

## NEW DRUGS

## Sofosbuvir with velpatasvir

*Aust Prescr 2017;40:200-1*

<https://doi.org/10.18773/austprescr.2017.063>

First published  
9 August 2017

### Approved indication: hepatitis C

#### Epclusa (Gilead)

#### tablets containing sofosbuvir 400 mg and velpatasvir 100 mg

#### Australian Medicines Handbook section 5.5

This is a fixed-dose combination tablet indicated for people with hepatitis C genotypes 1–6. In Australia, approximately 50% of all hepatitis C cases are genotype 1 and 35–40% are genotype 3.

Sofosbuvir is already available in combination with ledipasvir<sup>1</sup> and can be used concomitantly with daclatasvir,<sup>2</sup> peginterferon and ribavirin.<sup>3</sup> It is an inhibitor of the NS5B RNA polymerase and blocks viral replication. Velpatasvir is a newly approved drug. Like ledipasvir and daclatasvir, it inhibits the NS5A protein which is required for assembly and release of viral particles.

The efficacy of this combination has been investigated in four main trials (ASTRAL 1–4, see Table).<sup>4–6</sup> The trials enrolled treatment-naïve and treatment-experienced patients with genotypes 1–6. Compensated liver cirrhosis was allowed in all four studies, but those with decompensated liver

disease were only included in ASTRAL-4. The primary efficacy measure in the trials was the proportion of patients who achieved a sustained virologic response. This was defined as undetectable viral RNA in a blood test 12 weeks after the end of treatment.

Almost all patients in ASTRAL-1 (99%) had a sustained response to 12 weeks of treatment with sofosbuvir and velpatasvir. This was irrespective of their hepatitis C genotype, cirrhosis status or previous experience with treatment.<sup>4</sup> No one in the placebo group had a sustained virologic response.

In ASTRAL-2 and ASTRAL-3, sofosbuvir with velpatasvir was compared to treatments for genotype 2 (12 weeks of sofosbuvir plus ribavirin) and genotype 3 infection (24 weeks of sofosbuvir plus ribavirin). Sofosbuvir/velpatasvir was superior to the comparators for both genotypes (see Table).<sup>5</sup>

ASTRAL-4 only enrolled patients with decompensated cirrhosis (Child-Pugh B) infected with genotypes 1–4 and 6. Overall, sustained response rates to 12 weeks of sofosbuvir/velpatasvir were high (83%) and comparable to sofosbuvir/velpatasvir plus ribavirin (94%) and 24 weeks of sofosbuvir/velpatasvir (86%). However on further analysis of the different genotypes, only 50% of patients (13/26) with genotype 3 responded to 12 or 24 weeks of

Table Efficacy of sofosbuvir/velpatasvir\* in chronic hepatitis C

Trial (design)	Patient characteristics	Genotype	Treatment arm (duration)	Efficacy – patients with SVR12
ASTRAL-1 (double-blind) <sup>4</sup>	Treatment-naïve and experienced patients, with or without cirrhosis	1, 2, 4, 5 <sup>†</sup> , 6	sofosbuvir/velpatasvir (12 weeks)	99% (618/624)
			placebo (12 weeks)	0% (0/116)
ASTRAL-2 (open-label) <sup>5</sup>		2	sofosbuvir/velpatasvir (12 weeks)	99% (133/134)
ASTRAL-3 (open-label) <sup>5</sup>		3	sofosbuvir plus ribavirin <sup>‡</sup> (12 weeks)	94% (124/132)
			sofosbuvir/velpatasvir (12 weeks)	95% (264/277)
			sofosbuvir plus ribavirin <sup>‡</sup> (24 weeks)	80% (221/275)
ASTRAL-4 (open-label) <sup>6</sup>	Treatment-naïve and experienced patients with decompensated cirrhosis	1–4, 6 <sup>§</sup>	sofosbuvir/velpatasvir (12 weeks)	83% (75/90)
			sofosbuvir/velpatasvir plus ribavirin <sup>‡</sup> (12 weeks)	94% (82/87)
			sofosbuvir/velpatasvir (24 weeks)	86% (77/90)
ASTRAL-5 (open-label) <sup>7</sup>	Treatment-naïve and experienced patients co-infected with HIV	1–4	sofosbuvir/velpatasvir (12 weeks)	95% (99/104)

SVR12 sustained virologic response 12 weeks after the end of treatment

\* Sofosbuvir 400 mg and velpatasvir 100 mg was given once-daily.

<sup>†</sup> All 35 patients with genotype 5 infection received sofosbuvir/velpatasvir.

<sup>‡</sup> Ribavirin dose was weight-based and given twice-daily.

<sup>§</sup> There was only 1 patient with genotype 6 infection.

sofosbuvir/velpatasvir. When ribavirin was added to 12 weeks of sofosbuvir/velpatasvir, 85% (11/13) of people with genotype 3 had a sustained response.<sup>6</sup>

Another trial (ASTRAL-5) enrolled people with genotypes 1–4 who were co-infected with HIV. The overall response rate to 12 weeks of sofosbuvir/velpatasvir was 95%.<sup>7</sup>

In a pooled analysis of ASTRAL 1–3, the most common adverse events in people taking sofosbuvir/velpatasvir were headache (29% of patients), fatigue (21%), nausea (13%) and nasopharyngitis (12%). These occurred at a similar frequency in those receiving placebo in the ASTRAL-1 trial. Anaemia was common in people who received the combination with ribavirin, particularly in patients with decompensated cirrhosis.

Following oral administration, sofosbuvir is absorbed within an hour and velpatasvir within three hours. Absorption of velpatasvir decreases as gastric pH increases therefore antacids should be taken at least four hours before or after sofosbuvir/velpatasvir. H<sub>2</sub> receptor antagonists can be taken at the same time or 12 hours apart. Proton pump inhibitors, comparable to omeprazole 20 mg, can also be taken at the same time as sofosbuvir/velpatasvir and with food.

Sofosbuvir and velpatasvir are substrates of P-glycoprotein and velpatasvir is a substrate of cytochrome P450 (CYP) 2B6, CYP2C8 and CYP3A4. Potent inducers of these (e.g. carbamazepine, efavirenz, rifampicin, St John's wort), may decrease serum concentrations of one or both drugs in the combination and co-administration is not recommended. Sofosbuvir/velpatasvir may increase concentrations of digoxin, tenofovir and rosuvastatin, and close monitoring and possible dose adjustment of these drugs is recommended. Concomitant amiodarone can cause symptomatic bradycardia and is not recommended.

It is not known if sofosbuvir/velpatasvir is safe for pregnant women as there have been no adequate studies. No fetal effects were found at high doses in animal studies. It is not known if sofosbuvir and velpatasvir are excreted in human milk, but both were found in the milk of lactating rats. There were no observed effects on nursing rat pups.

When this combination is used with ribavirin, prescribers should be aware that ribavirin is teratogenic and toxic to embryos and is contraindicated in pregnant women and male partners of pregnant women. Female patients and female partners of male patients must use contraception during and for six months after the end of ribavirin treatment.

Patients must be screened for current or past hepatitis B (surface antigen, core antibody) before starting sofosbuvir/velpatasvir as hepatitis C treatment can cause reactivation of hepatitis B infection.

This fixed-dose combination of sofosbuvir and velpatasvir was effective in eradicating hepatitis C infections caused by genotypes 1–6. For most patients, the recommended dose is one tablet a day for 12 weeks. In those with genotype 3 infection who have compensated cirrhosis, the addition of ribavirin may be considered. Unlike some of the other direct-acting combination drugs for hepatitis C (e.g. elbasvir/grazoprevir,<sup>8</sup> paritaprevir/ritonavir/ombitasvir plus dasabuvir<sup>9</sup>), sofosbuvir/velpatasvir can be used in patients with decompensated liver disease. However, ribavirin should be added to the regimen in these patients. As yet, there are no clinical data for sofosbuvir/velpatasvir in patients with Child-Pugh C cirrhosis or those who have had a liver transplant. This combination is well tolerated but prescribers need to be aware of the numerous drug interactions that can occur.

**T T** [manufacturer provided additional useful information](#)

## REFERENCES

1. Ledipasvir with sofosbuvir for hepatitis C. *Aust Prescr* 2015;38:219-21. <https://doi.org/10.18773/austprescr.2015.078>
2. Daclatasvir for hepatitis C. *Aust Prescr* 2015;38:217-9. <https://doi.org/10.18773/austprescr.2015.077>
3. Sofosbuvir for hepatitis C. *Aust Prescr* 2014;37:172-9. <https://doi.org/10.18773/austprescr.2014.073>
4. Feld JJ, Jacobson IM, Hézode C, Asselah T, Ruane PJ, Gruener N, et al. Sofosbuvir and velpatasvir for HCV genotype 1, 2, 4, 5 and 6 infection. *N Engl J Med* 2015;373:2599-607. <https://doi.org/10.1056/NEJMoa1512610>
5. Foster GR, Afdhal N, Roberts SK, Bräu N, Gane EJ, Pianko S, et al. Sofosbuvir and velpatasvir for HCV genotype 2 and 3 infection. *N Engl J Med* 2015;373:2608-17. <https://doi.org/10.1056/NEJMoa1512612>
6. Curry MP, O'Leary JG, Bzowej N, Muir AJ, Korenblat KM, Fenkel JM, et al. Sofosbuvir and velpatasvir for HCV in patients with decompensated cirrhosis. *N Engl J Med* 2015;373:2618-28. <https://doi.org/10.1056/NEJMoa1512614>
7. Wyles D, Bräu N, Kottlilil S, Daar ES, Ruane P, Workowski K, et al. Sofosbuvir and velpatasvir for the treatment of HCV in patients coinfecting with HIV-1: an open-label, phase 3 study [Epub ahead of print]. *Clin Infect Dis* 2017. <https://doi.org/10.1093/cid/cix260>
8. Elbasvir/grazoprevir for hepatitis C. *Aust Prescr* 2017;40:32-4. <https://doi.org/10.18773/austprescr.2017.010>
9. Paritaprevir/ritonavir/ombitasvir plus dasabuvir/with ribavirin for chronic hepatitis C. *Aust Prescr* 2016;39:141-3. <https://doi.org/10.18773/austprescr.2016.045>

The Transparency Score is explained in [New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27](#).

At the time the comment was prepared, information about this drug was available on the websites of the [Food and Drug Administration](#) in the USA and the [European Medicines Agency](#).