NEW DRUGS

Elbasvir/grazoprevir

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Approved indication: hepatitis C

Zepatier (MSD)
tablets containing elbasvir 50 mg and grazoprevir 100 mg
Australian Medicines Handbook section 5.5

The management of chronic hepatitis C is rapidly changing, with newer regimens containing direct-acting antivirals without interferon.[1] This product is a fixed-dose combination tablet of elbasvir and grazoprevir indicated for people with hepatitis C genotypes 1 or 4.

Elbasvir inhibits the NS5A protein involved in the production and assembly of virus particles, and grazoprevir inhibits the NS3/4A protease involved in viral replication. After oral administration, peak plasma concentrations are reached within 2–3 hours. Steady-state concentrations are reached after six days of once-daily dosing. Almost all of the dose is excreted in the faeces as metabolites.

The approval of this combination is based on several trials in treatment-naïve and treatment-experienced patients infected with genotypes 1, 4 and 6. Studies included people co-infected with HIV, those with chronic kidney disease and people receiving opioid substitution therapy (see Table).[2-7] To be enrolled, patients had to have at least 10^4 IU/mL of hepatitis C viral RNA in their blood at baseline. Liver cirrhosis was allowed but those with decompensated liver disease were excluded from the trials.

The primary measure of effectiveness in the trials was the proportion of patients who achieved a sustained virologic response. This was defined as undetectable viral RNA in a blood test 12 weeks after the end of treatment (SVR12).

In the C-EDGE trial, which enrolled people who had not received previous treatment for hepatitis C, almost 95% of participants had a sustained virologic response to 12 weeks of treatment with elbasvir/grazoprevir.[2] Response rates were 92% (144/157) with genotype 1a, 99% (129/131) with genotype 1b, 100% (18/18) with genotype 4 and 80% (8/10) with genotype 6. Similarly high response rates were seen in treatment-naïve patients co-infected with HIV (C-EDGE CO-INFECTION).[3] In both trials, cirrhosis and high viral load at baseline did not seem to affect response rates.

Response rates to elbasvir/grazoprevir were high in patients who had failed on previous therapy with peginterferon/ribavirin (C-EDGE TE). Extending therapy to 16 weeks and adding ribavirin increased the response rate from 92% to 98%.[4]

Adding ribavirin to elbasvir/grazoprevir was also very effective in those who had failed previous therapy with peginterferon/ribavirin combined with boceprevir, telaprevir or simeprevir (C-SALVAGE).[5]

Another trial enrolled patients with stage 4 or 5 chronic kidney disease (C-SURFER) – 76% of participants were dependent on haemodialysis and 81% had stage 5 chronic kidney disease. After 12 weeks of treatment with elbasvir/grazoprevir, 94% had a sustained virologic response.[6]

In a trial of patients receiving opioid substitution therapy (C-EDGE CO-STAR), 92% had a sustained virologic response following a 12-week course of elbasvir/grazoprevir.[7]

Resistance to elbasvir/grazoprevir was observed in the trials. This was associated with single amino acid substitutions in the NS5A and NS3/4A proteins.

Fatigue, headache and nausea were the most common adverse effects in people taking elbasvir/grazoprevir,[2] including those co-infected with HIV[3] and those with advanced chronic kidney disease.[6] In patients who received the combination with ribavirin, anaemia was also common (14.8% of patients).[4]

Alanine aminotransferase elevations greater than five times the upper limit of normal occurred in 0.77% of patients given elbasvir/grazoprevir with or without ribavirin. Onset was generally eight weeks after starting treatment and usually resolved with ongoing therapy. Elevated bilirubin was also observed, often in those given ribavirin (6% of patients). Elbasvir/grazoprevir is contraindicated in moderate and severe hepatic impairment.

Both elbasvir and grazoprevir are partially metabolised by oxidation, primarily by cytochrome P450 (CYP) 3A, so there are numerous potential drug interactions. Strong inducers of CYP3A, such as the HIV drug efavirenz, phenytoin, carbamazepine and St John's wort, are contraindicated as they can reduce the concentrations of elbasvir and grazoprevir. Grazoprevir is also a substrate of OATP1B and co-administration with drugs that inhibit this transporter, such as cyclosporin and HIV drugs atazanavir, darunavir, lopinavir, saquinavir and tipranavir, may cause alanine aminotransferase elevations due to the increase in grazoprevir exposure. Interactions with other drugs may require dose changes and the product information should be consulted. For example, elbasvir/grazoprevir increases exposure to co-administered atorvastatin so the daily statin dose should not exceed 20 mg.

Table **Efficacy of elbasvir/grazoprevir with or without ribavirin in chronic hepatitis C**

Trial	Patient characteristics	Genotype	Treatment arm (duration)*	Efficacy – patients with SVR12
C-EDGE[2] (double-blind)	Treatment-naïve patients	1, 4, 6	elbasvir/grazoprevir (12 weeks)	94.6% (299/316)
C-EDGE CO-INFECTION[3] (open-label)	Treatment-naïve patients co-infected with HIV	1, 4, 6	elbasvir/grazoprevir (12 weeks)	96.3% (210/218)
C-EDGE TE[4] (open-label)	Previous treatment failure with peginterferon/ribavirin, with or without HIV co-infection	1, 4, 6	elbasvir/grazoprevir (12 weeks)	92.4% (97/105)
			elbasvir/grazoprevir+ribavirin (12 weeks)	94.2% (98/104)
			elbasvir/grazoprevir (16 weeks)	92.4% (97/105)
			elbasvir/grazoprevir+ribavirin (16 weeks)	98.1% (104/106)
C-SALVAGE[5] (open-label)	Previous treatment failure with peginterferon/ribavirin in combination with boceprevir, telaprevir or simeprevir	1	elbasvir/grazoprevir+ribavirin (12 weeks)	96.2% (76/79)
C-SURFER[6] (double-blind)	Stage 4 or 5 chronic kidney disease, treatment-naïve or experienced (previous treatment failure with peginterferon with or without ribavirin)	1	elbasvir/grazoprevir (12 weeks)	94.3% (115/122)
C-EDGE CO-STAR[7] (double-blind)	Treatment-naïve patients with or without cirrhosis receiving opioid substitution therapy	1, 4, 6	elbasvir/grazoprevir (12 weeks)	91.5% (184/201)

* elbasvir 50 mg and grazoprevir 100 mg given once-daily and ribavirin given twice-daily
SVR12 sustained virologic response 12 weeks after the end of treatment

The recommended elbasvir/grazoprevir dose for previously untreated patients or those who have relapsed since finishing a previous course is one tablet a day for 12 weeks. In patients who have had a null or partial response, or viral breakthrough during previous treatment, ribavirin should be added. This treatment should be given for 12 weeks in those with genotype 1b infection and for 16 weeks in those with 1a or 4 infection. Patients with severe renal impairment or end-stage renal disease should not be given ribavirin.

There have been no studies of the elbasvir/grazoprevir combination in pregnant women. Studies of high doses in rats and rabbits found no adverse effects on fetal development. It is not known if elbasvir and grazoprevir are excreted in human milk, however, in preclinical studies both drugs were excreted in lactating rats. No adverse effects were seen on nursing pups.

If ribavirin is added to elbasvir/grazoprevir, female patients and female partners of male patients must use contraception during and for six months after the end of treatment.

This fixed-dose combination of elbasvir and grazoprevir was very effective and generally well tolerated in people with chronic hepatitis C genotype 1 or 4. It seems to be suitable for people with HIV infection or advanced kidney disease. However, similar to paritaprevir/ritonavir/ombitasvir plus dasabuvir,[8] it is contraindicated in people with moderate to severe hepatic impairment. Other regimens such as ledipasvir with sofosbuvir[9] may be more suitable for these patients. The elbasvir/grazoprevir combination has numerous potential drug interactions, particularly with HIV medicines.

T T manufacturer provided additional useful information

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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.