

NEW DRUGS

New drugs



Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may be limited published data 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. As a result of fuller experience, initial comments may need to be modified. The Committee is prepared to do this. Before new drugs are prescribed, the Committee believes it is important that full information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

Telaprevir

Approved indication: hepatitis C

Incivo (Janssen-Cilag)

375 mg film-coated tablets

Australian Medicines Handbook section 5.4.3

Like boceprevir (Aust Prescr 2012;35:102), telaprevir is a protease inhibitor that can be added to standard treatment (peginterferon and ribavirin) for patients with hepatitis C genotype 1. It works by binding to the NS3 (non-structural 3) protease which is essential for viral replication.

The approval of telaprevir is based on safety and efficacy data from three phase III trials. Two trials were in previously untreated patients – ADVANCE¹ and ILLUMINATE² – and one in patients who had relapsed or failed to respond to previous treatment – REALIZE³. In each trial, telaprevir 750 mg (orally every eight hours) was added to peginterferon alfa 2a and ribavirin for 12 weeks. This was then followed by standard treatment alone for varying durations. The ADVANCE and REALIZE trials also included a control arm of placebo added to standard treatment.

Adding telaprevir compared to adding placebo significantly increased the rate of sustained virological responses in previously untreated and treated patients (ADVANCE and REALIZE trials).^{1,3} Similar responses to telaprevir were observed in the open-label ILLUMINATE trial (Table 1).²

In the trial of previously treated patients (REALIZE), sustained responses to telaprevir were more likely in people who had relapsed after previous treatment compared to those who had not responded or only partially responded to previous treatment (particularly those with cirrhosis) (Table 2).³ In many cases, distinct mutations in the viral protease were associated with treatment failure.

The most common adverse reactions (at least grade 2 in severity) to telaprevir were anaemia, pruritus, rash, nausea and diarrhoea in a cohort of 1346 people. Severe rash occurred in 4.8% of patients who added telaprevir compared to only 0.4% receiving standard treatment. Rashes can take several weeks to resolve and discontinuation of treatment and referral may be needed in severe cases. Stevens-Johnson syndrome and drug rash with eosinophilia and systemic symptoms have also been reported with telaprevir. Patients should be warned to report skin reactions.

Telaprevir increased the incidence of anaemia (haemoglobin <10 g/100 mL) compared to standard treatment alone (34% vs 14% of patients). Haemoglobin should therefore be measured at baseline and at least every four weeks. Reducing the dose of ribavirin may be needed to manage the anaemia.

Hyperbilirubinaemia, hyperuricaemia, hypokalaemia, decreased lymphocytes and platelet counts, and increased low-density lipoprotein and total cholesterol were more common with telaprevir than with standard treatment alone. With the exception of platelet counts, these had normalised by the end of treatment.

Following oral administration of telaprevir 750 mg, maximum plasma concentrations are reached after 4–5 hours. It is metabolised in the liver and is not recommended for patients with moderate to severe liver impairment or decompensated liver disease. Telaprevir and its metabolites are excreted mainly in faeces. Its elimination half-life is 4–4.7 hours.

Telaprevir is metabolised by cytochrome P450 (CYP) 3A4 and is a substrate for P-glycoprotein so there is a potential for many drug interactions. Contraindicated drugs include amiodarone, ergot alkaloids, simvastatin and atorvastatin, sildenafil (for pulmonary arterial hypertension), rifampicin, carbamazepine, phenytoin and phenobarbitone. As telaprevir increases the QT

Table 1 Patient responses to 12 weeks of telaprevir (added to standard treatment) for hepatitis C

Trial	Participants	Sustained virological response *	
		telaprevir	placebo
ADVANCE ¹	1088 previously untreated patients	75%	44%
ILLUMINATE ²	540 previously untreated patients	72%	–
REALIZE ³	662 previously treated patients	64–66%	17%

* proportion of patients who had undetectable viral RNA for six months after treatment

Table 2 The efficacy of telaprevir in previously treated patients³

Patients	Sustained virological response *	
	telaprevir	placebo
Previous relapse	83–88%	24%
Previous partial responders	54–59%	15%
Previous non-responders	29–33%	5%

* proportion of patients who had undetectable viral RNA for six months after treatment

interval, care should be taken when it is co-prescribed with other drugs that have a similar effect, such as methadone.

Telaprevir should be taken every eight hours with food. It should be started in combination with peginterferon and ribavirin and given for 12 weeks. If, however, viral RNA counts are above 1000 IU/mL after four weeks, telaprevir should be discontinued.

This drug is not recommended for patients who are co-infected with hepatitis B, and there are limited data in patients with HIV. Telaprevir with peginterferon and ribavirin is contraindicated in pregnancy, as ribavirin is teratogenic. Two forms of contraception are recommended for women, including partners of men taking telaprevir, during treatment and for four months after.

In patients with hepatitis C genotype 1, telaprevir significantly improves the rates of sustained virological responses when added to standard treatment. It is uncertain how telaprevir will compare to boceprevir. However, a meta-analysis comparing the two found that efficacy was comparable, but rash and pruritus were more common with telaprevir.⁴ Longer-term studies are needed to investigate telaprevir's effect on morbidity and mortality.

T manufacturer provided the product information

REFERENCES *†

1. Jacobson IM, McHutchison JG, Dusheiko G, Di Bisceglie AM, Reddy KR, Bzowej NH, et al. Telaprevir for previously untreated chronic hepatitis C virus infection. *N Engl J Med* 2011;364:2405-16.
2. Sherman KE, Flamm SL, Afdhal NH, Nelson DR, Sulkowski MS, Everson GT, et al. Response-guided telaprevir combination treatment for hepatitis C virus infection. *N Engl J Med* 2011;365:1014-24.
3. Zeuzem S, Andreone P, Pol S, Lawitz E, Diago M, Roberts S, et al. Telaprevir for retreatment for HCV infection. *N Engl J Med* 2011;364:2417-28.
4. Cooper CL, Druyts E, Thorlund K, Nachega JB, El Khoury AC, O'Regan C, et al. Boceprevir and telaprevir for the treatment of chronic hepatitis C genotype 1 infection: an indirect comparison meta-analysis. *Ther Clin Risk Manag* 2012;8:105-30.

The T-score (**T**) is explained in 'New drugs: T-score for transparency', *Aust Prescr* 2011;34:26-7.

* At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov).

† At the time the comment was prepared, a scientific discussion about this drug was available on the website of the European Medicines Agency (www.ema.europa.eu).