Glecaprevir/pibrentasvir

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Approved indication: hepatitis C

Maviret (Abbvie)
100 mg/40 mg tablets
Australian Medicines Handbook section 5.5

This fixed-dose combination tablet is indicated for people with hepatitis C genotypes 1–6. It contains two new antiviral drugs – glecaprevir, which is an NS3/4A protease inhibitor, and pibrentasvir, which inhibits the NS5A protein involved in viral replication.

Approval of the combination is based on several trials in approximately 2300 treatment-experienced and treatment-naïve patients, with and without cirrhosis. The primary efficacy outcome in the studies was the proportion of patients with a sustained virologic response 12 weeks after the end of the treatment course. Following 8, 12 or 16 weeks of glecaprevir/pibrentasvir (300 mg/120 mg), 91–100% of patients in the trials responded (see Table).[1-5] Most of the trials were open label and did not include an active comparator. However, in the Endurance-3 study, the efficacy of glecaprevir/pibrentasvir was comparable to sofosbuvir plus daclatasvir (95% vs 97%) in treatment-naïve participants (see Table).[2]

The combination has also been investigated in patients who had experienced treatment failure or relapsed after treatment with an NS3/4A protease inhibitor or an NS5A inhibitor, or both (Magellan-1 study). Participants did not have cirrhosis. In part 1 of the study, 86% (19/22) of patients with genotype 1 infection had a sustained response to 12 weeks of treatment.[6] In part 2 of the study, which enrolled patients with genotype 1 or 4 infection with or without cirrhosis, 89% (39/44) and 91% (43/47) responded to 12 and 16 weeks of treatment respectively.[7]

The combination has also been assessed in 104 people with severe chronic kidney disease with hepatitis C genotypes 1–6 (Expedition-4 study). Almost 20% of them had cirrhosis. After a 12-week course of treatment, 98% had a sustained virologic response 12 weeks later.[8]

Of all patients who participated in the trials, 0.1% discontinued treatment because of an adverse event. The most commonly reported events were headache (13.2%), fatigue (11.4%) and nausea (7.6%). In the severe kidney disease trial, 20% (21/104) of patients developed pruritis.[8]

As with other direct-acting antiviral drugs, there is a risk of hepatitis B reactivation with this combination. There have been no studies in pregnant or lactating women, however in preclinical studies there were no adverse outcomes in pregnant animals. Both glecaprevir and pibrentasvir were excreted in the breastmilk of rats.

Both drugs inhibit P-glycoprotein and BCRP (breast cancer resistance protein), and glecaprevir is a substrate of OATP1B1/3. The combination has the potential for many drug interactions and concomitant use of atazanavir, atorvastatin, simvastatin, dabigatran, contraceptives containing ethinylestradiol, and rifampicin are contraindicated.

The recommended treatment course for patients who have not previously been treated for hepatitis C and do not have cirrhosis is eight weeks. Longer courses (12 or 16 weeks) are recommended for people who have received previous hepatitis C regimens or who have compensated cirrhosis (Child Pugh A).

This combination is not recommended for those with moderate hepatic impairment and it is contraindicated in severe impairment. However, it can be used in patients who have had a liver transplant. Dose adjustment is not needed in renal impairment or for patients on dialysis.

The combination of glecaprevir and pibrentasvir seems to offer most people with hepatitis C a tolerable, effective option for treatment regardless of which genotype they have, and whether or not they have severe renal impairment or liver cirrhosis. However, patients who have been previously treated with an NS3/4A protease inhibitor or an NS5A inhibitor or both are less likely to have a sustained response. In Australia, the combination is not indicated for those with genotype 1 infection who have been previously treated with regimens containing both of these drug classes such as elbasvir/grazoprevir or paritaprevir/ombitasvir. Prescribers need to be aware that glecaprevir/pibrentasvir has the potential to cause numerous drug interactions.

T T manufacturer provided additional useful information

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NEW DRUGS

Table **Efficacy of glecaprevir/pibrentasvir for chronic hepatitis C**

Genotype	Study	Duration (weeks)	Patient history	Response rate*
Patients without cirrhosis				
1	Surveyor-I (phase 2, open label)[1]	8	treatment naïve or experienced	97% (33/34)
	Endurance-1 (phase 3, open label)[2]	8	treatment naïve or experienced	99.1% (332/335)
		12	treatment naïve or experienced	99.7% (331/332)
2	Surveyor-II (phase 2, open label)[1]	8	treatment naïve or experienced	98% (53/54)
		12	treatment naïve or experienced	96% (24/25)
	Endurance-2 (double-blind, placebo controlled)[3]	12	treatment naïve or experienced	99.5% (201/202)
3	Surveyor-II (phase 2, open label)[1]	8	treatment naïve	97% (28/29)
		12	treatment naïve or experienced	93% (28/30)
		12	treatment experienced	92% (22/24)
	Surveyor-II, part 3 (phase 3, open label)[4]	12	treatment experienced	91% (20/22)
		16	treatment experienced	95% (21/22)
	Endurance-3 (phase 3, open label)[2]	8	treatment naïve	95% (149/157)
		12	treatment naïve	95% (222/233)
		12 (sofosbuvir + daclatasvir)	treatment naïve	97% (111/115)
4, 5, 6	Surveyor-I (phase 2, open label)[1]	12	treatment naïve or experienced	100% (34/34)
	Surveyor-II, part 4 (open label)[3]	8	treatment naïve or experienced	93% (54/58)
	Endurance-4 (open label)[3]	12	treatment naïve or experienced	99% (120/121)
Patients with cirrhosis				
1, 2, 4, 5, 6	Expedition-1 (phase 3, open label)[5]	12	treatment naïve or experienced	99% (145/146)
3	Surveyor-II, part 3 (phase 3, open label)[4]	12	treatment naïve	98% (39/40)
		16	treatment experienced	96% (45/47)

* The primary efficacy outcome in the studies was the proportion of patients with a sustained virologic response 12 weeks after the end of the treatment course.

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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.