Paritaprevir/ritonavir/ombitasvir plus dasabuvir

Viekira Pak (AbbVie)
75 mg/50 mg/12.5 mg tablet plus 250 mg tablet

Paritaprevir/ritonavir/ombitasvir plus dasabuvir with ribavirin

Viekira Pak-RBV (AbbVie)
75 mg/50 mg/12.5 mg tablet plus 250 mg tablet with 200 mg tablet
75 mg/50 mg/12.5 mg tablet plus 250 mg tablet with 600 mg tablet

Aust Prescr 2016;39:141–3
http:/dx.doi.org/10.18773/austprescr.2016.045
First published online 20 May 2016

Approved indication: chronic hepatitis C
Australian Medicines Handbook section 5.5

The management of hepatitis C is rapidly changing with a move away from regimens containing interferon.[1] This new product contains four antiviral drugs, three of which are combined in one tablet. The product can also be packaged with ribavirin, so some patients will be treated with five drugs simultaneously.

Paritaprevir is a protease inhibitor aimed at the NS3/4A protease, which is essential for viral replication. Its plasma concentration is increased by combining it with ritonavir as this inhibits the metabolism of paritaprevir by cytochrome P450 3A4. Although ritonavir is an antiviral drug, it has no effect on the hepatitis C virus.

Ombitasvir acts on the NS5A protein which is also involved in viral replication. Dasabuvir is a non-nucleoside inhibitor of viral RNA polymerase. Ribavirin is a nucleoside analogue, but its mechanism of action against the hepatitis C virus is uncertain.

Two combined tablets of paritaprevir, ritonavir and ombitasvir are taken once a day while dasabuvir and ribavirin are taken twice a day. All these tablets should be taken with food. The four drugs are contraindicated in patients with severe hepatic impairment and their safety in patients with moderate impairment is unknown. No dose adjustment is recommended in renal impairment, but this would limit the use of ribavirin. The four- or five-drug regimen has the potential to interact with many other drugs including erythromycin, dabigatran, calcium channel blockers, frusemide, proton pump inhibitors and triazolam. There is a long list of contraindicated drugs which includes contraceptives containing ethinyloestradiol, simvastatin, salmeterol, antiepileptic drugs and St John's wort. As ribavirin is teratogenic it is contraindicated in pregnant women and men with pregnant partners. The safety of the four-drug regimen in pregnancy and lactation is unknown.

The regimens have been studied in untreated or previously treated patients with or without cirrhosis[2-6] (see Table). Patients were treated for 12 or 24 weeks with or without ribavirin. Efficacy was assessed as the proportion of patients who had a sustained virological response. This was defined as having a viral RNA concentration below 25 IU/mL 12 weeks after the end of treatment.

The Sapphire I trial involved 631 patients who were infected with hepatitis C genotype 1, but did not have

Table **Major efficacy trials of a four-drug regimen‡ for hepatitis C genotype 1**

Trial	Patients and treatment	Proportion achieving a sustained virological response§
Untreated patients without cirrhosis		
Sapphire I [2]	473 patients 4-drug regimen and ribavirin	96.2%
Pearl IV [4] (genotype 1a)	205 patients 4-drug regimen	90.2%
	100 patients 4-drug regimen and ribavirin	97%
Pearl III [4] (genotype 1b)	209 patients 4-drug regimen	99%
	210 patients 4-drug regimen and ribavirin	99.5%
Previously treated patients without cirrhosis		
Sapphire II [3]	297 patients 4-drug regimen and ribavirin	96.3%
Pearl II [5] (genotype 1b)	91 patients 4-drug regimen	100%
	88 patients 4-drug regimen and ribavirin	96.6%
Patients with cirrhosis		
Turquoise II [6]	208 patients 4-drug regimen and ribavirin	91.8%
	172 patients 4-drug regimen and ribavirin (24 weeks)	95.9%

‡ The four-drug regimen consisted of paritaprevir, ritonavir and ombitasvir plus dasabuvir given for 12 weeks (unless otherwise stated).
§ A sustained virological response is a concentration of hepatitis C RNA below 25 IU/mL 12 weeks after the end of treatment.

cirrhosis. One group of 473 patients was randomised to take the four-drug regimen with ribavirin for 12 weeks while 158 patients took a placebo regimen. Twelve weeks after their treatment concluded, 96.2% of the patients in the active treatment group had a virological response. Alanine aminotransferase returned to normal in 97% compared with 15% of those given placebo. Patients in the placebo group were later switched to a 12-week course of treatment. Both groups were to be followed up for 48 weeks after treatment to see if the virological response was sustained.[2]

The Sapphire II trial had a similar design but involved 394 patients who had not completely responded, or had relapsed following treatment with peginterferon and ribavirin. The active treatment was again the four-drug regimen plus ribavirin. Twelve weeks after 12 weeks of therapy, 96.3% of the 297 patients who took the active treatment had a sustained virological response.[3]

The Pearl trials compared the efficacy of the four-drug regimen with or without ribavirin in untreated and previously treated patients. All these trials studied 12 weeks of treatment. Twelve weeks after completing this treatment there was a sustained virological response in 90.2% of 205 people infected with genotype 1a who took the four-drug regimen. In the 100 patients who also took ribavirin the response rate was 97%.[4] For the 419 patients infected with genotype 1b the response rate was 99% without ribavirin and 99.5% with ribavirin.[4]

Pearl II was an open-label trial involving 179 patients whose previous treatments for genotype 1b had failed. The sustained virological response was 96.6% with ribavirin and 100% without.[5]

The Turquoise II trial investigated the five-drug regimen in 380 patients with mild (Child-Pugh class A) cirrhosis. Most of these patients had previously been treated with peginterferon and ribavirin. The patients were randomised to receive treatment for 12 or 24 weeks with efficacy assessed 12 weeks after the end of the course. The virological response was 91.8% with a 12-week course and 95.9% with a 24-week course. In previously untreated patients the response rate was 94–95%. Response rates were lower in patients who had not responded to previous therapy or had a history of injecting drugs.[6]

The five-drug regimen has also been tried in patients with hepatitis C genotype 1 and HIV infection. The Turquoise I trial randomised 31 patients to a 12-week course and 32 to a 24-week course. Most (65–69%) of the patients had not been previously treated for hepatitis C. Twelve weeks after treatment concluded the virological response rates were 94% for the 12-week course and 91% for the 24-week course. These regimens did not appear to lead to loss of control of the HIV infection.[7]

A small study has looked at patients who have recurrent infection with genotype 1 hepatitis C after liver transplantation. The 34 patients were treated with the five-drug regimen for 24 weeks. There was a virological response in 97% of the patients 12 weeks after treatment and this was sustained 24 weeks after treatment concluded.[8]

A problem with combination products is that it can be difficult to attribute adverse effects to a particular component. As there is previous experience with ritonavir and ribavirin, some adverse effects can be anticipated, but it may be harder to identify the adverse effects of paritaprevir, ombitasvir and dasabuvir when they are used in combination. While 1.2% of patients had to stop treatment because of adverse events, this was mainly in people treated with ribavirin. Only 0.3% of those taking the four-drug regimen had to discontinue.

The common adverse effects seen in the trials were fatigue, nausea, pruritus and insomnia. These symptoms tended to be more frequent when ribavirin was included in the regimen. Another adverse effect, which is probably due to ribavirin, is anaemia. This may cause problems in patients with cardiovascular disease. Suppression of the hepatitis C virus should see improvements in liver function tests, however, concentrations of alanine aminotransferase increase in some patients.

During the trials the virus developed drug resistance. This led to treatment failure in 3% of patients, usually presenting as a relapse after treatment concluded.

The efficacy of paritaprevir, ritonavir, ombitasvir and dasabuvir makes this combination suitable for treating patients infected with hepatitis C genotype 1b.[4,5] It may be possible to use this combination to treat patients infected with genotype 1a if they have not previously been treated and do not have cirrhosis, but the addition of ribavirin is needed to maximise the response.[4] While the five-drug regimen is very effective, it will require careful selection of patients and checking the product information to avoid drugs that either interact or are contraindicated. As the regimen involves three new drugs, unforeseen problems could emerge in the future. An alternative regimen of ledipasvir and sofosbuvir[9] may be easier to manage and avoids the adverse effects of ribavirin.

T T manufacturer provided additional useful information

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The Transparency score (T) is explained in 'New drugs: transparency', Aust Prescr 2014;37:27.

* 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).

A:

ANSWERS TO SELF-TEST QUESTIONS

1 True 2 False
3 True 4 False

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