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New drugs

Sofosbuvir/velpatasvir/voxilaprevir

Approved indication: hepatitis C

Vosevi (Gilead)
film-coated tablets containing 400 mg/100 mg/100 mg
Australian Medicines Handbook section 5.5, Antivirals for hepatitis C

Voxilaprevir is a new chemical entity recently approved in a fixed-dose combination with sofosbuvir[1,2] and velpatasvir.[3] Like glecaprevir and grazoprevir, voxilaprevir inhibits the NS3/4A protease involved in viral replication. Sofosbuvir is an NS5B nucleotide polymerase inhibitor and velpatasvir is an NS5A inhibitor.

The approval of this combination is primarily based on two 12-week studies in people who had previously failed treatment with direct-acting antiviral drugs (POLARIS-1 and -4).[4] The primary measure of efficacy in the trials was the proportion of patients who achieved a sustained virologic response, defined as undetectable viral RNA in a blood test 12 weeks after the end of treatment (SVR12).

Results of the POLARIS trials are summarised in the Table. Overall, sustained virologic response rates to once-daily sofosbuvir/velpatasvir/voxilaprevir were high in treatment-experienced patients.[4]

The most common adverse effects with 12 weeks of treatment were headache (26%), fatigue (22%), diarrhoea (17%) and nausea (17%). As with other direct-acting antivirals for hepatitis C, this combination comes with a warning about the risk of hepatitis B reactivation.

There are many potential drug interactions with this fixed-dose combination so checking the product information before prescribing is advisable. Its efficacy can be reduced by inducers of P-glycoprotein such as rifampicin, which is contraindicated with this product. Sofosbuvir has a potentially fatal interaction with amiodarone and concomitant use is not recommended. Other significant interactions include:

- anticonvulsants such as carbamazepine and phenytoin
- antiretrovirals such as atazanavir, lopinavir and efavirenz
- statins, particularly rosuvastatin, which is contraindicated
- St John's wort.

The solubility of velpatasvir decreases as gastric pH increases so antacids should be administered separately by four hours. Caution is urged with high doses of H_2 receptor antagonists and proton pump inhibitors.

There are no clinical studies of this combination in pregnancy. However, in animal studies, there did not appear to be any fetal adverse effects. All three drugs were found in the breast milk of lactating rats but there were no apparent adverse effects in the pups.

Following oral administration, peak plasma concentrations are reached after 2–4 hours. Dose adjustments are not required in mild–moderate renal impairment. There are no safety data in people with severe impairment or end-stage renal disease. Dose adjustments are not needed in mild hepatic impairment, but this combination is not recommended in moderate–severe hepatic impairment.

This fixed-dose combination eradicated hepatitis C infections in treatment-experienced people including those with decompensated liver cirrhosis. It was also effective in treatment-naïve patients as an eight-week treatment course (see Table).[5]

In Australia, the combination tablets are specifically indicated for treatment-experienced patients infected with:

- genotype 1, 2, 3, 4, 5 or 6 after failed previous treatment with an NS5A inhibitor such as daclatasvir, elbasvir, ledipasvir, ombitasvir or velpatasvir
- genotype 1a or 3 after failed previous treatment with a regimen containing sofosbuvir without an NS5A inhibitor. This includes those who have received sofosbuvir with or without peginterferon, ribavirin or an NS3/4A protease inhibitor such as boceprevir, simeprevir of telaprevir.

T manufacturer provided the product information

REFERENCES

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4. Bourlière M, Gordon SC, Flamm SL, Cooper CL, Ramji A, Tong M, et al. Sofosbuvir, velpatasvir and voxilaprevir for previously treated HCV infection. N Engl J Med 2017;376:2134-46. https://doi.org/10.1056/NEJMoa1613512
5. Jacobson IM, Lawitz E, Gane EJ, Willems BE, Ruane PJ, Nahass RG, et al. Efficacy of 8 weeks of sofosbuvir, velpatasvir, and voxilaprevir in patients with chronic HCV infection: 2 phase 3 randomized trials. Gastroenterology 2017;153:113–22. https://doi.org/10.1053/j.gastro.2017.03.047

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Some of the views expressed in the following notes on newly approved products should be regarded as preliminary, as there may be limited published data at the time of publication, and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

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

Patient characteristics	Treatment	SVR12
POLARIS-1 trial[4] – Treatment-experienced		
Previously taken DAA regimen containing an NS5A inhibitor Infected with genotypes 1–6, with or without cirrhosis	sofosbuvir/velpatasvir/voxilaprevir for 12 weeks (263 patients)	96% overall 93% in those with cirrhosis
	placebo for 12 weeks (152 patients, mostly genotype 1)	0%
POLARIS-4 trial[4] – Treatment-experienced		
Previously taken DAA regimen not containing an NS5A inhibitor Infected with genotypes 1–4, with or without cirrhosis	sofosbuvir/velpatasvir/voxilaprevir for 12 weeks (182 patients)	98% overall 98% in those with cirrhosis
	sofosbuvir/velpatasvir for 12 weeks (151 patients, genotype 1–3)	90% overall 86% in those with cirrhosis
POLARIS-2 trial[5] – Treatment-naïve		
Infected with genotypes 1–6, with or without cirrhosis except patients with genotype 3 and cirrhosis who were excluded	sofosbuvir/velpatasvir/voxilaprevir for 8 weeks (501 patients)	95% overall 92% in those with genotype 1a 91% in those with cirrhosis
	sofosbuvir/velpatasvir for 12 weeks (440 patients)	98% overall 99% in those with genotype 1a 99% in those with cirrhosis
POLARIS-3 trial[5] – Treatment-naïve		
Infected with genotype 3 and with cirrhosis	sofosbuvir/velpatasvir/voxilaprevir for 8 weeks (110 patients)	96% overall
	sofosbuvir/velpatasvir for 12 weeks (109 patients)	96% overall

DAA direct-acting antiviral
SVR12 sustained virologic response 12 weeks after the end of treatment, defined as undetectable viral RNA in a blood test

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, the European Medicines Agency and the Therapeutic Goods Administration.