Research Review
PRODUCT REVIEW

Elbasvir/Grazoprevir in the Treatment of Chronic Hepatitis C Virus Infection

About the Reviewer

Assoc. Prof. Catherine Stedman
MBChB, FRACP, PhD

Catherine is Associate Professor of Medicine at the University of Otago, Christchurch, and Consultant Gastroenterologist and Hepatologist in the Gastroenterology Department, Christchurch Hospital. She completed FRACP specialist training in both gastroenterology and clinical pharmacology in Christchurch and Sydney, and PhD studies in molecular pharmacology and hepatology at the University of Sydney, together with a clinical fellowship at Westmead Hospital, and research projects at the Salk Institute (California). Catherine has been principal investigator for over 50 HCV clinical trials from phase 1 through to phase 3, and a significant contributor to several pivotal proof-of- concept interferon-free trials for hepatitis C treatment.

This review summarises important pharmacological and clinical characteristics of elbasvir/grazoprevir (Zepatier®), which is an orally-administered fixed-dose combination direct-acting anti-viral agent for use in the treatment of hepatitis C viral infection. In New Zealand, elbasvir/grazoprevir is registered with Medsafe and is in the reimbursement process.

HCV infection

Hepatitis C virus (HCV) infection is a major societal health problem in NZ and most other countries.[1,2]

The latest estimate of total global HCV prevalence is 2.5% (range: 1.3-2.9%), or 177.5 million HCV-infected individuals.[2] The exact prevalence of HCV in NZ is unclear because many cases are underdiagnosed and only acute infection is notifiable.[3] Based on more accurate Australian epidemiological data indicating an HCV prevalence of 1.3%, it has been estimated that 54,000 New Zealanders are living with current or past HCV infection.

Acute infection leads to chronic infection in approximately 60–85% of infected individuals.[4] Chronic infection can progress to chronic liver disease, cirrhosis, end-stage liver disease, and even hepatocellular carcinoma (HCC).[4,5] It is also a major indication for liver transplantation. An estimated 20%–30% of people with chronic HCV will develop cirrhosis, generally after 20–30 years of infection.[4] It is not surprising therefore that while the prevalence of HCV infection in NZ may have already peaked (in 2010), due to a reduction in injecting drug use and improved harm reduction measures among people who inject drugs (PWID), the burden of HCV infection will continue to grow with the peak prevalence of cirrhosis predicted to occur after 2030.[3]

High-risk groups include the middle-aged and PWID. Most chronic HCV infections occur in individuals aged 40–60 years, making this group at highest risk of advanced liver disease and hence in greatest need of treatment.[3,6] In NZ, an HCV prevalence of 3.3–4% has been found in this age group in a single-urban centre study.[6] With the introduction of routine screening of donated blood in 1992, intravenous drug use has supplanted blood transfusion as the major mode of HCV transmission. HCV prevalence in PWID is known to be high.[7] In NZ, the prevalence of HCV infection in PWID receiving opioid substitution therapy is 75%.[8,9]

HCV genotype helps to inform the clinical management of patients with HCV infection. HCV genotype 1 is the most prevalent form of HCV worldwide (49.1%), followed by genotype 3 (17.9%), genotype 4 (16.8%), and genotype 2 (11.0%), with genotype 5 and genotype 6 responsible for the remaining <5%.[2] The genotype prevalence pattern appears to differ somewhat in Australasia. Based on combined Australian and NZ data, the most common HCV genotype is 1 (55.0%) followed by genotype 3 (36.0%) and genotype 2 (6.6%), with minimal percentages of genotypes 4 and 6 having been found and no genotype 5 cases yet identified.

It has been estimated that treatment uptake and cure rates for HCV infection in NZ are worryingly low.[3] Suboptimal rates of treatment and cure are likely due, in large part, to the toxicity and limited efficacy of interferon (INF)-based antiviral therapy.[3,10] Under-treatment and the aging-cohort effect, resulting in an increasing burden of disease related to HCV infection, emphasise the need for more effective treatments that are better tolerated.

HCV treatment and DAAs

Except for those with reduced life expectancy (<12 months) due to non-liver or non-HCV-related comorbidities, all people living with HCV should be considered for treatment.[10] The goal of treatment is cure, or sustained virologic response (SVR), which is defined as undetectable plasma HCV RNA at least 12 weeks after treatment has ceased (SVR12). People co-infected with HIV and HCV have higher HCV RNA loads and are at increased risk of severe liver disease compared with mono-infected patients.[11,12] As HCV eradication can prevent progression of liver disease and its complications, people with HIV/HCV co-infection should be prioritised for treatment of HCV.[10]

Direct-acting antiviral (DAA) agents, which target specific HCV proteins, were first approved for the treatment of HCV infection in 2011.[13] They have proven to be highly effective and well tolerated, and require a short treatment duration.[13-15] In fact, it is with the advent of DAAs that HCV cure has become a realistic clinical goal. Importantly, almost all patients are suitable for DAA therapy, including those previously intolerant of or ineligible for IFN-based regimens.

A modelling analysis based on NZ epidemiological data has demonstrated that a combination of increased treatment uptake and higher efficacy therapies will reduce HCV infection-related morbidity and mortality.[3] Widespread access to effective and well tolerated oral DAAs has the potential to halt the future transmission of the HCV and eliminate HCV infection as a major public health issue in NZ.

Elbasvir/grazoprevir

Elbasvir/grazoprevir (Zepatier®) is the most recent of the fixed-dose combination DAA agents to become available. Oral elbasvir/grazoprevir 50/100 mg once daily is approved in NZ for the treatment of adults with chronic HCV genotypes 1, 3 (only in combination with sofosbuvir), or 4 infection.[16]

The following is an overview of the key clinical and pharmacological properties of elbasvir/grazoprevir. For full details

of its pharmacology, drug interactions, contraindications, and recommended dosage and administration, the elbasvir/grazoprevir Data Sheet should be consulted.

Mechanism of action

Elbasvir is an inhibitor of the HCV NS5A protein, which is required for HCV RNA replication and viron assembly.[16] Grazoprevir is an inhibitor of the HCV NS3/4A protease, which cleaves the HCV-encoded polyprotein that is required for viral replication. The combination of two DAAs with distinct mechanisms of action targets the HCV at multiple steps in its lifecycle.

Pharmacokinetics

Following oral administration, peak plasma concentrations are reached at approximately 3 hours for elbasvir and 2 hours for grazoprevir.[16] Concentrations of elbasvir and grazoprevir reach steady-state within approximately 6 days. Administration of elbasvir/grazoprevir with a high-fat meal results in reduced exposure to elbasvir and increased exposure to grazoprevir. However, the differences are not considered clinically relevant and elbasvir/grazoprevir can be taken without regard to food.

Elbasvir and grazoprevir are highly plasma protein bound (both >98%), and plasma protein binding is not meaningfully altered by hepatic or renal impairment.[16] Elbasvir distributes into most tissues, including the liver, whereas grazoprevir distributes mainly into the liver.

Elbasvir and grazoprevir are partially eliminated by oxidative metabolism, predominantly by the cytochrome P450 3A4 system, with no metabolites of either agent detected in human plasma.[16] Elimination half-lives for elbasvir and grazoprevir are 24 and 31 hours, respectively, which allows for once-daily dosing. The primary route of elimination of both agents is through faeces.

Drug-drug interactions

The potential for drug-drug interactions (DDIs) should be considered for all IFN-free treatment regimens.[10] Important candidates for potential interactions with DAAs include proton pump inhibitors, H2-blockers, antacids, statins, St John's wort, antimicrobials, anti-epileptic agents, immunosuppressive agents, and antiretroviral therapy (ART) agents.

Elbasvir/grazoprevir is contraindicated in patients taking inhibitors of organic anion transporting polypeptides (OATP) 1B (e.g. atazanavir, cyclosporine). Grazoprevir is a substrate of OATP1B and co-administration of elbasvir/grazoprevir with OATP1B inhibitors may lead to clinically relevant increases of grazoprevir plasma concentrations.[16]

Elbasvir/grazoprevir is also contraindicated with strong cytochrome P450 3A4 inducers (e.g. rifampin, phenytoin, carbamazepine, St John's Wort) or efavirenz secondary to reduced concentrations and reduced therapeutic effects of elbasvir and grazoprevir with co-administration.[16]

Use of elbasvir/grazoprevir with moderate cytochrome P450 3A4 inducers (e.g. bosentan, etravirine, modafinil, nafcillin) is not recommended because co-administration may reduce elbasvir and grazoprevir plasma concentrations leading to reductions in therapeutic effects of elbasvir/grazoprevir.[16]

Co-administration of elbasvir/grazoprevir with strong cytochrome P450 3A4 inhibitors (e.g. ketoconazole and ritonavir) is not recommended as it may lead to elevated plasma concentrations of elbasvir and grazoprevir and increased risk of hepatotoxicity.[16]

Concomitant use of elbasvir/grazoprevir with the fixed-dose combination of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate or alafenamide is not recommended as co-administration may result in increases in elbasvir and grazoprevir plasma concentrations.[16]

Administration of elbasvir/grazoprevir with tacrolimus may result in elevated concentrations of tacrolimus; therefore, tacrolimus whole blood concentrations should be frequently monitored.[16]

Caution is advised if using elbasvir/grazoprevir with HMG-CoA reductase inhibitors (atorvastatin, rosuvastatin, fluvastatin, lovastatin, or simvastatin) as co-administration may increase the concentrations of these statins.[16] The lowest dose HMG-CoA reductase inhibitor possible should be used if this drug combination is necessary.

No dose adjustments are needed when elbasvir/grazoprevir is co-administered with proton pump inhibitors, H2-blockers, antacids, buprenorphine/naloxone, digoxin, dolutegravir, methadone, mycophenolate mofetil, oral contraceptive pills, phosphate binders, pitavastatin, pravastatin, prednisone, raltegravir, ribavirin, rilpivirine, tenofovir disoproxil fumarate, and sofosbuvir.[16] In addition, clinically-relevant DDIs are not expected when elbasvir/grazoprevir is co-administered with abacavir, emtricitabine, entecavir, and lamivudine.

Dosage and administration

Zepatier® is a fixed-dose tablet containing 50mg of elbasvir and 100mg of grazoprevir that is given once daily.[16] It is given with or without ribavirin for 12 or 16 weeks, depending on HCV genotype, previous treatment, and presence of baseline polymorphisms (resulting in variability in response).

Dosage reductions are not required in patients with mild, moderate, or severe renal dysfunction. No dosage adjustment is required in patients who are on dialysis.[16]

Dosage reduction is not required in patients with mild hepatic impairment.[16] However, elbasvir/grazoprevir is contraindicated in patients with moderate (Child-Pugh B) or severe hepatic impairment (Child-Pugh C).

Liver function tests should be performed prior to treatment and at treatment week 8 during a 12-week treatment course and at week 12 during a 16-week treatment course.[16]

Resistance

Pre-existing baseline resistance-associated polymorphisms and resistance selection contribute to treatment failure with DAAs.[17] Resistance-associated polymorphisms have been identified *in vitro* for all DAAs in clinical use.[10]

In terms of clinical data on resistance, the following is a summary of pooled analyses of phase II and III clinical studies of elbasvir/grazoprevir (with or without ribavirin) that were conducted to assess the association between baseline NS5A and/or NS3 polymorphisms and treatment response in patients who achieved SVR or experienced virologic failure and for whom baseline sequences were available.[16]

HCV genotype 1

Treatment failure rates with DAAs appear to be higher with HCV genotype 1a compared with genotype 1b.[17]

In vitro studies in genotype 1a replicon cells indicate that elbasvir/grazoprevir has a high genetic barrier to resistance.[18] In the pooled analyses of HCV genotype 1a-infected patients, SVR was achieved in 98% of treatment-naïve patients who did not have NS5A polymorphisms before starting treatment with elbasvir/grazoprevir compared with 55% of patients with baseline NS5A polymorphisms.[16] Among treatment-experienced patients, SVR was achieved in 99% of patients without baseline NS5A polymorphisms versus 50% of subjects with baseline NS5A polymorphisms.

An independent analysis of HCV drug resistance data submitted for regulatory approval confirmed that the failure to respond to 12 weeks of treatment with elbasvir/grazoprevir observed in a small proportion of patients with HCV genotype 1a is due to the presence of NS5A polymorphisms and suggested that pre-treatment resistance analyses can optimize treatment selection.[19]

For HCV genotype 1b-infected patients, the pooled analyses showed that the presence of baseline NS5A polymorphisms did not affect the response to elbasvir/grazoprevir in treatment-naïve individuals.[16] Among treatment-experienced patients, SVR was achieved in 100% of patients without baseline NS5A polymorphisms versus 86% of those with baseline NS5A polymorphisms.

In the pooled analyses, the presence of baseline NS3 polymorphisms did not affect treatment response to elbasvir/grazoprevir among HCV genotype 1a- and genotype 1b-infected patients.[16]

HCV genotype 4

In pooled analyses of HCV genotype 4-infected patients, neither NS5A nor NS3 polymorphisms present at the start of therapy affected the efficacy of elbasvir/grazoprevir in treatment-naïve and -experienced patients.[16] The independent analysis of regulatory data on HCV drug resistance confirmed that HCV genotype 4-infected patients with NS5A polymorphisms achieved SVR12 with elbasvir/grazoprevir treatment.[19]

HCV genotype 3

In a phase II study of sofosbuvir given with elbasvir/grazoprevir, neither NS5A nor NS3 polymorphisms present at the start of therapy affected treatment response in HCV genotype 3-infected patients.[16]

Comment:
Treatment experienced patients:

NS5A RAS: The presence of baseline resistance-associated substitutions (RAS) of the NS5A protein has been associated with lower SVR rates for HCV genotype 1a in response to 12 weeks of elbasvir/grazoprevir, but does not have an impact on efficacy of this regimen in HCV genotypes 1b or 4. The specific RAS associated

with reduced efficacy in HCV genotype 1a are M28, Q30, L31, and Y93; overall prevalence of these RAS is only 6% in treatment-naïve patients. The FDA has recommended baseline NS5A RAS testing to allow extension of treatment duration to 16 weeks and the addition of ribavirin to the subset of patients containing these RAS, which overcomes the impact of these RAS on SVR rates. However, this is not recommended by the NZ Data Sheet, probably because of the small number of patients likely to be affected.

NS5A-experienced patients: Elbasvir/grazoprevir is not recommended in patients who have failed DAA therapy with other regimens containing an NS5A inhibitor, because of the likelihood of selection of NS5A RAS in this group, and the persistence of these RAS.

NS3/4A protease inhibitor-experienced patients: Grazoprevir is a second-generation NS3A protease inhibitor with an improved resistance profile compared with earlier protease inhibitors (boceprevir, telaprevir, and simeprevir). The presence of the NS3A polymorphisms, including Q80K, do not appear to substantially impact treatment response, with overall SVR of 96%, in patients who were protease inhibitor-experienced, and 88% SVR in the subgroup with baseline NS3/4A RAS, treated with elbasvir/grazoprevir plus ribavirin. The NZ Data Sheet only recommends extension of therapy to 16 weeks, and addition of ribavirin to the subgroup with a prior history of on-treatment virologic failure.

Clinical efficacy and tolerability

Data from clinical trials demonstrate that elbasvir/grazoprevir is effective and well tolerated in treatment-naïve and -experienced HCV patients and those with and without cirrhosis across multiple HCV genotypes.[16] The data also demonstrate the efficacy safety of elbasvir/grazoprevir in patients with renal disease, especially those with end-stage renal disease and/or undergoing haemodialysis.

Analysis of pooled data from clinical trials reveals that the most frequently reported adverse effects (≥5%) are fatigue, headache, and nausea when elbasvir/grazoprevir is given without ribavirin.[16] When given with ribavirin, the most common adverse effects (≥5%) are fatigue, headache, anaemia, nausea, and pruritus.

The following are summaries of three key clinical trials of elbasvir/grazoprevir in the treatment of HCV infection, with expert commentary by Catherine Stedman on the implications of the study findings.

Elbasvir/grazoprevir to treat hepatitis C virus infection in persons receiving opioid agonist therapy: A randomized trial[20]

Authors: Dore GJ et al.

Aim: The main objective of this multicentre, randomised, placebo-controlled, phase III study (C-EDGE CO-STAR), which included sites in Australia, was to evaluate the efficacy and safety of elbasvir/grazoprevir in the treatment of HCV infection in PWID.

Methods: Treatment-naive patients with chronic HCV genotype 1, 4, or 6 infection who were ≥80% adherent to visits for opioid substitution therapy were randomised (2:1) to one of two treatment groups. The immediate-treatment group (ITG) received blinded elbasvir/grazoprevir for 12 weeks while the deferred-treatment group (DTG) received placebo for 12 weeks (placebo-phase DTG), followed by 4 weeks of follow-up, and then open-label elbasvir/grazoprevir for 12 weeks (active-phase DTG). Blinding was maintained until the 16-week visit to allow all safety data (through to week 12) to be reviewed before un-blinding. The primary outcome was SVR12, evaluated separately in the ITG and DTG.

Results: A total of 301 patients were randomised to treatment: 201 to the ITG and 100 to the DTG. The SVR12 was 91.5% (95% CI: 86.8–95.0%; 184/201) in the ITG and 89.5% (95% CI: 81.5–94.8%; 85/95) in the active phase of the DTG (**Table 1**). Drug use did not affect SVR12 or adherence to elbasvir/grazoprevir. Six of 18 patients with post-treatment viral recurrence at 24 weeks' follow-up had probable re-infection. If the probable re-infections were assumed to be responses, SVR12 was 94.0% (CI: 89.8–96.9%) in the ITG. One of 201 patients in the ITG and 1/100 patients in the placebo-phase DTG discontinued treatment because of an adverse event.

	Total	Genotype 1a	Genotype 1b	Genotype 4	Genotype 6
Intermediate treatment group					
SVR12 (95% CI; n/N)	91.5 (86.8–95.0; 184/201)	93.5 (88.4–96.8; 144/154)	93.3 (77.9–99.2; 28/30)	91.7 (61.5–99.8; 11/12)	20.0 (0.5–71.6; 1/5)
Deferred treatment group					
SVR12 (95% CI; n/N)	89.5 (81.5–94.8; 85/95)	90.1 (80.7–95.9; 64/71)	92.9 (66.1–99.8; 13/14)	100.0 (54.1–100.0; 6/6)	50.0 (6.8–93.2; 2/4)

Table 1. Summary of the efficacy of elbasvir/grazoprevir in the intermediate treatment and deferred treatment groups.[20] SVR12 = sustained virologic response at week 12 after end of treatment and assuming reinfections are failures.

Comment: The C-EDGE CO-STAR study is important because it specifically demonstrated the efficacy and safety of elbasvir/grazoprevir for the treatment of HCV in PWID who are engaged in opioid substitution therapy, including people engaging in ongoing drug use, confirmed by urine drug screening. Key findings included good adherence to DAA therapy, and high SVR12 rates in this group. Some reinfections were noted within the initial study timeframe but longer term follow-up data will also be of great interest with respect to reinfection rates. Effective engagement and safe DAA treatment in this group of PWID is essential to reduce incidence of new HCV infections, and is a key element of any strategy towards elimination of HCV from this country.

Grazoprevir plus elbasvir in treatment-naive and treatment-experienced patients with hepatitis C virus genotype 1 infection and stage 4–5 chronic kidney disease (the C-SURFER study): A combination phase 3 study[21]

Authors: Roth C et al.

Aim: This multicentre (including Australian sites), double-blind, phase III study assessed the efficacy and safety of elbasvir/grazoprevir without ribavirin in patients with HCV genotype 1 infection and stage 4 or 5 chronic kidney disease, including patients receiving haemodialysis.

Methods: Efficacy was assessed by observational study while safety was assessed by randomised study. Patients were randomised (1:1) to receive elbasvir/grazoprevir (immediate treatment group; ITG) or placebo (deferred treatment group; DTG) for 12 weeks. Patients in the DTG received matched placebo for 12 weeks and subsequently elbasvir/grazoprevir for 12 weeks after 4 weeks of follow-up. An additional cohort of non-randomised patients received elbasvir/grazoprevir open-label and underwent intensive pharmacokinetic sampling (pharmacokinetic treatment group; PTG). The primary efficacy outcome was a non-randomised comparison of SVR12 for the combined ITG + PTG with a historical control. A randomised comparison between the ITG and the DTG provided the primary safety outcome.

Results: Of 235 patients that received at least one dose of study drug, 224 patients were randomised to the ITG (n=111) or DTG (n=113), and 11 were included in the PTG. Of the 122 patients in the ITG + PTG, six were excluded from the primary efficacy analysis for reasons other than non-virologic failure. SVR12 in the ITG + PTG was 99% (95% CI: 95.3–100%; 115/116), with one relapse 12 weeks after end of treatment, versus a historical control SVR12 of 45% (p<0.001) that was based on meta-analyses of INF-based regimens in clinical trials of HCV patients on haemodialysis. Adverse events, which were classified as mild to moderate, occurred at similar frequencies in the ITG (76%) and DTG (84%). No patients in the ITG and five (4%) in the DTG discontinued because of an adverse event.

Comment: C-SURFER was a large phase III study of elbasvir/grazoprevir for people with HCV and renal impairment, including patients on haemodialysis. A major advantage of this regimen is that it is ribavirin-free, which significantly reduces treatment-related morbidity compared with many previous HCV treatment regimens in people with renal impairment. In this study, the 12-week regimen of standard doses of elbasvir/grazoprevir was demonstrated to have very high efficacy in both HCV genotype 1a and 1b, and treatment was well tolerated.

Efficacy and safety of grazoprevir (MK-5172) and elbasvir (MK-8742) in patients with hepatitis C virus and HIV co-infection (C-EDGE CO-INFECTION): a non-randomised, open-label trial[22]

Authors: Rockstroh JK et al.

Aim: This open-label, phase III study assessed the efficacy, safety, and tolerability of elbasvir/grazoprevir in patients with HCV and HIV co-infection.

Methods: Treatment-naive patients with chronic HCV genotype 1, 4, or 6 infection and HIV co-infection, with or without cirrhosis, were enrolled from nine countries, including Australia. Patients were either ART-naïve or had been stable on ART for ≥8 weeks. All patients received elbasvir/grazoprevir for 12 weeks.

Results: A total of 218 patients were treated. Elbasvir/grazoprevir produced an SVR12 of 96% (95% CI: 92.9–98.4; 210/218). One patient did not achieve SVR12 due to a non-virologic reason and seven patients without cirrhosis relapsed (two were subsequently confirmed as re-infections). All 35 patients with cirrhosis achieved SVR12. Only two patients (1%) experienced a serious adverse event and there were no treatment discontinuations due to an adverse event.

Comment: The C-EDGE CO-INFECTION study is important as it clearly demonstrates high efficacy of elbasvir/grazoprevir for the treatment of HCV in HIV co-infected patients. This has been a consistent finding, with other DAA regimens also demonstrating equivalent efficacy in this population compared with the mono-infected HCV infection. Treatment of co-infected people is a high priority because they are at increased risk of HCV-related complications. Drug-drug interactions are particularly important in this population and may well influence HCV therapeutic choices. Key HIV medications that are contraindicated with elbasvir/grazoprevir include atazanavir, darunavir, lopinavir, saquinavir, tipranavir, and efavirenz. Regimens that are not recommended in combination with elbasvir/grazoprevir include etravirine, or the combination of elvitegravir/cobicistat/emtricitabine/tenofovir because of alterations in the DAA drug concentrations and potential risks of lack of efficacy, or toxicity.

EXPERT'S CONCLUDING COMMENTS

The availability of elbasvir/grazoprevir is an important advance for the HCV community in New Zealand, particularly those infected with HCV genotypes 1 or 4. The majority of HCV genotype 1 and 4 patients can be successfully treated in a ribavirin-free regimen, which improves tolerability of therapy and reduces monitoring requirements. This is also the first ribavirin-free regimen that is suitable for both HCV genotype 1a and 1b patients with severe renal impairment. Although elbasvir/grazoprevir is safe and effective in patients with compensated cirrhosis, it is contra-indicated in people with decompensated Child-Pugh B or C cirrhosis.

TAKE-HOME MESSAGES

- The burden of HCV-related liver disease is high and is increasing.
- Elbasvir/grazoprevir is an orally-administered fixed-dose INF-free combination DAA agent.
- DAAs are recommended as a first-line therapy for chronic HCV infection.
- Elbasvir/grazoprevir has been demonstrated to be effective and well tolerated in treatment-naïve and -experienced HCV patients and those with/without cirrhosis across multiple HCV genotypes.
- Elbasvir/grazoprevir can be considered for use in patients with HIV/HCV co-infection or end-stage renal disease and in PWID.
- As with other DAAs, there is the potential for important DDIs to occur with elbasvir/grazoprevir.
- Prescribers should consider all concomitant medications for risk of interaction with elbasvir/grazoprevir.
- Elbasvir/grazoprevir is not suitable for people with decompensated cirrhosis (elbasvir/grazoprevir is contra-indicated in patients with Child-Pugh B/C cirrhosis).

REFERENCES

1. Saraswat V, et al. Historical epidemiology of hepatitis C virus (HCV) in select countries - volume 2. J Viral Hepat. 2015;22 Suppl 1:6-25.
2. Petruzziello A, et al. Global epidemiology of hepatitis C virus infection: An up-date of the distribution and circulation of hepatitis C virus genotypes. World J Gastroenterol. 2016;22(34):7824-40.
3. Gane E, et al. Impact of improved treatment on disease burden of chronic hepatitis C in New Zealand. N Z Med J. 2014;127(1407):61-74.
4. Westbrook RH, et al. Natural history of hepatitis C. J Hepatol. 2014;61(1 Suppl):S58-68.
5. Younossi ZM, et al. Hepatitis C infection: A multi-faceted systemic disease with clinical, patient reported and economic consequences. J Hepatol. 2016;65(1 Suppl):S109-19.
6. Vermunt J, et al. Prevalence and knowledge of hepatitis C in a middle-aged population, Dunedin, New Zealand. World J Gastroenterol. 2015;21(35):10224-33.
7. Nelson PK, et al. Global epidemiology of hepatitis B and hepatitis C in people who inject drugs: results of systematic reviews. Lancet. 2011;378(9791):571-83.
8. O'Connor P, et al. Prevalence of hepatitis C among injecting drug users attending drug clinics. N Z Med J. 2016;129(1434):44-8.
9. Robinson GM, et al. Hepatitis C prevalence and needle/syringe sharing behaviours in recent onset injecting drug users. N Z Med J. 1995;108(996):103-5.
10. Anonymous. Hepatitis C Virus Infection Consensus Statement Working Group. Australian recommendations for the management of hepatitis C virus infection: a consensus statement 2016. Melbourne: Gastroenterological Society of Australia. 2016. Available from: http://www.hepcguidelines.org.au/PDFs/HCV_consensus_statement_2016.pdf.
11. Sulkowski MS, et al. Therapeutic issues in HIV/HCV-coinfected patients. J Viral Hepat. 2007;14(6):371-86.
12. Graham CS, et al. Influence of human immunodeficiency virus infection on the course of hepatitis C virus infection: a meta-analysis. Clin Infect Dis. 2001;33(4):562-9.
13. Zhang X. Direct anti-HCV agents. Acta Pharm Sin B. 2016;6(1):26-31.
14. Gogela NA, et al. Enhancing our understanding of current therapies for hepatitis C virus (HCV). Curr HIV/AIDS Rep. 2015;12(1):68-78.
15. Majumdar A, et al. Treatment of hepatitis C in patients with cirrhosis: remaining challenges for direct-acting antiviral therapy. Drugs. 2015;75(8):823-34.
16. Anonymous. New Zealand data sheet. Zepatier (elbasvir/grazoprevir tablets). 01 December 2016. Newmarket, Auckland: Merck Sharp & Dohme (NZ) Limited. Available from: http://www.medsafe.govt.nz/Profs/datasheet/z/Zepatiertab.pdf
17. Cento V, et al. Resistance to direct-acting antiviral agents: clinical utility and significance. Curr Opin HIV AIDS. 2015;10(5):381-9.
18. Lahser FC, et al. The Combination of Grazoprevir, a Hepatitis C Virus (HCV) NS3/4A Protease Inhibitor, and Elbasvir, an HCV NS5A Inhibitor, Demonstrates a High Genetic Barrier to Resistance in HCV Genotype 1a Replicons. Antimicrob Agents Chemother. 2016;60(5):2954-64.
19. Komatsu TE, et al. Regulatory Analysis of Effects of Hepatitis C Virus NS5A Polymorphisms on Efficacy of Elbasvir and Grazoprevir. Gastroenterology. 2016.
20. Dore GJ, et al. Elbasvir-Grazoprevir to Treat Hepatitis C Virus Infection in Persons Receiving Opioid Agonist Therapy: A Randomized Trial. Ann Intern Med. 2016;165(9):625-34.
21. Roth D, et al. Grazoprevir plus elbasvir in treatment-naive and treatment-experienced patients with hepatitis C virus genotype 1 infection and stage 4-5 chronic kidney disease (the C-SURFER study): a combination phase 3 study. Lancet. 2015;386(10003):1537-45.
22. Rockstroh JK, et al. Efficacy and safety of grazoprevir (MK-5172) and elbasvir (MK-8742) in patients with hepatitis C virus and HIV co-infection (C-EDGE CO-INFECTION): a non-randomised, open-label trial. Lancet HIV. 2015;2(8):e319-27.

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