Application to increase access to Maviret through exemption to prescription status for pharmacists

Introduction

In late 2022, the Medicines Classification Committee recommended allowing nurses to supply a treatment for chronic hepatitis C (Maviret). This will be very helpful for remote outreach work in vulnerable populations. While the proposal originally suggested nurses treat the patients with Maviret dispensed by pharmacists as one option, such a model was not possible under legislation. The Medicines Classification Committee minuted "that they would be open to considering a separate submission to enable pharmacists to supply Maviret."

Therefore we are suggesting that, in addition to nurses treating patients with Maviret as recommended by the Medicines Classification Committee at their 69th meeting, a further approach allows a pharmacist-supply model.

This application seeks to widen access to a treatment for chronic hepatitis C infection to allow pharmacists with appropriate knowledge and experience, and in collaboration with specific nurses, to treat people with hepatitis C safely, thereby increasing community access and treatment uptake. This model will be finalised with stakeholders including the Pharmacy Council, Nursing Council, and the professional organisations.

New Zealand has a goal to eliminate hepatitis C as a major public health concern by 2030[1], as one of 194 countries which signed up to this World Health Organisation recommended goal in 2016.

> ***"New Zealand has a unique opportunity to eliminate hepatitis C as a major public health threat within the next 10 years. With the availability of publicly funded, highly effective, direct-acting antiviral treatment, we have a real prospect of curing … New Zealanders… living with chronic hepatitis C. We can also reduce liver cancer and the need for liver transplants."[1] Hon Dr Ayesha Verrall, Associate Minister of Health***

Despite having a very effective oral therapy available fully funded since early 2019, barriers to access need to be overcome to reach this target, and, particularly to ensure the most vulnerable members of our communities are able to access medicines. This reclassification seeks to help overcome some of these barriers, supporting a collaborative model for supply.

Chronic hepatitis C disproportionately affects marginalised populations (e.g. people who inject drugs, people in prison, people with chronic mental illness, people who are homeless). The label of hepatitis C is often accompanied with stigma and discrimination. Enabling different models of care to the traditional doctor-led approach is expected to remove barriers to treatment in these priority populations,[1, 2] to *"turn off the tap of new infections"* and to prevent the long-term complications of hepatocellular carcinoma and liver failure, associated with hepatitis C. Increasing access and treatment uptake will save our health system resources, by halting new infections and reducing the total pool of chronically infected individuals, thereby accelerating the progress to elimination, which will prevent thousands of deaths and liver transplants

This proposed reclassification has a strong equity component given the marginalised populations that it particularly seeks to help. Māori are likely to be disproportionately affected by hepatitis C because of increased prevalence rates and delayed diagnosis and treatment, which all result in increasing rates of complications.[1] This proposed reclassification should facilitate easier access and increased treatment uptake for Māori living with hepatitis C.

The subject of the proposed reclassification is for the combination medicine containing glecaprevir and pibrentasvir (Maviret), the treatment used to treat chronic hepatitis C infection in New Zealand.

This proposal would enable pharmacists with relevant knowledge and support to manage and treat people with chronic hepatitis C, including collaboration with nurses with direct benefits to these individuals, their communities and our health system.

Diagnosis of hepatitis C infection is straight forward (antibody and confirmatory RNA testing) and pretreatment assessment is well-established. The final treatment pathway for pharmacist supply needs to be decided in conjunction with the Pharmacy Council, Nursing Council and other stakeholders. The nurses and pharmacists will be able to seek advice from their local physicians experienced with hepatitis C for more complex or uncertain scenarios. Pharmacists and nurses will work together to enable a supply that will allow easy stock management, automatic updates of patient records with Maviret supply, the additional interaction checks in the pharmacy, and convenient supply.

We see this will work in two ways.

1. Nurse-initiated - nurses working in settings with higher risk for hepatitis C would have the initial contact with the client and work with a local pharmacy with an appropriately skilled and credentialed pharmacist, to work together collaboratively to start the patient on treatment through the pharmacist-supply model.
2. Pharmacist-initiated – the pharmacist finds a person in their setting with hepatitis C and works with a specific nurse experienced in hepatitis C to together agree on management including treatment. This would support the existing pharmacy test and treat model. It is likely the nurse, for whom this would be part of their agreed role, would be available by telephone and email within an agreed process.

We expect this reclassification to increase uptake of hepatitis C treatment, helping Aotearoa New Zealand to reach the target of eliminating hepatitis C as a major public health concern by 2030.

There is urgency in this application. Community access to hepatitis C testing has improved thanks to point-of-care testing programmes in needle exchanges, addiction services and in remote locations through the Mobile van outreach. However, community access to treatment remains restricted to registered medical practitioners. Very few hepatology nurse practitioners are able to prescribe Maviret. This delays getting the treatment to the client who in some cases may be lost after that window of opportunity. This proposed reclassification would reduce the steps required to treating a patient, reducing loss to follow-up, while ensuring patient records are complete and an expensive medication is well-managed. The more people treated now, particularly in the population at risk of transmission, the fewer we need to treat ahead, the sooner we eliminate this disease as a public health concern from New Zealand and the more lives, morbidity and burden on the health system we can save.

Part A

1. **International Non-proprietary Name of the medicine**
   Glecaprevir and pibrentasvir

2. **Proprietary name (s)**
   Maviret

3. **Name of company/organisation/individual requesting reclassification**
   Health New Zealand Long Term Conditions

4. Dose form(s) and strengths for which a change is sought

Tablets containing 100 mg glecaprevir and 40 mg pibrentasvir.

5. Proposed pack size, storage conditions and other qualifications

The current pack is a multipack containing 84 tablets (four weeks of therapy). It is expected that this reclassification will allow supply of two packs of 84 tablets or eight weeks of treatment. There are no special storage conditions.

See below regarding qualifications applicable to this reclassification. These are primarily related to the health care professionals it would apply to.

6. Indications for which change is sought

The indications for this medicine in New Zealand are as follows:
MAVIRET is indicated for the treatment of adults and adolescents 12 years and older with chronic hepatitis C virus (HCV).

We recommend for this reclassification that the indication is for adults and adolescents aged 16 years and older. Few people aged 12 years to 15 years of age inclusive will be infected with hepatitis C, and those who are will be more appropriately treated by a paediatric specialist.

7. Present classification of the medicines

Prescription medicine

8. Classification sought

We seek to enable a pharmacist-supply model to be able to facilitate the supply of glecaprevir-pibretasvir combination tablets in collaboration with a suitably qualified nurse. The exact model will be appropriately decided by the stakeholders including the Pharmacy Council and Nursing Council of New Zealand, with input from other pharmacy and nursing organisations as well as other relevant stakeholders, such as needle exchange, general practice, community hepatitis C nurses, and Te Whatu Ora. We are open to wording that best achieves this with suggested wording below.

Glecaprevir - prescription except when supplied in combination with pibretasvir for treatment of chronic hepatitis C virus infection to people aged 16 years or over who meet the clinical and eligibility criteria of the approved programme on hepatitis C provision by a pharmacist, in collaboration with a registered nurse who has specialty knowledge of hepatitis C*, or a nurse working in the community in a high-prevalence hepatitis C environment. [Any requirements of the pharmacist or nurse with respect to training will have input from the respective regulators and stakeholder organisations]

Pibrentasvir - prescription except when supplied in combination with Glecaprevir for treatment of chronic hepatitis C virus infection to people aged 16 years or over who meet the clinical and eligibility criteria of the approved programme on hepatitis C provision by a pharmacist, in collaboration with a registered nurse who has specialty knowledge of hepatitis C*, or a nurse working in the community in a high-prevalence hepatitis C environment. [Any requirements of the pharmacist or nurse with respect to training will have input from the respective regulators and stakeholder organisations]

*A registered nurse with speciality knowledge of hepatitis C could include hospital-based nurses working in gastroenterology, hepatology, or infectious diseases and community-based nurses in community hepatitis C roles or alcohol and drugs services including opioid treatment services, corrections, homeless, outreach and needle exchange.

OR
Glecaprevir - prescription except when supplied in combination with pibretasvir for treatment of chronic hepatitis C virus infection to people aged 16 years or over who meet the clinical and eligibility criteria of the approved programme on hepatitis C provision by a pharmacist who has successfully completed approved training and is working within the approved programme.

Pibrentasvir - prescription except when supplied in combination with Glecaprevir for treatment of chronic hepatitis C virus infection to people aged 16 years or over who meet the clinical and eligibility criteria of the approved programme on hepatitis C provision by a pharmacist, who has successfully completed approved training and is working within the approved programme.

The approved programme would be able to outline any collaboration.

9. Classification status in other countries (especially Australia, UK, USA, Canada)

Prescription status. However, a patient group directive has been used for nurses and pharmacists to prescribe this in Scotland.[2, 3]

10. Extent of usage in New Zealand and elsewhere (e.g. sales volumes) and dates of original consent to distribute

Sales volumes are confidential to the company. Over 5,000 patients have been treated with Maviret in New Zealand since it was first available (source: Pharmaceuticals Collection Office in the Ministry of Health to 1 May 2022).

Maviret was first registered in New Zealand on 20 June 2018. Funding for Maviret started 1 February 2019.

11. Local data or special considerations relating to New Zealand (if applicable)

New Zealand has signed up to the World Health Organisation (WHO) goal to eliminate hepatitis C as a public health concern by 2030.[1] To achieve this, and help our most vulnerable receive treatment we must reduce barriers to access to treatment wherever possible, without delay.

Maviret is the only funded first-line agent in New Zealand for hepatitis C infection. It is the most effective (>98% cure) and simplest regimen (3 tablets once a day for 8 weeks for all treatment-naïve patients with compensated liver disease, regardless of duration of infection, genotype, or cirrhosis status. Maviret is fully funded with no patient co-payment, and has no restrictions on prescribing, and can therefore be prescribed by specialists, general practitioners and nurse practitioners.

Nurse-led Maviret supplies

In New Zealand Maviret can be prescribed by Nurse Practitioners and, very recently, Designated Registered Nurse Prescribers. Feedback from the nurses involved in hepatitis C management has been that most are not willing to take up the prescribing pathway owing to the time involved.

The Nursing Council specifies that registered nurses who wish to prescribe in primary health and speciality teams need to have a minimum of three years full-time practice in the area they intend to prescribe in with at least one year of the total practice.[4] Further requirements include a need to complete a Council-approved postgraduate diploma in registered nurse prescribing for long-term and common conditions or equivalent as assessed by the Nursing Council. The post-graduate diploma is 120 credits, equivalent to one-year of full-time study. There is a prescribing practicum of a minimum of 150 hours of clinical practice. Recertification is required three-yearly including professional development of at least 20 hours relating to prescribing practice over the past three years. The July 2022 document about prescribing for registered nurses is attached as an appendix. The list of medicines that can be prescribed is focused on prescribing for long-term and common conditions.[4] Hepatitis C is an infection which, when diagnosed and treated for eight weeks is almost always cured, and for those 1-2% who are not cured, there are other treatment options to cure the condition. Thus, it no longer fits the typical long-term condition. Hepatitis C is not considered a common condition, occurring in under 1% of adults in Aotearoa New Zealand. In this special circumstance, where we want to enable nurse-led care, the prescribing pathway will not achieve the increased access we are particularly seeking given most nurses working in this field do not wish to commit to the study required. It is possible that some nurses will start with hepatitis C treatment through this reclassification and see an opportunity to do further education to become a registered nurse prescriber, and this will be encouraged.

A further prescribing alternative is Tapuhi kua rēhitatia tūtohu i te hauora hapori, registered nurse prescribing in community health.[5] This mechanism is designed for common and mild ailments and requires less education time than the registered nurse prescribing for long-term and common conditions outlined above.[6] There is a list of medicines that can be prescribed by these nurses in areas like sexual health, common skin conditions and ear or urinary tract infections.[7] Nurses "may prescribe where the diagnosis has already been made (e.g. rheumatic fever secondary prevention), where the diagnosis is relatively uncomplicated (e.g. determined through laboratory testing) or for minor ailments or illnesses." This mechanism appears problematic for hepatitis C management. Firstly, there are limited locations (eight on the Nursing Council website)[5] with approved programmes where this programme can be used, so it would not be available nationally. Secondly, there is a list of medicines which are for common and mild ailments, and hepatitis C does not fit that description. Glecaprevir in combination with pibretasvir has some complexities in diagnosis and referral, and we envisage availability as an exception from prescription to apply only to a small group of registered nurses with specific experience and additional assessment specific to this treatment.

The challenges of the pathways for increasing use of nurse-led hepatitis C treatment made a reclassification the best option for addressing the unmet need and helping overcome some barriers to access, and this was sought in 2022, with a positive response.

The Medicines Classification Committee consideration was minuted as follows:[8]
"The Committee recommended the classification of glecaprevir be reclassified to *'prescription except when supplied in combination with pibrentasvir for treatment of chronic hepatitis C virus infection to people who meet the clinical and eligibility criteria of the approved training programme, when provided by nurses who meet the requirements of the Nursing Council.* The Committee recommended the classification of pibrentasvir be reclassified to *'prescription except when supplied in combination with glecaprevir for treatment of chronic*

hepatitis C virus infection to people who meet the clinical and eligibility criteria of the approved training programme, when provided by nurses who meet the requirements of the Nursing Council."

This recommendation enables supply by specific nurses (subject to funding and distribution allowing this also). However, it creates several challenges:

1. It does not allow Maviret supply to be automatically added to the electronic patient record so that other health care workers managing this patient can see it and avoid potential drug-drug interactions.
2. There are logistical challenges with a very expensive medicine that is distributed through the manufacturer for specific patients through selected pharmacies only.
3. There may also be funding challenges with such an expensive medicine provided in advance to health professionals.
4. It will prevent automated data entry into the planned hepatitis C patient registry, with the potential for omissions or errors.

Additionally, a model using the pharmacy provides a second check on potential drug-drug interactions.

Therefore, we propose, in addition to the nurse-led model recommended by the MCC at the last meeting, that a further collaborative pharmacist and nurse availability.

Current role of pharmacists with Maviret

Maviret can only be dispensed in pharmacies which have been registered for the service and have one or more pharmacists who have successfully completed the Pharmaceutical Society of New Zealand training on Maviret. They are expected to identify drug interactions and address these with the patient and prescriber, if necessary, and provide counselling. The Maviret is typically dispensed for 4 weeks with one repeat.

In the Northern Region of New Zealand, over 60 pharmacies provide a pharmacy test and treat service. The pharmacy finds people who are positive on a hepatitis C point-of-care antibody test, or who have a blood test record of being RNA positive. They work with a clinical nurse specialist to help the person get the relevant blood tests and treatment is arranged via a prescription from a medical practitioner. This has been running since 2021 and shows the collaborative pharmacist-nurse model is a very workable one. This model has also been used as a three-way collaboration with Needle Exchange, the nearby pharmacy and the clinical nurse specialist. Pharmacists have used existing relationships with their clients or built relationships with those referred from elsewhere or new clients to help them get through the blood tests and start treatment. This has seen patients treated who have been long known to be positive. The proposed reclassification enabling pharmacists and nurses to work together to provide through a prescription except when classification would make this process easier and less reliant on the current single prescriber involved. Other regions have implemented a similar model or are looking to do so, and this proposal would support this work.

The proposed reclassification would also enable a faster linkage to care thereby reducing loss to follow-up. Point-of-care HCV RNA testing machines at community settings can produce a result within 45 minutes, permitting initiation of treatment that same day in previously "difficult-to-treat" populations.

New Zealand has a history of using *the "prescription except when"* facility to enable provision through groups of health care professionals with particular skill sets. Examples include podiatrists, optometrists, certain dental professionals, nurses and pharmacists. Occasionally additional qualifications on the classification exist, such as requiring additional training to be successfully completed as occurs with pharmacists supplying selected oral contraceptives, or scope of practice qualification. Examples are provided below.

Lignocaine has the following exception:

> *"for injection **except** when used as a local anaesthetic in practice by a nurse whose scope of practice permits the performance of general nursing functions or by a podiatrist registered with the Podiatry Board or by a dental therapist or oral health therapist registered with the Dental Council; for ophthalmic use **except** when used in practice by an optometrist registered with the Optometrists and Dispensing Opticians Board; for oral use **except** in throat lozenges in medicines containing 30 milligrams or less per dose form; for external use in medicines containing more than 10%; **except** in throat sprays in medicines containing 2% or less; **except** when specified elsewhere in this schedule."*

Ethinyloestradiol has the following exception:

> ***"except** when supplied at a strength of 35 micrograms or less in combination with either levonorgestrel or norethisterone for oral contraception to women who meet the clinical and eligibility criteria of the Pharmacy Council and the Pharmaceutical Society of New Zealand approved training programme on oral contraception, when sold in the manufacturer's original pack that has received the consent of the Minister or Director-General to their distribution as medicines, containing not more than 6 months' supply by a registered pharmacist who has successfully completed the approved training programme."*

12. Labelling or draft labelling for the proposed new presentation(s)

No labelling change is required, the medicine would remain prescription only with an exception.

13. Proposed warning statements (if applicable)

There would be no need for any additional warning statements as usage is virtually unchanged.

14. Other products containing the same ingredient(s) and which would be affected by the proposed change

Nil.

Part B

Reasons for requesting classification change including benefit-risk analysis

The proposed reclassification will help tāngata (people) who live with hepatitis C, including our most vulnerable and Māori, to receive the hepatitis C treatment they need through community-based initiatives including needle exchanges, homeless providers, addiction services, mobile van services and community pharmacies. This works with the "Closer to home, Ka aro mai ki te kāinga" part of the 2016 Health Strategy.

The 69th meeting of the Medicines Classification Committee recommended that glecaprevir be reclassified to *'prescription except when supplied in combination with pibrentasvir for treatment of chronic hepatitis C virus infection to people who meet the clinical and eligibility criteria of the approved training programme, when provided by nurses who meet the requirements of the Nursing Council.* The Committee also recommended pibrentasvir be reclassified to *'prescription except when supplied in combination with glecaprevir for treatment of chronic hepatitis C virus infection to people who meet the clinical and eligibility criteria of the approved training programme, when provided by nurses who meet the requirements of the Nursing Council.*

However, the Committee noted concerns about storage and recording of Maviret supply, and also minuted: "The Committee noted that some comments suggested development of a distribution model whereby nurses refer eligible/ suitable patients to pharmacists, who could be enabled (by scheduling) to provide Maviret. The Committee noted the important role pharmacists play in patient follow-up. Specifically, the model proposed by the Pharmacy Guild of New Zealand was noted however outside the current classification request. The Committee noted that they would be open to considering a separate submission to enable pharmacists to supply Maviret."

This application seeks to have a pharmacist-supply model through the "prescription except when" mechanism to aid storage, drug interaction checks, record-keeping and distribution. It would support both pharmacist-led and nurse-led pathways.

Trials support that Maviret treatment (usually 8 weeks) cures more than 98% of people with chronic HCV taking the full course.[9] Cure will reduce their life-time risk of the liver-related complications of hepatocellular carcinoma and liver failure.[10] Providing hepatitis C treatment to people with chronic HCV who inject drugs is recommended to reduce new infections is known as "treatment as prevention" or TasP. [11] This proposed reclassification to allow nurse and pharmacist to treat without doctor prescription should facilitate TasP in people who inject drugs.

Many challenges exist to diagnosing and treating people with chronic HCV, including the fact that it is often asymptomatic, stigma, and that people at risk of hepatitis C may not be accessing health services. [1, 10, 12] New Zealand needs to overcome these challenges, with WHO recommending simplified services delivered close to communities.[13]

Nurse-led models of care are increasingly seen in many developed countries to enable "on-site" care in priority community settings with higher HCV prevalence,[12, 14] such as needle exchanges, opioid substitution sites,[3] and prisons. These vulnerable populations are important from an equity perspective, and to stop transmission, as Professor Gane notes in the National Hepatitis C Action Plan:

> ***"Prioritising people who inject drugs for direct-acting antiviral therapy in community settings – treatment as prevention – will rapidly turn off the tap of new infections."[1] Professor Ed Gane, Hepatologist***

> ***"Community and facility providers are more likely to identify HCV infections in primary care and in high-risk difficult-to-reach populations such as OST clinics,… mental health facilities, and corrections.***

Treating individuals in their home clinic where they are diagnosed or in a setting they frequent and in which they feel comfortable is likely to increase [cure] rates, with multiple models of care emerging."[12] Biondi and Feld, Canada

We are seeing increasing collaboration between healthcare providers and community pharmacies in areas such as INR testing and gout management using standing orders, following the "One team, Kotahi te tīma" approach in the 2016 Health Strategy. We are seeing the same happening with hepatitis C with places such as needle exchanges linking with a pharmacy, or a medical centre that particularly caters for low-income and homeless people working closely with a pharmacy alongside. With shortages of GPs,[15] using a suitable nurse in such a medical practice will aid timely access to care reducing GP burden.

In the Northern Region pharmacy test and treat model, the pharmacist-nurse collaboration is also helping people access care with fewer barriers. Pharmacists are funded to do point-of-care tests, provide blood tests on the spot if necessary, and help patients start on Maviret where appropriate. Pharmacies are working with needle exchange to help linkage to care with people who are antibody positive. They are working with a clinical nurse specialist and hepatology specialist to do this. Similar models are being rolled out elsewhere, for example in the Midlands area. The proposed reclassification will enable this pharmacist-nurse collaboration to benefit people who have hepatitis C.

New Zealand, like a number of other countries, needs help to meet the WHO goal of elimination of hepatitis C as a major public health threat by 2030.[16] Modelling suggests the COVID-19 pandemic has had a significant impact on hepatitis C elimination efforts in most countries including New Zealand, because lockdowns and reallocation of resources have disrupted access to harm reduction, testing and treatment. This has resulted in increase in HCV infections and HCV-related deaths.[17] In New Zealand, in the year prior to the pandemic, 3500 people were cured, whilst in 2021, less than 500 were cured. Recent Markov modelling predicted that in order to meet the WHO 2030 Elimination Goals, annual treatment numbers in New Zealand will need to exceed 2300[18]. To reach this target, we will need to improve access to both testing and treatment across the motu. This includes work in community settings as noted by Professor Gane[1] and Biondi and Feld[12] above.

In other countries, nurses[3, 12] and pharmacists[2, 12, 19] have prescribed or supplied hepatitis C medicines using different mechanisms. Such mechanisms include patient group directions in the UK.[3] A review by Cunningham et al. reported that interventions facilitating same-day treatment initiation are likely to have a large effect on the uptake of treatment.[20] A nurse-led model in community sites including mobile sites has been encouraged in New Zealand.[1] While glecaprevir and pibrentasvir have recently been added to the medicines that can be prescribed by nurses with prescribing rights, this is a small proportion of nurses, most nurses working in the hepatitis C space have indicated that they do not want to do the required study to become prescribers, and thus, the nurse prescribing opportunity is not making a difference for hepatitis C at the community level. Using nurses and pharmacists together will reduce barriers to access.

We see this reclassification will follow two paths:

1. Nurse-initiated - nurses working in settings with higher risk for hepatitis C would have the initial contact with the client and work with a local pharmacy with an appropriately skilled and credentialed pharmacist, to together agree on treatment.
2. Pharmacist-initiated – the pharmacist finds a person in their setting with hepatitis C (or may be referred them from a place like needle exchange or an outreach provider) and works with a specific nurse to together agree on management including treatment. This would support the existing pharmacy test and treat model. It is likely the nurse, for whom this would be part of their agreed role, would be available by telephone and email within an agreed process.

1. Indications and dose

The full indications and dose are in the data sheet attached, with key points below:

MAVIRET is indicated for the treatment of adults and adolescents 12 years and older with chronic hepatitis C virus (HCV).

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), taken orally, once daily at the same time with food. Addition of ribavirin is not required.

Tables 1 and 2 provide the recommended MAVIRET treatment duration based on the patient population in HCV genotype (GT) 1, 2, 3, 4, 5 or 6 patients with compensated liver disease (with or without cirrhosis).

Table 1: Recommended duration for treatment-naïve patients

Patient Population	Recommended Treatment Duration	
	No Cirrhosis	Cirrhosis
GT 1-6	8 weeks	8 weeks

Includes patients co-infected with human immunodeficiency virus (HIV).

Table 2: Recommended duration 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).

The indications and dosage are appropriate for the proposed reclassification and are well-understood by the pharmacists for whom this reclassification is proposed. They are also well-understood by the nurses who may work with the pharmacists.

The diagnosis of active hepatitis C virus (HCV) infection is mandatory prior to starting antiviral therapy. This is through the detection of HCV RNA with a PCR RNA test, something these nurses will be used to ordering and interpreting. In some cases, these nurses, pharmacists or others suitably trained, will be conducting a point-of-care hepatitis C RNA test with a special GeneXPERT machine that provides results in 45 minutes. Pharmacists have been facilitating blood tests for patients and checking the results, with the assistance of a nurse in the Northern Region.

Pretreatment assessment is now very simple with the following issues to be resolved:

a. Prior failure of antiviral therapy: This is the only baseline factor that will influence the duration of Maviret. Previous treatment use in the patient, including its success or failure will be known to these health professionals who will have access to previous prescribing and medical records and can also ask the patient (in case of treatment in a different region or overseas). Nurses

and pharmacists may differ in terms of what they have access to, but it would be expected that it would be a requirement that between them they have access to the necessary patient records.

b. Presence of cirrhosis: Liver staging is part of the clinical pathway, depending on age. People aged 30 years or over with chronic HCV will have blood tests from which the nurse will calculate an APRI score (further details below) or may have an on-the-spot fibroscan. If the patient has cirrhosis which is compensated, he/she can still be treated safely in the community but after cure, he/she will need to receive 6 monthly surveillance for liver cancer with serum alphafetoprotein measurement and abdominal ultrasounds.

The APRI score is the AST-to-Platelet Ratio Index. AST increases and platelets fall with advancing fibrosis (an indication of cirrhosis). Calculating this score allows those at risk of cirrhosis to be identified and referred for fibroscan before starting treatment. The APRI score is calculated though entering the serum AST level and Platelet count in the mdcalc website https://www.mdcalc.com/ast-platelet-ratio-index-apri which uses the equation below:

$$\text{APRI} = \frac{\left(\frac{\text{Serum AST level}}{\text{AST upper limit of normal}}\right) \text{x100}}{\text{Platelet count (x10}^9\text{/Litre)}}$$

The majority of people will have an APRI score of < 1.0 so no fibroscan is necessary. If the APRI is ≥ 1.0, then 50% will have cirrhosis, and therefore they need to be referred for a fibroscan.

People aged under 30 years with chronic HCV are not at risk of cirrhosis and therefore the health pathway does not require an APRI score in this subgroup.[21]

Nurses involved under this proposed reclassification will be very familiar with the APRI score, will be familiar with management of patients with cirrhosis, will be able to refer patients who have an APRI score ≥ 1.0 for a fibroscan, and will have access to specialist advice where needed regarding the APRI score. Some of these nurses may be able to do an on-the-spot fibroscan where appropriate so that the person does not need to go to a lab for the blood test. Any credentialling or guidance for the nurses and pharmacists would have input from the regulators and professional organisations.

Pharmacists will generally be unfamiliar with these tests, but we expect they would receive training on them, understand that they are required, and have the nurse to help navigate through the tests. Note that some pharmacists may only see one or two patients per year, so providing them with all the training on interpreting these blood tests is a less practical approach than having the collaborative arrangement in which the nurse can help interpret the blood tests and advise on management.

2. Presentation

Tablets come in packs of 84 tablets (four weeks' supply). It is proposed that the nurse and pharmacist would be able to treat with the appropriate quantity for a course of treatment, as per the datasheet.

3. Consumer benefits

The consumer benefits of this reclassification are very significant, and it is important that the reclassification be enacted as soon as possible to achieve these benefits. Multiple benefits include:

1. Increasing likelihood of people with chronic hepatitis C being treated for this potentially deadly disease reducing the risk of morbidity and mortality from hepatitis C;
2. Increasing convenience for consumers;

3. Reducing the infection in the potentially transmitting population and therefore protecting other persons from being infected and reducing the future burden on the health system of finding and treating more people.

Hepatitis C is likely to disproportionately affect Māori, who have increase rates of exposure risk, infection and long-term complications.[1] Māori can have difficulty accessing health services in Aotearoa/New Zealand, and Māori with complications from hepatitis C have poorer outcomes than non- Māori with the same complications.[1] Recommendations following recent research by Hikaka et al[22] of Māori experiences of hepatitis C treatment included:

- Develop a coordinated treatment service that provides options for where and how to access care. This includes kaupapa Māori services, conveniently placed test and treat facilities (e.g. local pharmacies) as well as co-location of treatment with intravenous drug use and opiate clinics.
- Offers of treatment, health information and wraparound services should be made proactively.
- Ensure those involved in hepatitis C service delivery are very knowledgeable and supportive

Hepatitis C is a disease with significant stigma and one which likely disproportionately affects Māori in both infection rates and long-term complications.[1] In New Zealand, the majority of people with chronic HCV will have acquired it through shared needles with illicit drug use. For some this will be long-ago behaviour that they may not have revealed to others around them or their doctor. For others who are still injecting, the stigma is very real (including a concern others may consider them "dirty" in having shared needles). For those still injecting there may be other priorities, mental health, addiction and/or social issues that make accessing treatment difficult. We need to make it as easy as possible for these people to be tested and treated. Allowing appropriately trained, experienced and supported nurses who regularly see such people to treat their hepatitis C with the first-line treatment will reduce waiting times for people with hepatitis C and help them to start treatment while engaged. Similarly, allowing pharmacists who may be providing needles or opioid substitution treatment to these people to offer an easy solution to testing and treatment will overcome barriers.

In some cases, this reclassification will enable an immediate linkage to care – a point-of-care PCR RNA test that takes less than 1 hour in someone under 30 years, plus a urine pregnancy test (if indicated) will be sufficient to start a person on treatment that same day. Or in someone aged 30 years or over, a point-of-care PCR RNA test taking less than 1 hour plus a fibroscan and hepatitis B point-of-care test (or known previous fibroscan or APRI results, and previous hepatitis B results) would allow immediate treatment. This type of model could be used to deliver a community Test&Treat programme for the high risk populations at needle exchanges, pharmacies, prisons and the new mobile van outreach services (as will soon be available in multiple New Zealand regions).

4. Contraindications and precautions

Contraindications for Maviret are as follows[9]:

- Hypersensitivity to any ingredient
- Patients with severe hepatic impairment (Child-Pugh C)
- Concomitant use with atazanavir and rifampicin

These contraindications will be well-known to the nurses and pharmacists.

Warnings and precautions are as follows[9]:

Hepatitis B virus reactivation

Cases of severe liver injury have been reported in patients with untreated chronic hepatitis B virus (HBV) and HCV coinfection, during treatment with direct-acting antiviral agents. Therefore, all patients over the age of 30 (i.e. born before neonatal vaccination) should be screened for chronic HBV infection before initiation of treatment. Although the risk of sever liver injury is rare, any HBV/HCV co-infected patient who is not established on treatment for HBV should be monitored during DAA therapy and managed according to current clinical guidelines.

Patients with hepatic impairment

MAVIRET is not recommended in patients with moderate hepatic impairment (Child-Pugh B).

Patients with lactose intolerance

MAVIRET contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Potential effects of HCV clearance by Direct-Acting Antivirals (DAA) (class therapeutic effect)

Patients may experience improvement of liver function with HCV treatment resulting in improved glucose metabolism by the liver. In diabetic patients, this could lead to improved glucose control. Rare cases of symptomatic hypoglycaemia have been reported with the use of HCV DAAs. Therefore, close monitoring of blood glucose levels is recommended in diabetic patients to determine if dose adjustment of the anti-diabetes medication is required.

These warnings and precautions will be well-known to the nurses involved who already will have been providing patient advice about them. The pharmacists dispensing Maviret already have had training in this area.

Drug interactions

Please see the attached data sheet, section 4.5 for all information about interactions with other medicines. The Liverpool University site is well-known to pharmacists who have completed the Pharmaceutical Society training in Maviret, and nurses working in this area.

The data sheet[9] states the following:

"Glecaprevir and pibrentasvir are substrates of P-gp and/or BCRP. Glecaprevir is a substrate of OATP1B1/3. Co-administration of MAVIRET with medicinal products that inhibit hepatic P-gp, BCRP, or OATP1B1/3 may increase the plasma concentrations of glecaprevir and/or pibrentasvir. Co-administration of MAVIRET with medicinal products that induce P-gp/CYP3A may decrease plasma concentrations of glecaprevir and pibrentasvir."

Important clinically significant interactions between Maviret and specific medicines exist. This includes, for example, ethinyloestradiol, used in combined oral contraceptives, and provision with Maviret is not recommended, with important implications on contraception cover. Carbamazepine, statins and some second-line HIV anti-virals are other significant interacting medicines. The nurses covered by this reclassification pertains will already have existing knowledge of these interactions and how to deal with them (withholding or switching the guilty comedication). They will be working with pharmacists who have had additional training in the interactions with Maviret. Furthermore, they will have strong links to local expertise in the gastroenterology department to discuss management of difficult cases where necessary.

Pregnancy and breastfeeding

The data sheet reports the following:

"There are no or limited data from the use of glecaprevir or pibrentasvir in pregnant women.
Animal studies with glecaprevir or pibrentasvir do not indicate direct harmful effects on reproductive toxicity. Maternal toxicity in the rabbit precluded evaluation of glecaprevir at clinical exposures (see section 5.3). As a precautionary measure, MAVIRET use is not recommended in pregnancy.

It is unknown whether glecaprevir or pibrentasvir is excreted in human milk. Available pharmacokinetic data in animals have shown excretion of glecaprevir and pibrentasvir in milk, and a risk to newborns or infants cannot be excluded. Therefore, a decision must be made whether to discontinue breastfeeding or to discontinue/abstain from MAVIRET therapy, taking into account the benefits of breastfeeding for the child and the benefit of therapy for the woman."

All nurses and pharmacists involved in this model using the proposed reclassification would have the appropriate training, knowledge, understanding and access to patient medical history (blood tests, previous prescribing of hepatitis C medicines, current medication) to ensure safe administration of Maviret. Nurses will be able to order any necessary blood tests prior to or during treatment, and pharmacists have been already providing blood test forms to appropriate people to help reduce the loss to follow-up. The exact model and requirements would be decided with input from the Pharmacy Council, Nursing Council, and appropriate pharmacy, nursing and primary care organisations.

5. Undesirable effects

Maviret is extremely well-tolerated with permanent discontinuation for poor tolerability in under 0.1% of those treated in phase 2 and 3 studies[9].

See the data sheet attached for the full list of adverse effects. The most common adverse effects are: headache (13%), fatigue (11%), nausea (8%). Most (80%) of those experiencing adverse events had mild severity, and adverse reactions were at a similar frequency in those randomised to placebo as to active treatment.

These nurses and pharmacists will be familiar with the adverse event profile of Maviret, and will have received training that will include adverse events. The adverse event profile is very reasonable for a reclassification.

6. Overdose

The data sheet notes the following[9]:
"The highest documented doses administered to healthy volunteers were 1200 mg once daily for 7 days for glecaprevir, and 600 mg once daily for 10 days for pibrentasvir. In the case of overdose, the patient should be monitored for any signs and symptoms of toxicities, and appropriate symptomatic treatment should be implemented immediately. Glecaprevir and pibrentasvir are not significantly removed by haemodialysis."

There is no reason that overdose would be any more likely with the proposed reclassification as under existing prescribing.

7. Medication errors and abuse/misuse potential

Maviret is administered asthree tablets once a day, for eight weeks. This is a relatively straightforward regimen to follow, will be explained by the pharmacist or nurse, and included in the product label. The adverse effects of intentional or accidental overdose is minimal.

Minimal risk of medication errors exists, and risk of error should be no greater than that which currently exists with prescription status. Pharmacists have special training to be able to dispense Maviret, and the pack would be dispensed with a patient label.

Maviret is not a medicine with psychoactive effect and is very unlikely to be abused or misused.

8. Communal harm and/or benefit

The primary reason for this application is for the pharmacist-supply model, in conjunction with nurses as appropriate, to remove barriers to treatment uptake in the community for vulnerable populations who have been very difficult to treat in the traditional secondary and primary care models of care. There is communal benefit of having increased uptake of a hepatitis C treatment in these vulnerable populations. Cure with DAAs (direct acting antivirals) has been associated with improved life expectancy, quality of life and engagement with harm reduction services in PWID (people who inject drugs). Cure of PWID will rapidly reduce HCV transmission in that community and is key to achieving an 80% reduction in incidence of HCV in New Zealand by 2030, one of the goals of the WHO Elimination Targets and the New Zealand Hepatitis C Action Plan.[1]

Those who will be targeted with this service will include people who are not currently accessing health services, people who have other challenges in their lives making prioritising management of their hepatitis C difficult, people worried about stigma who are reluctant to raise hepatitis C with their usual health care professional, and transient populations, such as people who are homeless, those with chronic mental illness and those who have recently been in prison. People attending pharmacies for needle exchange or opioid substitution services, or other reasons will be able to be tested and treated easily in this community setting, where they are comfortable and have trust in the peer support, nurses and pharmacists. Some of these may be people who could be at greatest risk of transmission to others.

The community will also benefit from treating the individuals who have had chronic hepatitis C, both through feeling healthier (hepatitis C can cause fatigue and reduce health-related quality of life[23]) and reduced risk of complications which require considerable resource to address, e.g. on-going monitoring, liver transplant, or have early mortality. Having these people able to function well is beneficial for themselves, their families and society.

There is no communal harm likely. The theoretical risk of generating and transmitting antiviral resistant virus within active PWID population through inappropriate or intermittent use of direct acting antivirals in PWID population has never been reported despite more than 10 million individuals successfully treated to date.

9. Integrated benefit-risk statement

The overall benefit strongly outweighs any risk which will be managed through:

- pharmacists who have completed specific training,
- identifying an appropriate small group of nurses working in the right setting for whom this reclassification applies and who are willing to work collaboratively in this model,
- use of a guideline and criteria for supply (e.g. minimum age of 16 years, and referral points such as previous treatment failure),
- a clear referral pathway, and

- an ability for the nurse and pharmacist to see advice from a physician with considerable experience in hepatitis C or a gastroenterology department if required for a specific patient.

The benefit is improving ready access to treatment, having more appropriately trained health care professionals able to be proactive in treating patients, and therefore reducing the attrition commonly seen in community settings when a person is found to be hepatitis C positive. Within this community group there is often distrust of the health system, many will be mobile with a chaotic lifestyle, and some will be concerned about stigma and legal consequences of engaging in criminal behaviour. These people often become lost to follow up. This proposed reclassification brings hepatitis C treatment closer to their home, making it more convenient for people with hepatitis C to be treated, and therefore reducing transmission and complications of hepatitis C.

This reclassification proposal will provide the greatest benefit for marginalised populations and Māori, by removing inequities of access and the stigma associated with hepatitis C.

10. Risk mitigating strategies

There is minimal risk with this reclassification because the registered nurses concerned will have the necessary knowledge and support to ensure they are able to deliver hepatitis C treatment in a best practice manner, and the pharmacists will receive special training. Already pharmacists need to receive special training through a Pharmaceutical Society training programme to dispense Maviret, and this training could easily be extended to include the pharmacist-supply function, ensuring the pharmacists have the necessary information.

A meeting will be held with the Pharmacy Council and Nursing Council and other appropriate stakeholders to discuss the model and requirements for the two health professionals. A Health Pathway guideline (see appendices) provides guidance where necessary. Any nurses involved will be encouraged to be members of the Hepatology Subgroup of the New Zealand Nurses Organisation Gastroenterology Nurses' College (which is open to nurses with an interest in liver health).

The registered nurses working in hepatology are very experienced with excellent knowledge of the disease, how to diagnosis it, liver effects, the medicine, the contraindications, precautions and drug interactions, and the tests required before treatment starts. In most cases these nurses are working within a multi-disciplinary team in the gastroenterology department. The registered nurses working in community with hepatitis C will be appropriate qualified and supported. We expect both nurses and pharmacists to have ready access to local hepatitis specialists (this will include anyone experienced with treating hepatitis C, such as gastroenterologists, infectious diseases specialists, addiction specialists or experienced GPs).

In this model, the pharmacist will dispense the medicine. This provides a safety net, as for general practitioner prescriptions, as only specific pharmacies where the pharmacist has successfully completed Maviret training can dispense the medicine. It also ensures the patient electronic record is up-to-date for other health providers to see the medication prescribed.

This reclassification will only be useful if funding is also made available for treatment provided according to this reclassification. Note that Pharmac has agreed to fund Maviret through pharmacist provision under a standing order in the Northern Region in New Zealand, so this would not be dissimilar and enables access.

Treatment failures will involve secondary services as they will need testing for NS5A resistance and consideration of the national retreatment programme. People with hepatitis B, APRI ≥ 1, or HIV will be referred to secondary services, as will children under 16 years. Women who are pregnant or breastfeeding will have treatment initiation delayed until they are no longer pregnant or breastfeeding. Clinically significant interactions will be managed as is recommended, with the prescribing doctor of the interacting medicine contacted where necessary.

11. Potential risk of harm to the consumer as a result of the proposed change, and factors to mitigate this risk

Potential harms for the consumer are stated below:

a. The consumer is treated when they are antibody positive and not RNA positive (so do not need the treatment), or have not had the other required tests (which could indicate referral is needed). The risk of harm to the consumer is negligible but this would incur costs of course of care, including the Maviret medication.

   Mitigation: All nurses and pharmacists concerned will have the knowledge and understanding of the necessary blood tests, and how to treat appropriately. There is a clear Health Pathway for management of hepatitis C. There will be an appropriate flow chart available for the pharmacist to work through.

b. The consumer's full medical history and other medications may not be known at a community site if they receive medical services elsewhere.

   Mitigation: there is a mechanism used to look up electronic patient records, to see the medicines being taken, blood test results, previous treatment of hepatitis C, and to ask them. Note that patients are already being managed at needle exchanges, emergency departments, and clinics for vulnerable people, and information accessed to aid in decision making.

c. Some may suggest that consumers in these environments may not take the full treatment and then end up with an infection that is resistant. This risk is small and treatment duration as short as 4-6 weeks will often achieve cure.

   Response: This is a well-known risk that is worth taking as many of these patients will take the medicine and be cured, and note above the treatment as prevention strategy.[1, 11] These nurses and pharmacists will help with adherence advice.

d. Risk that the consumer's general practice or other prescriber will be unaware that the consumer is receiving Maviret and may prescribe an interacting medicine.

   Mitigation: With consumer consent, the consumer's general practice or other prescribers involved in their care (e.g. alcohol and drug services, mental health services) will be informed of the consumer's treatment with Maviret. This is usual with most of these services already. The prescribing record for the patient will include Maviret as it will be provided from a pharmacy.

e. If the community service is a mobile one, there is a risk that the consumer will not get follow-up care.

   Mitigation: Any hepatitis C service set up will include follow-up care, which may be by telehealth. Consumers will be encouraged to become enrolled at a general practice if they are not already. Note that this is an already known risk of this population, that they can be difficult to engage, and we need to reduce barriers to access for hepatitis C treatment as much as possible with this group, as is the intent of this reclassification.

f. Risk that the patient will be provided with the treatment despite being inappropriate for it, because of previous use of this medication. A second course of Maviret for patients who reinfected after previously been cured with Maviret is safe and effective. A second course of Maviret for

patients who previously failed Maviret will be safe and may be ineffective if DAA resistance developed after the first course. This risk is negligible - of the 5500 New Zealanders treated with Maviret, less than 60 have failed treatment with DAA resistance. All have been offered retreatment in a study at NZLTU and all but one has been cured.

Mitigation: knowledge, training and the ready access to clinical records and the secondary care team, and asking questions of the patient.

g. Risk that the patient will be recommended the wrong duration of treatment. The risk is that of unnecessary cost of prolonged duration of therapy. There are no additional risks of treatment failure, adverse effects, or DAA resistance.

   Mitigation: training, Health Pathways and the ready access to secondary care team and ability to know when to ask questions and work relationship/environment that encourages questions.

h. Risk that the patient will not receive treatment because they do not get the hepatitis C RNA test or do not return for the results.

   Mitigation: this risk already exists in most environments in which people at risk of hepatitis C are and is unlikely to be any greater with nurse-led care than for other prescribers in these settings. This application helps reduce some barriers for these patients. Other mitigations may be needed here, such as incentives for getting the test, peer support, or having a point-of-care RNA testing machine, which are being used in some community settings in New Zealand.

i. Risk that the patient will have other health concerns that could not be resolved at the same time.

   Mitigation: Other health concerns are possible in this population. All nurses and pharmacists treating patients under this reclassification would be advised to always recommend that the patient sees a general practitioner regularly for their wider health needs. This is important given that the mean age of hepatitis C patients in New Zealand is over 50 years and they have high rates of alcoholism and mental illness. Pharmacists routinely refer people to general practice, so are well-versed in doing this.

   To meet the goal of elimination of hepatitis C by 2030, and prevent transmission of hepatitis C to other patients, we need to increase the access to treatment through patient-centred models. We anticipate that some patients may become more motivated about their health needs on building a relationship with a nurse or pharmacist who helps them treat an important problem, and then encourages them to get enrolled with a general practitioner for other care.

12. Further information

We greatly appreciate the assistance of Te Kaunihera Tapuki o Aotearoa, The Nursing Council of New Zealand, and pharmacy organisations in feedback regarding the reclassification. A meeting of stakeholders is planned to decide on the details of a model.

Summary

New Zealand has signed up to the WHO goal of elimination of hepatitis C as a public health threat by 2030. We need to remove barriers to access for care in those vulnerable populations most at risk of hepatitis C. Some may not be diagnosed, whilst others already diagnosed are unable or unwilling to access primary health care services.

Adopting this exception to prescription status for the pharmacist-supply of Maviret will reduce many barriers to access while retaining patient safety. It should help community nurse-led services maintain people in the treatment pathway. This model will also support the pharmacy test and treat programme. The ability to treat without waiting for a doctor's prescription should increase treatment uptake and cure in our most vulnerable populations.

Maviret is a well-tolerated medicine with predictable contraindications and precautions, with few well known drug-drug interactions. There is a written healthcare pathway for treatment of patients with hepatitis C. The proposed reclassification will see competent trained health professionals very well-placed to manage the treatment of patients with this medicine and increase uptake as a result of the collaborative model.

Nurse-led models of care are becoming more popular internationally to improve access to hepatitis C treatments in the community. The prescribing course necessary to become either a Nurse Practitioner or Designated Registered Nurse Prescriber requires considerable study which most nurses working in this space do not wish to do. For this small area of treatment that they are already very competent in, it is reasonable to consider other mechanisms to enable nurse-led care in Aotearoa New Zealand. The pharmacist-supply model assists the nurse-led model of care through a collaboration with the pharmacist while minimising the burden of managing expensive stock and automating prescribing record updates. It also supports the pharmacist-led care where the pharmacist identifies someone in need of treatment and seeks a nurse's advice where needed.

This reclassification has multiple benefits for people with hepatitis C, for their community, and for the health system in the potential savings from preventing complications associated with chronic hepatitis C infection. Risks are minimal. Enabling new care models is needed urgently to help achieve the government goal of elimination by 2030, and maximise the potential gains from such care.

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