

NZ SOCIETY OF GASTROENTEROLOGY HCV TREATMENT GUIDELINES

Initial assessment

Hepatitis C Virus virology	
Anti-HCV (serology) HCV RNA level (viral load) HCV GT	<ul style="list-style-type: none"> Indicates HCV exposure Confirms HCV infection Determines treatment regimen
Liver staging	
Liver Elastography Scan (Fibroscan or Shear Wave Elastography) [†]	<p>Excludes cirrhosis if:</p> <ul style="list-style-type: none"> LSM <10.5 kPa. If LSM 10.5–12.5 kPa, assume bridging fibrosis/transition to cirrhosis; refer to secondary care for long-term follow-up. If the Liver Elastography Scan is unavailable or technically unsuccessful, perform serum fibrosis markers (Fibrotest, Fibrosure, APRI). † APRI ‡ <1.0 is consistent with no cirrhosis. <p>Likely cirrhosis if:</p> <ul style="list-style-type: none"> LSM >12.5 or APRI ‡ >1.0. Refer to secondary care for assessment, treatment and long-term HCC surveillance.
Evidence of decompensated chronic liver disease	
Physical Examination	<ul style="list-style-type: none"> Confusion, jaundice, ascites
LFTs and INR	<ul style="list-style-type: none"> Low albumin, elevated bilirubin, elevated INR reflect liver synthetic dysfunction associated with advanced cirrhosis. Refer to secondary care for treatment and long-term HCC surveillance.
Ultrasound	<ul style="list-style-type: none"> Ascites
Additional laboratory data	
Haemoglobin and platelet count	<ul style="list-style-type: none"> 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. Patient may need gastroscopy to assess for varices.
HCV Genotype 1	
Pre-treatment assessment for access to treatment with DAAs	
<p>The approved treatments for patients with HCV GT 1 are (i) VIEKIRA PAK±RBV (paritaprevir/ritonavir/ombitasvir with dasabuvir ±ribavirin); (ii) HARVONI (sofosbuvir/ledipasvir ±ribavirin); 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 NPPA or Special Authority forms.</p>	
U&Es and eGFR	<ul style="list-style-type: none"> Ribavirin needs dose reduction if eGFR <50 mL/min and discontinuation if eGFR <30 mL/min. HARVONI (sofosbuvir) is not recommended for eGFR <30.
HCV treatment history (Peg-IFN and RBV)	<ul style="list-style-type: none"> Affects treatment regimen (e.g. most patients with GT1 HCV should have 12 weeks treatment with VIEKIRA PAK±RBV, except for previous NULL responders with HCV GT 1a and cirrhosis, who need 24 weeks of treatment with VIEKIRA PAK-RBV).
Check MELD score (if patient has decompensated)	<ul style="list-style-type: none"> VIEKIRA PAK is contraindicated in patients with decompensated liver disease (Childs B or C). Use Child-Pugh Score Calculator Patients with MELD score >14 may be considered for PHARMAC-funded HARVONI. Use MELD Score Calculator[§].
Potential for non-adherence?	<ul style="list-style-type: none"> Consider medical, psychiatric, and social issues that decrease medication adherence. Counsel patient regarding the importance of adherence.
Alcohol / cannabis intake/ metabolic syndrome / HBsAg and HIV AB	<ul style="list-style-type: none"> 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. Patients with a current or previous HBV/HCV coinfection should be monitored for possible reactivation of HBV All coinfectd patients should be treated in secondary care in close consultation with an ID physician.
Pregnancy discussion [¶]	<ul style="list-style-type: none"> RBV and VIEKIRA PAK are both contraindicated during pregnancy. There are no safety data for the use of any DAA regimen during pregnancy or lactation. Pregnancy should be avoided for all patients and their partners during VIEKIRA PAK. Both women and men should be counselled about the risk of teratogenicity and the importance of avoiding pregnancy during treatment. Reliable contraception (i.e. two methods, including barrier contraception) is essential for both men and women. For those who are also receiving RBV (i.e. VIEKIRA PAK-RBV), pregnancy should also be avoided for 6 months post-treatment Check for DDIs that may affect contraception efficacy. Women treated with VIEKIRA PAK should avoid ethinylestradiol-containing contraceptives because of possible hepatotoxicity with VIEKIRA PAK. Patients taking ethinylestradiol-containing contraceptives should be switched to other effective contraceptives ≥2 weeks prior to starting VIEKIRA PAK until ≥2 weeks after finishing treatment.
Check for DDIs	<ul style="list-style-type: none"> Refer to Hepatitis Drug Interactions Checker[§] Includes prescribed, over-the-counter, complementary/herbal, illicit drugs
HCV Genotypes 2,3,4,5,6	
<p>The approved treatments for patients with HCV GT 2-6 infection are: either (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 for 12 weeks; or (iv) sofosbuvir plus RBV for 12 or 24 weeks. None of these are currently funded by PHARMAC, unless they are considered eligible for HARVONI by PHARMAC's Expert Panel. Peg-IFN-based therapy is the only funded therapy for compensated patients with these genotypes but in most cases it is preferable to wait for funding of DAAs. Alternative access to DAAs may include:</p> <ul style="list-style-type: none"> Import 12 weeks supply of sofosbuvir and daclatasvir or 12 weeks supply of sofosbuvir and ledipasvir for private use under a personal importation scheme (e.g. FixHepC Buyers Club[¶] approx. \$2,000–\$3,000). Purchase HARVONI (ledipasvir/sofosbuvir) from Gilead Sciences without subsidy (approximately \$75,000 excl GST per 3-month supply). Participate in a clinical trial with either next-generation DAAs or approved DAAs in difficult-to-treat populations. 	

* Liver Elastography Scan must be performed before starting treatment.

† 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.

‡ APRI Score Calculator website: <http://www.hepatitisc.uw.edu/page/clinical-calculators/apri>.

§ MELD Score Calculator website: <http://www.mdcalc.com/original-meld-score-pre-2016-model-for-end-stage-liver-disease/>.

¶ Hepatitis Drug Interactions Checker website: <http://hep-druginteractions.org/checker> (Search under tradename [VIEKIRA PAK] or generic name [OBV/PTV/r + DSV]).

‡ FixHepC Buyers Club website: <http://fixhepc.com>.

Abbreviations: APRI = aspartate aminotransferase-to-platelet ratio index; DAA = direct-acting antiviral; DDI = drug-drug interactions; eGFR = estimated glomerular filtration rate; GT = genotype; HBsAg = hepatitis B surface antigen; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HCV RNA = hepatitis C virus ribonucleic acid; HIV = human immunodeficiency virus; HIV AB = human immunodeficiency virus antibody; INR = international normalised ratio; LFT = liver function test; U&E = urea and electrolytes; LSM = Liver stiffness measurement; MELD = Model for End-Stage Liver Disease; RBV = ribavirin; Peg-IFN = pegylated interferon; SVR12 = sustained virologic response ≥12 weeks after treatment (= cure).

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Monitoring

On-treatment and post-treatment monitoring

Pre-treatment Week 0	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Monitor FBC if on RBV. Monitor LFTs in patients with cirrhosis. Assess for medication adherence, side effects and new concomitant meds (and potential DDIs).
Post-treatment Week 12 (24 weeks after starting treatment)	<ul style="list-style-type: none"> 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: 200mg bid; if eGFR <30mL/min- no RBV.
On-treatment dose adjustment for anaemia	<p>No significant vascular disease:</p> <p>Hb <100g/L: reduce to 200mg mane, 400mg nocte. Hb <85g/L: Stop RBV. Weekly Full Blood Count and restart RBV 200mg mane, 400mg nocte when Hb >100g/L, and consider further increasing to 400mg bd.</p> <p>Significant vascular disease (symptomatic ischemic heart disease, recent TIA, or CVA, claudication):</p> <p>Hb <100g/L: Stop RBV. Weekly Full Blood Count and restart at 200mg bd when Hb >110g/L</p>

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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Management Guidelines for treating hepatitis C virus infection with VIEKIRA PAK: SUMMARY

VIEKIRA PAK protocols for people with HCV infection and compensated liver disease*					
Regimen	HCV subtype	No cirrhosis		Cirrhosis	
		Treatment-naïve	Treatment-experienced	Treatment-naïve	Treatment-experienced
Paritaprevir–ritonavir (150mg/100mg), daily + ombitasvir 25mg, orally, daily + dasabuvir 250mg, orally, twice daily	1a (or 1 not subtypable)	12 weeks + ribavirin ^{#,†}	12 weeks + ribavirin [†]	12 weeks + ribavirin [†]	12 or 24 weeks [‡] + ribavirin [†]
	1b	12 weeks	12 weeks	12 weeks	12 weeks
Treatment of side effects and common comorbidities:	<ul style="list-style-type: none"> • 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:	<ul style="list-style-type: none"> • 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, fusidic acid, atorvastatin, rifampicin, simvastatin, and St Johns' wort. 				
Precautions:	<ul style="list-style-type: none"> • 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 [§]					
Recreational drug use:	<ul style="list-style-type: none"> • 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). 				
Transportation and storage	<ul style="list-style-type: none"> • Room temperature (<25°C, in a dry place). 				

PHARMAC website: www.pharmac.govt.nz/hepatitis-c-treatments

Medsafe website: [VIEKIRA PAK](#) and [VIEKIRA PAK-RBV](#) Data Sheets.

AbbVie VIEKIRA PAK website: www.viekira.co.nz, HCP Username GT1, Password GT1.

* 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 non-cirrhotic treatment-naïve patients with genotype 1a

† 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.

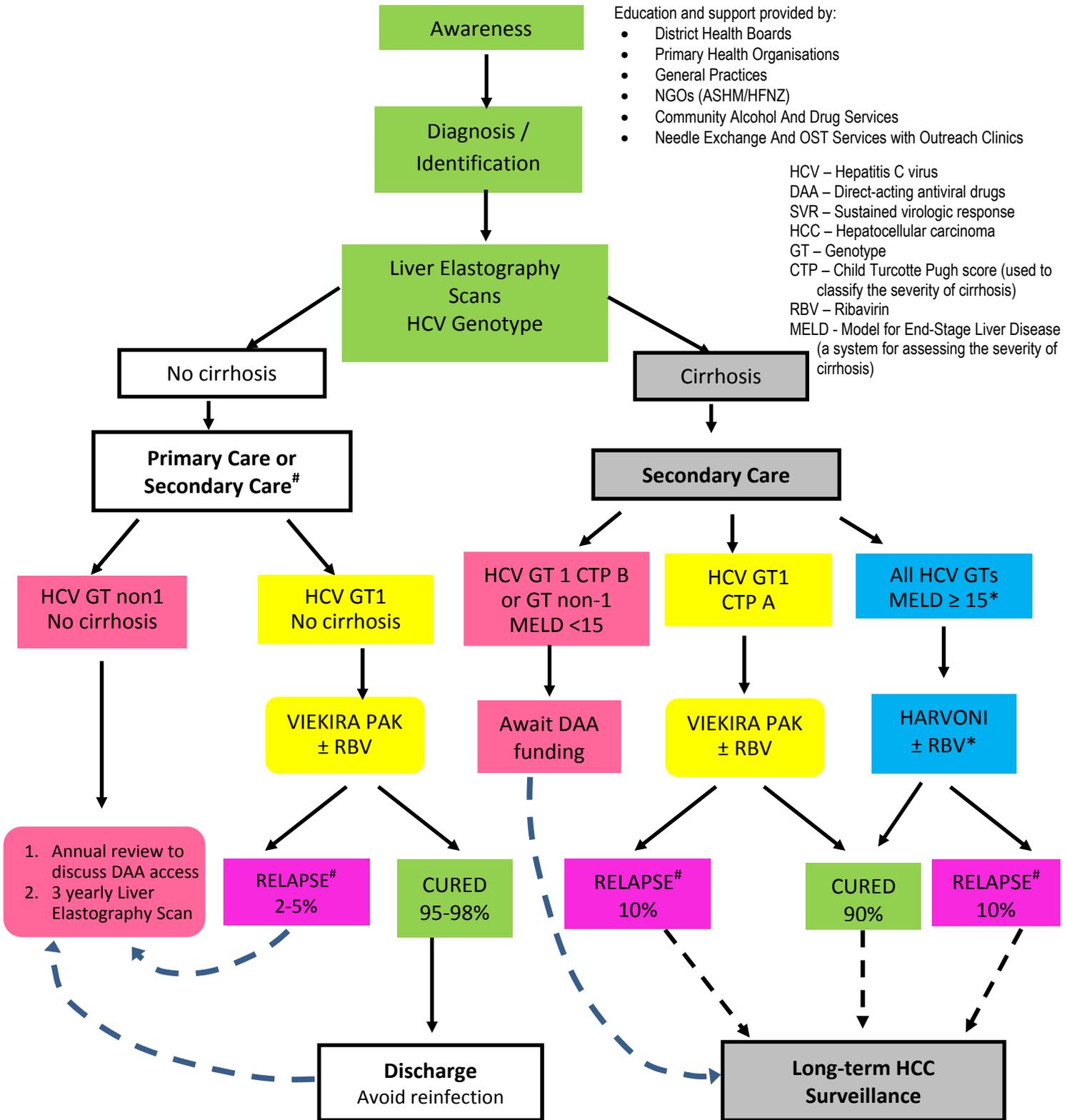
¥ DermNet NZ website: <http://www.dermnetnz.org/>.

|| For a full list of contraindications, see the [VIEKIRA PAK](#) and [VIEKIRA PAK-RBV](#) Data Sheets.

§ Hepatitis Drug Interactions Checker website: <http://hep-druginteractions.org/checker>.

Abbreviations: DDIs = drug-drug interactions; eGFR = estimated glomerular filtration rate; Peg-IFN = pegylated interferon.

Appendix: DRAFT Clinical pathway for hepatitis C from 1st July 2016 (Ministry of Health HCV Implementation Committee, June 2016)



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.

*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.

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