NZ SOCIETY OF GASTROENTEROLOGY HCV TREATMENT GUIDELINES

Initial assessment

<table>
<thead>
<tr>
<th>Hepatitis C Virus virology</th>
<th>HCV Genotypes 2,3,4,5,6</th>
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<tbody>
<tr>
<td>Anti-HCV (serology) HCV RNA level (viral load) HCV GT</td>
<td>The approved treatments for patients with HCV GT 2-6 infection are: (i) VIEKIRA PAK±RBV (paritaprevir/ritonavir/ombitasvir + dasabuvir +ribavirin); (ii) SOVALDI (sofosbuvir/ledipasvir; and (iii) SOVALDI (sofosbuvir + peg-IFN/RBV or sofosbuvir +RBV). VIEKIRA PAK is funded for patients with HCV GT1, except for patients with decompensated cirrhosis (Child-Pugh B or C). Applications for VIEKIRA PAK should be submitted to PHARMAC. HARVONI is funded for Patients with MELD score ≥15. Applications for HARVONI should be submitted to the HepC Treatment Panel and not through NPHS or Special Authority forms.</td>
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</table>

Liver staging

| Liver Elastography Scan (Fibroscan or Shear Wave Elastography)†‡ | The approved treatments for patients with HCV GT 1 are: (i) VIEKIRA PAK±RBV (paritaprevir/ritonavir/ombitasvir with dasabuvir +ribavirin); (ii) HARVONI (sofosbuvir/ledipasvir; and (iii) SOVALDI (sofosbuvir + peg-IFN/RBV) or SOVALDI (sofosbuvir +RBV). VIEKIRA PAK is funded for patients with HCV GT1, except for patients with decompensated cirrhosis (Child-Pugh B or C). Applications for VIEKIRA PAK should be submitted to PHARMAC. HARVONI is funded for Patients with MELD score ≥15. Applications for HARVONI should be submitted to the HepC Treatment Panel and not through NPHS or Special Authority forms. |

Evidence of decompensated chronic liver disease

<table>
<thead>
<tr>
<th>Physical Examination</th>
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<tr>
<td>LFTs and INR</td>
<td>Physical Examination</td>
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<tr>
<td>Ultrasound</td>
<td>Physical Examination</td>
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<tr>
<th>Additional laboratory data</th>
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<tr>
<td>Haemoglobin and platelet count</td>
<td>Additional laboratory data</td>
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</table>

HCV Genotype 1

Pre-treatment assessment for access to treatment with DAAs

The approved treatments for patients with HCV GT 1 are: (i) VIEKIRA PAK±RBV (paritaprevir/ritonavir/ombitasvir with dasabuvir +ribavirin); (ii) HARVONI (sofosbuvir/ledipasvir; and (iii) SOVALDI (sofosbuvir + peg-IFN/RBV or sofosbuvir +RBV). VIEKIRA PAK is funded for patients with HCV GT1, except for patients with decompensated cirrhosis (Child-Pugh B or C). Applications for VIEKIRA PAK should be submitted to PHARMAC. HARVONI is funded for Patients with MELD score ≥15. Applications for HARVONI should be submitted to the HepC Treatment Panel and not through NPHS or Special Authority forms. |

U&Es and eGFR

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<td>HCV treatment history (Peg-IFN and RBV)</td>
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<tr>
<td>Check MELD score (if patient has decompensated)</td>
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<td>Potential for non-adherence?</td>
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<tr>
<td>Alcohol / cannabis intake/ metabolic syndrome / HBsAg and HIV AB</td>
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Pregnancy discussion

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HCV Genotypes 2,3,4,5,6

The approved treatments for patients with HCV GT 2-6 infection are: (i) sofosbuvir plus daclatasvir for 12 weeks; (ii) sofosbuvir plus ledipasvir for 12 weeks (plus ribavirin in GT 3); or (iii) sofosbuvir plus peg-IFN/RBV or sofosbuvir +RBV. VIEKIRA PAK is funded for patients with HCV GT1, except for patients with decompensated cirrhosis (Child-Pugh B or C). Applications for VIEKIRA PAK should be submitted to PHARMAC. HARVONI is funded for Patients with MELD score ≥15. Applications for HARVONI should be submitted to the HepC Treatment Panel and not through NPHS or Special Authority forms. |

* Liver biopsy does not have a routine role in staging, but may be useful if there is diagnostic uncertainty about the liver fibrosis stage or cause of liver disease.
† Liver Elastography Scan must be performed before starting treatment.
‡ APRI Score Calculator website: http://www.hepatitis.uc.edu/page-clinical-calculator-apri.
¶ FixHepC Buyers Club website: http://www_fixhepc.com
*
"Cofactor for progression to cirrhosis. VIEKIRA PAK may increase exposure to recreational drugs (including cannabis, ecstasy). Patients with HIV/HCV coinfection may require alteration in HIV therapy if possible DDIs. All coinfected patients should be treated in secondary care in close consultation with HIV physician."

Confusion, jaundice, ascites

| Baseline low haemoglobin identifies patients at highest risk of anaemia from RBV-induced haemolysis. RBV is recommended for all patients with HCV GT 1a infection and patients with HCV GT 1b infection and cirrhosis. Baseline low platelet count suggests cirrhosis and portal hypertension. Refer to secondary care for treatment and long-term HCC surveillance. | Baseline low haemoglobin identifies patients at highest risk of anaemia from RBV-induced haemolysis. RBV is recommended for all patients with HCV GT 1a infection and patients with HCV GT 1b infection and cirrhosis. Baseline low platelet count suggests cirrhosis and portal hypertension. Refer to secondary care for treatment and long-term HCC surveillance. |

Professor Ed Gane and Associate Professor Catherine Stedman
Monitoring

**On-treatment and post-treatment monitoring**

### Pre-treatment Week 0
- Review concomitant medications for potential interaction with VIEKIRA PAK.
- Review serum HCV RNA and HCV GT (within last 5 years) to confirm active infection with HCV GT 1 and determine need for addition of RBV.
- Review LSM (within last 3 years). If evidence of cirrhosis or transition to cirrhosis (i.e. LSM >10.5 kPa) then refer to secondary care for treatment.
- Check baseline FBC, U&Es and creatinine, LFTs, HCV RNA levels.

### Treatment Week 2,4,8
- Monitor FBC if on RBV.
- Monitor LFTs.
- Assess for medication adherence, side effects and new concomitant meds (and potential DDIs).

### Post-treatment Week 12 (24 weeks after starting treatment)
- Check HCV RNA – if negative, then patient has achieved SVR12 (i.e. cure).
- Check LFTs – if elevated despite SVR12 then monitor and if remains abnormal then investigate according to local pathways/ refer to Liver Clinic.

Note: An isolated elevation in unconjugated bilirubin is common and is caused by both enzyme inhibition (paritaprevir) and haemolysis (RBV). However, an elevation in ALT/AST accompanied by an elevation in conjugated bilirubin is consistent with VIEKIRA PAK hepatotoxicity. In this case, treatment should be discontinued immediately.

Note: Do NOT repeat HCV RNA testing during treatment because on-treatment responses do NOT predict relapse.

**Abbreviations:** FBC = full blood count. ALT = alanine aminotransferase. AST = aspartate aminotransferase.

### Ribavirin management

**Baseline dosing**
- Weight-based dosing: 600mg bid if >75kg; 400mg mane, 600mg nocte if <75kg.
- Renal function-based dosing: if eGFR <50ml/min: 200 mg bid; if eGFR <30ml/min- no RBV.

**On-treatment dose adjustment for anaemia**
- **No significant vascular disease:**
  - Hb <100g/L: reduce to 400mg bd
  - Hb <85g/L: Stop RBV. Weekly Full Blood Count and restart RBV 200mg bd when Hb >100g/L
- **Significant vascular disease (symptomatic ischaemic heart disease, recent TIA, or CVA, claudication):**
  - Hb <100g/L: Stop RBV. Weekly Full Blood Count and restart at 200mg bd when Hb >110g/L

Note: RBV dose modification reduces morbidity and has NO effect on SVR rates.

**Abbreviations:** TIA = transient ischemic attack. CVA = Cerebrovascular accident.

### Ongoing monitoring of people after successful hepatitis C treatment (SVR)

- **SVR, normal LFTs, no pre-treatment cirrhosis** (pre-treatment LSM <10.5 kPa): discharge with no follow-up
  - Note: Most patients remain anti-HCV antibody-positive lifelong despite successful treatment. Patients should be reminded that cure does NOT protect against reinfection following re-exposure. Patients should be counselled to avoid high-risk behaviours, including injecting drug use, tattooing/body piercing with unsterilised equipment, and unprotected sex with multiple partners (MSM)

- **SVR, pre-treatment cirrhosis ± post-treatment elevated LFTs:** refer to liver clinic for long-term HCC surveillance. Continue surveillance in secondary care
  - Note: LFTs may remain mildly elevated in cirrhotic patients following SVR

- **SVR, pre-treatment no cirrhosis + post-treatment elevated LFTs:** investigate for presence of other diseases, especially fatty liver or alcoholic liver disease. Consider referral to secondary care
  - Note: Liver Elastography Scan/ Shear Wave Elastography should not be performed to determine cirrhosis status following SVR because liver stiffness drops dramatically following viral suppression and ALT normalisation. Only liver biopsy can be used to determine cirrhosis status following SVR. For this reason, all patients should have cirrhosis status confirmed prior to starting DAA therapy.

### Ongoing management in people who relapse following treatment

Fortunately, the rate of virologic failure following both VIEKIRA PAK and HARVONI in compensated patients treated in the real world is only 5%, which is similar to that reported in the respective clinical trial programmes – between 5 and 10%. Almost all virologic failures have relapsed in the first 4 weeks post-treatment with HCV, which is resistant to current NS5A inhibitors. Currently, there are no retreatment options available for these patients but several potential regimens are now in development (Gilead, Merck, and Janssen triplets, and AbbVie Next-Gen doublet). Patients who relapse following VIEKIRA PAK and HARVONI should be discussed with Liver Clinics and reviewed at least annually so that they can be offered retreatment when this is available.

**Abbreviations:** NS5A = non-structural protein 5A.

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This treatment guidance document was developed by Professor Ed Gane and Associate Professor Catherine Stedman under an unrestricted educational grant from AbbVie New Zealand Limited, and has been endorsed by the New Zealand Society of Gastroenterology, the Australasian Society for Infectious Diseases, and the Royal NZ College of General Practitioners.

Professor Ed Gane and Associate Professor Catherine Stedman
**Management Guidelines for treating hepatitis C virus infection with VIEKIRA PAK: SUMMARY**

<table>
<thead>
<tr>
<th>Regimen</th>
<th>HCV subtype</th>
<th>No cirrhosis</th>
<th>Treatment-naive</th>
<th>Treatment-experienced</th>
<th>Cirrhosis</th>
<th>Treatment-naive</th>
<th>Treatment-experienced</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paritaprevir–ritonavir (150mg/100mg), daily + ombitasvir 25mg, orally, daily + dasabuvir 250mg, orally, twice daily</td>
<td>1a (or 1 not subtypable)</td>
<td>12 weeks</td>
<td>12 weeks</td>
<td>12 weeks</td>
<td>12 weeks</td>
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<tr>
<td></td>
<td>1b</td>
<td>+ ribavirin†</td>
<td>+ ribavirin‡</td>
<td>+ ribavirin†</td>
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### Treatment of side effects:

- **Fatigue:** Check haemoglobin level and adjust ribavirin dosage accordingly.
- **Insomnia:** Consider advice on improved sleep hygiene. If severe, then consider using zopiclone at half the recommended dose (3.75mg nocte) OR temazepam at the full recommended dose (10mg nocte).
- **Nausea:** Consider ondansetron at the standard recommended dosage.
- **Depression:** Citalopram or e-citalopram are allowed.
- **Skin rash:** Use 10% urea cream or fatty cream. For further advice, consult DermNet NZ.

### Contraindications include:

- Decompensated cirrhosis (Child-Pugh class B or C).
- Pregnancy.
- Midazolam, triazolam (other benzodiazepines allowed), carbamazepine, colchicine, efavirenz, ergotamine and its derivatives, gemfibrozil, phenobarbital, phenytoin, quetiapine, rilpivirine, ritonavir, sildenafil for pulmonary arterial hypertension, salmeterol, terfenadine, ethinyl estradiol, atorvastatin, rifampicin, simvastatin, and St Johns’ Wort should be avoided.

### Precautions:

- Use caution when administering VIEKIRA PAK with fluticasone or other glucocorticoids that are metabolised by CYP3A4. Concomitant use of inhaled glucocorticoids metabolised by CYP3A can increase systemic exposures of the glucocorticoids and cases of Cushing’s syndrome and subsequent adrenal suppression have been reported with ritonavir-containing regimens.

### Notes:

- Many drugs can be stopped for the duration of treatment with VIEKIRA PAK (e.g. statins) or switched to a safer alternative (e.g. beclomethasone instead of fluticasone and progesterone-only oral contraceptives instead of ethinylestradiol-containing contraceptives). For a full list of DDIs, consult the Hepatitis Drug Interactions Checker §
- Ongoing use of recreational drugs is not an absolute contraindication, but regular use should be discouraged because of the associated impact on adherence and risk of infection. In addition, the exposure to certain recreational drugs may be increased by VIEKIRA PAK, including cannabis, amphetamine, methamphetamine, and MDMA (Ecstasy).
- Room temperature (<25°C, in a dry place).

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* All patients living with chronic HCV benefit from antiviral therapy, including those with no fibrosis and those with normal LFTs.
† No dose adjustment of VIEKIRA PAK is required in patients with mild, moderate, or severe renal impairment; however, ribavirin dose modification is required, as listed under “Ribavirin Management”.
‡ 24 weeks is the recommended treatment duration for patients with GT 1a-infection with cirrhosis who have had a previous NULL response to Peg-IFN + ribavirin.
**AbbVie VIEKIRA PAK website:** [www.viekira.co.nz](http://www.viekira.co.nz), HCP Username GT1, Password GT1.

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* AbbVie VIEKIRA PAK website: [www.viekira.co.nz](http://www.viekira.co.nz), HCP Username GT1, Password GT1.
* Medsafe website: [VIEKIRA PAK and VIEKIRA PAK-RBV Data Sheets](http://www.medsafe.govt.nz/therapeutics/)
* All patients living with chronic HCV benefit from antiviral therapy, including those with no fibrosis and those with normal LFTs.
* If RBV is contraindicated because of vascular disease, anaemia, or allergy, then VIEKIRA PAK without RBV can be considered for treatment-naive patients with genotype 1a.
* For a full list of contraindications, see the VIEKIRA PAK and VIEKIRA PAK-RBV Data Sheets.
Appendix: DRAFT Clinical pathway for hepatitis C from 1st July 2016
(Ministry of Health HCV Implementation Committee, June 2016)

Education and support provided by:
- District Health Boards
- Primary Health Organisations
- General Practices
- NGOs (ASHM/HFNZ)
- Community Alcohol And Drug Services
- Needle Exchange And OST Services with Outreach Clinics

HCV – Hepatitis C virus
DAA – Direct-acting antiviral drugs
SVR – Sustained virologic response
HCC – Hepatocellular carcinoma
GT – Genotype
CTP – Child Turcotte Pugh score (used to classify the severity of cirrhosis)
RBV – Ribavirin
MELD - Model for End-Stage Liver Disease (a system for assessing the severity of cirrhosis)

Liver Elastography Scans
HCV Genotype

No cirrhosis
Primary Care or Secondary Care#

HCV GT non1
No cirrhosis

HCV GT1
No cirrhosis

HCV GT 1 CTP B or GT non-1
MELD <15

Wait for DAA funding

HCV GT1
CTP A

HCV GT1 CTP C

MELD ≥ 15*

HARVONI ± RBV*

1. Annual review to discuss DAA access
2. 3 yearly Liver Elastography Scan

RELAPSE* 2-5%
CURED 95-98%

RELAPSE* 10%
CURED 90%
RELAPSE* 10%

Discharge
Avoid reinfection

Long-term HCC Surveillance

*It is likely that initially, many patients with HCV GT 1 and without cirrhosis will still be treated in secondary care. But in the future, improved GP education and simpler regimens should facilitate community treatment for all non-cirrhotic patients.

*Note: Cure or relapse is evident 3 months post treatment.

*All applications for HARVONI in decompensated HCV cirrhosis will be assessed by Expert Panel. Patients with CTP C who are potential candidates for liver transplantation should be discussed with NZLTU prior to initiating treatment. Deferring treatment until after transplant may be preferred.