Japanese trial of patients who were intolerant to or ineligible for interferon, 10 patients discontinued because of elevations in liver enzymes and one because of myasthenia gravis.[6] When peginterferon and ribavirin were added to daclatasvir and asunaprevir, 18 patients discontinued. The most common reasons were rash, malaise, neutropenia and vertigo (2 cases of each).[7]

Cardiac arrhythmias, including severe bradycardia, have been reported in patients taking amiodarone with daclatasvir and sofosbuvir, so close monitoring is recommended with this combination.

Daclatasvir should not be used in pregnancy. In animal studies, it has been shown to cross the placenta, and maternal and embryofetal toxicity have been observed at high doses. Contraception should be used during treatment and for five weeks afterwards. Daclatasvir is also excreted in milk and breastfeeding is not recommended.

The safety and efficacy of daclatasvir 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, the regimen should be discontinued.

Drug interactions

Daclatasvir is mainly metabolised by cytochrome P450 (CYP) 3A4. It is contraindicated in combination with strong inducers of CYP3A4 (e.g. phenytoin, carbamazepine, rifampicin, dexamethasone and St John's wort), as these drugs may lower daclatasvir exposure. The daily daclatasvir dose should be increased to 90 mg with moderate CYP3A4 inducers. Conversely, the dose should be reduced to 30 mg per day with strong CYP3A4 inhibitors (e.g. clarithromycin, boceprevir, telaprevir, atazanavir, ritonavir, ketoconazole).

As daclatasvir inhibits P-glycoprotein, co-administered digoxin and other P-glycoprotein substrates with a narrow therapeutic index, such as dabigatran, should be used with caution. Care is also urged with the statins as rosuvastatin concentrations are increased with daclatasvir.

Conclusion

In general, daclatasvir-containing regimens were very effective at clearing hepatitis C virus in patients with chronic disease. This included those who had not adequately responded to previous treatments and patients who were co-infected with HIV. With the daclatasvir and sofosbuvir combination, adding ribavirin did not seem to give further benefit. Patients with genotype 3 infection who had cirrhosis were less likely to have a sustained response after 12 weeks of daclatasvir and sofosbuvir compared to those who did not have cirrhosis. This combination was not assessed in patients with genotype 1 disease and cirrhosis. The combination of daclatasvir and asunaprevir (with or without peginterferon and ribavirin) was effective in a range of patients with genotype 1 or 4 infection.

Daclatasvir regimens were generally well tolerated but prescribers should be mindful of adverse reactions to other drugs in the treatment regimen. As daclatasvir is metabolised by CYP3A4, there are numerous drug interactions that need to be considered. Most importantly, concomitant use of strong CYP3A4 inducers is contraindicated as this may reduce the efficacy of daclatasvir.

T T manufacturer provided additional useful information

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Ledipasvir with sofosbuvir

Approved indication: hepatitis C
Harvoni (Gilead)
90 mg/400 mg tablets
Australian Medicines Handbook section 5.5

Sofosbuvir (Aust Prescr 2014;37:177-8) is a nucleotide analogue antiviral drug that is used in combination with other drugs to treat chronic hepatitis C. As the effectiveness of regimens containing interferon can be limited by adverse effects, there is interest in studying other drugs to use in combination with sofosbuvir.

Ledipasvir is an antiviral drug aimed at a protein (NS5A) in the hepatitis C virus. As this protein is

involved in viral replication, ledipasvir will reduce the amount of virus in infected patients. Ledipasvir is rapidly absorbed. As the solubility of ledipasvir is pH-dependent, antacids, proton pump inhibitors and H_2-receptor antagonists can decrease absorption. Ledipasvir is minimally metabolised with most of the dose being excreted unchanged in the faeces. The median half-life is 47 hours. No dose adjustment is required in patients with hepatic impairment.

The fixed-dose combination of ledipasvir and sofosbuvir has mainly been studied in patients with genotype 1 infection. Its approval is based on open-label clinical trials which assessed the virological response (see Table). A sustained virological response was defined as a viral RNA in the patient's serum below 25 IU/mL 12 weeks after the end of treatment. However, the World Health Organization has previously considered a sustained response to be the absence of viral RNA six months after the end of treatment.

In ION-1, 865 previously untreated patients were randomised to take the combination, with or without ribavirin, in either 12- or 24-week regimens. There was a sustained viral response in 97–99% of the patients. This response was achieved by 94–100% of the patients who had cirrhosis (16% of the trial participants).[1]

The ION-2 trial used the same four treatment regimens as ION-1, but studied 440 patients who had not responded to other treatments for genotype 1 infections. Approximately 20% of these patients had cirrhosis. Twelve weeks after completing 12 weeks of treatment, there was a virological response of 94–96%. In patients who were treated for 24 weeks a viral RNA below 25 IU/mL was achieved in 99%. The response rate was significantly lower in patients with cirrhosis who were treated for 12 weeks compared with 24 weeks (82–86% vs 100%).[2]

The ION-3 trial assessed the efficacy of a shorter treatment regimen in previously untreated patients without cirrhosis. It randomised 647 patients to take the combination of ledipasvir and sofosbuvir, with or without ribavirin, for eight weeks, or the combination alone for 12 weeks. There was a sustained virological response in 94% of the patients who took the combination for eight weeks (93% with ribavirin) compared with 95% who took it for 12 weeks.[3] An eight-week regimen can therefore be considered in previously untreated patients without cirrhosis who have pre-treatment viral RNA concentrations below 6 million IU/mL.

ION-4 was an open-labelled study involving 335 patients who were infected with hepatitis C virus and HIV. Using a 12-week regimen, a sustained response against hepatitis C was achieved by 96% of the patients. Results were similar irrespective of the treatments used for HIV in the trial, and whether or not the patients had cirrhosis.[4]

Less than 1% of the patients treated with ledipasvir and sofosbuvir had to stop treatment because of adverse effects. Without ribavirin, the most frequent adverse events with the combination were fatigue, headache, nausea and insomnia. There are no human data in pregnancy and lactation, but the combination had no effect on fetal development in animal studies.

Drug interactions can occur with one or both components of the combination, so it is best to check the product information before prescribing. Its efficacy could be reduced by inducers of P-glycoprotein such as rifampicin and St John's wort. There is a potentially fatal interaction with amiodarone. Other interactions include digoxin, antiepileptic drugs, and statins particularly rosuvastatin. There is no known interaction with oral contraception.

Resistance to ledipasvir can develop during treatment. This should be considered in patients who do not have a sustained virological response.

Table **Efficacy of ledipasvir and sofosbuvir in hepatitis C**

Trial	Patients	Sustained virological response for patients taking 12-week regimens ‡	
		Ledipasvir/sofosbuvir	Ledipasvir/sofosbuvir plus ribavirin
ION-1[1]	865 previously untreated patients	99% (211/214)	97% (211/217)
ION-2[2]	440 previously treated patients	94% (102/109)	96% (107/111)
ION-3[3]	647 previously untreated patients without cirrhosis	95% (206/216)	-
ION-4[4]	335 patients coinfected with HIV	96% (322/335)	-

‡ Primary outcome was the proportion of patients who had no quantifiable RNA in their sera 12 weeks after treatment

A once-daily, interferon-free treatment, which in most cases only needs to be taken for 12 weeks, that has very high efficacy is an advance. While further research is needed for other genotypes, the combination of ledipasvir and sofosbuvir is probably the treatment of choice for genotype 1 hepatitis C infection in 2015. However, until similar antiviral drugs arrive, cure comes with a high cost.[5] The Pharmaceutical Benefits Advisory Committee estimates that the cost of treatment in Australia will exceed $3 billion over five years.[6]

T manufacturer provided the product information

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Ponatinib

Approved indication: chronic myeloid leukaemia, acute lymphoblastic leukaemia

Iclusig (Ariad Pharmaceuticals)

15 and 45 mg film-coated tablets

Australian Medicines Handbook section 14.2.3

Along with imatinib (Aust Prescr 2001;24:129), dasatinib (Aust Prescr 2007;30:50-5) and nilotinib (Aust Prescr 2008;31:49-55), ponatinib is a tyrosine kinase inhibitor for patients who have leukaemia with the Philadelphia chromosome (Ph). This chromosome results in an abnormal tyrosine kinase that causes uncontrolled growth of malignant cells. Almost all patients with chronic myeloid leukaemia and approximately 20–25% of those with acute lymphoblastic leukaemia have the chromosome.

Ponatinib is indicated for patients with chronic myeloid leukaemia who are resistant or intolerant to at least two previous tyrosine kinase inhibitors, or have the T315I mutation. Patients with this mutation are resistant to imatinib, dasatinib and nilotinib.

Ponatinib is also indicated for those with Ph-positive acute lymphoblastic leukaemia who are resistant or intolerant to dasatinib, cannot be given imatinib or have the T315I mutation.

The approval of ponatinib is primarily based on a phase II, single-arm trial. The study enrolled 449 people with chronic myeloid leukaemia (n=417) or Ph-positive acute lymphoblastic leukaemia (n=32). Almost all of the patients had experienced treatment failure with imatinib.[1]

Patients were started on ponatinib 45 mg once a day. Those with chronic myeloid leukaemia were grouped into cohorts according to whether they had chronic-, accelerated- or blast-phase disease. The primary end point for those with chronic-phase disease was a major cytogenetic response (when the proportion of Ph-positive white blood cells has fallen to 35% or less) within the first 12 months. For patients with accelerated- and blast-phase chronic myeloid leukaemia or Ph-positive acute lymphoblastic leukaemia, the primary end point was a major haematological response (normal number of white blood cells or no evidence of leukaemia) in the first six months.[1]

Just over half of the patients with chronic- and accelerated-phase chronic myeloid leukaemia responded to treatment. Response rates were lower in people with blast-phase chronic myeloid leukaemia and Ph-positive acute lymphoblastic leukaemia (see Table). Pre-specified subgroup analyses revealed that fewer previous treatments, younger age and shorter duration between diagnosis and treatment tended to predict a better response to ponatinib.[1]

Adverse reactions were very common in the trial with 67% of patients having at least one dose interruption because of an adverse event. The most common treatment-related events (any grade) were thrombocytopenia (37% of patients), rash (34%), dry skin (32%), vascular occlusion (23%), abdominal pain (22%), neutropenia (19%) and anaemia (13%).[1] Infections occurred in over half of the people who received ponatinib – these were serious in 20% of cases and some were fatal.

Serious adverse events (grade 3 or 4) included pancreatitis (5%), abdominal pain (2%), increased lipase (2%), thrombocytopenia (2%), diarrhoea (1%), fever (1%), myocardial infarction (1%), anaemia (1%), neutropenia (1%), febrile neutropenia (1%) and pancytopenia (1%).[1] Thrombocytopenia was the most common reason for treatment interruption.

During the study, 18/449 patients died. Five deaths were thought to be related to treatment and were a result of pneumonia, fungal pneumonia, gastric haemorrhage, acute myocardial infarction and cardiac arrest. Other deaths deemed unrelated to