledipasvir/sofosbuvir FDC is contraindicated for use in patients with a known hypersensitivity to the active ingredients or any other component of the tablets, and should not be administered concurrently with other medicines that contain the same active ingredients.[1]

Currently approved for use in patients with genotype 1 HCV infection only

At the time of writing, ledipasvir/sofosbuvir was approved by the Therapeutic Goods Administration and PBS listed for treatment of patients with chronic genotype 1 HCV infection only.[2, 10]

Clinical data to support use of ledipasvir/sofosbuvir in patients with genotype 3 infection are limited, and efficacy has not been studied in patients with genotype 2 infection.[1]

There are data to support effectiveness of ledipasvir/sofosbuvir (with or without ribavirin) in patients with genotype 4[11] or 6 infection;[12] however, ledipasvir/sofosbuvir is not currently TGA approved or PBS listed for these patient populations.[2, 10] Australian consensus recommendations state it is likely that these regimens will be approved in Australia for genotypes 4 and 6 in the near future.[9]

Caution in patients who are pregnant or breastfeeding

There have been no adequate or well-controlled studies of ledipasvir/sofosbuvir in pregnant women, and it is unknown if ledipasvir, sofosbuvir or metabolites of sofosbuvir are present in human breast milk. Carefully consider the potential benefits and risks of using ledipasvir/sofosbuvir during pregnancy or breastfeeding.[1]

Where does it fit?

From 1 March 2016 several new treatment options for patients with chronic genotype 1 HCV infection became available on the PBS. The place in therapy for the ledipasvir/sofosbuvir FDC product is outlined below.

A first-line treatment option for patients with chronic genotype 1 HCV

Among adult patients with chronic genotype 1 HCV infection, ledipasvir/sofosbuvir is a first-line treatment option[9] and is now listed on the PBS. Depending on the patient's cirrhotic status and whether they are treatment-naive or treatment-experienced, recommended treatment duration is 8, 12 or 24 weeks.[13]

Note that sofosbuvir with daclatasvir, with or without ribavirin, is another option for first-line treatment of chronic genotype 1 HCV available on the PBS.[13] For information about the PBS-listed daclatasvir combination treatment regimen see the separate *NPS RADAR* review 'Daclatasvir with sofosbuvir and/or ribavirin for chronic hepatitis C' on page 10.[6-8]

Additional treatment options for patients with chronic genotype 1 HCV

Sofosbuvir and peginterferon with ribavirin is also PBS listed for patients with genotype 1 infection; however, it is not recommended as a first-line treatment option.[9, 13] For information on the sofosbuvir and peginterferon with ribavirin treatment regimen see the interferon-based treatment wrap-up on page 27.

NOTE: A third interferon-free, direct-acting antiviral regimen (paritaprevir/ritonavir/ombitasvir and dasabuvir [Viekira-Pak]) with or without ribavirin is also TGA approved for patients with chronic genotype 1 HCV infection, although it is not yet PBS listed.[9, 14, 15]

How does it compare?

The high level of efficacy of the ledipasvir/sofosbuvir FDC had been demonstrated in three key studies of patients with chronic genotype 1 infection, across treatment-naive and treatment-experienced patients, with and without cirrhosis.[3-5]

High rates of SVR in patients with chronic genotype 1 HCV infection

In the randomised open-label ION-1 trial, previously untreated patients with genotype 1 infection showed SVR rates of 99% (95% CI 96 to 100) after 12 weeks of treatment with ledipasvir/sofosbuvir (n = 214), and 98% (95% CI 95 to 99) after 24 weeks of treatment (n = 217).[5]

Similar SVR rates were reported in patients treated with ledipasvir/sofosbuvir and ribavirin (97% [95% CI 94 to 99; n = 217)] and 99% [95% CI 97 to 100; n = 217] after 12 and 24 weeks of treatment, respectively).[5] Approximately 16% of patients in this study had cirrhosis, and 67% had genotype 1a infection.[5]

ION-2 was a randomised open-label study involving treatment-experienced patients who had not achieved SVR after treatment with peginterferon and ribavirin, with or without a protease inhibitor.

High rates of SVR were seen among patients treated for 12 weeks (n = 109) or 24 weeks (n = 109) with ledipasvir/sofosbuvir (94% [95% CI 87 to 97] and 99% [95 to 100], respectively).

This was similar to SVR rates for 12 (n = 111) or 24 weeks (n = 111) of treatment with ledipasvir/sofosbuvir with ribavirin (96% [95% CI 91 to 99] and 99% [95 to 100], respectively).

CI: confidence interval

Collectively, 20% of these patients had cirrhosis, and 79% had HCV genotype 1a infection.[4]

The efficacy of a shorter treatment regimen in patients without cirrhosis was then studied in the ION-3 non-inferiority trial. In terms of SVR rates, 8 weeks of treatment with ledipasvir/sofosbuvir was found to be non-inferior to 12 weeks of treatment with ledipasvir/sofosbuvir, and 8 weeks of ledipasvir/sofosbuvir with ribavirin (94% [95% CI 90 to 97] versus 95% [92 to 98] and 93% [89 to 96], respectively).[3]

An additional trial, ION-4, confirmed the efficacy of ledipasvir/sofosbuvir in patients with chronic HCV infection (genotype 1 or 4) and HIV-1 co-infection, while receiving an anti-retroviral regimen. Of these patients, 55% had been previously treated for HCV, and 20% had cirrhosis. Overall, 96% of patients (95% CI 93 to 98) had an SVR after 12 weeks of treatment with ledipasvir/sofosbuvir.[7]

Safety issues

The safety of ledipasvir/sofosbuvir FDC has been assessed in key trials. The FDC was found to be well tolerated, with a favourable safety profile compared with that of ledipasvir/sofosbuvir with ribavirin.

Ledipasvir/sofosbuvir FDC is well tolerated

Generally ledipasvir/sofosbuvir was well tolerated across key trials. The most common adverse events were fatigue, headache, insomnia and nausea. Discontinuation rates due to adverse events were low or absent for patients taking ledipasvir/sofosbuvir for 8, 12 or 24 weeks (0–2% across studies).[3-5]

The rate of serious adverse events was higher among patients treated for 24 weeks (6–8%) [4, 5] compared with those receiving ledipasvir/sofosbuvir treatment for 8 or 12 weeks (0–2%),[3-5] and those receiving a regimen containing the FDC with ribavirin for 24 weeks (< 1% to 3%).[4, 5]

For information about reporting adverse reactions to the TGA, or to report suspected adverse reactions online, see the TGA website.

ADDITIONAL INFORMATION

TGA website:
www.tga.gov.au/safety/problem.htm#medicine

Co-administration of amiodarone not recommended

Postmarketing reports of symptomatic bradycardia, fatal cardiac arrest and cases requiring pacemaker intervention have been reported when amiodarone has been taken with ledipasvir/sofosbuvir.[1]

Patients are at increased risk of symptomatic bradycardia with co-administration of amiodarone if they are also taking beta blockers, have underlying cardiac comorbidities, and/or advanced liver disease.[1]

Avoid combination with potent P-glycoprotein inducers

Potent P-glycoprotein inducers of the intestine (eg, rifampicin, St John's wort) should not be used with ledipasvir/sofosbuvir, as they may significantly decrease plasma concentration of ledipasvir and sofosbuvir, leading to reduced therapeutic effect of the FDC product.[1]

Reason for PBS listing

The PBAC recommended the listing of the ledipasvir/sofosbuvir FDC for treatment of chronic genotype 1 hepatitis C infection in treatment-naive and treatment-experienced patients with or without cirrhosis, based on cost-effectiveness over 'no treatment'.[8]

The PBAC considered the most appropriate comparator for the ledipasvir/sofosbuvir treatment regimen was 'no treatment' in view of the broader context of infected individuals whose treatment preference is interferon-free therapies. Ledipasvir/sofosbuvir was found to have superior comparative effectiveness and inferior comparative safety to 'no treatment'.[8]

Although many of the trials that assessed safety and efficacy of the ledipasvir/sofosbuvir FDC were single-arm and had limited sample sizes, they were regarded as the best available and sufficient evidence to support listing on the PBS.[8]

Dosing issues

The ledipasvir (90 mg)/sofosbuvir (400 mg) FDC is a tablet that is taken once daily, orally with or without food.[1] Treatment durations are outlined in the *General Statement for Drugs for the Treatment of Hepatitis C.*

No dose adjustment required for elderly patients

IIn clinical trials including patients aged 65 years or over, the response rate for those over 65 was similar to that of younger patients. However, exercise caution when prescribing in the elderly because of greater incidence of renal, hepatic or cardiac dysfunction, concomitant diseases and use of other medicines.[1]

No dose adjustment required for mild or moderate renal impairment

No dose adjustment is required for patients with mild or moderate renal impairment; however, there is a lack of information on dose recommendations for patients with severe renal impairment and end-stage renal disease requiring haemodialysis, who may have higher exposure of the predominant sofosbuvir metabolite.[1]

No dose adjustment required for mild, moderate or severe renal impairment

No dose adjustment is required for patients with mild, moderate or severe hepatic impairment; however, the safety and efficacy of this product has not been established in patients with decompensated cirrhosis.[1]

Co-administration with proton pump inhibitors

Proton pump inhibitors (PPIs) may reduce absorption of ledipasvir by increasing gastric pH[16] and should not be taken before ledipasvir/sofosbuvir.[1] PPI doses comparable to omeprazole 20 mg can be taken with, or up to 2 hours after, ledipasvir/sofosbuvir. There are currently no data for other omeprazole doses.[16]

ADDITIONAL INFORMATION

PBS website, General Statement for Drugs for the Treatment of Hepatitis C: www.pbs.gov.au/info/healthpro/explanatory-notes/general-statement-hep-c

Information for patients

Advise patients taking the ledipasvir/sofosbuvir FDC product as follows.[17]

- Do not take Harvoni if you are also taking any another medicine that contains sofosbuvir.
- Before taking Harvoni, let your doctor know if you are pregnant or think you may be pregnant, or are planning to have a baby.
- You should not breastfeed while you are taking Harvoni.
- Tell your doctor if you are taking medicines for heart conditions, high cholesterol, HIV infection, epilepsy, heartburn, stomach ulcers or reflux, antibiotics or St John's wort, because they may interact with Harvoni.
- If you are taking an antacid, take it at least 4 hours before or after taking Harvoni. If proton pump inhibitor treatment is required (eg, omeprazole), it should be taken at the same time, or up to 2 hours after, taking Harvoni. Do not take proton pump inhibitors before Harvoni.
- Let your doctor know if you have any other liver problems besides hepatitis C, if you have hepatitis B, any other medical condition, or kidney problems.

Discuss the ledipasvir/sofosbuvir FDC (Harvoni) Consumer Medicine Information (CMI) leaflet with the patient.

ADDITIONAL INFORMATION

ledipasvir/sofosbuvir FDC (Harvoni) CMI: www.nps.org.au/medicines/infections-and-infestations/antiviral-medicines/ledipasvir-sofosbuvir/harvoni-tablets

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FULL REVIEW

Daclatasvir with sofosbuvir, with or without ribavirin

for chronic hepatitis C

(dac-LAT-as-veer)

Now PBS listed as a first-line interferon-free combination treatment option for chronic HCV genotypes 1 and 3

KEY POINTS

Daclatasvir is a direct-acting antiviral (DAA) agent
It selectively inhibits HCV viral replication by targeting the hepatitis C virus (HCV) NS5A protein; it is used in combination with the HCV NS5B RNA polymerase inhibitor sofosbuvir.[1]

PBS listed as an interferon-free, all-oral combination treatment for HCV genotypes 1 and 3
In combination with sofosbuvir for HCV genotypes 1 or 3, or in combination with sofosbuvir plus ribavirin for patients with cirrhosis and infection with HCV genotype 1.[2]

High rates of sustained virological response in patients with genotype 1 or 3 infection
Demonstrated in treatment-naïve and treatment-experienced patients with or without cirrhosis, and in those co-infected with HIV-1.[3, 4]

Available on the General Schedule (S85) and S100 Highly Specialised Drugs program
Community pharmacists can only dispense prescriptions written under the General Schedule, not those written under S100 arrangements.[5]

PBS listing

Authority required (written or by phone)

From 1 March 2016 daclatasvir (Daklinza), became available on the PBS General Schedule 'Section 85' and Section 100 (S100) Highly Specialised Drugs (HSD) Program for **oral combination treatment with sofosbuvir** for patients who are 18 years or older with:[5]

- genotype 1 HCV – for 12 weeks in patients without cirrhosis who are treatment-naïve, 12 or 24 weeks for those without cirrhosis who are treatment-experienced, or 24 weeks for those without cirrhosis who are treatment-naïve or treatment-experienced
- genotype 3 HCV – in treatment-naïve or treatment-experienced patients without cirrhosis for 12 weeks, and in treatment-naïve or -experienced patients with cirrhosis for 24 weeks.[5]

Daclatasvir is also available on the General Schedule and S100 HSD program as a **combination treatment with sofosbuvir and ribavirin** for 12 weeks in treatment-naïve or -experienced patients who are 18 years or older with genotype 1 HCV and cirrhosis.[5]

At the time of *Authority* application, the hepatitis C virus genotype and patient's cirrhotic status (non-cirrhotic or cirrhotic) must be provided, and evidence of chronic hepatitis C infection (repeatedly testing positive for antibody to HCV [anti-HCV positive] and for hepatitis C virus ribonucleic acid [HCV RNA positive] and the hepatitis C virus genotype must be documented in the patient's medical records.

PBS patient and prescriber eligibility is the same whether the medicines is prescribed under the PBS General Schedule or the HSD program.[5]

EVIDENCE SNAPSHOT

WHAT IS KNOWN ABOUT THIS DRUG?

Treatment with daclatasvir in combination with sofosbuvir with or without ribavirin for 12–24 weeks was shown to achieve a high rate of sustained virological response (SVR) in treatment-naïve and treatment-experienced patients with chronic genotype 1 or 3 HCV infection, with or without cirrhosis.[3, 4]

Combination treatment with daclatasvir was well tolerated, and the most common adverse events related to fatigue, headache and nausea.[4]

AREAS OF UNCERTAINTY

To date, the key evidence for efficacy and safety of daclatasvir and sofosbuvir, with and without ribavirin, has been established from one open-label, randomised non-comparative study, with no head-to-head trials comparing efficacy with other treatment options for chronic HCV genotypes 1 and 3.[4, 6]

However, as the current best available evidence, the unadjusted SVR rates of daclatasvir and sofosbuvir were considered by the Pharmaceutical Benefits Advisory Committee to have non-inferior comparative efficacy and similar safety profile to those of:[6]

- ledipasvir with sofosbuvir fixed-dose combination for treatment-naïve patients with genotype 1 chronic hepatitis C (CHC) without cirrhosis
- sofosbuvir and ribavirin for treatment-naïve patients with genotype 3 CHC without cirrhosis.

WHAT DOES NPS SAY?

Daclatasvir and sofosbuvir, with or without ribavirin, is an interferon-free first-line treatment option for patients with genotype 1 or genotype 3 CHC infection,[7] which is well tolerated and achieves high rates of response.[4]

ADDITIONAL INFORMATION

PBS General Statement for Drugs for the Treatment of Hepatitis C: www.pbs.gov.au/info/healthpro/explanatory-notes/general-statement-hep-c

New supply arrangements for some S100 medicines: www.nps.org.au/radar/articles/new-supply-arrangements-for-some-s100-medicines

As well as daclatasvir and sofosbuvir, with or without ribavirin, three additional all-oral HCV treatment combinations were also identified in the recommended prescribing matrix for PBS listing from 1 March 2016, as follows:[5]

- ledipasvir with sofosbuvir (see the separate *NPS RADAR* review 'Ledipasvir with sofosbuvir fixed-dose combination for chronic hepatitis C' on page 4)
- sofosbuvir with ribavirin (see the 'Sofosbuvir treatment combinations for chronic hepatitis C' RADAR review on page 17)
- sofosbuvir with peginterferon alfa-2a and ribavirin (see the section on interferon in the 'New listings wrap-up' on page 27).[5]

May be prescribed by specialists or GPs

Gastroenterologists, hepatologists or infectious-disease physicians experienced in the treatment of chronic hepatitis C infection can prescribe daclatasvir on the PBS. Other health professionals, including GPs, can also prescribe daclatasvir under the PBS, provided that it is done in consultation (by phone, mail, email, or videoconference) with one of these specialists.[5]

Community pharmacists can only dispense under the General Schedule

Daclatasvir will not be available under the new S100 HSD Community Access arrangements (see the September 2015 *NPS RADAR* brief item 'New supply arrangements for some S100 medicines' introduced on 1 July 2015. Approved pharmacists in the community will be able to dispense when a prescription is issued under the General Schedule. However, if the prescription has been written under S100 HSD arrangements in a public hospital, approved pharmacists in the community will not be able to dispense.

ADDITIONAL INFORMATION

University of Liverpool Hepatitis Drug Interactions: www.hep-druginteractions.org

What is it?

Daclatasvir is a direct-acting antiviral (DAA) agent that selectively inhibits the HCV non-structural protein NS5A, an essential component of the HCV replication complex.[1]

Daclatasvir is an oral tablet used as a component of a combination HCV antiviral treatment regimen, and can be used in combination with sofosbuvir, with or without ribavirin, to treat chronic HCV infection.

Who is it for?

Use in a combination antiviral regimen for patients with genotype 1 or 3 HCV infection

PBS-listed daclatasvir is suitable for patients with genotype 1 or genotype 3 HCV infection in combination antiviral treatment regimens with sofosbuvir, with or without ribavirin depending on the HCV genotype and treatment history.[5] Refer to the section 'Where does it fit' for detailed place in therapy.

There are limited data to support the use of daclatasvir in patients with genotype 2 HCV infection,[1] and it is not PBS listed for this use.[5]

Available for use in patients with decompensated liver disease

Although the manufacturer's product information states that daclatasvir combination regimens have not been studied in patients with decompensated cirrhosis,[1] the PBS-listed HCV treatment regimens for daclatasvir do not distinguish between patients with compensated versus decompensated cirrhosis.[2, 7]

Available for use in patients co-infected with HIV or hepatitis B virus

Although the manufacturer's product information states that safety and efficacy of daclatasvir treatment regimens for the treatment of chronic HCV infection has not been established in patients who are co-infected with HIV or hepatitis B virus (HBV),[1] treatment regimens for chronic HCV infection in these populations should be the same as those used for HCV mono-infection.[7]

Careful assessment of potential interactions with concurrent medicines should be used to guide selection of an appropriate direct-acting antiviral (DAA) treatment regimen. Australian consensus recommendations direct practitioners to the University of Liverpool's Hepatitis Drug Interactions website.[7]

Not for use during pregnancy

There are no adequate and well-controlled trials to support using daclatasvir in pregnant women. Ensure women of childbearing potential use contraception during, and for 5 weeks after completing, treatment involving daclatasvir.

Because ribavirin is contraindicated in pregnancy, when using daclatasvir in combination with ribavirin, extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients, for 6 months after completion of therapy.[1]

Where does it fit?

Australian Consensus recommendations recommend daclatasvir and sofosbuvir, with or without ribavirin, as a first-line option for treatment of patients with chronic genotype 1 or genotype 3 hepatitis C infection.[7] Patients with compensated and decompensated cirrhosis are also eligible for PBS-listed daclatasvir combination treatment regimens.[7]

Daclatasvir is PBS listed with sofosbuvir as a 12- or 24-week interferon- and ribavirin-free treatment regimen for both treatment-naïve and treatment-experienced patients 18 years or older with genotype 1 or 3 HCV infection regardless of their cirrhotic or non-cirrhotic status, or as a 12-week interferon-free regimen with sofosbuvir and ribavirin for treatment-naïve or -experienced patients aged 18 years or older with genotype 1 HCV infection and cirrhosis.[5]

Although daclatasvir is approved by the Therapeutic Goods Administration for use with asunaprevir or with peginterferon alfa and ribavirin,[1] these combinations are not PBS listed.[5] Daclatasvir should not be used as monotherapy.[1]

The contraindications applicable to the other individual antiviral agents are applicable when used in combination with daclatasvir. Refer to the respective Product Information for sofosbuvir or ribavirin for a list of contraindications for these medicines.[1]

As well as daclatasvir and sofosbuvir, with or without ribavirin, three additional HCV treatment combinations were also listed on the PBS for treatment of chronic hepatitis C from 1 March 2016:[5]

- ledipasvir with sofosbuvir (see 'Ledipasvir with sofosbuvir fixed-dose combination for chronic hepatitis C' on page 4)
- sofosbuvir with ribavirin (see 'Sofosbuvir treatment combinations for chronic hepatitis C' on page 17)
- sofosbuvir with peginterferon alfa-2a and ribavirin (see interferon wrap-up on page 27).

How does it compare?

The PBAC considered that the appropriate comparator should be 'no treatment', as many HCV patients are not undertaking therapy because of adverse effects associated with current interferon-based therapies.[6]

For the purposes of PBS listing the results of a single non-comparative open label trial were considered by the PBAC.[4] The PBAC accepted this study as sufficient evidence of clinical effectiveness of daclatasvir in achieving SVR, while noting the limitations of the study, including the small sample size.[6]

Combination treatment with daclatasvir for 12 weeks achieves high rates of SVR for genotype 1 and 3 HCV infection

In the study considered by the PBAC, patients infected with HCV genotypes 1, 2 or 3 but without cirrhosis were randomly assigned, in a 1:1:1 ratio to receive treatment as follows:[4]

- combination of daclatasvir and sofosbuvir for 23 weeks following treatment with sofosbuvir alone during a 1-week run-in period, or
- combination of daclatasvir and sofosbuvir for 24 weeks, or
- combination of daclatasvir, sofosbuvir and ribavirin for 24 weeks.

Of the 211 patients who received daclatasvir, 44 were infected with genotype 2 or 3 HCV and 167 had genotype 1 infection, with mostly treatment-naïve treatment history.

After 12 weeks an overall SVR was achieved by 98% of patients infected with HCV genotype 1 and 91% of patients infected with genotypes 2 and 3.[4] The submission noted the numerically lower SVR rate seen in patients with genotype 2 or 3 compared with genotype 1 infection.[6]

High rates of SVR (95% to 100%) were also observed in treatment-experienced patients who received daclatasvir with sofosbuvir (with or without ribavirin) for 24 weeks; however, this included only 41 patients who had previously experienced virological failure with telaprevir or boceprevir and peginterferon alfa–ribavirin combination treatment.[4]

Two other small studies have established similarly high rates of SVR after 12 weeks, mostly against genotype 1 infection in patients without cirrhosis who were co-infected with HIV-1 in both treatment-naïve and treatment-experienced groups,[3] as well as in genotype 3 infection in mostly treatment-naïve patients without cirrhosis.[9] In the latter study, 86% of 51 treatment-experienced patients achieved SVR.

Follow the prescribing matrix outlined by the PBAC

The PBAC has outlined a prescribing matrix based on treatment history and HCV genotype for antiviral treatment regimens that are supported by evidence and available for PBS rebate.

The PBAC noted that evidence of clinical efficacy for daclatasvir with sofosbuvir was insufficient in the following groups:[6]

- treatment-experienced patients with HCV genotypes 2–6
- patients with documented cirrhosis
- treatment-naïve patients with HCV genotype 4, 5 or 6
- patients with HIV or HBV co-infection.[9]

While some clinical efficacy was observed in patients with cirrhosis in one study, the proportion of patients achieving SVR was lower than for patients without cirrhosis.[9] Another study showed

ADDITIONAL INFORMATION

PBS General Statement for Drugs for the Treatment of Hepatitis C: www.pbs.gov.au/info/healthpro/explanatory-notes/general-statement-hep-c

CI: confidence interval

ADDITIONAL INFORMATION

PBS hepatitis C fact sheet: www.pbs.gov.au/info/publication/factsheets/hep-c/hepatitis-c-medicines-factsheet-for-community-based-prescribers

similar rates of SVR in patients with and without cirrhosis; however, this was in a population of patients co-infected with HIV.[3] Both these studies were limited by the small number of patients with cirrhosis studied.

Read more about the new hepatitis C medicines available on the PBS on the PBS website.[6]

Safety issues

There were insufficient data to reliably determine the safety profile of daclatasvir with sofosbuvir, especially with respect to uncommon or rare treatment-related adverse events.[6]

Combination treatment with daclatasvir is well tolerated

In the pivotal trial involving 211 patients, two (< 1%) discontinued during treatment and 15 patients (7.1%) experienced serious adverse events during the treatment period (including five events of overdose with no clinically significant effects). The most common adverse events were fatigue (37%), headache (29%) and nausea (19%).[4]

The most common grade 3 or 4 laboratory abnormalities were low phosphorus and elevated glucose levels.[4]

Other trials showed a similarly low rate of serious adverse events and discontinuations.[3, 9]

For information about reporting adverse reactions to the TGA, or to report suspected adverse reactions online, see the TGA website.

Read more about the efficacy and safety of daclatasvir in *Australian Prescriber.*

Potential drug interaction with amiodarone

Severe bradycardia and heart block have been reported in patients using amiodarone who underwent HCV antiviral treatment with daclatasvir and sofosbuvir, regardless of whether other medicines that lower heart rate were being used. Bradycardia resolved after discontinuation of HCV treatment.

Consider an alternative antiarrhythmic treatment. For patients with no alternative treatment options, warn patients of the symptoms of bradycardia and heart block. Closely monitor cardiac activity when co-administering amiodarone with daclatasvir and sofosbuvir.[1]

Contraindicated in combination with strong CYP3A4 inducers

Do not use daclatasvir in combination with drugs that strongly induce CYP3A4, as these may lead to lower exposure and loss of efficacy of daclatasvir.

Contraindicated medicines include, but are not limited to, phenytoin, carbamazepine, oxcarbazepine, phenobarbital, rifampicin, rifabutin, dexamethasone and St John's wort.[1]

A dose adjustment is required when daclatasvir is used in combination with moderate inducers of CYP3A4 (see 'Dosing issues').[1]

Dosing issues

Daclatasvir is for oral administration and may be taken with or without food. The recommended dose is 60 mg once daily taken in a combination antiviral regimen with other medicines.[1] For specific dosing recommendations for other medicines taken with daclatasvir in an antiviral regimen, refer to the respective Product Information.

Daclatasvir is not for use as monotherapy

Avoid treatment interruption after therapy with daclatasvir has started. If treatment interruption of any agent used in combination with daclatasvir is necessary, discontinue daclatasvir.[1]

Dose adjustment required if co-administered with moderate inducers or strong inhibitors of CYP3A4

A 30 mg daclatasvir tablet is also available for use when dose adjustment is required.

Daclatasvir is a substrate of CYP3A, and the major CYP isoform responsible for its metabolism is CYP3A4.[1]

ADDITIONAL INFORMATION

Information on/reporting suspected adverse reactions to the TGA online: www.tga.gov.au/safety/problem.htm#medicine

Efficacy and safety of daclatasvir: www.nps.org.au/australian-prescriber/articles/daclatasvir

The dose of daclatasvir should be increased to 90 mg once daily when used in combination with moderate inducers of CYP3A4.[1] Moderate CYP3A4 inducers include, but are not limited to, bosentan, modafinil and efavirenz.[10] Note that strong inducers of CYP3A4 are contraindicated with daclatasvir (see 'Safety issues').[1]

Strong inhibitors of CYP3A4 may increase the plasma levels of daclatasvir, and the dose of daclatasvir should be reduced to 30 mg once daily when administered concomitantly with strong inhibitors of CYP3A4.[1] These include, but are not limited to, boceprevir, clarithromycin and ketoconazole.[10]

Discontinue treatment if virological breakthrough is confirmed

Australian Consensus Recommendations do not mandate testing for HCV RNA during antiviral treatment; however, they note it may be considered when there is a concern over non-adherence to treatment, and for patients with cirrhosis.[7]

If a patient experiences an increase in HCV RNA (from nadir) of greater than 1 log 10 IU/mL, it is recommended daclatasvir be discontinued. The effectiveness of treatment with daclatasvir in patients with prior exposure to an NS5A inhibitor has not been established.[1]

No dose adjustment required for renal or hepatic impairment

When administering daclatasvir in patients with mild, moderate or severe hepatic or renal impairment, no dose adjustment is needed.[1] However, the safety of sofosbuvir has not been assessed in patients with severe renal impairment (eGFR < 30 mL/min/1.73m^2) or end-stage renal disease requiring haemodialysis, and there are no data to support use of sofosbuvir in patients with severe renal failure.[11] Combination treatment with daclatasvir and sofosbuvir should therefore not be used in these patients.

No dose adjustment required for older people

Clinical trials of daclatasvir have included cohorts of patients 65 years and older, with no differences in safety or efficacy observed compared with younger people. No dose adjustment of daclatasvir is advised at this time.[1]

Information for patients

Advise patients talking daclatasvir with sofosbuvir, with or without ribavirin, as follows.[8]

- Daclatasvir should not be taken alone to treat chronic hepatitis C. It should be used together with other antiviral medicines such as sofosbuvir, with or without ribavirin, which are also PBS listed.
- Daclatasvir is sometimes used with ribavirin, which may cause birth defects or death of your unborn baby. If you are pregnant or are planning to become pregnant or your sexual partner is pregnant or plans to become pregnant, do not take these medicines.
- Do not take daclatasvir if you are currently taking any of these medicines:
  - carbamazepine
  - dexamethasone
  - oxcarbazepine
  - phenobarbital
  - phenytoin
  - rifabutin
  - rifampicin
  - St John's wort.

  If you are unsure, talk to your doctor or pharmacist.

Discuss the daclatasvir (Daklinza) Consumer Medicine Information (CMI) leaflet with the patient, especially when daclatasvir is used in combinations that are not PBS listed and therefore not considered here (eg, with Sunvepra or Pegasys-RBV).

ADDITIONAL INFORMATION

daclatasvir (Daklinza) CMI: www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2015-CMI-01991-1&d=20160307161146224121

eGFR: estimated glomerular filtration rate

Reason for PBS listing

The PBAC recommended the listing of daclatasvir in combination with sofosbuvir for treatment of genotype 1 chronic hepatitis C (CHC) in treatment-naïve patients without cirrhosis, based on acceptable cost effectiveness over no treatment.[6]

The listing of daclatasvir in combination with sofosbuvir for the treatment of genotype 3 CHC was also recommended on the basis of acceptable cost-effectiveness over no treatment.[6]

However, following the recommendation to list sofosbuvir-containing regimens, the PBAC considered these sofosbuvir-containing regimens to be the appropriate comparator for all other oral HCV treatments because they were likely to become the standard of care, while accepting that the listing of daclatasvir could only progress if sofosbuvir is available on the PBS.[6]

The PBAC considered that the SVR achieved with 12 weeks' combination treatment with daclatasvir and sofosbuvir was non-inferior in comparative efficacy with that of:[6]

- ledipasvir with sofosbuvir fixed-dose combination in treatment-naïve patients with genotype 1 CHC but no cirrhosis
- sofosbuvir and ribavirin treatment over 24 weeks in treatment-naïve patients with genotype 3 CHC but no cirrhosis.

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FULL REVIEW

Sofosbuvir treatment combinations

for chronic hepatitis C

(soe-FOS-bue-veer)

Now PBS listed as a first-line interferon-free treatment option for chronic HCV genotypes 1, 2 and 3

KEY POINTS

Sofosbuvir inhibits replication of hepatitis C virus (HCV)
It is a nucleotide analogue inhibitor of HCV-specific NS5B RNA polymerase, which is essential for HCV replication.

Multiple sofosbuvir-based treatment regimens now available on the PBS
Most sofosbuvir combinations are oral and interferon-free, and patients are eligible for PBS subsidy irrespective of treatment experience and cirrhotic status; however, these factors influence treatment regimen and duration.

High rates of sustained virological response (SVR) for patients with chronic HCV infection
Sofosbuvir treatment regimens are highly effective in patients with chronic HCV across multiple genotypes, irrespective of treatment experience or cirrhotic status.

Community pharmacists can only dispense under the General Schedule
If the prescription is written under S100 Highly Specialised Drug arrangements, approved community pharmacists will not be able to dispense.

PBS listing

Authority required

Sofosbuvir (Sovaldi) is listed on the General Schedule (S85) and PBS Section 100 Highly Specialised Drugs (S100 HSD) program for treatment-naïve or treatment-experienced patients, with or without cirrhosis, as part of an interferon-free, oral treatment regimen with:[13]

- ribavirin, for genotype 2 or 3 HCV infection
- ledipasvir, as part of a fixed-dose combination product, for patients with genotype 1 HCV infection (see the separate *NPS RADAR* review 'Ledipasvir with sofosbuvir fixed-dose combination for chronic hepatitis C' on page 4)
- daclatasvir, with or without ribavirin, for genotype 1 or 3 HCV infection (see separate review 'Daclatasvir with sofosbuvir, with or without ribavirin, for chronic hepatitis C' on page 10).

Sofosbuvir is also PBS listed for combination with ribavirin and peginterferon.[13] See the interferon-based treatment wrap-up on page 27 for more information.

Specific treatment combinations and treatment duration depend on the HCV genotype, whether the patient has received previous treatment for hepatitis C, and the patient's cirrhotic status. Treatment regimens are outlined in a prescribing matrix *General Statement for Drugs for Treatment of Hepatitis C* on the PBS website.

When applying for authority to prescribe, the hepatitis C virus genotype and the patient's cirrhotic status (non-cirrhotic or cirrhotic) must be provided.

In addition, evidence of chronic hepatitis C infection (repeatedly testing positive for antibody to hepatitis C virus [anti-HCV] and hepatitis C virus ribonucleic acid [HCV RNA]) and the hepatitis C virus genotype must be documented in the patient's medical records.

ADDITIONAL INFORMATION

PBS General Statement for Drugs for the Treatment of Hepatitis C: www.pbs.gov.au/info/healthpro/explanatory-notes/general-statement-hep-c

EVIDENCE SNAPSHOT

WHAT IS KNOWN ABOUT THIS DRUG?

Sofosbuvir is a nucleotide analogue inhibitor of the HCV-specific RNA polymerase NS5B, which prevents replication of HCV.[1, 2] It is used as a component of combination treatment for chronic HCV genotype 1–6 infection,[2] and key clinical trials have demonstrated high rates of sustained virological response (SVR) when sofosbuvir is used in an interferon-free regimen with:

- ledipasvir, in a fixed-dose combination for patients with genotype 1 infection[3-5]
- daclatasvir, with or without ribavirin, for genotype 1, 2 or 3 infection[6]
- ribavirin, for genotype 2 or 3 infection[7-9]

An interferon-containing regimen consisting of sofosbuvir, peginterferon and ribavirin can also achieve high rates of SVR in patients with genotype 1, 3, 4, 5 or 6 infection;[8, 10] however, it is less well-tolerated than interferon-free regimens, and is likely to be reserved for:

- patients for whom first-line interferon-free therapies fail[11] or are not tolerated,[12] or
- those with genotype 4–6 infection.[11, 13]

AREAS OF UNCERTAINTY

Head-to-head comparisons of the efficacy and safety of sofosbuvir with ribavirin with other interferon-free sofosbuvir combination regimens are currently lacking, and more clinical trials are required to establish efficacy and safety for patients who are co-infected with HIV or HBV.[14]

WHAT DOES NPS SAY?

Interferon-free combination treatments with sofosbuvir are highly effective first-line options for patients with chronic genotype 1, 2 or 3 HCV infection, irrespective of treatment experience and cirrhotic status.

Head-to-head comparative data with other interferon-free, first-line treatment options in patients with HCV would assist health professionals in selecting the most appropriate treatment regimen for their patient.

ADDITIONAL INFORMATION

New supply arrangements for some S100 medicines: www.nps.org.au/radar/articles/new-supply-arrangements-for-some-s100-medicines

PBS patient and prescriber eligibility is the same whether the medicine is prescribed under the PBS General Schedule or the HSD program.[15]

May be prescribed by specialists or GPs

Gastroenterologists, hepatologists or infectious-disease physicians experienced in the treatment of chronic hepatitis C infection can prescribe sofosbuvir on the PBS. Other health professionals, including GPs, can also prescribe sofosbuvir under the PBS, provided that it is done in consultation with one of these specialists.[15]

Community pharmacists can only dispense under the General Schedule

Sofosbuvir will not be available under the new S100 HSD Community Access arrangements introduced on 1 July 2015. Approved pharmacists in the community will be able to dispense when a prescription is issued under the General Schedule. However, if the prescription has been written under S100 HSD arrangements in a public hospital, approved pharmacists in the community will not be able to dispense.[15]

What is it?

Sofosbuvir is a nucleotide analogue inhibitor of HCV-specific NS5B RNA polymerase, which prevents replication of HCV.[14] As a pro-drug, sofosbuvir is extensively metabolised in the liver to an active uridine analogue triphosphate, and has selective in vitro activity against all six HCV genotypes (1a and b, 2a, 3a, 4a, 5a and 6a).[1, 2,16]

Sofosbuvir is an oral tablet used as a component of a combination HCV antiviral regimen for treatment of chronic HCV infection.[14]

This article focuses predominantly on data concerning the combination of sofosbuvir with ribavirin. See:

- the ribavirin wrap-up on page 26 for details on the separate PBS listing of ribavirin
- the full *NPS RADAR* review 'Ledipasvir with sofosbuvir fixed-dose combination for chronic hepatitis C' on page 4 for details on the fixed-dose combination with ledipasvir
- the full RADAR review 'Daclatasvir with sofosbuvir, with or without ribavirin, for chronic hepatitis C' (page 10) for combination with daclatasvir.
- the interferon wrap-up on page 27 for combination with ribavirin and peginterferon.

Who is it for?

Sofosbuvir is a Therapeutic Goods Administration – approved treatment option for adults (18 years or older) with chronic HCV, as a component of a combination antiviral treatment regimen.[17] Note that use of sofosbuvir as a monotherapy is not recommended and is not PBS listed.[14]

Sofosbuvir combination treatment regimens are PBS listed for patients with chronic HCV infection with or without cirrhosis, including those who are treatment-naïve or treatment-experienced.[13] Here, the combination of sofosbuvir with ribavirin is discussed in detail.

Interferon-free, dual oral treatment options for genotype 2 and 3 infection

Sofosbuvir and ribavirin are PBS listed for patients with chronic genotype 2 or 3 HCV infection with or without cirrhosis, who are treatment-naïve or treatment-experienced.[13]

Uncertain safety and efficacy in patients with decompensated cirrhosis

The safety and efficacy of sofosbuvir has not been established in patients with decompensated cirrhosis; however, these patients are not excluded from receiving the PBS subsidy.[13] No dose adjustment of sofosbuvir is required for patients with mild, moderate or severe hepatic impairment.[14]

Use in pregnancy

There have been no adequate or well-controlled clinical studies of sofosbuvir in pregnant women (pregnancy category B1), and it must not be used as a monotherapy in this population. Avoid breastfeeding while taking sofosbuvir.[14] Note that ribavirin is contraindicated for patients who are pregnant or breastfeeding.[2]

When using sofosbuvir in combination with ribavirin, extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients, for approximately 6 months after completion of therapy.[14]

Use in patients co-infected with hepatitis B or HIV

The safety and efficacy of sofosbuvir has not been established in patients co-infected with hepatitis B virus, and there are limited data on safety and efficacy in patients co-infected with HIV.[14]

Note that the precautions and contraindications of other direct-acting antivirals, ribavirin or peginterferon alfa also apply when sofosbuvir is used in combination with any of these agents.[14] See the Product Information under precautions and contraindications.

Where does it fit?

Consensus recommendations list the following interferon-free sofosbuvir combination treatment regimens as first-line treatment options:[11]

- sofosbuvir and ledipasvir, or sofosbuvir and daclatasvir (with or without ribavirin) for patients with genotype 1 HCV infection
- sofosbuvir and ribavirin for patients with genotype 2 HCV infection
- sofosbuvir and daclatasvir, or sofosbuvir and ribavirin for patients with genotype 3 HCV infection.[11]

In addition, an interferon-containing treatment regimen of sofosbuvir, ribavirin and peginterferon is the first-line treatment for patients with genotype 4, 5 or 6 infection.[11] Although this treatment regimen is also PBS listed for genotypes 1 and 3,[13, 18] it is less well-tolerated and likely to be considered a second-line option for patients who are intolerant of,[12] or fail to respond to,[11] first-line treatment with interferon-free regimens.

How does it compare?

Dual treatment with sofosbuvir and ribavirin has been evaluated for safety and efficacy in five key phase 3 trials in patients with chronic hepatitis C.[7-9] Across these studies, the primary clinical outcome was the proportion of patients achieving SVR.

Dual combination treatment with sofosbuvir and ribavirin at least as effective as standard of care for treatment-naïve genotype 2 or 3

The efficacy of a 12-week, interferon-free, dual combination treatment regimen consisting of sofosbuvir and ribavirin (n = 256) was compared with standard-of-care treatment with 24 weeks of peginterferon alfa-2a and ribavirin (n = 243) in a randomised non-inferiority study (FISSION) of treatment-naïve patients with genotype 2 or 3 infection.[8]

In this patient population, 12 weeks of sofosbuvir and ribavirin (SOF + RBV) was at least as effective as 24 weeks of peginterferon alfa-2a and ribavirin (PEG + RBV) treatment for achieving SVR 12 weeks after treatment ($p < 0.001$), with nearly identical overall SVR rates (67%) for both groups.[8]

Key term	Definition
Sustained virological response (SVR)	Negative HCV RNA and normal alanine aminotransferase (ALT) level 6 months after completing treatment for HCV infection.[19] In key clinical trials SVR was defined as HCV RNA below the lower limit of detection 12 weeks after the end of treatment.[7-9] Testing for SVR 12 weeks after the end of treatment is recommended[10]
Chronic hepatitis C	Hepatitis C infection that persists for more than 6 months[19]
Virological breakthrough	The return of detectable HCV RNA during treatment after previous undetectable levels during treatment[20]
Virological relapse	A subsequent recurrence of detectable HCV RNA after undetectable levels at the end of treatment[21]

Superior efficacy of with sofosbuvir and ribavirin compared with no treatment for treatment-experienced patients

An interferon-free regimen of SOF + RBV was studied in two key phase 3 trials (POSITRON and FUSION) in patients with genotype 2 or 3 infection.[7]

In patients for whom interferon was not an option (due to absolute or relative contraindications; POSITRON, randomised), treatment with SOF + RBV (n = 207) for 12 weeks produced SVR rates of 78% (95% CI 72 to 83) 12 weeks after treatment, compared with 0% ($p < 0.001$) for placebo (n = 71).[7] None of the patients with SVR 12 weeks after treatment with SOF + RBV showed virological relapse for up to 24 weeks after treatment.[7]

The second study (FUSION) focussed on patients with genotype 2 or 3 infection who had either not responded to prior interferon therapy, or displayed virological breakthrough during the prior interferon treatment or virological relapse afterward.

Patients were randomised to either 12 weeks of SOF + RBV followed by 4 weeks of matching placebo (n = 103), or 16 weeks of SOF + RBV (n = 98). Overall, longer duration of treatment with SOF + RBV was associated with higher rates of SVR 12 weeks after treatment (72.6% vs 50% for 16 and 12 weeks, respectively).[7]

Longer treatment duration necessary for genotype 3

Patients with chronic HCV genotype 3 consistently showed lower rates of response to SOF + RBV in the POSITRON, FUSION and FISSION studies, compared with those with genotype 2 infection.[7, 8]

Of patients treated with SOF + RBV in the FISSION study, lower rates of SVR were observed in those with genotype 3 infection (56% [95% CI 48.2 to 63.1]) compared with those with genotype 2 infection (97% [95% CI 90 to 100).[8]

Similarly, the POSITRON study also reported lower rates of SVR in patients with genotype 3 infection who were treated with SOF + RBV (61.2% [95% CI 51 to 71]), compared with genotype 2 (92.7% [95% CI 86 to 97]).[7]

Extending the duration of SOF + RBV treatment was shown to improve SVR rates for patients with genotype 3 infection. The FUSION study demonstrated that extending treatment from 12 to 16 weeks improved SVR rates, particularly for patients with genotype 3 infection, with response rates rising from 30% (95% CI 19 to 42) to 62% (95% CI 49 to 74).[7]

When treatment duration was extended from 12 to 24 weeks in the VALENCE study, the SVR rates for patients with genotype 3 infection increased from 27% (95% CI 6 to 61) to 85% (95% CI 80 to 89).[9]

Low rate of virological breakthrough during treatment but relapse varies

In the POSITRON and FUSION studies, no patient receiving sofosbuvir had virological breakthrough during treatment.[7, 8]

A low rate of virological breakthrough was observed during 12 weeks of SOF + RBV treatment for patients with genotype 2 or 3 infection in the FISSION trial (< 1%), compared with 7% in patients treated with PEG + RBV for 24 weeks.[8]

One case of virological breakthrough was reported in the 24-week SOF + RBV treatment group in the VALENCE study; however, this was likely due to non-adherence, as no drug was detected in that patients' blood during weeks 12–24 of treatment.[9]

Relapse, however, occurred in all four studies at varying rates. For treatment-naïve patients with genotype 1, 4, 5 or 6 infection receiving sofosbuvir in combination with ribavirin and peginterferon, relapse occurred at a rate of 8%.[8] For patients with genotype 2 or 3 infection, relapse rates after 12 weeks of treatment with SOF + RBV were 29%, 20% and 46% (FISSION, POSITRON, FUSION, respectively).[7, 8]

The higher relapse rates observed in the last of these studies were obtained in a patient group that had not responded to previous interferon treatment, and extending treatment duration to 16 weeks improved rates of relapse to 27%.[7]

For details on the interferon-containing sofosbuvir-based regimen that has been PBS listed for patients with chronic genotype 1, 3, 4, 5 or 6 HCV infection, see the wrap-up article on interferon-containing sofosbuvir combination treatment in this issue.

CI: confidence interval

Safety issues

Safety data for the interferon-free, dual oral treatment regimen containing SOF + RBV for chronic hepatitis C infection comes mainly from key clinical trials.[7-9] The long-term safety profile for sofosbuvir beyond 24 weeks is not yet known.[14]

More favourable safety profile of interferon-free treatment compared with interferon-based treatment

An interferon-free, dual combination treatment regimen consisting of SOF + RBV over 12, 16 or 24 weeks was associated with common adverse effects (> 10%) which typically related to:[7, 8]

- fatigue
- headache
- nausea
- insomnia
- anaemia.

Influenza-like symptoms and fever, which occur frequently in people receiving interferon treatment,[20] only occurred in 1–4% of patients taking SOF + RBV.[8]

Extending duration of SOF + RBV treatment to 16 or 24 weeks resulted in a similar frequency of most adverse events compared with the 12-week group,[7, 9] although diarrhoea and irritability were more common in those receiving 24 weeks of treatment.[9]

Treatment discontinuation rates due to adverse events were low in patients receiving dual therapy for 12–24 weeks (ranging from 1–2% across studies).[7-9] By comparison, standard of care treatment with PEG + RBV for 24 weeks resulted in a discontinuation rate of 11% due to adverse events.[8]

Rates of serious adverse events during treatment for patients receiving SOF + RBV for 12, 16 or 24 weeks were generally low (0–5%).[7-9] These included anaemia (0.4%),[8] cellulitis (0.4–0.5%),[7, 8] chest pain (0.4–0.5%)[7, 8] and arrhythmia (0.4%).[9]

For treatment-experienced patients who did not respond to previous interferon treatment, serious adverse event rates were 5% and 3% after receiving SOF + RBV for 12 and 16 weeks, respectively.[7]

The serious adverse event rate for patients receiving treatment for 24 weeks was higher than that observed in the 12-week and placebo groups (4% vs 0% vs 2%, respectively).[9] However, no single serious adverse event occurred in more than 1% of patients taking SOF + RBV during 24 weeks of treatment.[9]

Available for use in patients co-infected with hepatitis B or HIV

The safety and efficacy of sofosbuvir has not been established in patients co-infected with hepatitis B virus, and there are limited data for patients co-infected with HIV.[14] However, treatment regimens for chronic HCV infection in these populations should be the same as those used for HCV mono-infection.[11]

Avoid combination with potent P-glycoprotein inducers

Potent P-glycoprotein inducers of the intestine (eg, rifampicin, tipranavir, or St John's wort) should not be used with sofosbuvir, as they may significantly decrease sofosbuvir plasma concentration, leading to reduced therapeutic effect of sofosbuvir.[14]

For information about reporting adverse reactions to the TGA, or to report suspected adverse reactions online, see the TGA website.

ADDITIONAL INFORMATION

Information on/reporting suspected adverse reactions to the TGA online: www.tga.gov.au/safety/problem.htm#medicine

Reason for PBS listing

The Pharmaceutical Benefits Advisory Committee recommended the listing of sofosbuvir in combination with ribavirin for the treatment of genotype 2 chronic hepatitis C (12 weeks) and genotype 3 chronic hepatitis C (24 weeks) on the basis of cost-effectiveness of the treatment over 'no treatment'.[1]

The PBAC considered 'no treatment' to be the most appropriate comparator in view of the broader context of infected individuals whose treatment preference is interferon-free therapies.[1]

Dosing issues

The recommended dose of sofosbuvir in dual combination with ribavirin is 400 mg taken once daily, orally with or without food.[14]

No dose adjustment required for mild or moderate renal impairment

No dosage adjustment of sofosbuvir is required in patients with mild or moderate renal impairment, based on results of pharmacokinetic studies. However, the safety of sofosbuvir has not been assessed in patients with severe renal impairment (eGFR < 30 mL/min/1.73m^2) or end-stage renal disease.[14] Sofosbuvir is currently not recommended in patients with severe renal impairment.[11]

No dose adjustment required for mild, moderate or severe hepatic impairment

Sofosbuvir is extensively metabolised in the liver; however, no dosage adjustment of sofosbuvir is required for patients with mild, moderate or severe hepatic impairment.[1]

Avoid use of combination treatment if pregnant or breastfeeding

There are no adequate and well-controlled clinical studies of sofosbuvir in pregnant women (pregnancy category B1), and it is not known whether sofosbuvir and its metabolites are excreted in human breast milk.[14]

Due to the significant teratogenic and/or embryocidal effects of ribavirin, patients should not undergo dual therapy with sofosbuvir and ribavirin if pregnant. Women of childbearing potential and their male partners must use effective contraception during treatment with ribavirin and for approximately 6 months after the treatment has concluded.[14]

Use in children and the elderly

The safety and effectiveness of sofosbuvir has not been established in children under the age of 18 years.[14]

No dose adjustment is required for sofosbuvir in elderly patients. However, exercise caution when prescribing sofosbuvir combination treatment to elderly patients due to greater frequency of anaemia, potential for impaired renal, hepatic and cardiac function, and concurrent medicines.[14]

Information for patients

Advise patients taking sofosbuvir as follows:[22]

- sofosbuvir must always be taken together with other hepatitis C medicines, as it will not work on its own
- ask your health professional for advice before taking this medicine if you are pregnant, think you may be pregnant or are planning to have a baby, or if you are breastfeeding, or planning to breastfeed
- tell your health professional if you are taking rifampicin, St John's Wort, amiodarone, anti-epileptic medicines, or any other medicines, herbal supplements or vitamins
- talk to your health professional if you have liver problems (other than hepatitis C), hepatitis B, HIV infection, severe kidney problems, you are on haemodialysis, or have any other medical condition

Discuss the sofosbuvir (Sovaldi) Consumer Medicine Information (CMI) leaflet with the patient.

ADDITIONAL INFORMATION

sofosbuvir (Sovaldi) CMI: www.nps.org.au/medicines/infections-and-infestations/antiviral-medicines/sofosbuvir/sovaldi-tablets

eGFR: estimated glomerular filtration rate

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Date published: April 2016

IN BRIEF

A digest of news items about new drugs and medical tests, changes to PBS and MBS listings, and updates of past *NPS RADAR* reviews.

Itraconazole (Lozanoc) for systemic fungal infections

From 1 April itraconazole 50 micrograms (Lozanoc) is PBS listed *(Authority Required – Streamlined)* for the management of systemic fungal infections.[1] This listing is in line with the currently listed itraconazole 100 microgram (Sporanox) capsule for fungal infections.[1]

Lozanoc capsules have higher bioavailability than the currently available itraconazole capsule.[2] Pharmacokinetic studies have shown that the 50 microgram Lozanoc capsules can be considered therapeutically equivalent to the 100 microgram Sporanox capsules.[2]

If switching patients to Lozanoc, GPs should ensure that patients are aware of their new dosing regimen and their new itraconazole brand.

PBS listing for systemic mycoses only

Itraconazole 50 and 100 microgram are approved by the Therapeutic Goods Administration for superficial and systemic mycoses. However, the PBS listing is for the following systemic mycoses only:[1]

- systemic aspergillosis
- systemic sporotrichosis
- systemic histoplasmosis
- disseminated and chronic pulmonary histoplasmosis infection
- oropharyngeal or oesophageal candidiasis.

Itraconazole is not PBS listed for superficial mycoses.

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PBS: Pharmaceutical Benefits Scheme MBS: Medical Benefits Schedule

WRAP-UP

Information about other medicines that have been PBS listed for which full *NPS RADAR* reviews or brief items are not available

April 2016 new listings wrap-up

The new listings wrap-up section of *NPS RADAR* is designed to provide you with information about other medicines that have been listed on the PBS for which full RADAR reviews or brief items are not available.

April 2016 sees:

- the listing of arsenic for a type of leukaemia
- the separate listing of ribavirin
- a combination of sofosbuvir, ribavirin and peginterferon for treatment of chronic hepatitis C infection.
  (NB: full RADAR reviews are included in this issue for the listings of sofosbuvir, daclatasvir, and the fixed-dose combination ledipasvir with sofosbuvir for chronic hepatitis C infection).

Arsenic for acute promyelocytic leukaemia

Arsenic (Phenasen) has been listed in section 100 of the PBS for the first-line treatment of acute promyelocytic leukaemia (APL).

What is it?

The mechanisms of action for arsenic in APL are uncertain. However, arsenic has been observed to induce partial differentiation and cell death in leukaemia cells in vitro.[3]

Who is it for?

APL is a form of acute myeloid leukaemia with specific biological markers.[4] This type of leukaemia is frequently associated with coagulation disorder and a sensitivity to certain antineoplastic medicines such as arsenic.[4]

Remission rates for this type of leukaemia can be as high as 80% when patients are identified and treated early.[4]

Safety issues

Arsenic can cause QT-interval prolongation.[3] Caution should be taken when prescribing other medicines also known to prolong the QT interval. For more information on the QT interval see the NPS MedicineWise *Health News and Evidence* article 'Fatal arrythmias – drugs and the QT'.

Ribavirin for chronic hepatitis C – separate PBS listing

Ribavirin has been listed on the PBS General Schedule (Section 85) and S100 Highly Specialised Drugs program for use as a component of combination treatment for chronic hepatitis C virus (HCV) infection.[5]

Specific treatment combinations and duration depend on the viral genotype, as well as the patient's cirrhotic status and whether they have previously received treatment for HCV infection. Treatment regimens can be found in the *General Statement for Drugs for the Treatment of Hepatitis C.*

This is the first time ribavirin has been listed on the PBS separately to peginterferon,[6] paving the way for prescription of interferon-free hepatitis C treatments, a number of which are now listed on the PBS.

What is it?

Ribavirin is a nucleoside analogue with antiviral activity[7] that interferes with RNA and DNA synthesis to inhibit protein synthesis and viral replication.[8]

ADDITIONAL INFORMATION

Fatal arrythmias – drugs and the QT:
www.nps.org.au/publications/health-professional/health-news-evidence/2013/drugs-QT-invterval

PBS General Statement for Drugs for the Treatment of Hepatitis C:
www.pbs.gov.au/info/healthpro/explanatory-notes/general-statement-hep-c

Who is it for?

Ribavirin is PBS listed for use in the following interferon-free treatment regimens:[5, 9]

- in combination with daclatasvir and sofosbuvir (12 weeks) for patients with chronic genotype 1 HCV infection
- in combination with sofosbuvir (12 weeks) for patients with chronic genotype 2 HCV infection, with or without cirrhosis, who are treatment naïve or treatment experienced
- in combination with sofosbuvir (24 weeks) for patients with chronic genotype 3 HCV infection, with or without cirrhosis, who are treatment naïve or treatment experienced.

Safety issues

Ribavirin is contraindicated in:[7]

- women who are pregnant
- men whose partners are pregnant
- patients with:
  - haemoglobinopathies (eg, thalassaemia major or sick-cell anaemia)
  - hypersensitivity to ribavirin or its excipients
  - history of severe pre-existing cardiac conditions, including unstable or uncontrolled cardiac disease, in the previous 6 months.

Ribavirin is also contraindicated in combination with didanosine due to reports of fatal hepatic failure, peripheral neuropathy, pancreatitis and symptomatic hyperlactataemia or lactic acidosis in clinical trials.[7]

When ribavirin is used in combination with other anti-HCV treatments, the relevant contraindications and precautions for those agents also apply.[7]

ADDITIONAL INFORMATION

PBS General Statement for Drugs for the Treatment of Hepatitis C: www.pbs.gov.au/info/healthpro/explanatory-notes/general-statement-hep-c

Sofosbuvir with ribavirin and peginterferon for chronic hepatitis C

The treatment regimen sofosbuvir with ribavirin and peginterferon has been PBS listed for patients with chronic genotype 1, 3, 4, 5 or 6 HCV infection, irrespective of their treatment experience and cirrhotic status.[5]

Further details of treatment protocols can be found in the *General Statement for Drugs for the Treatment of Hepatitis C.*

What is it?

Sofosbuvir is a nucleotide analogue inhibitor of the HCV-specific RNA polymerase NS5B, and prevents replication of HCV.[10]

Both ribavirin and peginterferon are non-specific inhibitors of viral replication. Ribavirin is a nucleoside analogue,[7] while peginterferon alfa 2a shows the same antiviral activity as interferon alfa-2a in vitro, which works by activating cellular signalling and gene transcription, causing immunomodulation and inhibiting viral replication in infected cells.[11]

Who is it for?

Sofosbuvir with peginterferon and ribavirin is a first-line treatment option for patients with chronic genotype 4, 5 or 6 hepatitis C infection.[5]

Although this treatment regimen is also PBS listed for genotypes 1 and 3, it is not as well tolerated as first-line interferon-free regimens[12] and is likely to be considered for patients who cannot tolerate,[13] or fail to respond to,[14] first-line treatment with direct-acting antivirals.

ADDITIONAL INFORMATION

Child–Pugh classification of liver disease: www.nps.org.au/radar/articles/child-pugh-classification-of-liver-disease-additional-content-rivaroxaban-xarelto-for-stroke-prevention-in-non-valvular-atrial-fibrillation

Safety issues

Common adverse effects of sofosbuvir with peginterferon and ribavirin include fatigue, headache, nausea, insomnia, pruritus, anaemia and influenza-like illness.[10]

Peginterferon and ribavirin are contraindicated in:[11]

- pregnant women, or in men whose female partners are pregnant or are not using adequate contraception. Extreme care must be taken to avoid pregnancy during, and for 6 months after stopping, treatment
- women who are breastfeeding
- patients with known hypersensitivity to alfa interferons, to *Escherichia coli*-derived products, to ribavirin or any other component of the injection or tablet
- autoimmune hepatitis or decompensated cirrhosis
- patients with HIV co-infection with cirrhosis and a Child–Pugh score of ≥ 6,[9] except if due only to indirect hyperbilirubinaemia caused by medicines such as atazanavir and indinavir
- patients with a history of severe pre-existing cardiac disease, including unstable or uncontrolled cardiac disease in the previous 6 months
- patients with haemoglobinopathies (eg, thalassaemia, sick-cell anaemia)
- neonates and infants up to the age of 3 years, because of the excipient benzyl alcohol.

Potent P-glycoprotein inducers of the intestine (eg, rifampin, St John's wort) should not be used with sofosbuvir.[10]

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RADAR
Rational Assessment of Drugs and Research

INDEX APR 2015 – APR 2016

The following full reviews were published on the *NPS RADAR* website (www.npsradar.org.au) in the last 12 months.

Look for the *NPS RADAR* index under the **Browse** menu.

NPS RADAR **reviews are also available in GP prescribing software** (*Best Practice, Genie, Medical Director* and *Medtech 32*).

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