New Zealand Hepatitis C Guideline for Antiviral Treatment of People who have Cirrhosis and/or are HCV Treatment-Experienced (Secondary Care Guideline)

Introduction

These guidelines are for treatment of Hepatitis C (HCV)-infected people with cirrhosis, or those who have already failed prior HCV treatment with interferon or direct acting antivirals, who should be treated in secondary care. All other patients should wherever possible be treated in primary care.

The guidelines have been written to reflect the New Zealand (NZ) funding environment, so focus primarily on medications that are funded or otherwise available in NZ.

All HCV-infected, treatment-naïve, noncirrhotic people should be treated with MAVIRET@ (glecaprevir/pibrentasvir) three tablets once daily for 8 weeks. MAVIRET@ has few side effects and requires no monitoring in patients without cirrhosis. Efficacy is greater than 99.5% in both clinical studies and the real-world series. This safe, effective and simple regimen is ideal for GP prescribing. GP engagement is vital to improve awareness, testing and linkage to care, all necessary if New Zealand is to meet the WHO targets of HCV elimination. There are separate NZ guidelines for treatment of this group of people in primary care (1).

1. Assessment and Investigations of Anti-HCV Positive Person Prior to Considering HCV Antiviral Therapy

Clinical assessment:

- Prior or current symptoms of liver decompensation
- Cofactors for liver disease
- Signs of chronic liver disease

Medication History

- Carefully document any prior HCV therapy including date, regimen and response
- Check prescribed, OTC, supplements and complementary and alternative medicines, recreational drugs for drug-drug interactions (DDI) with proposed antiviral regimen. NZ Formulary http://nzformulary.org/ or www.hep-druginteractions.org

Liver fibrosis assessment:

- Evaluation of liver fibrosis stage must be made prior to initiation of antiviral therapy
- If APRI≥1 then transient elastography/ Fibroscan® should be performed

- Transient elastography: Fibroscan® ≥12.5KPa confirms cirrhosis
- Some people with Fibroscan® score between 10-12.5KPa may be regarded as cirrhotic if there is additional evidence to suggest cirrhosis. e.g. thrombocytopaenia, ultrasound (USS) features of portal hypertension.

Bloods:

- CBC, LFT (includes albumin), INR, creatinine and sodium
- Hepatitis C RNA/viral load if previous result not available.
- HCV Core Antigen testing will soon be provided by community laboratories. All HCV Ab positive samples will be reflex tested for HCV Core Ag test, providing immediate confirmation of active infection, without the need for further blood sample. The HCV Core Ag test is significantly cheaper than HCV RNA test.
- HCV Genotyping is not required in treatment-naïve people without cirrhosis or with compensated cirrhosis because MAVIRET@ is pangenotypic. Genotyping may be useful in treatment failures and patients with decompensated cirrhosis (because regimens may differ depending on HCV genotype)
- Hepatitis B virus (HBV) HBsAg, anti-HBc, anti-HBs, Hepatitis A virus (HAV), HIV serology
  - Vaccinate if non-immune to HBV or HAV
  - If active HBV coinfection (i.e. HBsAg positive), there is a small (approximately 9%) risk of HBV reactivation-related hepatitis when HCV is suppressed by DAAs (2).
    - If patient meets criteria for starting oral antiviral therapy at baseline (noncirrhotic and ALT >ULN and HBV DNA >3 logs OR cirrhotic and HBV DNA detectable) then start entecavir or tenofovir during DAA therapy and continue long-term
    - If patient does NOT meet criteria for starting oral antiviral therapy at baseline, then monitor for flares/reactivation during direct acting antiviral (DAA) therapy. Check ALT and HBV DNA after 4 and 8 weeks and start entecavir or tenofovir if HBV DNA increases >1 log above baseline AND ALT increases >2xULN.
  - If resolved HBV infection (i.e. HBsAg negative and anti-HBcore positive), there is minimal risk of virus reactivation (1.4%) but no HBV reactivation-related hepatitis has been reported to date (2) and so no specific on-treatment monitoring is recommended.

2. HCV Antiviral Therapy in Compensated Cirrhosis (Treatment Naïve)

Additional investigations in those with cirrhosis:

- USS/AFP to exclude hepatocellular carcinoma (HCC)
- Gastroscopy to screen for varices if:
  - Platelets <150 x10(9)/L or
  - Fibroscan® ≥ 20KPa (3), or
  - Features of portal hypertension seen on USS
  - Clinical decompensation
- Calculate Child-Turcotte-Pugh (CTP) Score (see Appendix 1)

  MAVIRET® is absolutely contraindicated in patients with CTP Class C.

  MAVIRET® is not recommended in those with CTP-Class B, or prior episodes of decompensation.

  Any patient with CTP-Class B or C can be considered for treatment with sofosbuvir-based regimens including HARVONI® plus ribavirin (Section 3).

Drug-Drug interactions

- DDIs are relatively uncommon with MAVIRET®. The few important DDIs are ethinyl oestradiol (combined OC, HRT), statins, and some anticonvulsants and HIV medicines. Please check any concomitant meds on http://hep-druginteractions.org/

Treatment with Glecaprevir/Pibrentasvir (MAVIRET®):

- MAVIRET® (fixed dose combination of glecaprevir 100mg /pibrentasvir 40mg): 3 tablets once daily with food. No dose adjustment required in renal impairment.
- Treatment duration: 12 weeks for all HCV genotypes 1-6.
- Monitor LFT, INR monthly during treatment.

Sustained virological response (SVR) or cure

SVR rates are 97-100% with MAVIRET® treatment (4-7). If patients who are lost to follow-up after treatment are excluded, then the SVR rate is 99.5%. Check LFT, HCV viral load 12 weeks after end of treatment.

- *HCV viral load undetectable*
  - Sustained virologic response achieved
  - No indication for further HCV viral load testing unless risk of reinfection exists
  - If LFT remain abnormal then complete full liver screen for other liver pathology
- *HCV detectable:*
  - SVR not achieved
  - Check HCV genotype (HCV GT) and send blood to LabPlus Auckland for HCV NS5A resistance testing-include detail of previous HCV therapy
  - Consider retreatment if possible (see Section 4)

Follow-up in all patients with cirrhosis:

- Continue HCC surveillance*- 6 monthly USS +/-AFP (EASL and AASLD guidelines also recommend HCC surveillance in people with F3 fibrosis).
- Lifestyle/risk factor advice- abstinence from alcohol, healthy diet (including bedtime snacks), exercise, avoid cannabis.
- Monitor for signs of clinical or biochemical decompensation.

Recommended Treatment for Treatment Naïve Compensated Cirrhosis (Child Pugh A)		
Regimen	Genotypes	Duration
Glecaprevir/Pibrentasvir (MAVIRET®)	1, 2, 3, 4, 5, 6	12 weeks

3. HCV Antiviral Therapy in Decompensated Cirrhosis

Additional Investigations/Considerations in those with Liver Decompensation:

- HCV genotype (GT) should be tested in all people with decompensated cirrhosis
- Calculate CTP (Appendix 1) and MELD scores (http://www.mdcalc.com/original-meld-score-pre-2016-model-for-end-stage-liver-disease/)
  Consider discussion with NZLTU physician prior to antiviral treatment if:
  - MELD ≥15 or previous clinical decompensation
  - Current significant clinical decompensation and patient is a potential candidate for liver transplantation
  - Patients with CTP Class C should be considered for transplantation and if eligible, should be treated after liver transplantation with MAVIRET, with NZLTU advice.
- Perform baseline ECG if >50 years or person with cardiac risk factors
- Contraception: Ribavirin is teratogenic so both men and women should be counselled about the risks of pregnancy and should be advised that two forms of contraception are required while taking ribavirin, and for 6 months after treatment.

Therapeutic Options in New Zealand

Option 1: HARVONI® (Ledipasvir/Sofosbuvir) with Ribavirin

HARVONI® (ledipasvir 100mg/sofosbuvir 400mg fixed dose combination) with ribavirin is currently the only funded HCV antiviral therapy for decompensated cirrhosis in New Zealand. It is approved in NZ for all HCV genotypes.

- **HCV Genotypes 1,2,4:** HARVONI® with ribavirin is an effective therapy for HCV GT1,2 and 4 with decompensated cirrhosis. SVR rates were 86-87% in GT 1 and 4 in SOLAR-1 and SOLAR-2 studies with 12 weeks therapy in people with decompensated cirrhosis(8, 9).
- **HCV genotype 3:** HARVONI® is a suboptimal therapy for HCV GT 3 and significantly lower SVR rates are expected, but HARVONI® should be used if no other therapy is available. See below (Section3; Option 3) for alternative options for HCV GT 3.

Drug-Drug Interactions

- Check NZ Formulary http://nzformulary.org/ or www.hep-druginteractions.org
- Ledipasvir/sofosbuvir is contraindicated with amiodarone and for up to 3 months after discontinuing amiodarone (risk of life-threatening arrhythmias).
- Proton pump inhibitors and H2 R antagonists should be discontinued or used at lowest possible dose and taken at the same time as HARVONI®.

Treatment

- Application must be made by specialist to PHARMAC for ledipasvir/sofosbuvir (Harvoni®) plus ribavirin funding https://www.pharmac.govt.nz/2016/06/30/SA1605.pdf
- HARVONI® - one tablet once daily (with or without food) plus weight-based ribavirin is funded for 12 weeks, or 24 weeks if ribavirin is contraindicated.
- No dose adjustment required for mild-moderate renal impairment.

- Severe renal impairment (eGFR<30ml/min) or end stage renal disease: higher exposures of sofosbuvir metabolite GS-331007 occur, but there is no evidence of toxicity in Gilead or real-world studies. There has been no recent update on dose recommendation in ESRD but there is now considerable safety data to support use of standard dosing of sofosbuvir, HARVONI® and EPCLUSA® in this patient group if risk benefit ratio is carefully considered (10, 11).
- Ribavirin dosing is weight-based:
  - Weight ≥75Kg- 600mg BD
  - Weight <75Kg: ribavirin 600mg mane, 400mg nocte
  - Consider lower ribavirin initial dose of 600mg/day if:
    - Significant clinical hepatic decompensation (Child Pugh C)
    - Mild-moderate renal impairment
    - Baseline anaemia
  - In ESRD ribavirin dose should be reduced to 200mg/day with close monitoring

Monitoring during treatment:

- Haemoglobin, LFT, INR monthly
- Mild-moderate anaemia is common with ribavirin therapy. Dose reduce ribavirin if haemoglobin decreases below 100g/L or symptomatic.

Option 2: Sofosbuvir/Velpatasvir with Ribavirin
(Non-funded recommended therapy for HCV genotype 3 with decompensated cirrhosis)

Recommended therapy for HCV genotype 3 with decompensated cirrhosis is daily fixed dose combination of sofosbuvir (400mg)/velpatasvir (100mg) with ribavirin for 12 weeks. SVR of 85% was found with this regimen in the ASTRAL-4 study(12).

Sofosbuvir/Velpatasvir is approved in NZ (as EPCLUSA®) but is not currently funded.

Options for private purchase of sofosbuvir/velpatasvir plus ribavirin:

a. Self-funded generic sofosbuvir/velpatasir and ribavirin through the Fix Hep C Buyers Club.(https://fixhepc.com/buyers-club.html) Approximate cost $2000 for 12 weeks
b. Self-funded branded EPCLUSA@ from Gilead Sciences. Approximate cost $70000

Recommended Treatment for Treatment Naïve Decompensated Cirrhosis			
Regimen	Genotypes	Duration	Comments
Ledipasvir/Sofosbuvir (HARVONI®) with Ribavirin	1, 2, 3, 4, 5, 6	12 weeks	Funded in NZ Suboptimal for GT3 HCV
Sofosbuvir/Velpatasvir (EPCLUSA®) with Ribavirin	1,2,3,4,5,6	12 weeks	Unfunded in NZ Optimal for GT3 HCV

4. HCV Antiviral Therapy for People with Prior Treatment Experience

These guidelines only refer to prior antiviral therapies that have been funded or widely available in New Zealand. There may be some people who have previously received other therapies overseas or in the context of a clinical trial. In this situation it is essential to determine exactly what therapy has been received and discuss with an HCV expert.

Investigations:

- **HCV Genotyping**: all HCV treatment-experienced patients should have HCV genotype testing performed. If HCV GT has changed, this may help to differentiate reinfection from virological failure/relapse. If reinfection is present then retreatment is appropriate.
- **Fibroscan®:** non-cirrhotic patients should have recent Fibroscan® (within 1 year) to confirm presence or absence of cirrhosis prior to retreatment of HCV.
- **NS5A resistance testing:** for those with prior NS5A treatment experience (see section 4.4)

4.1 Treatment of HCV in People with Prior Interferon Experience: Received Interferon but no Prior DAA Experience

Option 1: MAVIRET®

MAVIRET® is appropriate therapy for all non-cirrhotic patients and patients with compensated cirrhosis who have prior treatment experience with interferon-based therapy who have not been treated with direct acting antiviral drugs (DAAs).

MAVIRET® Treatment Duration in Those with Prior Interferon Treatment:				
HCV Genotype	Non-cirrhotic Treatment Duration	SVR (reference)	Cirrhosis Treatment Duration	SVR (reference)
1a/1b	8 weeks	99% (13)	12 weeks	98% (4)
2	8 weeks	98% (14)	12 weeks	100% (4)
3	16 weeks	96%(15)	16 weeks	96%(15)
4	8 weeks	93%(14, 16)	12 weeks	100%(4)
5	8 weeks	100%(17, 18)	12 weeks	100%(18)
6	8 weeks	90%(17-19)	12 weeks	100%(18)

4.2 Treatment of HCV in people with prior DAA-treatment experience: Received NS3-Protease Inhibitor + Peginterferon/Ribavirin

This includes people who have only been exposed to a protease inhibitor DAA (e.g. peginterferon/ribavirin plus boceprevir or telaprevir) without an NS5A inhibitor.

Option 1: **MAVIRET®**

These people should be retreated with MAVIRET®

MAVIRET® treatment duration should be 12 weeks for HCV genotypes 1a and 1b.

SVR rate of 92% was seen in MAGELLAN-1 trial with this regimen (20).

This does NOT apply to those treated with combinations of PI and NS5A (e.g. VIEKIRA PAK®)

Recommended Treatment for Treatment Experienced with Interferon plus NS3/4 Protease Inhibitor			
Regimen	Genotypes	Duration	Comments
Glecaprevir/Pibrentasvir (MAVIRET®)	1a, 1b	12 weeks	cirrhotic and non-cirrhotic

4.3 Treatment of HCV in people with prior DAA-treatment experience: Received NS5A inhibitor + Sofosbuvir without NS3 Protease Inhibitor

Option 1: MAVIRET®

This includes prior treatment experience with sofosbuvir/ledipasvir or sofosbuvir/daclatasvir treatment failures, including generics purchased from the FixHepC Buyers Club.

The NZ MAVIRET® label recommends treatment of all HCV genotypes with prior treatment experience with an NS5A inhibitor plus sofosbuvir without an NS3/4 protease inhibitor to be treated with MAVIRET® for 16 weeks. However, there is only limited data from Magellan-1 Part 2 study to support this with SVR of 94% in 18 patients with HCV GT 1 or 4. There is no supporting trial data for other HCV genotypes including HCV GT3 (20).

Option 2: Sofosbuvir/Velpatasvir/Voxilaprevir (VOSEVI®; unfunded)

Other HCV guidelines recommend the fixed dose combination of sofosbuvir (400mg)/velpatasvir (100mg)/voxilaprevir (100mg) (VOSEVI®) for these people, particularly in HCV GT3 (21).

Recommended Treatment for Treatment Experienced with sofosbuvir plus NS5A Inhibitor			
Regimen	Genotypes	Duration	Comments
Glecaprevir/Pibrentasvir (MAVIRET®)	1,4,	16 weeks	Small trial numbers

Glecaprevir/Pibrentasvir (MAVIRET®)	2,3,5,6	?16 weeks	Approved in NZ label but no data
Sofosbuvir/Velpatasvir/Voxilaprevir (VOSEVI®)	1,2,3,4,5,6	12 weeks	Approved but not funded

4.4 Treatment of HCV in people with prior DAA-treatment experience: Received NS5A inhibitor + NS3 protease inhibitor, including VIEKIRA PAK®

Additional investigations:

NS5A Resistance testing:

- Blood should be sent for HCV NS5A resistance testing to assist decisions regarding further antiviral therapy. (This should be sent via local laboratory with instructions to send to LabPlus Auckland; requires 5x EDTA tubes and prior therapy should be stated on request form)
- People who were non-adherent with previous DAA therapy, or who achieved SVR and have reinfection will not usually have NS5A resistance, and if NS5A resistance is not detected they may be considered for MAVIRET therapy (Option 3).

Therapeutic Options in New Zealand

Option 1: MAVIRET® plus Sofosbuvir ± Ribavirin (off-label and partially funded)

An unlicensed DAA combination for retreatment, that appears effective with limited trial evidence, is to combine MAVIRET® with sofosbuvir +/- ribavirin in those without cirrhosis, or with compensated cirrhosis.

In MAGELLAN-3 study, 23 people who previously failed therapy with glecaprevir/pibrentasvir were retreated with MAVIRET® plus sofosbuvir 400mg/day plus ribavirin (22).

- People with HCV genotype 1,2,4,5,6 without cirrhosis, and naïve to NS3/4A protease inhibitors and NS5A inhibitors prior to virologic failure with glecaprevir/pibrentasvir received 12 weeks treatment.
- People with HCV genotype 3 and/or compensated cirrhosis (any genotype), and /or experience with NS3/4A protease and NS5A inhibitors prior to virologic failure with glecaprevir/pibrentasvir (any genotype) received 16 weeks treatment.

Overall SVR12 was 96% with this regimen – but note that this study had very small numbers.

In 2 Real World studies (23, 24), 31 people (including 27% GT3; 42% cirrhotic) who previously failed therapy with a regimen including both NS5A inhibitors and NS3 protease inhibitors were retreated with 12 weeks MAVIRET® plus sofosbuvir without ribavirin. All 19 patients who have had SVR12 tests were cured.

MAVIRET® is funded for HCV without restriction in New Zealand. However sofosbuvir +/- ribavirin therapy is approved but not funded. Options for private purchase of sofosbuvir plus ribavirin:

a. Self-funded generic sofosbuvir and ribavirin through the Fix Hep C Buyers Club (https://fixhepc.com/buyers-club.html) Approximate cost $900 for 12 weeks, $1200 for 16 weeks
b. Self-funded branded SOVALDI® from Gilead Sciences. Approximate cost $60,000 for 12 weeks, RBV accessed locally through NPPA

Option 2: Sofosbuvir/Velpatasvir/Voxilaprevir (VOSEVI®; approved but unfunded)

Recommended retreatment therapy for those who are either non-cirrhotic or have compensated cirrhosis and have received prior therapy with both an NS5A inhibitor and NS3 protease inhibitor is daily fixed dose regimen of sofosbuvir (400mg)/velpatasvir (100mg)/voxilaprevir (100mg) +/-ribavirin (for HCV genotype 3 cirrhosis) for 12 weeks (25).

This regimen is approved in NZ as VOSEVI®, but is not currently funded.

Option 3: MAVIRET®

Treatment guidelines do not recommend MAVIRET® for treatment of people previously exposed to the combination of both an NS5A inhibitor (e.g. ombitasvir, elbasvir or ledipasvir) and an NS3 protease inhibitor (e.g. paritaprevir, grazoprevir) because the combination of NS5A and NS3 resistance reduces the efficacy of retreatment with MAVIRET® to less than 50%.

This includes VIEKIRA PAK® and ZEPATIER® **(**elbasvir/grazoprevir**)** treatment failures (21, 26, 27).
However, other retreatment options are not fully funded in New Zealand. Therefore, it is reasonable to test VIEKIRA PAK® failures for NS5A resistance, and if NS5A RASs are not detected, then retreatment with MAVIRET® for 16 weeks may be given.

Recommended Treatment for Treatment Experienced with NS3 Protease Inhibitor plus NS5A Inhibitor including VIEKIRA PAK®			
Regimen	Genotypes	Duration	Comments
Glecaprevir/Pibrentasvir (MAVIRET®) plus Sofosbuvir ±Ribavirin	1,2,3,4,5,6	12-16 weeks (see text)	Not licenced Partial funding- MAVIRET® funded; sofosbuvir/ ribavirin unfunded
Sofosbuvir/Velpatasvir/Voxilaprevir (VOSEVI®)	1,2,4,5,6 (any) 3 (non-cirrhotic)	12 weeks	Approved but not funded
Sofosbuvir/Velpatasvir/Voxilaprevir (VOSEVI®) +Ribavirin	3 (cirrhotic)	12 weeks	Not funded
Glecaprevir/Pibrentasvir (MAVIRET®)	1	16 weeks	Funded. Only consider if NS5A RAS not detected

4.5 Treatment of HCV in people with prior DAA-treatment experience AND Decompensated cirrhosis:

Option 1: Sofosbuvir/Velpatasvir plus Ribavirin for 24 weeks (unfunded)

Options for private purchase of sofosbuvir/velpatasvir plus ribavirin:

a. Self-funded generic sofosbuvir/velpatasvir and ribavirin through the Fix Hep C Buyers Club (https://fixhepc.com/buyers-club.html) Approximate cost $3500
b. Self-funded branded EPCLUSA@ from Gilead Sciences. Approximate cost $150,000 (for 24 weeks). RBV accessed locally through NPPA

If person is a potential transplant candidate then physician should discuss with NZLTU prior to commencing therapy, as treatment may be more effective after transplantation.

Recommended Treatment for Decompensated Cirrhosis AND Prior DAA Experience			
Regimen	Genotypes	Duration	Comments
Sofosbuvir/Velpatasvir (EPCLUSA®) with Ribavirin	1,2,3,4,5,6	24 weeks	Not funded

Appendix 1: Child-Turcotte-Pugh Classification of Severity of Cirrhosis

Child -Turcotte-Pugh (CTP) Classification of the Severity of Cirrhosis			
Factor	**1 Point**	**2 Points**	**3 Points**
Total bilirubin (µmol/L)	<34	34-50	>50
Serum albumin (g/L)	>35	28-35	<28
INR	<1.7	1.71-2.3	>2.3
Ascites	None	Mild	Moderate to Severe
Hepatic encephalopathy	None	Grade I-II (or supressed with medication)	Grade III-IV (or refractory)

Child Pugh A 5-6 points
Child Pugh B 7-9 points
Child Pugh C 10-15 points

Appendix 2: Abbreviations

Abbreviation	Explanation
AFP	Alpha fetoprotein
APRI	AST to Platelet Ratio
CBC	Complete blood count
CTP	Child-Turcotte-Pugh
DAA	Direct acting antiviral drugs
DDI	Drug-Drug Interaction
ESRD	End Stage Renal Disease
GT	Genotype
HCC	Hepatocellular carcinoma
HAV	Hepatitis A virus
HBV	Hepatitis B virus
HCV	Hepatitis C virus
LFT	Liver function tests
MELD	Model of End Stage Liver Disease Score
NS3A	Nonstructural Protein 3A
NS5A	Nonstructural protein 5A
OTC	Over the counter medication
RAS	Resistance Associated Substitution
RBV	Ribavirin
SVR	Sustained virological response
USS	Ultrasound scan

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