Application to increase access to Maviret through exemption to prescription status for specific nurses

Introduction

This application seeks to widen access to a treatment for chronic hepatitis C infection to allow nurses with appropriate knowledge and experience to treat people with hepatitis C safely, thereby making the medicine more accessible and increasing uptake.

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 the [now 40,000] New Zealanders estimated to be 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, New Zealand is currently not on track, and barriers to access need to be overcome to reach this target. This reclassification seeks to help overcome some of these barriers, enabling nurse-led clinics.

Chronic hepatitis C disproportionately affects marginalised populations (e.g. people who inject drugs, people in prison, homeless), and has considerable stigma. Nurse-led management is one of the recommendations of the National Hepatitis C Action Plan[1] to help reach these important populations, to *"turn off the tap of new infections"* and also to prevent complications such as hepatocellular carcinoma and liver failure. Increasing access and treatment uptake will save our health system resources with fewer new infections to find and treat and fewer people with complications to be managed. Increasing treatment uptake will save lives.

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 in both infection numbers and complications,[1] and enabling easier access with fewer steps to getting treated, including through outreach work, will increase treatment for Māori.

The subject of the reclassification is the combination medicine containing glecaprevir and pibrentasvir (Maviret), the key treatment used to treat chronic hepatitis C infection in New Zealand. With just eight weeks of once daily tablets (in most people), Maviret will cure around 98% of people with hepatitis C, and it is well-tolerated.[2]

This proposal would enable a group of nurses with relevant knowledge and support to manage and treat people with chronic hepatitis C, to benefit individuals, the communities they work with and the health system. Hepatitis C is straight-forward to diagnose. Referral criteria are clear. We recommend successful completion of a short training programme developed for this initiative be a requirement. The nurses will have support from their local gastroenterology team or physicians experienced with hepatitis C.

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 an urgency in this application. Mobile van services are being implemented in multiple regions, and work in needle exchanges and community outreach work are already underway, but only one nurse practitioner in hepatology currently prescribes with others needing to arrange a doctor's prescription. This reclassification would reduce the steps required to treating a patient, reducing loss to follow-up. 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 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**
   Essentially we wish to enable nurses who are hospital-based or in the community with appropriate knowledge and who are the principal health professionals managing patients with hepatitis C to be able to facilitate the supply of glecaprevir-pibretasvir combination tablets. We are open to wording that best achieves this and have made several suggestions 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 training programme on hepatitis C provision by nurses, when recommended or supplied by a registered nurse who has specialty knowledge of hepatitis C*, or a nurse working in the community in a high-prevalence hepatitis C environment, who has successfully completed the approved training programme, and who meet the criteria of the training 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 training programme on hepatitis C provision by nurses, when recommended or supplied by a registered nurse who has specialty knowledge of hepatitis C*, or a nurse working in the community in a high-prevalence hepatitis C environment, who has successfully completed the approved training programme, and who meet the criteria of the training programme.

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

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.[3, 4]

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] We are currently **not on track** to achieving this and it is imperative that we 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 pangenotypic, i.e. this medicine can be used for all genotypes of hepatitis C. It 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.

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 prescriber, if necessary, and provide counselling. The tablets are typically given as a 4-week course with one repeat.

In New Zealand, in the pharmacy test and treat model used in the Northern Region, the model allows for standing orders to be used by pharmacists to supply Maviret without requiring a prescription. This is not a useful option for nurses managing hepatitis C, as standing orders do not allow prescribing.[5]

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. There is currently only a single nurse (a Nurse Practitioner) who is a clinical nurse specialist in hepatology in New Zealand who prescribes Maviret.

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.[6] 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.[6] Hepatitis C is an infection which, when diagnosed and treated for eight weeks is almost always cured, and for those 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.[7] 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.[8] 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.[9] 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)[7] 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 existing pathways for increasing use of nurse-led hepatitis C treatment make the proposed reclassification the best option for addressing the unmet need and helping overcome some barriers to access.

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. An example is provided below for the Lignocaine exception from prescription.

> *"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."*

This reclassification of Maviret will apply to registered nurses with specialist knowledge about hepatitis C working in hepatology clinics or in community and who are the principal health professionals managing patients with hepatitis C.

As background information, below is described the three scopes of practice for nurses in New Zealand, as per the Nursing Council.

Enrolled nurse (**Tapuhi Kua Whakauru)**[10] **-** practises under the direction and delegation of a registered nurse or nurse practitioner to deliver nursing care and health education across the life span to health consumers in community, residential or hospital settings. This is a small group with only 2456 registered in 2020. **Note: it is not proposed that this reclassification will apply to an enrolled nurse**

Registered nurse (Tapuhi Kua Rēhitatia)[11] – uses nursing knowledge and complex nursing judgment to assess health needs and provide care, and to advise and support people to manage their health. They practise independently and in collaboration with other health professionals, perform general nursing functions, and delegate to and direct enrolled nurses, health care assistants and others. They provide comprehensive assessments to develop, implement, and evaluate an integrated plan of health care, and provide interventions that require substantial scientific and professional knowledge, skills and clinical decision making. This occurs in a range of settings in partnership with individuals, families, whānau and communities.
Registered nurses may practise in a variety of clinical contexts depending on their educational preparation and practice experience. Registered nurses may also use this expertise to manage, teach, evaluate and research nursing practice. Registered nurses are accountable for ensuring all health services they provide are consistent with their education and assessed competence, meet legislative requirements and are supported by appropriate standards.

There will be conditions placed in the scope of practice of some registered nurses according to their qualifications or experience limiting them to a specific area of practice. Some nurses who have completed the required additional experience, education and training will be authorised by the Council to prescribe some medicines within their competence and area of practice. In 2020 there were 57,000 registered nurses in New Zealand.

Nurse practitioner (Mātanga Tapuhi)[12] - has advanced education, clinical training and the demonstrated competence and legal authority to practise beyond the level of a registered nurse. Mātanga tapuhi nurse practitioners work autonomously and in collaborative teams with other health professionals to promote health, prevent disease, and improve access and population health outcomes for a specific patient group or community. They prescribe medicines within their area of competence. In 2020 there were 459 nurse practitioners in New Zealand. **Note: this reclassification is not relevant to nurse practitioners as they already have prescribing rights.**

Nurse with prescribing rights (other than a nurse practitioner) – there were 335 registered nurses with prescribing rights in NZ in 2020, 60 of whom were for diabetes.[13] This is approximately 0.6% of the registered nurse workforce. These registered nurses have completed a postgraduate diploma or clinical masters and assessment against prescribing competencies. See the attached appendix for more information about the training requirements that were summarised above.

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

> ***"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 the [now 40,000] New Zealanders estimated to be 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***

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 and mobile van services. Trials support that Maviret treatment (usually 8 weeks) cures around 98% of people with chronic HCV taking the full course.[2] Cure will reduce their risk of hepatocellular carcinoma, liver failure.[14] Providing hepatitis C treatment to people with chronic HCV who inject drugs is recommended to reduce new infections, this is known as "treatment as prevention",[15] and we have the opportunity to maximise this work in needle exchanges and outreach settings using nurse-led care.

Many challenges exist to diagnosing and treating people with chronic HCV, including the fact that it is often asymptomatic.[14, 16] New Zealand needs to overcome these challenges, with WHO recommending use of trained nurses for testing and treatment for hepatitis C and simplified services delivered close to communities.[17] Indeed, the WHO theme for World Hepatitis Day 2022 is "Bringing hepatitis care closer to you".[17]

Nurse-led models of care are increasingly seen in many developed countries as the answer to enable closer "on-site" care,[16, 18] particularly in locations with higher HCV prevalence, such as needle exchanges, opioid substitution sites or collection points,[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."[16] Biondi and Feld, Canada***

New Zealand, like a number of other countries, is not on track to meet the WHO goal of elimination of hepatitis C as a major public health threat by 2030.[19] Modelling suggests COVID-19 has affected hepatitis C programmes causing excess liver deaths and other harms.[20] New Zealand will be no exception. During COVID-19 lockdowns and infection in the community affecting staff availability, testing programmes in some locations were suspended at times, or greatly reduced and treatment numbers have been low. Catch up will be vital, and to achieve the 2030 elimination goal diagnosis and treatment of hepatitis C needs to be more accessible to the community. This includes work in community settings as noted by Professor Gane[1] and Biondi and Feld[16] above.

Internationally, nurses[3, 16] and pharmacists[4, 16, 21] 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.[22] 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.

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. They are clear and will be very well-known and well-understood by the nurses for whom this reclassification is proposed.

Chronic hepatitis C virus (HCV) infection is easily identified by a PCR RNA test, something these nurses will be used to ordering and reading and this will be required before anyone is treated for hepatitis C. In some cases, these nurses or others suitably trained, will be conducting a hepatitis C RNA test on the spot with a special machine that provides results in one hour.

Previous treatment use in the patient, including its success or failure will be known to the nurses 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).

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.

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 values in the mdcalc website https://www.mdcalc.com/ast-platelet-ratio-index-apri which uses the equation below:

$$\text{APRI} = \frac{\left(\frac{\text{Serum AST level}}{\text{AST upper limit of normal}}\right) \times 100}{\text{Platelet count } (\times 10^9/\text{Litre})}$$

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.[23]

Nurses able to treat patients 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. We propose that nurses concerned would need to successfully complete a training that includes a test to ensure all had the correct knowledge.

2. Presentation

Tablets come in packs of 84 tablets (four weeks' supply). It is proposed that the nurse would be able to treat with the appropriate quantity for a course of treatment, as per the datasheet. We propose that the nurses would need to successfully complete a training that includes an assessment to provide evidence of having the correct knowledge.

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.

Hepatitis C is likely to disproportionately affect Māori in infection rates 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[24] 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.

In some cases, this reclassification will enable a "one-stop-shop" approach – a point-of-care PCR RNA test that takes one hour in someone under 30 years, plus a urine pregnancy test (if indicated) will be sufficient to start a person on treatment. Or in someone aged 30 years or over, a point-of-care PCR RNA test taking one 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 at a needle exchange facility, with community testing e.g. mobile van (as will soon be available in multiple New Zealand regions), at a medical practice serving a high-risk population, in outreach, or for prisons.

4. Contraindications and precautions

Contraindications for Maviret are as follows[2]:

- 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.

Warnings and precautions are as follows[2]:

Hepatitis B virus reactivation

Cases of hepatitis B virus (HBV) reactivation, some of them fatal, have been reported during treatment with direct-acting antiviral agents. All patients should be screened for HBV before initiation of treatment. HBV/HCV co-infected patients are at risk of HBV reactivation, and should therefore be monitored 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.

Drug interactions

Please see the attached data sheet, section 4.5 for all information about interactions with other medicines.

The data sheet[2] 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 HIV anti-virals are other significant interacting medicines. The nurses for whom this reclassification pertains will have existing knowledge of these interactions and will have had to deal with them before, but it will also be covered in the training to ensure they are very well-versed in how to manage these interactions. 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 are 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 who would be enabled to recommend or supply Maviret using the proposed reclassification would have the appropriate training, knowledge, understanding and access to information (blood

tests, previous prescribing of hepatitis C medicines, current medication to ensure they could recommend or supply the treatment safely with respect to contraindications, precautions and interactions. They will be able to order blood tests. We propose the requirement to successfully complete a training that includes a test to ensure all have the correct knowledge before they start treating patients.

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[2].

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

6. Overdose

The data sheet notes the following[2]:

"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 tablets are taken as three tablets once a day, usually for eight weeks. This is a relatively straightforward regimen to follow, will be explained by the nurse, and included in the product label.

Minimal risk of medication errors exists, and risk of error should be no greater than that which currently exists with prescription status. Maviret is the primary funded treatment for hepatitis C in New Zealand and nurses for whom this exemption from prescription status would apply know Maviret well. Nurses would typically recommend the medicine to then be dispensed by the pharmacist, so it would receive a normal dispensing label with dosage on it.

Where concerns exist that the patient may need to receive the medicine themselves directly (e.g. in a remote area), there may be the potential for provision by the nurse directly to the patient for whom they have recommended it (subject to funding and manufacturer approval). Selection error would be unlikely in this instance as the nurses know it so well and they are unlikely to be holding any other similar medicine.

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 to reduce barriers to uptake of this medicine, and helping people with chronic hepatitis C to be cured, with a nurse-led model particularly helpful for those with the greatest difficulty of access. There is communal benefit of having increased uptake of a hepatitis C treatment, particularly in this more vulnerable population. Increasing uptake will increase the proportion of people who have chronic hepatitis C who are treated and therefore reduce the risk of transmission in the future. Reducing transmission is a key aim of the Hepatitis C Action Plan to help meet the goal to stop hepatitis C being a public health threat by 2030.[1] Those who will be targeted with this service will include those 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. 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[25]) 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. While normally resistance is a consideration with reclassification of an anti-microbial, use will be limited to those who have tested hepatitis C RNA positive, so there is no risk of over-usage.

9. Integrated benefit-risk statement

The overall benefit strongly outweighs any risk which has been managed through:

- identifying an appropriate small group of nurses working in the right setting for whom this reclassification applies,
- the requirement to successfully complete training,
- 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
- support from a physician with considerable experience in hepatitis C or a gastroenterology department.

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, some will be mobile with a chaotic lifestyle, and some will be concerned about stigma. These people often become lost to follow up. By the appropriate nurses being able to provide treatment, this 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.

A particular benefit is likely for marginalised populations and Māori, owing to inequities of access and the stigma associated with hepatitis C which this reclassification will help to address.

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.

We propose that all nurses for whom this applies complete a short on-line training session and pass a test, to ensure all have the necessary knowledge, and that all will have appropriate support. A HealthPathway guideline (see appendices) provides guidance where necessary. These nurses 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 may also be very experienced, or may be newer to the role where they will be managing hepatitis C. In either case, they will complete the training mentioned above, pass the test, and work closely with their local gastroenterology team or hepatitis C physician (this will include anyone very experienced with treating hepatitis C, such as infectious diseases, addiction specialists or GPs who have treated many patients). There will be no greater risk in these nurses treating a person with chronic hepatitis C following this training than a general practitioner who prescribes Maviret possibly once every year or two and has not had recent training in the new DAAs for hepatitis C.

We anticipate (subject to the final reclassification statement) that in most cases the pharmacy 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. If the nurse was to provide it directly, they can check with a pharmacist or the gastroenterology team on interactions advice if needed.

To ensure pharmacists know which nurses have successfully completed the training, a website (host site to be confirmed) can list which nurses have successfully completed the training and therefore are legally able to treat the patient with Maviret. Pharmacies providing Maviret will be informed of the reclassification if it is enacted and where to find details of the nurses it applies to. Furthermore, the nurses will be encouraged to contact pharmacies they are likely to use for the product recommendation and introduce themselves.

This reclassification will only be useful if funding is also made available for treatment provided according to this reclassification, and discussion with Pharmac is already underway. 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.

A potential concern could be that nurses could supply Maviret directly themselves without going through pharmacy and therefore not being entered into dispensing software which puts it into the electronic patient record. For mobile services with a "one-stop-shop" model, provision by the nurse directly may be useful. However, further work would be required before this could be put in place and

could be a requirement of funding and stock supply, so should not prevent a reclassification decision, and it is recommended that any reclassification decision would be future proofed to allow this to happen in the future if appropriate.

Treatment failures will be referred to 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).
   Mitigation: All nurses concerned will have the knowledge and understanding of the necessary blood tests, and how to treat appropriately. This will be ensured through the successful completion of training.
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.
   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, 15] These nurses will help with adherence advice which will also be covered within the training.
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: The training will cover the need for the nurse to (with consumer consent) inform the consumer's general practice or other prescribers involved in their care (e.g. alcohol and drug services, mental health services) of the consumer's treatment with Maviret. This is usual with most of these services already.
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 – this will be included in the training. 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 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
   Mitigation: training and the ready access to clinical records and the secondary care team, and ability to know when to ask questions

g. Risk that the patient will be recommended the wrong duration of treatment.
   Mitigation: training 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 treating patients under this reclassification would be advised to always recommend that the patient sees a general practitioner regularly for their wider health needs.
   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 a nurse-led model. We anticipate that some patients may become more motivated about their health needs on building a relationship with a nurse 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 members of the Hepatology subgroup of the NZNO Gastroenterology Nurses' College in feedback regarding the reclassification including wording. Any reclassification would have training and criteria developed in conjunction with both organisations.

Summary

New Zealand has signed up to the WHO goal of elimination of hepatitis C as a public health threat by 2030. We are currently not on track to achieve this, and need to reduce barriers to access. The population most at risk of hepatitis C is vulnerable with stigma concerns about the disease. Many will not be accessing health care services, or may not have been tested by these services. Some are known to have chronic HCV infection, but have barriers to treatment that need to be overcome.

Allowing registered nurses who are experienced in hepatology or working in community with a high prevalence of hepatitis C patients, who have successfully completed approved training on hepatitis C for this role, and who have strong support to treat patients with hepatitis C with Maviret will reduce some barriers to access. It will help reduce the attrition of patients who do not get treatment and help community nurse-led services to be more effective. Patients will not need to wait for a prescription to be obtained from a doctor.

Maviret is a well-tolerated medicine with clear contraindications and precautions, and some important interactions. There is a written pathway for treatment of hepatitis C with clear requirements for referral. 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 nurse-led model.

Nurse-led models of care are becoming more popular internationally to aid access to hepatitis C treatments and have been proven to do this. The prescribing course 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.

A positive reclassification decision would be followed by prompt development of training and criteria for supply in consultation with the Te Kaunihera Tapuki o Aotearoa, The Nursing Council of New Zealand and members of the Hepatology subgroup of the NZNO Gastroenterology Nurses' College.

This reclassification has benefits for people with hepatitis C, for prevention of new hepatitis C infections in the community, and for the health system in the potential savings from complications associated with chronic hepatitis C infection and additional infections to be treated following transmission. Enabling nurse-led care is needed urgently to help achieve the government goal of elimination by 2030, and maximise the potential gains from nurse-led care.

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