NEW DRUGS

New drugs

Asunaprevir

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Approved indication: hepatitis C

Sunvepra (Bristol-Myers Squibb)
100 mg capsules
Australian Medicines Handbook section 5.5

Asunaprevir is a direct-acting antiviral drug for hepatitis C.[1] It works by inhibiting the viral non-structural 3/4A serine protease required for viral replication. Asunaprevir is indicated in combination with daclatasvir[2] for people with compensated liver disease, including cirrhosis. Daclatasvir is also a direct-acting antiviral and works by inhibiting the non-structural 5A protein involved in viral replication.

The safety and efficacy of asunaprevir (100 mg twice daily) with daclatasvir (60 mg daily) have been assessed in three main trials (see Table).[3-5] An open-label study of 643 patients with genotype 1b infection[3] enrolled three types of participants:

- treatment-naïve patients
- patients who had not responded or only partially responded to previous peginterferon and ribavirin
- patients intolerant to, and/or ineligible for, peginterferon and ribavirin (this included patients with depression, anaemia, or neutropenia, or compensated advanced fibrosis or cirrhosis with thrombocytopenia).

Patients with cirrhosis were present in all three groups (16%, 31% and 47%). After 24 weeks of asunaprevir and daclatasvir, most patients had a sustained virological response (see Table). This was defined as a viral RNA concentration less than the lower limit of quantification in serum 12 weeks after the end of treatment. Rates of sustained responses were similar in patients with cirrhosis and without cirrhosis (84% vs 85%). A high viral titre at baseline (≥800 000 IU/mL) or the presence of viral variants associated with non-structural 5A protein resistance predicted a poor response to treatment.[3]

Another open-label trial enrolled 222 patients with genotype 1b disease.[4] They were classified as non-responders to previous interferon and ribavirin or as intolerant to, or ineligible for, interferon-based

Table **Efficacy of asunaprevir (100 mg twice daily) and daclatasvir (60 mg daily) regimens in hepatitis C**

Study	Treatment regimen§	Viral genotype	Sustained virological response‡		
			Treatment-naïve patients	Treatment-experienced patients	Intolerance/ ineligible patients
Manns[3]	asunaprevir + daclatasvir	1b	90% (182/203)	82% (168/205)	82% (192/235)
Kumada[4]	asunaprevir + daclatasvir	1b	-	80% (70/87)	88% (119/135)
Jensen[5]	asunaprevir + daclatasvir + peginterferon + ribavirin	1 (including 1a and 1b)	-	Overall 93% (329/354) Patients with cirrhosis 90% (66/73)	-
Jensen[5]	asunaprevir + daclatasvir + peginterferon + ribavirin	4	-	Overall 98% (43/44) Patients with cirrhosis 95% (19/20)	-

‡ Defined as the proportion of patients with viral RNA less than the lower limit of quantification in serum measured 12 weeks after the end of treatment
§ Treatment given for 24 weeks

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.

treatment. They were given 24 weeks of asunaprevir and daclatasvir. Up to 88% of participants had a sustained viral response (see Table), including 20 of the 22 patients with cirrhosis.[4]

A third trial investigated asunaprevir and daclatasvir with peginterferon and ribavirin in 398 patients with genotype 1 or 4 infection.[5] Participants had been previously treated with peginterferon and ribavirin but had either not responded or had only partially responded. After 24 weeks of treatment with the new regimen, most of them had a sustained virological response (see Table).[5]

A preliminary trial of 75 people who were co-infected with HIV and hepatitis C (genotype 1 or 4) has also been conducted. Patients were all receiving raltegravir-based regimens. After 24 weeks of daclatasvir and asunaprevir with peginterferon and ribavirin, 96% of participants had a sustained virological response.[6]

In the safety cohort of 918 patients, the most common adverse events were headache (23%), fatigue (17%), diarrhoea (15%), nasopharyngitis (14%) and nausea (10%). In one of the trials, 10/643 patients discontinued because of an adverse event. Reasons included increased liver enzymes (7 patients) and prolonged QT interval (1 patient).[3] In another trial, 10/222 patients discontinued because of elevations in liver enzymes and one because of myasthenia gravis.[4] When peginterferon and ribavirin were added to daclatasvir and asunaprevir, 18/398 patients discontinued. The most common reasons were rash, malaise, neutropenia and vertigo (2 cases of each).[5]

Liver enzymes were elevated (at least 5 times the upper limit of normal) in 3–4% of patients and bilirubin was increased (at least 2.6 times the upper limit of normal) in 1% of patients. Liver enzymes and bilirubin concentrations should be monitored at least every two weeks for the first 12 weeks of treatment and then monthly after that until therapy is finished. Treatment should be stopped immediately if alanine aminotransferase increases tenfold or more, and if alanine aminotransferase increases fivefold or more with a total bilirubin increase of twofold or more.

Asunaprevir in combination with daclatasvir is not recommended in pregnancy as maternal and embryofetal toxicity has been observed with daclatasvir. The combination should only be used with adequate contraception. In animal studies, asunaprevir was excreted in breast milk and is not recommended during breastfeeding.

Asunaprevir can interact with the oral contraceptive pill and women receiving asunaprevir should be advised to take a pill containing at least 30 microgram of ethinylestradiol combined with norethisterone.

The safety and efficacy of asunaprevir in people who are co-infected with hepatitis B have not been established as these patients were generally excluded from the trials.

Resistance to daclatasvir can occur. If patients experience an increase in viral RNA during treatment, their treatment should be reviewed to ascertain if resistance is a factor.

The recommended dose of asunaprevir is 100 mg twice daily. The dose should be reduced to once daily in patients with renal impairment (creatinine clearance <30 mL/min). Although asunaprevir is indicated for patients with compensated liver disease (including cirrhosis), it is contraindicated in those with moderate to severe hepatic impairment or decompensated liver disease.

After oral administration, peak plasma concentrations are reached in 1–4 hours and steady state is reached after seven days. The dose is extensively metabolised.

Asunaprevir and daclatasvir are metabolised by cytochrome P450 (CYP) 3A and asunaprevir is a moderate inhibitor of CYP2D6 so there is a potential for numerous drug interactions. The combination is contraindicated with moderate and strong inducers of CYP3A, such as phenytoin, carbamazepine, rifampicin, dexamethasone and St John's wort as these drugs may reduce asunaprevir and daclatasvir concentrations. CYP3A inhibitors such as ketoconazole, clarithromycin, verapamil, and several HIV drugs are also contraindicated. Organic anion transporting polypeptide 1B1 (OATP 1B1) is involved in the distribution of asunaprevir in the liver so strong inhibitors of this transporter are contraindicated (e.g. rifampicin, cyclosporin and gemfibrozil). Other drugs that may interact include dabigatran, tricyclic antidepressants, dextromethorphan, digoxin, midazolam and statins.

Asunaprevir appears to be effective when used in combination with daclatasvir in patients with genotype 1b disease, and with daclatasvir, peginterferon and ribavirin in those with genotype 1 or 4. This included those who had not adequately responded to previous treatments and patients with cirrhosis. Preliminary results suggest it is also effective in patients co-infected with HIV. However, there are numerous potential drug interactions with asunaprevir and daclatasvir and the product information should be consulted before prescribing. In short, concomitant use of many CYP3A inducers and inhibitors are contraindicated, as are inhibitors of the OATP 1B1 transporter. Other co-administered drugs may need close monitoring or dose adjustment.

T manufacturer provided the product information

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Idelalisib

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Approved indication: chronic lymphocytic leukaemia, follicular lymphoma

Zydelig (Gilead)
100 mg and 150 mg tablets
Australian Medicines Handbook section 14.2.4

Like ibrutinib,[1] idelalisib is an oral anticancer drug that targets B-cell cancers. It works by inhibiting phosphatidylinositol 3-kinase. This enzyme is overactive in B-cell cancers and is involved in driving proliferation, migration and survival of malignant cells.

Idelalisib is registered for two indications:

- in combination with rituximab for chronic lymphocytic leukaemia and small lymphocytic lymphoma when chemotherapy is not suitable, in people who have relapsed after treatment or have the chromosome 17p deletion or TP53 mutation
- monotherapy for refractory follicular lymphoma.

Chronic lymphocytic leukaemia

The approval of idelalisib for relapsed chronic lymphocytic leukaemia is based on a pivotal phase III trial of 220 patients.[2] The median age of randomised patients was 71 years. Two-thirds of them had advanced disease and the median time since initial diagnosis was nine years. Patients were heavily pre-treated (regimens included rituximab, cyclophosphamide, fludarabine and bendamustine) and were considered too unwell for chemotherapy.

In total, 80% of the patients lacked somatic hypermutation of the gene encoding the immunoglobulin heavy-chain variable region, and 40% carried the 17p deletion or TP53 mutation. These genetic characteristics are generally associated with poorer outcomes.

Patients received intravenous rituximab with either oral idelalisib or placebo. After 24 weeks, the rate of progression-free survival was significantly higher with idelalisib than with placebo ($p<0.001$, see Table 1). The overall response rate, assessed using serial CT or MRI of the neck, chest, abdomen and pelvis, was significantly higher in the idelalisib group compared to the placebo group (81% vs 13%, $p<0.001$). These were all partial responses.[2]

Idelalisib was also better than placebo in subgroup analyses of patients with unmutated immunoglobulin

Table 1 **Efficacy of idelalisib in relapsed chronic lymphocytic leukaemia** [2]

Outcome	Idelalisib‡ plus rituximab§ (110 patients)	Placebo plus rituximab§ (110 patients)
Progression-free survival after 24 weeks	93%	46%
Median duration of progression-free survival	Not reached	5.5 months
Overall survival after one year	92%	80%
Overall response rate (all partial responses)#	81% (of a total of 88 patients that could be evaluated)	13% (of a total of 88 patients that could be evaluated)

‡ Oral idelalisib 150 mg twice a day
§ Intravenous rituximab 375 mg/m^2 body surface area, followed by 500 mg/m^2 body surface area every 2 weeks for 4 doses and then every 4 weeks for 3 doses, for a total of 8 infusions
# Assessed using serial CT or MRI of the neck, chest, abdomen and pelvis