Medicines Adverse Reactions Committee

Meeting date	**11 June 2020**	Agenda item	3.2.4
Title	**Protease inhibitors for Hepatitis C and risk of serious liver injury**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice

Active constituent	**Medicines**	**Sponsors**
Glecaprevir/pibrentasvir	Maviret	AbbVie Limited
Elbasvir/grazoprevir	Zepatier	Merck Sharp & Dohme NZ Ltd
Sofosbuvir/velpatasvir/voxilapresvir	Vosevi	Gilead Sciences (NZ)

Funding	Maviret is funded.
Previous MARC meetings	Protease inhibitors for Hepatitis C and the risk of serious liver injury has not been discussed previously.
International action	FDA (see section 2.2.2) August 2019
Schedule	Prescription medicine
Usage data	Maviret has been funded since February 2019. Since then there has been 7,800 dispensings of Maviret to 3,230 patients. (Pharmaceutical Collection data)
Advice sought	**The Committee is asked to advise whether:** – The data sheets for protease inhibitors used for treatment of hepatitis C should be updated regarding the risk of serious liver injury. – This topic requires further communication other than MARC's Remarks in *Prescriber Update*.

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1.0 PURPOSE

In August 2019 the US Food and Drug Administration (FDA) issued a warning concerning the rare occurrence of serious liver injury affecting some patients with advanced liver disease who were treated with the hepatitis C medicines Maviret, Zepatier, and Vosevi (1). The warning was based on 63 reported cases of worsening liver function in relation to treatment with these medicines, sometimes leading to liver failure and death.

Maviret, Zepatier and Vosevi all contain a hepatitis C virus (HCV) protease inhibitor. Maviret is the only product that is currently marketed and funded for use in New Zealand; Zepatier and Vosevi are approved but not available. Maviret can be used in patients with chronic hepatitis C with none to mild liver impairment; it is not recommended in patients with moderate liver impairment and is contraindicated in patients with severe liver impairment.

Most of the patients in the cases reported to the FDA had moderate to severe liver impairment. In some cases, patients were reported to have none or mild liver impairment, but the classification was not always correct.

The FDA emphasized the importance of assessing severity of liver disease at baseline and to closely monitor for signs and symptoms of worsening liver function and stop treatment if that occurs. Patients should be aware that the risk of serious liver injury is rare but know to contact their health care professional right away if they develop signs of liver injury. Product information in the US have been updated with this information.

Because this potential risk is serious and Maviret is funded in New Zealand, Medsafe considers that this safety concern should be reviewed by the MARC. As Maviret is the only funded (and available) protease inhibitor in NZ, this report focuses on Maviret.

2.0 BACKGROUND

2.1 Hepatitis C

Hepatitis C is an infection of the liver, caused by the hepatitis C virus (HCV). More than 50,000 people in New Zealand are infected with the hepatitis C virus, although it is estimated only half are currently diagnosed (2). There are about 1000 new cases in NZ each year. Worldwide, about 200 million people have been infected with hepatitis C (3).

Hepatitis C can be acute or chronic. The first phase of the infection is the acute phase which is self-limited, rarely causes hepatic failure, and usually (about 3 out of 4 infected individuals) leads to chronic infection. Chronic HCV infection often follows a slowly progressive course over many years and may not result in any clinically apparent liver disease. However, chronic hepatitis C can for some patients ultimately result in cirrhosis, hepatocellular carcinoma, and the need for liver transplantation (4, 5).

2.1.1 Symptoms

Although many patients with chronic HCV infection are symptomatic, most symptoms are nonspecific and not clearly a result of the HCV infection itself. The most frequent complaints are fatigue and sleep disturbances; other symptoms include nausea, diarrhoea, abdominal pain, anorexia, myalgia, arthralgia, weakness, weight loss, depression and anxiety. Even if cirrhosis develops, many patients have only nonspecific symptoms. There is wide variability in serum aminotransferase levels among individual patients with chronic HCV infection over time. Viral levels of HCV, on the contrary, remain generally constant, although significant fluctuations can occur.

Generally, there is a poor correlation between aminotransferase levels and liver histology but despite this, aminotransferase levels have been incorporated into formulas that are used as non-invasive markers of liver fibrosis.

Several extrahepatic diseases have been associated with chronic HCV infection. Most cases appear to be directly related to the viral infection. These include:

- Hematologic diseases, such as essential mixed cryoglobulinemia and lymphoma
- Renal disease, particularly membranoproliferative glomerulonephritis
- Autoimmune disorders, such as thyroiditis and the presence of autoantibodies
- Dermatologic conditions, such as porphyria cutanea tarda and lichen planus
- Diabetes mellitus

The frequency of such findings is uncertain.

Approximately 5 to 30 percent of chronically infected individuals develop cirrhosis over a 20- to 30-year period, although slower and faster rates of progression have been described. The development of cirrhosis is silent in the majority of patients for whom it occurs (5).

2.1.2 Natural history

According to the Ministry of Health, up to 20–25% of infected individuals in NZ will develop cirrhosis of the liver if left unchecked. Without successful treatment, 2–5% of those with cirrhosis will progress to life-threatening liver cancer or liver failure each year. Hepatitis C is the leading cause of liver transplantation in New Zealand. Of the infected population, 50–60% remain undiagnosed and unaware of the risks associated with the disease (2).

The natural history of chronic HCV infections, and especially predictions of outcome for individual patients, are difficult to clearly define. Chronic HCV infection results in liver fibrosis and ultimately cirrhosis in approximately 20-30% of patients (7). A systematic review of 111 studies analysing the natural history of HCV infection estimated that the prevalence of cirrhosis 20 years after infection was 16 percent. In a large French series, the mean time to cirrhosis was 30 years. It was estimated that 31 percent of patients would show no evidence of cirrhosis for at least 50 years (5).

Cirrhosis is the end stage of any chronic liver disease. There are 2 clinical stages of cirrhosis: compensated and decompensated. The stages are dynamic and progressive, but there is potential reversibility from the decompensated to compensated stage if the aetiology of the liver disease is resolved.

Patients with compensated cirrhosis are asymptomatic do not have ascites, variceal haemorrhage, hepatic encephalopathy, or jaundice and can remain stable for years. Liver biopsy may be necessary for diagnosis. Overall the median survival time is > 12 years. Presence of varices is the key prognostic factor for compensated patients and indicates higher likelihood of decompensation.

Figure 1: Stages of liver damage (3)

Patients with decompensated cirrhosis have had at least one complication including ascites, jaundice, variceal haemorrhage or hepatic encephalopathy, and overall, they have median survival times of 2

years (8). Almost all HCV-infected patients who develop these complications have cirrhosis; however, not all patients with cirrhosis develop these complications.

Patients who presented clinically with chronic hepatitis tend to report a more aggressive course with a high risk of cirrhosis (and subsequent consequences of decompensation and hepatocellular carcinoma). Once an individual has developed advanced fibrosis, the risk of progression to cirrhosis is high.

Hepatocellular carcinoma in patients with HCV occurs almost exclusively in those with cirrhosis. In the United States, HCV accounts for approximately one-third of hepatocellular carcinoma cases. Estimates of the risk of developing hepatocellular carcinoma once cirrhosis has developed have varied from 0 to 3 percent per year in various reports.

Overall survival is decreased in patients with chronic HCV infection, especially in those who have developed cirrhosis. HCV-associated mortality, however, is more likely to be due to end stage liver disease rather than hepatocellular carcinoma (5).

2.1.3 The Child-Pugh score

The Child-Pugh score consists of five clinical features and is used to assess the prognosis of chronic liver disease and cirrhosis. The score is used together with another newer scoring system, Model for End-Stage Liver Disease (MELD), to determine priority for liver transplantation.

The NPS Medwise (Australia) Child-Pugh scoring system is shown in Table 1.

Table 1: The Child-Pugh score (9)

Parameter	Points assigned = 1	Points assigned = 2	Points assigned = 3
Ascites	Absent	Slight	Moderate
Bilirubin, micromol/L	<11	11–45	>45
Albumin, g/L	>35	28–35	<28
Prothrombin time – seconds over control or INR	<4 <1.7	4–6 1.7–2.3	>6 >2.3
Encephalopathy	None	Grade 1–2	Grade 3–4

Total score of 5–6 is grade A or well compensated disease (1 and 2 year survivals are 100% and 85%)

Total score of 7–9 is grade B or disease with significant functional compromise (1 and 2 year survivals are 80% and 60%)

Total score of 10–15 is grade C or decompensated liver disease (1 and 2 year survivals are 45% and 35%)

Unlike the NPS Medicinewise scoring system, many tables, such as those from mdcalc.com or medscape.com) include approximately the following numbers instead for Total bilirubin:

Table 2: Variation of limits for bilirubin in the Child-Pugh score

Parameter	Points assigned = 1	Points assigned = 2	Points assigned = 3
Bilirubin, micromol/L	< 34	34-50	> 50

2.1.4 Genotypes

There are different strains of the hepatitis C virus. These are called genotypes. The genotypes have different distributions throughout the world. The estimation for New Zealand, is that of those infected with hepatitis C virus:

- 55% have genotype 1 (which is further divided into genotype 1a and 1b)
- 35% have genotype 3
- 8% have genotype 2
- 1% have genotype 4 or 6.

Most people are infected by a single, dominant genotype, but it is possible to have more than one at the same time (called a mixed infection).

There is limited evidence about how the progression of the condition is affected by the different genotypes. For example, in a recent retrospective cohort study including 180 patients with HCV related HCC, the authors note that patients with HCV genotype 1 and 3 infection may have an increased risk of developing liver cancer. The results of this study showed that patients with HCV genotype 2 had longer overall survival than those with other genotypes (10)

The virus genotype that a person carries may affect treatment options. However, some medicines, such as Maviret, are pangenotypic treatments, which means that they are effective in all genotypes (11).

2.2 Treatment of Hepatitis C

The goal of antiviral therapy in patients with chronic hepatitis C is to eradicate HCV RNA, which is predicted by attainment of a sustained virologic response (SVR), defined as an undetectable RNA level 12 weeks following the completion of therapy (4).

Direct-acting antivirals (DAAs) are medicines targeting specific nonstructural proteins of HCV and thus disrupting viral replication and infection. The introduction of these medicines has revolutionized therapy of HCV infection. Highly effective, well-tolerated, all-oral regimens are now the treatment of choice for the vast majority of HCV-infected patients who have access to these agents.

2.2.1 DAAs – Mechanism of action

HCV is a virus that makes its own proteins to help it replicate. Some of these proteins, are called NS3/4A proteases, NS5B RNA-dependent RNA polymerases and NS5A proteins.

The infectious viral structure is comprised of envelope glycoproteins that contain the viral core protein and RNA. After cell entry, the viral RNA is translated through host machinery into a polyprotein (a non-functional “large” protein that is cleaved at specific sites into smaller proteins by proteases). The polyprotein is cleaved during and after translation by both host and viral-encoded proteases into 10 mature viral proteins, including a number of nonstructural (NS) proteins.

One of the viral proteases involved in this post-translational processing is a complex of the NS3 and NS4A proteins (NS3/NS4A). Synthesis of new viral RNA occurs in a highly structured replication complex that consists of NS3, NS4A, NS4B, NS5A, and NS5B. The RNA polymerase NS5B is essential for viral replication. NS5A has a role in organization and regulation of replication. It is also involved in assembly of the viral particle that is released from the host cell (12).

Direct-acting antivirals are inhibitors of the NS3/4A protease, the NS5A protein, and the NS5B polymerase, see figure below:

Figure 2: DAAs targeting specific steps within the HCV life cycle (12)

There are three classes of DAAs, which are defined by their mechanism of action and therapeutic target:

- Nonstructural proteins 3/4A (NS3/4A) protease inhibitors (PIs)
- NS5B polymerase inhibitors (NPIs) (sometimes divided into two classes)
- NS5A inhibitors

The tables below present some of the different DAAs. DAAs are typically taken in combination with other DAAs to improve the efficacy.

Pan-genotypic medicines: medicines which treat all genotypes:

Table 3: Pan-genotypic medicines

Brand name	Ingredients	Class	In NZ
Maviret	Glecaprevir/pibrentasvir	PI/NS5A	Yes, funded
Epclusa	sofosbuvir/velpatasvir	NPI/NS5A	Not available
Vosevi	sofosbuvir/velpatasvir/voxilapresvir	NPI/NS5A/PI	Not available

Genotype specific medicines:

Table 4: Medicines used for treatment of Genotype 1

Brand name	Ingredients	Class	In NZ
Daklinza + Sovaldi	daclatasvir + sofosbuvir	NS5A + NPI	Approval lapsed + Consent given
Harvoni	ledispasvir/sofobuvir	NS5A/NPI	Consent given, funded (SA*)
Viekira Pak	ombitasvir/paritaprevir/ritonavir; dasabuvir	NS5A/PI/PI/NS5A	Approval lapsed
Zepatier	elbasvir/grazoprevir	NS5A/PI	Not available

*Funded with Special authority

Table 5: Medicines used for treatment of Genotype 2

Brand name	Ingredients	Class	In NZ
Sovaldi	Sofosbuvir	NPI	Consent given

Table 6: Medicines used for treatment of Genotype 3

Brand name	Ingredients	Class	In NZ
Daklinza + Sovaldi or only Sovaldi	daclatasvir + sofosbuvir	NS5A+NPI	Approval lapsed + Consent given

Table 7: Medicines used for treatment of Genotype 4

Brand name	Ingredients	Class	In NZ
Harvoni or only Sovaldi	ledispavir/sofosbuvir	NS5A/NPI	Consent given (Harvoni funded SA)
Zepatier	elbasvir/grazoprevir	NS5A/PI	Not available

Table 8: Medicines used for treatment of Genotype 5

Brand name	Ingredients	Class	In NZ
Harvoni	ledispavir/sofosbuvir	NS5A/NPI	Consent given, funded (SA)

Table 9: Medicines used for treatment of Genotype 6

Brand name	Ingredients	Class	In NZ
Harvoni	ledispavir/sofosbuvir	NS5A/NPI	Consent given, funded (SA)

History of protease inhibitors

The first-generation protease inhibitors boceprevir and telaprevir were associated with a relatively high frequency of adverse reactions. Later PIs have fewer adverse reactions, can be used against more HCV genotypes and the dosing is easier. A later wave of first-generation PIs included simeprevir, asunaprevir and paritaprevir, while the second-generation PIs include grazoprevir, glecaprevir and voxilalapresvir (12). Liver injury has been reported with several of the HCV protease inhibitors, particularly asunaprevir which has been linked to acute hepatitis with immunoallergic features, sometimes as a part of a generalized hypersensitivity reaction (6).

Comment: The following protease inhibitor containing medicines are approved in NZ: Maviret, Zepatier and Vosevi. Maviret is currently funded and is dispensed from registered pharmacies. Zepatier and Vosevi are not available but Vosevi has a published NZ data sheet. Harvoni is the other funded DAA for patients who meet special authority criteria, including patients with advanced liver complications, e.g. decompensated cirrhosis or awaiting a liver transplant. However, Harvoni does not include a PI and is therefore not explored further in this report.

2.3 Regulatory action in the US

In August 2019, the FDA issued a warning concerning rare occurrence of serious liver injury with use of hepatitis C medicines Maviret, Zepatier, and Vosevi in some patients with advanced liver disease. These three medicines all include protease inhibitors and are indicated for use in patients with chronic hepatitis C and no or mild liver impairment (Child-Pugh A).

Maviret is not recommended for patients with moderate liver impairment (Child-Pugh B) and is contraindicated if liver impairment is severe (Child-Pugh C). Zepatier is contraindicated in moderate or severe liver impairment. Vosevi is not recommended in moderate or severe liver impairment.

FDA had received 63 reports about use of Maviret (n=46), Zepatier (n=14), and Vosevi (n=3) to treat patients with moderate to severe liver impairment resulting in worsening of liver function (liver decompensation) or liver failure.

Ten cases reported isolated hyperbilirubinemia and jaundice without concomitant evidence of increased transaminase levels or other hepatic decompensation events, and eight cases reported deaths.

The median time to onset of a liver-related event or liver decompensation after initiating treatment was 22 days, ranging from 2 days to 16 weeks. The most frequently reported liver-related events were hyperbilirubinemia (n=42), jaundice (n=32), ascites (n=27), and hepatic encephalopathy (n=12). Discontinuation of the drug resulted in resolution of symptoms or reduced liver biochemical values in 39 of the 63 cases, and there were two cases of recurrence of symptoms upon re-initiating treatment.

Of the 63 cases, 13 were in patients without cirrhosis, 18 with compensated cirrhosis, 21 with decompensated cirrhosis, and 11 with unknown liver function status at baseline. More than half of the cases that reported no cirrhosis or compensated cirrhosis (Child-Pugh A) at baseline were incorrectly classified and had evidence of advanced liver disease or pre-existing risk factors such as decreased platelets at baseline, portal hypertension, and alcohol abuse, or other serious medical illnesses impacting the liver prior to receiving treatment that may have signified or directly contributed to the development of hepatic decompensation or liver failure.

The advice was to:

- continue to prescribe Maviret, Zepatier, or Vosevi as indicated (Child-Pugh A)
- assess severity of liver disease at baseline and closely monitor for signs and symptoms of worsening liver function.
- assessment and close monitoring are especially important for those with pre-existing significant liver problems or risk factors, such as hepatocellular carcinoma or alcohol abuse, which can also contribute to clinical worsening of liver function or liver failure during treatment.
- discontinue these medicines in patients who develop signs and symptoms of liver decompensation or as clinically indicated.
- Maviret and Zepatier should not be prescribed in patients with any history of prior hepatic decompensation. Vosevi is indicated for patients who have previously failed certain other HCV treatments and is not recommended in patients with any history of hepatic decompensation unless the benefits outweigh the risk of liver injury, liver failure or death.
- patients should be aware that the risk of serious liver injury is rare but be informed to contact their health care professional right away if they develop fatigue, weakness, loss of appetite, nausea and vomiting, yellow eyes or skin, or light-colored stools as these may be signs of liver injury.
- patients should talk to their health care professional about liver impairment or other pre-existing risk factors that can worsen liver function such as a history of alcohol abuse (1).

Comments: In many of the reported cases, serious liver reactions occurred in patients who had signs and symptoms of moderate to severe liver impairment or other serious liver problems and should not have been treated with these medicines. In some cases, it was clear that patients had been classified as having no/compensated cirrhosis with mild liver impairment when they were more severely sick or had other risk factors such as high alcohol use. This may leave about 10 cases where the patient possibly had no or mild liver impairment, however, no specific information on these cases is included in the warning statement.

2.4 Protease inhibitors in NZ – Maviret

The reference to this section is the NZ data sheet (13) for Maviret unless another reference is stated. The last update of the data sheet was in April 2020.

2.4.1 Indication

The approved indication for Maviret in NZ is:

- for the treatment of adults and adolescents 12 years and older with chronic hepatitis C virus (HCV) (see sections 4.2, 4.4 and 5.1).

This is stated in section 4.1 of the data sheet. In the sections referred to, more information is outlined:

Section 4.2 specifies recommended treatment duration based on if patients are infected with genotype 1, 2, 3, 4, 5 or 6, with compensated liver disease (with or without cirrhosis) and if patients are treatment-naïve or treatment experienced (see also section 2.4.2).

No dose adjustment of Maviret is required in patients with mild hepatic impairment (Child-Pugh A). Maviret is not recommended in patients with moderate hepatic impairment (Child-Pugh B), (this is also listed in section 4.4). Maviret is contraindicated in patients with severe hepatic impairment (Child-Pugh C) (this is also listed in section 4.3).

Section 5.1 presents results from studies involving patients from the different patient groups.

Comments: Maviret is indicated for treatment of chronic hepatitis C. To see which severities of chronic hepatitis C it is supposed to be used in, and where it should not be used, one has look at the sections referred too. There it says that Maviret is not recommended in patients with Child-Pugh B and contraindicated in patients with Child-Pugh C.

The company's website about Maviret for patients in NZ only refers to Maviret as an 8-week Hep C treatment for patients who have not been treated for hep C before and are without liver scarring (cirrhosis). However, it mentions that some patients may have to be treated for 12 or 16 weeks (14).

Note that Vosevi is not recommended in moderate or severe liver impairment. Zepatier does not have a NZ data sheet, but according to US product information, it is contraindicated in moderate or severe liver impairment (Child-Pugh B or C).

2.4.2 Dosing

The recommended dose of Maviret in adults and adolescents 12 years and older is 300 mg/120 mg (three 100 mg glecaprevir/40 mg pibrentasvir tablets), once daily at the same time and with food (see section 5.2). Addition of ribavirin is not required.

Table 10 below describes the recommended Maviret treatment durations for patients infected with HCV genotype 1, 2, 3, 4, 5 or 6, with compensated liver disease (with or without cirrhosis) and with or without previous treatment experience.

Table 10: Recommended treatment duration for different patient groups

For treatment-naïve patients.

Patient Population	Recommended Treatment Duration	
	No Cirrhosis	Cirrhosis
GT 1, 2, 4, 5, 6	8 weeks	8 weeks
GT3	8 weeks	12 weeks
Includes patients co-infected with human immunodeficiency virus (HIV).		

For treatment-experienced patients.

Patient Population	Recommended Treatment Duration	
	No Cirrhosis	Cirrhosis
NS5A inhibitor-naïve* GT 1, 2, 4, 5, 6	8 weeks	12 weeks
NS5A inhibitor-experienced GT 1, 2, 4, 5, 6	16 weeks	16 weeks
GT 3 (any experienced)		

* experienced with PR, SOF + PR, SOF + R, SMV + SOF, SMV + PR, TVR + PR or BOC + PR.
PR = (peg)interferon + ribavirin; SOF = Sofosbuvir; R = Ribavirin; SMV = Simeprevir; TVR = Telaprevir; BOC = Boceprevir.
Includes patients co-infected with human immunodeficiency virus (HIV).

Maviret may be used for 12 weeks in liver or kidney transplant recipients. A 16-week treatment duration should be considered in transplant patients who are NS5A inhibitor-experienced or genotype 3-infected patients who are treatment experienced.

2.4.3 Pharmacokinetics

Following oral administration of the individual components of glecaprevir/pibrentasvir in healthy subjects, peak concentrations for both glecaprevir and pibrentasvir are reached in 5 hours. Administration with meals high in fat increases exposure of both substances.

Glecaprevir and pibrentasvir are highly plasma protein bound (97.5% and greater than 99%, respectively).

The elimination half-life of glecaprevir is 6 hours, while it is 13 hours for pibrentasvir. Both substances are primarily eliminated via the biliary-fecal route, with greater than 90% of the dose excreted in the faeces. Metabolism via cytochrome P450 (CYP-450) 3A is a secondary means of elimination for glecaprevir while pibrentasvir is not subject to biotransformation. Less than 1% of the dose of either component is excreted in the urine. The t½ is 6 hours for glecaprevir and 13 hours for pibrentasvir.

Relative to healthy subjects (N=230), glecaprevir Cmax was 51% lower and AUC24,ss was similar (10% difference) in non-cirrhotic patients with HCV; pibrentasvir Cmax and AUC24,ss were 63% and 34% lower, respectively (15).

<u>Patients with kidney impairment</u>
No dose adjustment is necessary in patients with mild, moderate, or severe renal impairment, including those on dialysis.

<u>Patients with liver impairment</u>

- In HCV-infected patients with mild hepatic impairment (Child-Pugh A) and compensated cirrhosis, glecaprevir exposure was increased approximately 2-fold while pibrentasvir exposure was similar to that of noncirrhotic HCV-infected subjects.
- In non–HCV-infected subjects with moderate hepatic impairment (Child-Pugh B), glecaprevir exposure was 100% higher than in subjects with normal hepatic function, while pibrentasvir exposure was 26% higher.
- In patients with severe hepatic impairment (Child-Pugh C), glecaprevir exposure was 11-fold higher than in subjects with normal hepatic function, while pibrentasvir exposure was 114% higher.

2.4.4 Drug interactions

There are several medicines that may interact with Maviret. (17) P-glycoprotein 1 (P-gp) is an important protein of the cell membrane that pumps many foreign substances out of cells. Breast

cancer resistance protein (BCRP) plays an important role in intestinal absorption and biliary excretion of drugs. Organic anion transporting polypeptide (OATP) 1B1/3 is a bile acid transporter.

Glecaprevir and pibrentasvir are inhibitors of P-gp, BCRP and OATP 1B1/3. Maviret may increase plasma concentrations of medicinal products that are substrates of these proteins, for example dabigatran and digoxin.

Glecaprevir and pibrentasvir are substrates of P-gp and/or BCRP and Glecaprevir is a substrate of OATP1B1/3. Co-administration of Maviret with medicinal products that inhibit hepatic P-gp, BCRP, or OATP1B1/3, such as ciclosporin, may increase the plasma concentrations of glecaprevir and/or pibrentasvir.

Co-administration of Maviret with medicinal products that induce P-gp/CYP3A, such as carbamazepine, may decrease plasma concentrations of glecaprevir and pibrentasvir.

Coadministration is contraindicated with atazanavir and rifampin. Other coadministration that is not recommended is carbamazepine, ethinyl estradiol-containing medications (such as oral contraceptive agents), St. John's wort, efavirenz, darunavir, lopinavir, ritonavir, and certain statins (atorvastatin, lovastatin, and simvastatin).

If Maviret is coadministered with a vitamin K antagonist, close monitoring of INR is recommended. This is due to liver function changes during treatment with Maviret.

Glecaprevir and pibrentasvir are weak inhibitors of cytochrome P450 (CYP) 3A, CYP1A2, and uridine glucuronosyltransferase (UGT) 1A1. Significant interactions are not expected when MAVIRET is co-administered with substrates of CYP3A, CYP1A2, CYP2C9, CYP2C19, CYP2D6, UGT1A1, or UGT1A4.

The data sheet also includes a list of medicines without clinically significant interactions with Maviret.

2.4.5 Safety

The safety assessment for Maviret in patients with compensated liver disease (with or without cirrhosis) was derived from Phase 2 and 3 studies, which evaluated approximately 2,300 adult patients with chronic HCV genotype 1, 2, 3, 4, 5 or 6 who received Maviret for 8, 12, or 16 weeks. Headache and fatigue were reported as very common and nausea as common. Of the patients, 0.1% permanently discontinued treatment due to adverse reactions.

The types and severity of adverse reactions in patients with compensated cirrhosis were comparable to those seen in patients without cirrhosis and there were no differences between treatment durations.

In a patient population with renal impairment, including dialysis, pruritus and asthenia (decreased muscle strength) were also reported. The overall safety profile in liver or kidney transplant recipients was comparable to that observed in patients in the Phase 2 and 3 studies and most reactions were mild. Through post-market use, also angioedema has been reported.

Elevations in total bilirubin of at least 2 x upper limit normal (ULN) were observed in 1% of subjects related to glecaprevir-mediated inhibition of bilirubin transporters and metabolism. Bilirubin elevations were asymptomatic, transient, and typically occurred early during treatment. Bilirubin elevations were predominantly indirect and not associated with ALT elevations.

Hepatitis B virus reactivation Cases of hepatitis B virus (HBV) reactivation, some of them fatal, have been reported during treatment with direct-acting antiviral agents. All patients should be screened for HBV before initiation of treatment.

The data sheet does not give recommendations for patient monitoring of patients at risk, except if the patient is HBV/HCV co-infected or diabetic. According to Bpac information (16), patients without cirrhosis who are treated in primary care do not need blood tests for monitoring safety or efficacy during Maviret treatment. Neither HCV RNA assays during treatment is usually necessary. However, a follow-up visit after four weeks of treatment is recommended to discuss whether patients are experiencing any adverse effects.

The effectiveness of treatment in eradicating HCV infection is determined by conducting an HCV RNA assay or HCV core antigen assay 12 weeks after treatment has finished. Liver function tests can be ordered at the same time in order to assess whether additional follow-up is required.

Comments: South Korea published guidelines for treatment of chronic hepatitis C in 2017 (17). There it is stated that elevation of ALT more than 5 times the upper limit of normal was reported in 3 to 4% of patients on asunaprevir, and in 1% of patients at week 4 on treatment including paritaprevir (in Viekira Pak) or including grazoprevir at week 8 (in Zepatier). Bilirubin elevation more than 2.6 times the upper limit of normal was reported in 1% of asunaprevir treated patients. Therefore, frequent monitoring of liver function is required.

It is also stated that hepatic decompensation and hepatic failure, including liver transplantation or fatal outcomes, have been reported in patients treated with ombitasvir/paritaprevir/ritonavir and dasabuvir (Viekira Pak), mostly in patients with advanced cirrhosis, warranting close monitoring. Asunaprevir (Sunvepra), paritaprevir (in Viekira Pak) and grazoprevir (in Zepatier) are all protease inhibitors.

For glecaprevir/pibrentasvir (Maviret), the guideline does not mention elevation of ALT or bilirubin as a problem.

2.4.6 Usage data

Maviret was funded in February 2019. Usage data from Pharmaceutical Collection shows that since then there has been [redacted]. The number of dispensings have decreased over time, see figure below.

Sixty-five percent of the patients were male. Figure 4 shows the ethnicity and age of patients receiving Maviret.

Figure 3: Number of Maviret dispensings per month from February – December 2019.

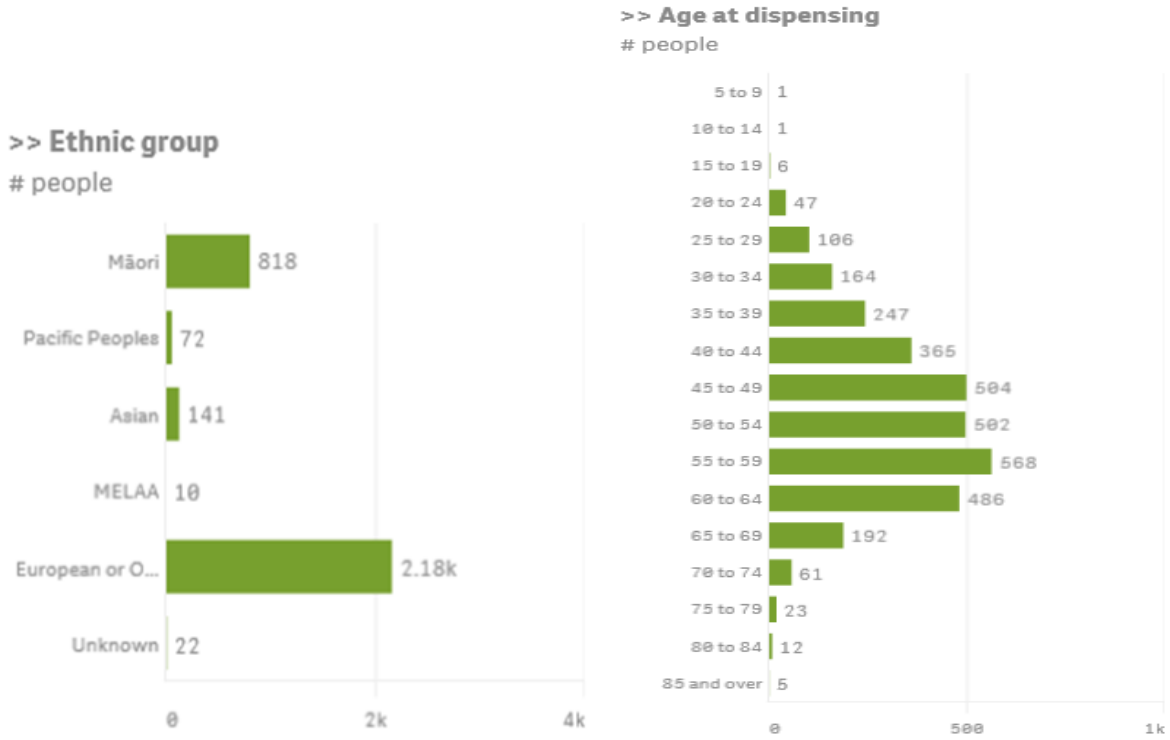

Figure 4: Ethnicity and age of patients prescribed Maviret.

Comments: Maviret is usually prescribed for one month at the time. It is unclear why amount of dispensings have decreased over time.

2.5 Data sheets

2.5.1 New Zealand (updated 9 April 2020)

The NZ data sheet does not list hepatic decompensation or hepatic failure as adverse reactions or advice on monitoring of liver function (13).

The CMI, last updated December 2019, lists the following symptoms to be aware of: feeling very tired, headache, nausea, swelling of the face, lips, tongue or throat and itching. No specific liver related symptoms are listed. However, the CMI includes the following text: 'Tell your doctor or pharmacist as soon as possible if you do not feel well while you are taking Maviret' (18).

2.5.2 US (updated 8 May 2020)

The US product information for Mavyret contains the following information under 'Warning and precautions' (19):

Risk of Hepatic Decompensation/Failure in Patients with Evidence of Advanced Liver Disease

Postmarketing cases of hepatic decompensation/failure, including those with fatal outcomes, have been reported in patients treated with HCV NS3/4A protease inhibitor-containing regimens, including MAVYRET. Because these events are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

The majority of patients with severe outcomes had evidence of advanced liver disease with moderate or severe hepatic impairment (Child-Pugh B or C) prior to initiating therapy with MAVYRET, including some patients reported as having compensated cirrhosis with mild liver impairment (Child-Pugh A) at baseline but with a prior decompensation event (i.e., prior history of ascites, variceal bleeding, encephalopathy). Rare cases of hepatic decompensation/failure were reported in patients without cirrhosis or with compensated cirrhosis (Child-Pugh A); many of these patients had evidence of portal hypertension. Events also occurred in patients taking a concomitant medication not recommended for coadministration, or in patients with confounding factors such as serious liver-related medical or surgical comorbidities. Cases typically occurred within the first 4 weeks of treatment (median of 27 days).

In patients with compensated cirrhosis (Child Pugh A) or evidence of advanced liver disease such as portal hypertension, perform hepatic laboratory testing as clinically indicated; and monitor for signs and symptoms of hepatic decompensation such as the presence of jaundice, ascites, hepatic encephalopathy, and variceal hemorrhage. Discontinue MAVYRET in patients who develop evidence of hepatic decompensation/failure.

In the section Adverse reactions, post-market experience, the following is listed:
Hepatobiliary Disorders: Hepatic decompensation, hepatic failure

2.5.3 Australia (updated 19 March 2020)

The Australian product information for Maviret does not list hepatic decompensation or hepatic failure as adverse reactions or advice on monitoring of liver function (20).

2.5.4 UK (updated 30 April 2020)

The UK product information for Maviret does not list hepatic decompensation or hepatic failure as adverse reactions or advice on monitoring of liver function (21).

2.5.5 Canada (updated 28 February 2020)

The Canadian product information for Maviret does not list hepatic decompensation or hepatic failure as adverse reactions or advice on monitoring of liver function (22).

3.0 SCIENTIFIC INFORMATION

3.1 Published literature

A literature search for publications on protease inhibitors and hepatic adverse reactions resulted in a few case reports and one publication only, which are described below.

3.1.1 Yoon JH et al 2019. A case report of glecaprevir/pibrentasvir-induced severe hyper-bilirubinemia in a patient with compensated liver cirrhosis (23)

A 77-year-old man with chronic hepatitis C-related compensated liver cirrhosis visited hospital due to severe jaundice after 3 weeks of glecaprevir/pibrentasvir treatment.

He had previously been treated for hepatic carcinoma and tuberculosis. The tuberculosis medicines included rifampicin and as there is an interaction between Maviret and rifampicin, the hepatitis C treatment had started 3 months after the pulmonary tuberculosis treatment ended. He also had underlying hypertension and benign prostate hyperplasia.

When he came to hospital, the total/direct bilirubin level was markedly elevated to 21.56 from 1.81 mg/dL while the alanine aminotransferase and aspartate aminotransferase levels were within normal range. The plasma drug concentration level of glecaprevir was more than 15 times higher than the drug concentration level verified in normal healthy adults.

Glecaprevir/pibrentasvir was stopped and after 2 months the serum total bilirubin levels had normalised. Twelve weeks after the end of treatment and HCV RNA could not be detected.

The advice is to monitor patients closely during follow-up laboratory exams, especially if they are elderly and cirrhotic.

Comment: The case report is partly confusing as stated time periods do not match between abstract and the more detailed description of the case. Elevations in total bilirubin of at least 2 x upper limit normal (ULN) is listed as an adverse reaction in the data sheet. Note that the patient only got treatment with Maviret for 3 weeks but still no HCV RNA could be detected 12 weeks later.

3.1.2 Hammami MB et al 2019. Glecaprevir/pibrentasvir-associated acute liver injury in non-cirrhotic, chronic HCV infection without HBV co-infection (24)

A woman aged 53 years with a 20-year history of treatment-naïve, chronic HCV infection (genotype 1b) had grade 3 hepatitis and stage 2 portal and periportal fibrosis and no cirrhosis on a liver biopsy performed 1 year prior. CT of the abdomen before starting treatment with glecaprevir/pibrentasvir showed normal liver contour with no cirrhotic changes, normal spleen size and no ascites.

Two weeks into treatment, she experienced fatigue that was complicated over 1 week by abdominal pain, vomiting and jaundice, which prompted hospitalisation. AST, ALT and bilirubin levels were elevated more than 10 times baseline levels. A CT of the abdomen and pelvis with contrast showed a mild hepatic periportal oedema consistent with acute hepatitis.

Treatment was stopped after completion of 3 weeks and symptoms resolved 1 week later. Fourteen weeks after treatment was stopped, HCV RNA was undetectable indicating sustained virologic response (SVR).

The authors discuss whether the acute liver injury was caused by glecaprevir, pibrentasvir or their combination. It could be an effect of protease inhibitors. However, this patient had contaminant diseases and was on pantoprazole and budesonide. Glecaprevir is largely metabolised by the liver, and so is pantoprazole and budesonide, potentially increasing the risk of drug-drug interactions and subsequent liver injury.

This is one of the cases found in the ADIS data base, see section 3.1.5.

Comments: Budesonide and pantoprazole are largely metabolised by cytochrome P450. According to the data sheet, Glecaprevir and pibrentasvir are weak inhibitors of cytochrome P450 (CYP) 3A, CYP1A2, and uridine glucuronosyltransferase (UGT) 1A1, and significant interactions are not expected via this mechanism. Even if omeprazole is on the data sheet list of medicines without clinically significant interactions with Maviret, pantoprazole and budesonide are not. Note that also this patient had undetectable HCV RNA after 3 weeks of treatment.

3.1.3 Livertox. 2018 Clinical and Research Information on Drug-Induced Liver Injury: Glecaprevir, Grazoprevir and Simeprevir (6)

This publication describes protease inhibitors in general and also includes additional sections about individual protease inhibitors, sometimes including case reports.

Glecaprevir and grazoprevir

While therapy with Mavyret or Zepatier can be associated with transient mild-to-moderate serum aminotransferase elevations, these medicines have not been convincingly linked to cases of clinically apparent liver injury, such as acute decompensation of HCV-related cirrhosis. As for all DAAs, there is a risk of reactivation of hepatitis B in susceptible patients.

Simeprevir

Simeprevir (Olysio) is one of the older protease inhibitors. In large randomized controlled trials, simeprevir was not linked to an increased rate of serum enzyme elevations during treatment or with instances of clinically apparent liver injury. Simeprevir could cause a mild increase in serum indirect bilirubin and some patients became jaundiced.

After its approval and more wide scale use, however, simeprevir has been implicated in at least one case of an acute hepatitis (Case 1). The latency to onset was 7 weeks and pattern of injury was hepatocellular without immunoallergic or autoimmune features. Recovery was rapid and complete once therapy was stopped.

Simeprevir, in combination with other agents, has also been linked to rare instances of acute, seemingly spontaneous decompensation of HCV related cirrhosis (see Case 2). This complication is probably more common in patients with more advanced liver disease, Child's Class B cirrhosis and those with a previous history of liver decompensation. The role of simeprevir as opposed to the other HCV antivirals used in combination was often unclear and the decompensation may also be incidental and unrelated to the antiviral therapy.

Case 2 concerned a man with genotype 1a, and Child's Class B cirrhosis who developed worsening fatigue, anorexia and jaundice with rises in serum ALT and INR 4 weeks after starting oral therapy with simeprevir and sofosbuvir. He had a history of excessive alcohol use but had stopped drinking years before. The treatment was stopped, and he underwent a successful liver transplantation 4 weeks later and was also found to be HCV RNA negative.

The advice is to monitor patients closely, especially during the first 4 weeks.

3.1.4 Gane E et al. 2019 Safety and Pharmacokinetics of Glecaprevir/Pibrentasvir in Adults with Chronic Genotype 1–6 Hepatitis C Virus Infections and Compensated Liver Disease (7)

This was an integrated analysis reporting the safety, efficacy, and pharmacokinetics of glecaprevir/pibrentasvir (G/P) in patients with chronic HCV genotype 1–6 infections and compensated liver disease, including patients with chronic kidney disease stages 4 or 5 (CKD 4/5). The authors came

from New Zealand, Canada, Germany, US, France and Belgium and the study (as well as the 9 studies included in the analysis) were sponsored by the company behind Maviret.

Method

Data from 9 Phase II and III clinical trials, assessing the efficacy and safety of G/P treatment for 8–16 weeks, in all patients who received at least one dose of G/P were included. The presence of cirrhosis was determined at screening using a liver biopsy, transient elastography, or serum biomarkers.

Patients with decompensated liver disease were excluded. Patients were treatment naïve or had prior treatment experience with interferon (IFN)/pegylated IFN ± RBV or sofosbuvir + RBV ± pegylated IFN or (for one study) prior treatment failures with NS5A inhibitors and/or NS3/4A protease inhibitors.

The primary objective was to determine the safety of G/P by evaluating the characteristics of reported adverse events (AEs) and the number and percentage of G/P-treated patients who reported treatment-emergent AEs and laboratory abnormalities, both in total and stratified by cirrhosis status and the presence or absence of CKD stages 4 or 5. Patients were monitored for AEs throughout G/P treatment and until 30 days post-treatment for nonserious and serious AEs and up to 24 weeks post-treatment for all spontaneously reported serious AEs. Additional objectives included the rate of sustained virologic response at post-treatment week 12 (SVR12), and steady-state PK by cirrhosis status.

Results

Among 2369 patients, 308 (13%) were Child-Pugh Class A and 304 of these had compensated cirrhosis, including 20 with CKD 4/5. Overall, <1% of patients experienced an adverse event (AE) that led to G/P discontinuation or G/P-related serious AEs (SAEs).

The most common AEs were headache and fatigue, occurring at similar frequencies with (74%) and without (67%) cirrhosis. SAEs were more common in patients with CKD 4/5, but all were unrelated to G/P.

There were no cases of drug-induced liver injury or clinically relevant hepatic decompensation. De novo HCC (hepatic carcinoma) was reported in 6 patients (5 with compensated cirrhosis), of which 3 cases were classified as treatment-emergent based on criteria described in the Methods. None were considered related to G/P but were considered related to underlying cirrhosis or long-standing chronic HCV infection.

No ALT elevations consistent with hepatotoxicity were seen. Grade 3 (>3 × upper limit of normal) elevations in total bilirubin occurred in approximately 1% of patients, regardless of cirrhosis status, and most of these patients had pre-existing indirect bilirubin elevations (Grade 1 or 2). Most Grade 3 elevations in total bilirubin were transient.

PK analysis demonstrated a 2.2-fold increase in glecaprevir exposure, but not pibrentasvir exposure, in patients with compensated cirrhosis.

The authors note that first-generation protease inhibitors, such as simeprevir, paritaprevir, and asunaprevir, were associated with safety concerns in patients with cirrhosis, such as elevations in alanine aminotransferase (ALT). Next-generation protease inhibitors, like grazoprevir, glecaprevir, and voxilaprevir, exhibit more favourable safety profiles in patients with compensated cirrhosis, including low (<2%) rates of clinically relevant ALT elevations.

Comments: This study only includes patients with no or mild liver impairment and it is a summary of clinical trials, so no post-market use included. Most of the FDA cases involved patients with Child-Pugh Class B or C, however some patients were possibly Child-Pugh A.

3.1.5 ADIS Insight

[redacted]

3.1.6 Vigilyze

[redacted]

[redacted]

[redacted]

[redacted]

3.1.7 Regulatory action – other countries than US

Japan

In February 2019, the Japanese PMDA (The Pharmaceuticals and Medical Devices Agency) decided to amend the package insert for Maviret to include:

1. A cautionary statement concerning 'Hepatic impairment, jaundice' in the Important Precautions section.

2. Addition of a Clinically Significant Adverse Reactions section with 'Hepatic impairment, jaundice' listed within.

The background of the revision was reports of 11 cases of hepatic impairment (including 5 cases for which a causal relationship to the product could not be ruled out) over the last 3 years in Japan. One patient had died, but a causal link to the product could not be established. PMDA concluded that revision of the package insert was necessary based on the results of their investigation of the currently available evidence and in consultation with expert advisors.

Abbvie analysed the adverse reaction reports from Japan and concluded that the data did not support a safety concern related to hepatic function disorders and hepatic laboratory abnormalities (25).

Comments: No regulatory action relating to protease inhibitors used in chronic hepatitis C and liver reactions has been taken by regulatory authorities in Canada, Australia or by the EMA. The company informed Medsafe in February 2019 that 'based on AbbVie's ongoing evaluation of global safety data, to date, existing data do not indicate a safety concern related to hepatic dysfunction in GLE/PIB-treated patients.' Therefore, the Company Core Data Sheet was not updated.

3.2 Company report

3.2.1 Abbvie Limited

[redacted]

[redacted]

3.3 CARM data

CARM has received a total 45 reports related to Maviret (glecaprevir + pibrentasvir) and there are no reports of any liver related adverse reactions.

CARM has not received any reports for Zepatier or Vosevi.

4.0 DISCUSSION AND CONCLUSIONS

In 2019, FDA issued a warning regarding rare occurrence of serious liver injury with use of hepatitis C medicines Maviret, Zepatier, and Vosevi in some patients with advanced liver disease. As a result of the warning, US product information has been updated with this rare adverse reaction and the need to monitor patients at risk for signs and symptoms of hepatic decompensation.

Maviret, Zepatier, and Vosevi all contain protease inhibitors. All three medicines are approved in NZ but Zepatier and Vosevi are not available. Maviret was approved in NZ in June 2018 and PHARMAC funding started on 1 Feb 2019 with about 3000 patients accessing treatment since funding started. This report focused on Maviret.

Maviret can be used for treatment of all genotypes of HCV in patients with no or mild liver impairment (Child-Pugh A). It is not recommended for patients with moderate liver impairment (Child-Pugh B) and is contraindicated if liver impairment is severe (Child-Pugh C). The reason is that exposure, especially for glecaprevir, is heavily increased in patients with impaired liver function which increases the risk of adverse reactions.

However, in clinical practice, health care providers could use GLE/PIB in specific patients with moderate hepatic impairment in whom the benefits of using GLE/PIB may outweigh the risks.

No hepatic adverse reactions are listed in the data sheet for Maviret. Patients with Child-Pugh B or C were excluded from clinical trials. Data on potential hepatic adverse reactions in association with Maviret use are very limited and consist of case reports.

No cases describing liver injury have been reported in NZ. The reported international cases contain some uncertainties. More than half of the FDA cases (note: cases reported for Maviret, Zepatier and Vosevi) that reported Child-Pugh A at baseline were incorrectly classified patients who had signs and symptoms of moderate to severe liver impairment or other serious liver problems and should not have been treated with these medicines.

For other case reports there were several other factors that could have contributed to the liver injury, such as concomitant illness and medication, pre-existing risk factors (e.g. decreased platelets at baseline or portal hypertension), alcohol abuse or the natural history of progression of the liver disease.

There is currently not enough evidence to support a casual association between Maviret, used the way it is intended to, and serious liver injury. However, it is still important to ensure that patients meet the indication criteria, liver status is monitored for patients at risk and that patients know to contact their health care professional if they experience symptoms from the liver.

The data sheet currently does not include advice on monitoring of patients at risk. Monitoring of patients with cirrhosis who are treated in primary care is described in Bpac guidelines as not needed. However, Bpac recommends a visit after 4 weeks of treatment.

There is no advice on monitoring of patients with cirrhosis or patients with moderate hepatic impairment (Child Pugh B). Maviret is not recommended for patients with Child-Pugh B but is likely to be used if benefits outweighs the risk. The warning statement does not include the reason for why it is not recommended (due to likely increase of in glecaprevir levels).

The CMI does not include to watch out for symptoms from the liver as such but instructs patients to contact HCP if they are feeling unwell.

5.0 ADVICE SOUGHT

The Committee is asked to advise whether:

- The data sheets for protease inhibitors used for treatment of hepatitis C should be updated regarding the risk of serious liver injury.
- This topic requires further communication other than MARC's Remarks in *Prescriber Update*.

6.0 REFERENCES

1. Food and Drug Administration. FDA warns about rare occurrence of serious liver injury with use of hepatitis C medicines Mavyret, Zepatier, and Vosevi in some patients with advanced liver disease 2019 [19 May 2020]. Available from: https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-rare-occurrence-serious-liver-injury-use-hepatitis-c-medicines-mavyret-zepatier-and.

2. NZ Ministry of Health. Hepatitis C 2019 [19 May 2020]. Available from: https://www.health.govt.nz/your-health/conditions-and-treatments/diseases-and-illnesses/hepatitis-c.

3. The Hepatitis Foundation of NZ. Hepatitis C [19 May 2020]. Available from: https://www.hepatitisfoundation.org.nz/hepatitis/hepatitis-c.

4. UpandGo. Overview of the management of chronic hepatitis C virus infection 2018 [11 May 2020]. Available from: https://www.uptodate.com/contents/overview-of-the-management-of-chronic-hepatitis-c-virus infection?search=hepatitis%20c&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1).

5. UpandGo. Clinical manifestations and natural history of chronic hepatitis C virus infection 2019 [11 May 2020]. Available from: https://www.uptodate.com/contents/clinical-manifestations-and-natural-history-of-chronic-hepatitis-c-virus-infection?search=hepatitis%20c&source=search_result&selectedTitle=5~150&usage_type=default&display_rank=5.

6. livertox.nih.gov. LiverTox: Clinical and Research Information on DrugInduced Liver Injury, Protease Inhibitors (HCV) 2018 [20 May 2020]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK548887/

7. Gane E, Poordad F, Zadeikis N, Valdes J, Lin CW, Liu W, et al. Safety and Pharmacokinetics of Glecaprevir/Pibrentasvir in Adults With Chronic Genotype 1-6 Hepatitis C Virus Infections and Compensated Liver Disease. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2019 Oct 30;69(10):1657-64. PubMed PMID: 30923816. Pubmed Central PMCID: PMC6821220. Epub 2019/03/30. eng.

8. US Department of Veterans Affairs. Viral hepatitis and Liver disease. Stages of cirrhosis [11 May 2020]. Available from: hepatitis.va.gov/cirrhosis/background/stages.asp.

9. NPS Medicinewise. Prescribing in liver disease 2009 [19 May 2020]. Available from: https://www.nps.org.au/australian-prescriber/articles/prescribing-in-liver-disease-1.

10. Park HK Lee SS et al. Hepatitis C virus genotype affects survival in patients with hepatocellular carcinoma. BMC Cancer. 2019;19(1):822. Published 2019 Aug 20. doi:10.1186/s12885-019-6040-3. BMC Cancer. 2019;19(1):822.

11. Health Navigator. Hepatitis C 2020 [19 May 2020]. Available from: https://www.healthnavigator.org.nz/health-a-z/h/hepatitis-c/.

12. UpandGo. Direct-acting antivirals for the treatment of hepatitis C virus infection 2019 [10 May 2020]. Available from: https://www.uptodate.com/contents/direct-acting-antivirals-for-the-treatment-of-hepatitis-c-virus-infection?search=hepatitis%20c%20treatment&source=search_result&selectedTitle=10~150&usage_type=default&display_rank=10.

13. AbbVie Limited. Maviret NZ data sheet 2018 [updated 9 April 202019 May 2020]. Available from: https://medsafe.govt.nz/profs/Datasheet/m/mavirettab.pdf.

14. AbbVie. Maviret (patient information) 2020 [19 May 2020]. Available from: https://maviret.co.nz/?gclid=CjwKCAjw-YT1BRAFEiwAd2WRtqNmv0YRXyzCMsBt-8ifAR--4_VUb4NhHXd0YFHCad9UrPUYem38aBoCJEYQAvD_BwE.

15. Levien TL Baker DE. Formulary Drug Reviews: Glecaprevir/ Pibrentasvir. Hospital pharmacy. 2018;53(2):75-84.

16. The Best Practice Advocacy Centre, Bpac. Management and follow-up of patients prescribed glecaprevir+pibrentasvir 2019 [19 May 2020]. Available from: https://bpac.org.nz/2019/hepc/management.aspx.

17. The Korean Association for the Study of the Liver. 2017 KASL clinical practice guidelines management of hepatitis C: Treatment of chronic hepatitis C. Clin Mol Hepatol. 2018;24(3):169-229.

18. AbbVie Limited. New Zealand Consumer Medicine Information Maviret 2019 [20 May 2020]. Available from: https://medsafe.govt.nz/Consumers/cmi/m/maviret.pdf.

19. AbbVie Inc. Mavyret US Drug Label Information 2020 [20 May 2020]. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=7bf99777-0401-9095-8645-16c6e907fcc0.

20. AbbVie Limited. Maviret Australian PI 2020 [20 May 2020]. Available from: https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2018-PI-01074-1&d=202005191016933.

21. AbbVie Ltd. Maviret UK Product Information 2020 [20 May 2020]. Available from: https://www.medicines.org.uk/emc/product/763/smpc.

22. AbbVie Corporation. Maviret Canadian Product Information 2020 [20 May 2020]. Available from: https://pdf.hres.ca/dpd_pm/00055691.PDF.

23. Yoon JH M, Kim SM et al. A case report of glecaprevir/pibrentasvir-induced severe hyperbilirubinemia in a patient with compensated liver cirrhosis. Medicine (Baltimore). 2019;98(39):e17343.

24. Hammami MB, Aboushaar R et al. Glecaprevir/pibrentasvir-associated acute liver injury in non-cirrhotic, chronic HCV infection without HBV co-infection. BMJ Case Rep 2019;12:e226622. doi:10.1136/bcr-2018-226622

25. Pharmaceuticals and Medical Devices Agency, Japan. Summary of Investigation Results Glecaprevir hydrate/pibrentasvir 2019 [20 May 2020]. Available from: https://www.pmda.go.jp/files/000228061.pdf.