## Medicines Adverse Reactions Committee

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|---|---|---|---|
| Meeting date | 10/06/2021 | Agenda item | 3.2.3 |
| Title | **Options for minimising opioid abuse, misuse and dependence** | | |
| Submitted by | Medsafe Pharmacovigilance Team | Paper type | For advice |
| **Active ingredient**<br>Buprenorphine<br>Codeine<br>Dihydrocodeine<br>Fentanyl<br>Methadone<br>Morphine<br>Oxycodone<br>Pethidine<br>Tramadol | **Product name** | **Sponsor** | |
| PHARMAC funding | All opioids listed above have at least one product funded on the Hospital and Community Schedules. | | |
| Previous MARC meetings | 184th meeting – held 3 December 2020: Opioids and abuse, misuse and dependence<br>169th meeting – held 9 March 2017: Concomitant use of opioids, benzodiazepines and other CNS depressants and the risk of serious side effects | | |
| International action | • FDA - Risk Evaluation and Mitigation Strategy (REMS) required for all opioids; prescribing information updates<br>• MHRA – warnings on package labelling, updates to prescribing information, safety leaflets for patients<br>• TGA – smaller pack sizes, boxed warnings and class statements in prescribing information and consumer medicine information, narrowing of indications<br>• Health Canada – Mandatory risk management plans for prescription opioids, Warning sticker and patient information handout | | |
| *Prescriber Update* | The following is a list of recent articles only.<br>• Opioid-induced hyperalgesia (for publication June 2021)<br>• Spotlight on tramadol including updated advice for use in children June 2020<br>• Spotlight on Codeine June 2018<br>• Medicines Interacting with Methadone June 2018<br>• Transdermal Opioid Patches - Stick to the Correct Application March 2020 | | |
| Classification | See Table 1. Medicines Regulations 1984 and the Misuse of Drugs Act 1975. | | |
| Usage data | See section 2.3 | | |
| Advice sought | **The Committee is asked to advise:**<br>• Which of the suggested options does the Committee consider will minimise the risk of opioid abuse, misuse and dependence in New Zealand? | | |

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# 1 PURPOSE

In December 2020, Medsafe presented a paper to the Committee regarding opioid abuse, misuse and dependence [1]. This paper reviewed the available data on opioid use to try and ascertain if there is a problem in New Zealand, or a recent increase in problems as seen in other countries.

At the meeting, the Committee noted that from the global data, New Zealand is doing comparatively well with the issue of opioid abuse, misuse and dependence [2]. There have been concerted efforts across New Zealand in both primary and secondary care to minimise the use of strong opioids. For example, in secondary care, some hospitals have developed policies on the appropriate amount of opioids to prescribe to patients on discharge from hospital and educating junior doctors on these policies.

The Committee discussed that strong opioids in New Zealand are tightly regulated in terms of dispensing and the re-supply of repeats [2]. Nevertheless, the Committee agreed that there is some evidence of abuse, misuse and dependence in New Zealand.

The Committee recommended [2]:

1. that Medsafe bring back an options paper concentrating on actions for weak opioids but also considering appropriate changes to data sheets, other regulatory options, education of prescribers and consumers and working with other agencies if appropriate
2. Medsafe to develop a consumer leaflet that highlights the risk of opioid use
3. raising awareness to prescribers that the WHO Analgesic Ladder is a tool intended to manage chronic cancer pain, and to highlight the issue of hyperalgesia with the use of opioids in a future edition of *Prescriber Update*.

The purpose of this paper is to provide options for minimising opioid abuse, misuse and dependence in New Zealand.

# 2 BACKGROUND

The following information was extracted from the paper presented to the Committee in December 2020 [1]. It is provided for background only and no new information has been added.

## 2.1 Approval, classification and funding

There are many opioid products approved in New Zealand. Table 1 below is a summary, by active ingredient, of the classification and funding status for the opioids currently approved in New Zealand. All opioids are classified as prescription medicines under the Medicines Regulations 1984, and most are also classified as Class B or C controlled drugs under the Misuse of Drugs Act 1975. Note that all codeine-combination medicines were reclassified from pharmacy only or restricted medicines to prescription medicines on 5 November 2020; codeine-only medicines were already prescription medicines [3].

**Table 1: Summary of opioids approved in New Zealand by active ingredient – classification and funding status (community and hospital)**

| Opioid | Classification | | Funded | |
|---|---|---|---|---|
| | Medicines Regulations 1984 | Misuse of Drugs Act 1975 | Community[a] | Hospital[b] |
| Alfentanil | Prescription | Class B3 Controlled Drug | No | Yes |
| Buprenorphine | Prescription | Class C4 Controlled Drug | No | No |
| Buprenorphine with naloxone | Prescription | Class C4 Controlled Drug | Yes | Yes |
| Codeine | Prescription | Class C2 Controlled Drug<br>Class C6 Controlled Drug[c] | Yes | Yes |
| Codeine combination products | Prescription[d] | - | Yes[e] | Yes[e] |
| Dihydrocodeine | Prescription | Class C2 Controlled Drug<br>Class C6 Controlled Drug[c] | Yes | Yes |
| Fentanyl | Prescription | Class B3 Controlled Drug | Yes | Yes |
| Methadone | Prescription | Class B3 Controlled Drug | Yes | Yes |
| Morphine | Prescription<br>Pharmacy only[f] | Class B1 Controlled drug | Yes | Yes |
| Oxycodone | Prescription | Class B3 Controlled Drug | Yes | Yes |
| Pethidine | Prescription | Class B3 Controlled Drug | Yes | Yes |
| Remifentanil | Prescription | Class B3 Controlled Drug | No | Yes |
| Tramadol | Prescription | - | Yes | Yes |

a. PHARMAC. 2020. Online Pharmaceutical Schedule – November 2020. URL: https://pharmac.govt.nz/pharmaceutical-schedule/community-section-b/ (accessed 3 November 2020).

b. PHARMAC. 2020. Online HML – November 2020. URL: https://schedule.pharmac.govt.nz/HMLOnline.php (accessed 3 November 2020).

c. A Class C6 Controlled drug when: (i) Compounded with one or more other pharmacologically active ingredients in such a way that the substance cannot be recovered by readily applicable means or in a yield which would constitute a risk to health; and (ii) Containing not more than 100 milligrams of the substance in each dosage unit and with a concentration of not more than 2.5 percent in undivided preparations.

d. All codeine combination products were reclassified from pharmacy only or restricted medicines to prescription medicines on 5 November 2020.

e. Paracetamol with codeine is the only funded codeine combination product.

f. Morphine is pharmacy only in medicines for oral use containing not more than 0.2% of morphine, when combined with 1 or more active ingredients in such a way that the substance cannot be recovered by readily applicable means or in a yield that would constitute a risk to health, when sold in a pack approved by the Minister or the Director-General for distribution as a pharmacy-only medicine.

### 2.1.1 Regulation of controlled drugs

Prescribing of controlled drugs is more tightly controlled than prescribing of other medicines, reflecting the need to restrict access to, and minimise the misuse of, controlled drugs [4]. Class A and B controlled drugs have more restrictions than Class C controlled drugs.

There are restrictions by professional group on the maximum period of supply for controlled drug prescriptions, prescription form requirements (a triplicate controlled drugs prescription form or an electronic form generated from an approved system) and requirements for dispensing within a certain time. In addition, there are further restrictions under s24 of the Misuse of Drugs Act 1975 for treatment of people dependent on controlled drugs [4].

Medicines Control is a regulatory team within the Ministry of Health that oversees the local distribution chain of medicines and controlled drugs within New Zealand [5]. Drug abuse containment activities are carried out by Medicines Control staff in conjunction with two Medical Officers of Health who have wide powers under both the Misuse of Drugs Act 1975 and the Medicines Act 1981 [6].

Activities include [7]:

- liaising with doctors, pharmacists and addiction services in relation to drug abuse and misuse issues
- monitoring controlled drug prescribing
- working with the Medical Officers of Health in the preparation of Restriction Notices for drug seekers and writing to practitioners if there are any concerns regarding possible aberrant prescribing of controlled drugs or medicines
- advising health professionals of current drug misuse issues
- liaising with Police and other agencies locally and nationally on drug misuse
- preparing reports for the disciplinary processes of the Medical Council, Dental Council and Pharmacy Council
- providing advice on the requirements of the Misuse of Drugs Act and Medicines Act.

Where particular drugs are causing problems, there is the ability to reclassify a drug through a process involving the Expert Advisory Committee on Drugs (EACD) who would consider the risk of harm posed.

## 2.2 Indications

Opioids are used to relieve moderate to severe acute pain [8]. They are also used in palliative care patients, with morphine, oxycodone, fentanyl and methadone most commonly used to treat pain in these patients [9]. Opioids are not recommended for treating chronic non-cancer pain (CNCP). This is due to concerns over the long-term efficacy and safety of treatment, including the risk of misuse and addiction [8].

Methadone and buprenorphine with naloxone are used as opioid substitution therapy (OST), for treating patients with opioid dependence [8]. Naloxone is an opioid receptor antagonist that can reverse the effects of agonists such as morphine and methadone [10]. Opioid antagonists with a high affinity for opioid receptors can dislodge opioid agonists from the receptor, thereby precipitating withdrawal. Naloxone is often used therapeutically to reverse the effects of opioid overdose.

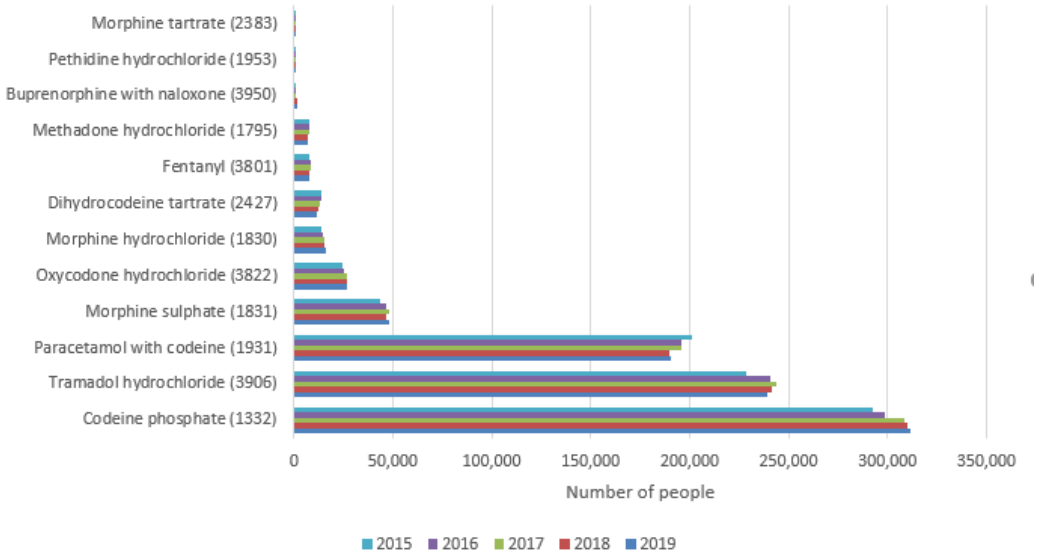
Alfentanil and remifentanil are potent, short-acting opioid analgesics that are chemically related to fentanyl [8]. They are indicated for use as analgesics during surgical procedures and as anaesthetic induction/maintenance agents. Alfentanil and remifentanil are not prescribed in the community for pain management.

## 2.3 Usage data

Data extracted from the Pharmaceutical data web tool are summarised below. This tool provides summary data from the Pharmaceutical Collection about prescriptions and dispensings that were dispensed in the community and funded by the New Zealand Government. It does not provide the indication for use, nor whether the patient took their dispensed medicine as prescribed.

Figure 1 below shows the number of number people dispensed an opioid (by chemical) for 2015 to 2019. Codeine phosphate, tramadol hydrochloride and paracetamol with codeine were dispensed to the greatest number of people. The number of people dispensed codeine phosphate has increased each year, whereas tramadol peaked in 2017 but decreased in 2018 and 2019.

**Figure 1: Number of people dispensed a particular opioid (by chemical ID), 2015 to 2019**

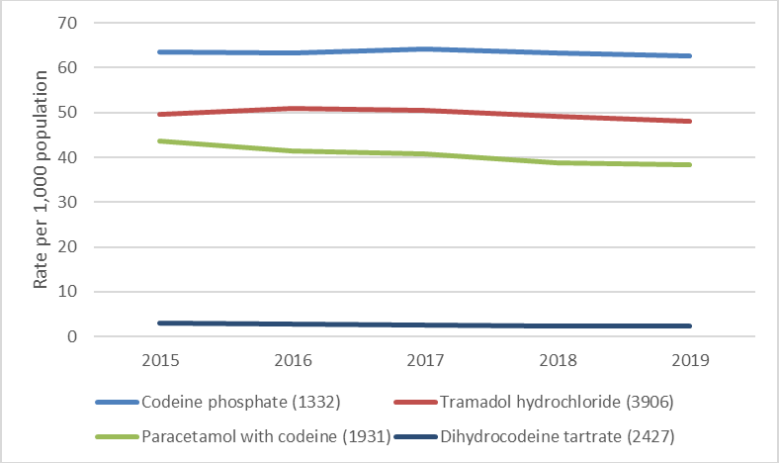



Notes:
The number of people dispensed an opioid is the number of people who received a dispensing of the pharmaceutical product as a named person from a pharmacy at least once during the year, as an initial dispensing or all at once (excludes people who only received a repeat dispensing during the year).
The approval for morphine tartrate lapsed in January 2020; there are now no approved morphine tartrate products available in New Zealand.

Source: Ministry of Health's Pharmaceutical Collection, extracted on 05 March 2020. URL: https://minhealthnz.shinyapps.io/pharmaceutical_data_web_tool/ (accessed 11 November 2020).

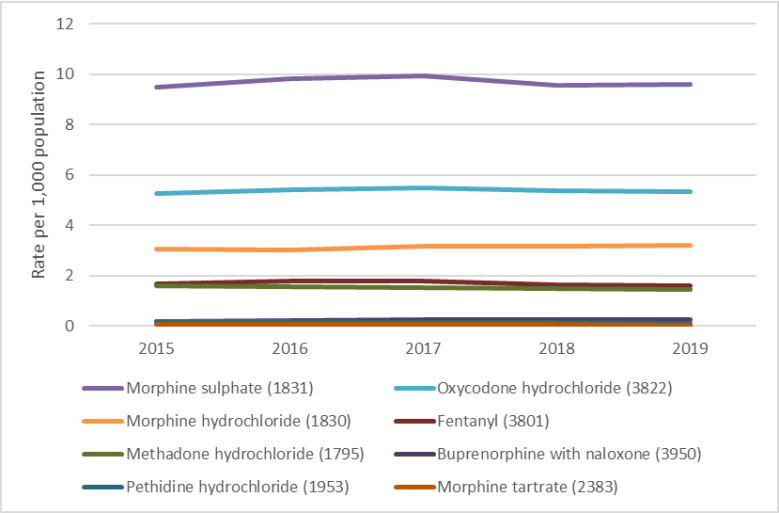
Figure 2 shows the people dispensed a weak opioid and Figure 3 the people dispensed a strong opioid, as rates per 1,000 population, from 2015 to 2019. While the absolute numbers of people dispensed a weak opioid have increased over the time period (Figure 2 above), the rates per 1,000 population have been relatively stable, with a decreasing trend since 2017. The rates per 1,000 population for strong opioids are also stable.

**Figure 2: People dispensed a weak opioid (by chemical ID), rate per 1,000 population, 2015 to 2019**




Sources:
Ministry of Health's Pharmaceutical Collection, extracted on 05 March 2020. URL: https://minhealthnz.shinyapps.io/pharmaceutical_data_web_tool/ (accessed 11 November 2020).
NZ.Stat Subnational population estimates, by age and sex, at 30 June 1996-2020. URL: http://nzdotstat.stats.govt.nz/wbos/Index.aspx?DataSetCode=TABLECODE7509# (accessed 11 November 2020).

**Figure 3: People dispensed a strong opioid (by chemical ID) – rate per 1,000 population, 2015 to 2019**




Sources:
Ministry of Health's Pharmaceutical Collection, extracted on 05 March 2020. URL: https://minhealthnz.shinyapps.io/pharmaceutical_data_web_tool/ (accessed 11 November 2020).
NZ.Stat Subnational population estimates, by age and sex, at 30 June 1996-2020. URL: http://nzdotstat.stats.govt.nz/wbos/Index.aspx?DataSetCode=TABLECODE7509# (accessed 11 November 2020).

## 2.4 Opioid harm

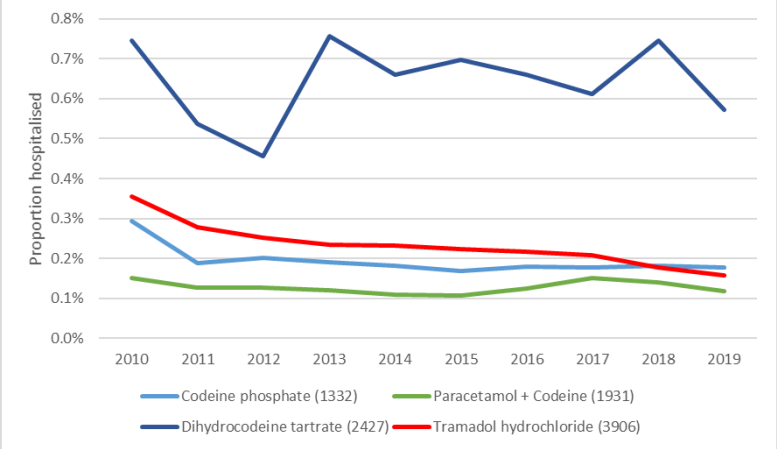
### 2.4.1 National collections

The data below is a linked administrative data set from the Pharmaceutical Collection, the National Minimum Dataset (hospital discharges) and the Mortality Collection of patients who were prescribed a particular opioid between 2010 and 2019. The data set includes unidentifiable information on the first and last date of opioid dispensing, along with hospital discharges and mortality information for ICD-10/ICD-10-AM clinical codes associated with mental and behavioural disorders due to psychoactive substance use (F11 and F19) and poisoning due to narcotics and dysleptics (T40, X42, X62, Y12).

Figure 4 shows the proportion of people hospitalised in the same year as the initial weak opioid dispensing compared to those that were dispensed that opioid and not hospitalised. Figure 5 shows the strong opioids, excluding the opioid substitution treatments (OST), methadone and buprenorphine with naloxone.

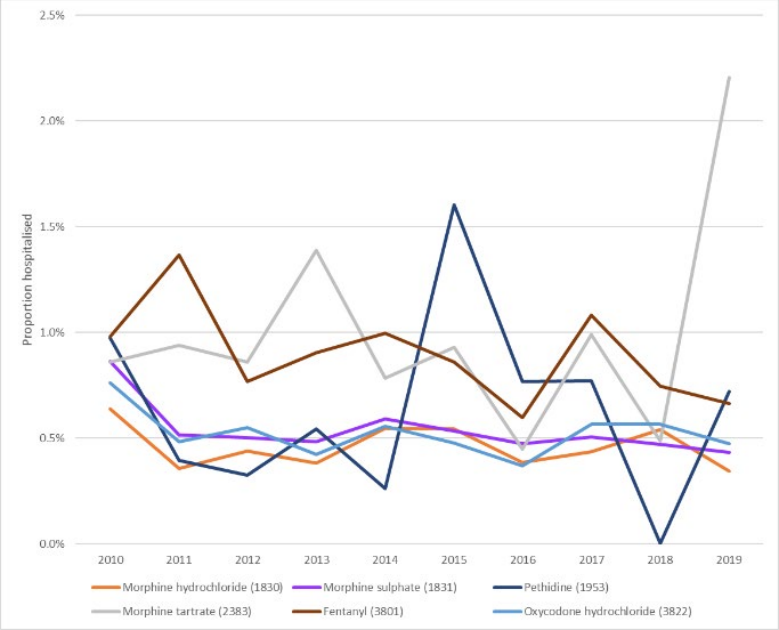
Of the weak opioids, a greater proportion of people were hospitalised with a poisoning or substance abuse code following a dispensing of dihydrocodeine compared to the other opioids. Compared to the weak opioids, the proportions fluctuate more and are higher for the strong opioids. This may be in part due to the lower numbers of people who received strong opioids. Due to their increased potency, strong opioids may also be more likely to contribute to a hospitalisation event within 12 months of dispensing compared to a weak opioid.

**Figure 4: Proportion[a] of people dispensed a weak opioid who were hospitalised with a substance abuse or poisoning clinical code[b] in the same year as the initial dispensing[c], 2010 to 2019**




a. Numerator: number of people hospitalised who had an initial opioid dispensing in that year; Denominator: all people who had an initial opioid dispensing in that year
b. Clinical codes: F11 Mental and behavioural disorders due to use of opioids; F19 Mental and behavioural disorders due to multiple drug use & use of psychoactive substances; T40 code (Poisoning by narcotics and psychodysleptics [hallucinogens] (T40.2, T40.3, T40.4 and T40.6 only); X42 Accidental poisoning by and exposure to narcotics and psychodysleptics, not elsewhere classified; X62 Intentional self-poisoning by and exposure to narcotics and psychodysleptics, not elsewhere classified; Y12 Poisoning by and exposure to narcotics and psychodysleptics, not elsewhere classified.
c. Excludes repeat discharges in the same calendar year.

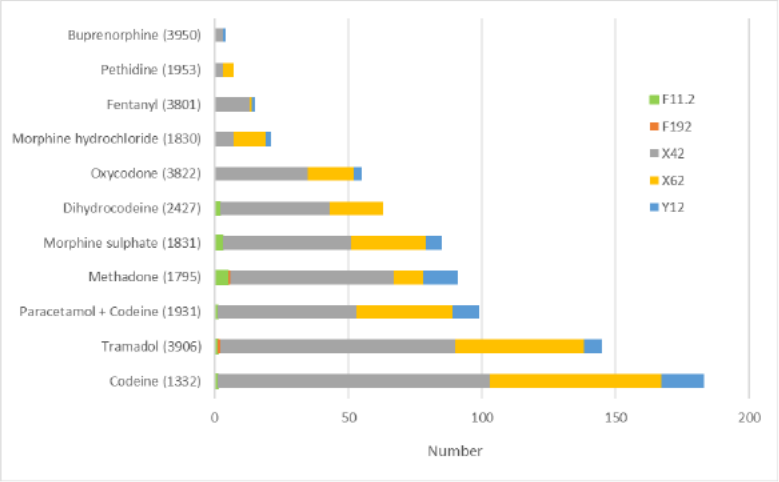
**Figure 5: Proportion[a] of people dispensed a strong opioid[b,c] who were hospitalised with a substance abuse or poisoning code[d] in the same year as the initial dispensing[e], 2010 to 2019**




a. Numerator: number of people hospitalised who had an initial opioid dispensing in that year; Denominator: all people who had an initial opioid dispensing in that year
b. Excludes the strong opioids methadone and buprenorphine with naloxone that are used for opioid substitution treatment.
c. As at January 2020, morphine tartrate was no longer approved in New Zealand.
d. Clinical codes: F11 Mental and behavioural disorders due to use of opioids; F19 Mental and behavioural disorders due to multiple drug use & use of psychoactive substances; T40 code (Poisoning by narcotics and psychodysleptics [hallucinogens] (T40.2, T40.3, T40.4 and T40.6 only); X42 Accidental poisoning by and exposure to narcotics and psychodysleptics, not elsewhere classified; X62 Intentional self-poisoning by and exposure to narcotics and psychodysleptics, not elsewhere classified; Y12 Poisoning by and exposure to narcotics and psychodysleptics, not elsewhere classified.
e. Excludes repeat discharges in the same calendar year.

Codeine, tramadol, paracetamol + codeine and methadone were the dispensed opioids associated with the greatest number of deaths per year (Figure 6). With the exception of morphine hydrochloride, accidental poisoning (X42) was most frequently recorded as the primary cause of death for the dispensed opioids, followed by intentional self-poisoning.

**Figure 6: Total deaths between 2010 and 2016 due to substance abuse or poisoning clinical codes[a], by dispensed opioid**




a. Clinical codes: F11.2: Mental and behavioural disorders due to use of opioids: dependence syndrome; F19.2 Mental and behavioural disorders due to multiple drug use & use of psychoactive substances: dependence syndrome; X42 Accidental poisoning by and exposure to narcotics and psychodysleptics, not elsewhere classified; X62 Intentional self-poisoning by and exposure to narcotics and psychodysleptics, not elsewhere classified; Y12 Poisoning by and exposure to narcotics and psychodysleptics, not elsewhere classified.

### 2.4.2 CARM data

Since the year 2000, there have 51 cases reported to CARM where the suspect medicine was an opioid and the reported reactions were assessed as abuse, misuse or dependence terms (Table 2).

[redacted]

### 2.4.3 National Poisons Centre data

There were 1,889 calls to the National Poisons Centre for opioid exposures between 1 January 2017 and 30 June 2020 (Table 3). Codeine and tramadol were the most prevalent opioid exposures reported to the NPC, accounting for 828 (1,137 when including codeine+paracetamol) and 601 exposures, respectively.

**Table 3: Overall prevalence of opioid substances in contacts to the National Poisons Centre, 1 January 2017 to 30 June 2020**

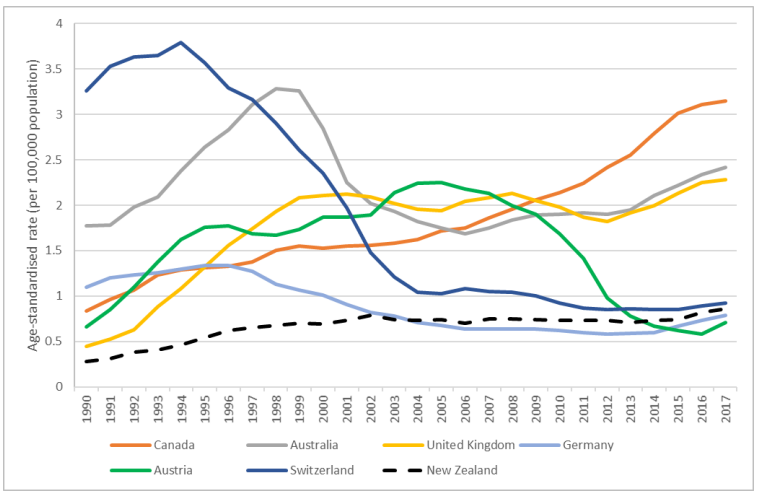
| | 2017 | 2018 | 2019 | 2020* | Grand Total |
|---|---|---|---|---|---|
| Total patients with one or more of the opioids of interest indicated | 530 | 547 | 542 | 270 | 1,889 |
| % of all human exposure patients | 2.5% | 2.6% | 2.4% | 2.3% | 2.5% |
| Total human exposure patients | 21,066 | 21,311 | 22,925 | 11,798 | 77,100 |
| Patients "positive" for specific substance of interest (substance present)** | | | | | |
| Buprenorphine + naloxone | 0 | 1 | 4 | 1 | 6 |
| Codeine | 233 | 242 | 219 | 134 | 828 |
| Codeine + paracetamol | 81 | 91 | 107 | 30 | 309 |
| Dihydrocodeine | 6 | 7 | 8 | 4 | 25 |
| Fentanyl | 3 | 3 | 6 | 7 | 19 |
| Methadone | 2 | 11 | 9 | 1 | 23 |
| Morphine | 66 | 56 | 68 | 31 | 221 |
| Oxycodone | 20 | 17 | 17 | 11 | 65 |
| Pethidine | 0 | 2 | 0 | 3 | 5 |
| Tramadol | 177 | 185 | 163 | 76 | 601 |

*To 30 June 2020. **NOTE: a single patient may have multiple opioids involved in their exposure; therefore total numbers of substance cases do not necessarily match total opioid-positive patients.

### 2.4.4 International comparisons - mortality

Rates of death from opioid-use disorders in New Zealand are low compared to many other Western countries (Figure 7), and much lower than in the USA. The rate of death has also been reasonably stable in NZ, compared to other countries.

**Figure 7: Age-standardised rates of death due to opioid-use disorders (cause B7.2.1), selected countries (excluding USA), 1990 to 2017**




Source: Global Health Data Exchange. *GBD Results Tool*. URL: http://ghdx.healthdata.org/gbd-results-tool?params=gbd-api-2017-permalink/569cfab3777a4c822ca0ec07c4a578f9 (accessed 30 September 2020).

## 2.5 International regulatory action

There has been international concern over increases in opioid prescribing, mainly attributed to prescribing for chronic non-cancer pain [11]. The opioid epidemics in the USA and Canada coincided with sharp increases in prescription opioid-related deaths and overdoses. National governments and their respective medicines regulators have implemented various legislative changes and regulatory actions with the aim of limiting opioid harm in their jurisdictions. These actions are summarised in Table 4 below.

**Table 4: Summary of recent international regulator actions for opioids**

| **Medicine Regulator/Country** | **Action** |
|---|---|
| Food and Drug Administration (FDA) - USA | Manufacturers required to submit Risk Evaluation and Mitigation Strategy (REMS) for all opioids.<br>Updates to prescribing information (labels) for all opioids to include information about naloxone, tapering, central sleep apnoea, drug interactions, REMS.<br>Limit prescription cough and cold medicines containing codeine or hydrocodone to adults only and include information in the Boxed Warnings for misuse, abuse, addiction, overdose, death, and slowed or difficult breathing.<br>Considering safety-packaging (blister packs) for immediate-release opioids. |
| Medicines and Healthcare products Regulatory Agency (MHRA) – UK | Warnings on package labelling<br>Updates to prescribing information<br>Safety leaflet for patients |
| Therapeutic Goods Administration (TGA) - Australia | Smaller pack sizes<br>Indication review<br>Review labels and CMI<br>Increase health professional awareness of alternatives to opioids for chronic pain management |
| Health Canada - Canada | Mandatory risk management plans for prescription opioids<br>Warning sticker and patient information handout to be provided at time of dispensing<br>Restricted advertising to healthcare professionals – must be pre-cleared by an advertising preclearance agency and can only contain information from the product monograph as authorised by Health Canada<br>Considering re-scheduling low-dose codeine and tramadol<br>Removed indication for children from cough and cold products containing opioids |

# 3 OPTIONS

The international regulatory actions for opioids can be broadly grouped into the following categories:

- changes to product information (data sheets)
- enhanced safety monitoring
- labelling changes
- prescribing restrictions
- communication activities.

How each of these actions could be applied in New Zealand is discussed below, under the respective categories.

The effectiveness of most of these international regulatory actions has not been evaluated, but new information is also provided below, where available. Note that for some countries, it may be difficult to separate the effect of the regulatory actions from the effect of the COVID-19 pandemic on opioid prescribing and usage.

## 3.1 Changes to product information (data sheets)

### 3.1.1 Narrowing of indications

The opioid reforms in Australia resulted in narrowing of the indications for opioids [12].

- The product information (data sheets) for immediate release products reinforce that opioids should only be used when other products are not suitable or effective.
- Modified release products should only be used when other products are not suitable or effective, and only used where the pain is opioid-responsive, and the patient requires continuous long-term treatment.
- Fentanyl patches should only be prescribed to treat pain in patients with cancer, patients in palliative care and those with exceptional circumstances.

Low-dose codeine products are not indicated for severe pain in Australia, so the indications for these products (<30 mg codeine per dosage unit and in combination with paracetamol, ibuprofen and/or sedating antihistamine) were not changed.

Medsafe can ask for indications to be changed but it should be noted that no evidence on efficacy has been reviewed, prescribers can legally prescribe outside the approved indications and we cannot mandate any changes. Enforcing an indication change to an approved product in New Zealand requires a section 36(1) review. Under this section of Medicines Act 1981, Medsafe may request the sponsor to provide evidence that a product is safe and effective for the therapeutic purpose for which it is sold. If the sponsor is unable to satisfy Medsafe that the product is safe and effective for its therapeutic purpose, conditions on the use of the medicine may be imposed or the consent for distribution of the product may be revoked.

However, to use this route, we would need to consider how the risks of abuse, misuse and dependence impacts the benefit-risk profile of the product. For most opioid products, we do not have that information – as New Zealand is not experiencing an opioid epidemic as has occurred in other countries.

### 3.1.2 New safety warnings

Regulatory actions in Australia, the USA, Canada and the UK resulted in significant changes to opioid prescribing information, including enhanced safety warnings for misuse, abuse and dependence. Note that international regulators can mandate that sponsors make changes to prescribing information but Medsafe does not have similar regulatory powers under the Medicines Act 1981.

Many products marketed in Australia are also marketed in New Zealand, and in some instances, the prescribing information is very similar for both countries. If the Committee agrees, Medsafe could request that the safety warnings in the New Zealand data sheets are updated to align with the Australian safety warnings (see Annex 1). Table 5 is a comparison of the New Zealand data sheets against the Australian safety warnings (this table has been updated since the December 2020 report).

**Table 5: Comparison of New Zealand data sheets (funded products only) against the Australian boxed warnings and opioid class statements**

| Australian boxed warning and Precautions and Warning Class Statement (all opioids) | New Zealand opioid product data sheets - Australian wording[a] included in section 4.3: Special warnings and precautions for use: Yes or No | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Buprenorphine Naloxone BNM | Codeine Phosphate PSM | DHC Continus Modified release | Fentanyl Sandoz<br>Fentanyl Solution for injection Boucher & Muir | Biodone Oral solution<br>Methatabs<br>Methadone Injection BP<br>Solution for injection (AFT) | RA Morph | Biomed m-Eslon<br>Sevredol<br>DBL Morphine Sulfate Injection | Oxycodone Sandoz modified release<br>OxyNorm | Paracetamol + codeine (Relieve) | Pethidine (PSM)<br>DBL Pethidine Hydrochloride Injection BP | Tramal SR<br>Arrow - Tramadol |
| Boxed warning[b] | No | No | No | No | No | No | DBL only | No | No | DBL only | No |
| Hazardous and harmful use | No | No | No | No | No | No | DBL only | No | No | DBL only | No |
| Respiratory depression[c] | Yes | No | Yes | Yes | No | Yes | Yes | OxyNorm only | No | Yes | Yes |
| Risks from concomitant use of benzodiazepines or other CNS depressants, including alcohol | Yes | No | Yes | Yes | Biodone and Methadone Yes | Yes | Yes | Yes | Yes | Yes | Yes |
| Use of opioids in chronic (long-term) non-cancer pain (CNCP) | No | No | No | No | No | No | DBL only | Sandoz only | No | DBL only | No |
| Tolerance, dependence and withdrawal | Yes | Yes | Yes | Yes | No | Yes | Yes | Yes | No | Yes | No |
| Accidental ingestion/ exposure | Yes | No | No | Fentanyl Sandoz (patch) only | No | No | DBL only | No | No | DBL only | No |
| Hyperalgesia | No | No | No | No | No | Yes | DBL only | Yes | No | DBL only | No |
| Ceasing opioids | Yes | No | No | No | No | No | DBL only | No | No | DBL only | No |

a. The New Zealand wording may be similar but not identical to the Australian wording.
b. The boxed warning includes: Limitations of use, Hazardous and harmful use, Life threatening respiratory depression, Concomitant use of benzodiazepines and other central nervous system (CNS) depressants, including alcohol. There is no requirement in New Zealand to include boxed warnings at the beginning of data sheets.
c. The respiratory sedation warning is separate from the respiratory sedation associated with concomitant use of benzodiazepines and other CNS depressants.

Sources:
Data sheets published on the Medsafe website. URL: https://www.medsafe.govt.nz/Medicines/infoSearch.asp (accessed 24 May 2021).
Community funding information from the Online Pharmaceutical Schedule – June 2021. URL: https://schedule.pharmac.govt.nz/ScheduleOnline.php (accessed 24 May 2021).
Hospital funding information from the HML Online – June 2021. URL: https://schedule.pharmac.govt.nz/HMLOnline.php (accessed 24 May 2021).

## 3.2 Enhanced safety monitoring

### 3.2.1 Periodic Benefit Risk Evaluation Report (PBRER)

A PBRER is a comprehensive, concise, and critical analysis of new or emerging information on the risks and benefits of a medicine compiled by the sponsor [13].

Under section 6.2 of the Pharmacovigilance Guidelines, PBRERs are required to be routinely submitted for the following types of medicines:

- vaccines that are included in the routine National Immunisation Schedule
- biological medicines (excluding vaccines)
- biosimilars medicines
- where a specific requirement for the submission of PBRERs has been imposed as a condition of approval.

Medsafe may occasionally request the submission of a PBRER for a specific medicine if closer monitoring of its safety is required.

Note that under section 3.5.4 of the Pharmacovigilance Guidelines, reports of intentional misuse or abuse where no suspected adverse reactions are associated do not need to be forwarded to either CARM or Medsafe. Sponsors should routinely follow up on these reports and include them in their PBRER. If serious adverse reactions are associated with valid case reports of misuse or abuse, they should be forwarded to CARM.

Medsafe does not currently require submission of PBRERs for opioids. Given the large number of approved opioid products available in New Zealand, it is not feasible for Medsafe to request and review PBRERs for every product. We could instead request PBRERs for those products with the highest use, ie, PHARMAC-funded codeine and tramadol products.

However, most funded opioid products are generics and the sponsors may not produce PBRERs. Medsafe does not have the regulatory authority to force sponsors to produce PBRERs for their products. Also, the information in the PBRER may be of limited use, especially if there is limited adverse event reporting to the sponsor of misuse, abuse and dependence in New Zealand. Medsafe usually only reviews PBRERs when looking at safety signals for new medicines or for higher-risk medicines, such as vaccines and biologicals.

### 3.2.2 Risk Management Plans (RMPs)

RMPs are ongoing appraisals that aid both the sponsor and the regulator in maintaining confidence in the benefit-risk balance of the medicine based on the regulatory options currently imposed (such as approved indications, warnings, labelling) and those yet available (eg, limiting the indications, expanding warnings and precautions, creating contraindications, rescheduling, re-labelling or restricting use to a subset of the population) [13].

Medsafe does not require routine submission of Risk Management Plans (RMPs). However, under section 6.3 of the Pharmacovigilance Guidelines, Medsafe may request these for specific medicines during the evaluation of a new medicine application as a condition of approval or in response to a safety issue.

As with the PBRER discussion above, we could request RMPs for those products with the highest use, ie, PHARMAC-funded codeine and tramadol products. But as with PBRERs, sponsors of generic products may not produce RMPs and Medsafe does not have the regulatory authority to force them to do so.

Medsafe could also request RMPs as part of new medicine applications for any opioid. However, this would need to be included in a future update to the Guidelines on the Regulation of Therapeutic Products in New Zealand.

## 3.3 Labelling changes

In Canada, mandatory handouts and stickers are required for any marketed product containing an active ingredient as included on Part A of the List of Opioids. This includes any prescription opioid that could be

dispensed by a retail pharmacy, with the exception of those authorised and indicated for the treatment of an opioid use disorder.

Based on the results of a survey of pharmacists about these new requirements, Health Canada issued a reminder for healthcare professionals to counsel patients about important safety and usage information contained in the patient information handout and to affix the warning stickers when required [14].

### 3.3.1 Label Statements Database

The Label Statements Database (LSD) lists the warning and advisory statements that are required on medicine and related product labels under regulations 13(1)(i) and 14(1)(f) of the Medicines Regulations 1984. Generally, the LSD warning statements do not apply to prescription medicines, unless otherwise stated.

The LSD already has a warning for codeine that must be on the package labels for any codeine-containing product:

- Codeine is an addictive substance.

Medsafe could add new warning statements for all opioids, for example, one or all of the following:

- [*name of opioid*] is an addictive substance
- use of this medicine has the risks of overdose and dependence
- contains opioid.

Updating the LSD requires a public consultation, and if new warning statements are confirmed, time for sponsors to implement the changes.

Note that under regulation 25 of the Misuse of Drugs Regulations 1977, there are already labelling requirements for controlled drugs, including directions for use and its controlled drug classification statement. Any new warning statement required under the LSD would be in addition to the controlled drug labelling requirements..

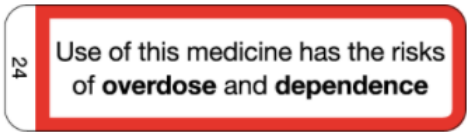
### 3.3.2 Cautionary and Advisory Labels (CALs)

LSD warning statements are not required on the bottle that is dispensed from the pharmacy [15]. CALs would be an alternative option for pharmacy dispensings.

The Pharmaceutical Society of New Zealand (PSNZ) CALs are additional instructions or advice added to the medicine container or dispensing label at the time of dispensing [16]. They are intended to prompt further discussion between patients and health providers. CALs may be applied using the brightly coloured stickers (preferred), or abbreviated forms can be used in on the dispensing label itself. PSNZ is responsible for CALs. They are also hosted on the NZ Formulary.

Medsafe could discuss the feasibility of an opioid CAL with PSNZ. The image below is the Australian CAL for opioids.

**Figure 8: Australian cautionary advisory label for opioids**




Source: Australian Pharmacist. 2020. New label 24 to help pharmacists reduce opioid risks. URL: https://www.australianpharmacist.com.au/new-opioid-cautionary-advisory-label-available/ (accessed 21 May 2021).

## 3.4 Prescribing restrictions

In the USA, the SUPPORT Act 2018 (Substance Use-Disorder Prevention that Promotes Opioid Recovery and Treatment for Patients and Communities Act) was signed into law in 2018. The Act combined more than 70 bills and involves multiple agencies and departments, including the FDA, Department of Health and Human

Services (HHS), Medicare and Medicaid, and the Substance Abuse and Mental Health Services Administration (SAMHSA).

As part of the requirements of the Act, HHS, FDA, CDC, National Institutes of Health and SAMHSA submitted a report to Congress on the impact of federal and state laws and regulations that limit the length, quantity or dosage of opioid prescriptions [17]. The following information is from that report.

> Prescribing limits were defined as anything that required an action at any point within the course of patient care, for example, prior authorisation, urine drug-testing, safety edits, Prescription Drug Monitoring Program (PDMP) checks if the prescription exceeded any value of days supplied, morphine milligram equivalent or dosage units prescribed.
>
> As at April 2020, 33 states had statutory limits on opioid prescriptions (ranging from 3–14 days). There are no federal laws or regulations requiring opioid prescribing limits. There are federal guidelines and policies that have been used as the basis for state laws and regulations. State and federal laws, regulations, policies, and guidelines often have additional components to prescribing limits such as PDMP checks, pain clinic laws, urine drug testing, and patient contracts. Other organisations are also requiring or recommending limits to opioid analgesic prescriptions and contributing to changes in patient care, such as pharmacies, payers, medical and pharmacy associations and organizations, hospitals and health systems, and medical and pharmacy boards.
>
> Published literature provide most of the evidence evaluating opioid analgesic prescribing limits at the federal and state level, to date. A literature review identified 29 studies published from 2013 through 2019 evaluating federal and state opioid analgesic prescribing limits. Among these studies, most assessed changes to opioid analgesic prescription or dispensing patterns after implementation of prescribing limits and generally reported decreasing trends in the dose, duration, and quantity of opioid analgesic prescriptions after implementation of prescribing limits. Thirteen studies evaluated outcomes beyond changes in prescribing and dispensing, such as patient outcome, patient burden, prescriber burden, or financial implications for insurance.
>
> Among the studies evaluating patient outcomes (n=12), most showed no change or modest improvement in patient outcomes after implementation of the prescribing limit and one study found a small but statistically significant increase in pain scores after implementation of the prescribing limit. Most studies did not adjust for any decreases in opioid analgesic prescribing already occurring before the implementation of prescribing limits or control for other interventions that could impact opioid analgesic prescribing. Importantly, while measurement of prescription and dispensing trends is a critical first step in assessing the impact of prescribing limits, far fewer studies included other patient, provider, or health outcomes. Only 12 of the studies included more informative outcomes to assess the effectiveness and unintended consequences of prescribing limits such as patient health outcomes, refill rates/attempts, patient burden, prescriber burden, and public health outcomes.
>
> Many of the studies suffered from methodological flaws that limited the HHS's understanding of the impact of prescribing limits on prescription, patient, provider, and health outcomes. Overall, the evidence indicates that opioid analgesic prescribing limits are likely effective in decreasing the dose, quantity of dosage units, or number of opioid analgesic prescriptions. However, the impact of these prescribing limits on the patient, their pain level, their quality of life, and other important health outcomes has not been well studied and the limited evidence that is available shows mixed results. There is some limited evidence that prescribing limits may not affect some patient outcomes or might result in a decrease in unneeded refills and associated decrease in the number of patients transitioning to chronic opioid analgesic use after implementation. However, there is also evidence that patient outcomes such as effective pain management could be negatively affected. Most importantly, most of the current literature does not sufficiently evaluate patient outcomes in a rigorous manner, and many other important patient outcomes are not evaluated at all. Additionally, there is anecdotal evidence of negative impacts on some patient outcomes not included in the literature, such as mental health conditions or suicidality, stigmatisation, difficulty finding a provider,

and increased patient burden. Other outcomes, such as prescriber burden, should also be more thoroughly studied.

In their conclusion, the HHS recommended careful consideration of the evaluation phase prior to implementing new prescribing limits or changing existing prescribing limits so meaningful outcomes can be assessed in the affected population before implementation for comparison. Other gaps can be addressed in future studies by using more sophisticated methods to control for existing trends in prescribing, by isolating the impact of prescribing limits within larger interventions around opioid analgesic prescribing, and by isolating the impact of state and federal prescribing limits from other interventions.

### 3.4.1 Up-scheduling and reclassifying

#### *3.4.1.1 Codeine*

In Australia, codeine was up-scheduled to prescription only in 2018. An evaluation of evidence 12 months after the change concluded that codeine reclassification successfully reduced harm from codeine, and the amount of codeine used [18]. There was a reduction in calls to the poisons centre involving codeine overdose (for the formulations containing ≤15 mg of codeine affected by the reclassification). Sales of products containing ≤15 mg of codeine from suppliers to community pharmacies and hospitals dropped approximately ten-fold, with no significant change in sales of higher strength codeine.

In New Zealand, all codeine-combination medicines were reclassified from pharmacy only or restricted medicines to prescription medicines on 5 November 2020; codeine-only medicines were already prescription medicines. Updated package labelling for these products should have been transitioned by May 2021 [19]. Advice to healthcare professionals on managing the clinical aspects of change was provided by bpac$^{nz}$ [18, 20]. Prescribing data is not yet available to review any impact of this change.

#### *3.4.1.2 Tramadol*

[redacted]

### 3.4.2 Reduced pack sizes and repeat dispensings

In June 2020, changes to the Australian Pharmaceutical Scheme (PBS) came into effect to support the TGA's regulatory changes, including funding for smaller quantities, changes to the indications that are funded, and changes to the authority process required for opioids to be subsidised [23]. Before prescribing high-strength opioids such as morphine and fentanyl under the PBS, prescribers must ensure that patients with chronic non-cancer pain are unresponsive or intolerant or have not achieved adequate pain relief from lower strength opioids. There are no repeat dispensings for the treatment of non-cancer pain. Additional changes to the PBS came into effect from 1 October 2020 to ensure continued and unimpeded access for palliative care patients receiving opioid analgesic medications.

In New Zealand, PHARMAC's is responsible for medicines funding. If limiting pack sizes and repeat dispensings for opioids is a preferred option for the Committee, Medsafe could write a letter to PHARMAC about this issue on your behalf.

Note that PHARMAC has been consulting on changes to dispensing frequency rules [24]. When dispensed in the community (eg, prescribed by a general practitioner and dispensed at a community pharmacy), publicly funded medicines are usually dispensed as a Monthly Lot or a 90-day Lot. For medicines on the Safety Medicines list, the prescriber determines the dispensing quantity and frequency. Under this rule, more frequent dispensings (and therefore smaller quantities) of the medicine can occur. Dihydrocodeine and tramadol are the only opioids with funded products that are not on the Safety Medicines list. If the consultation changes are implemented, more frequent dispensing could be prescribed for any product, for any reason. The Safety Medicines list would be disestablished. Based on stakeholder feedback, the consultation is currently postponed and there is no set date for it to be reopened. Medsafe could put in a submission on the Committee's behalf when this consultation reopens.

### 3.4.3 Prescription monitoring programmes

#### *3.4.3.1 USA*

As discussed above, the USA has implemented prescription drug monitoring programmes (PDMPs) in many states. PDMPs are databases that track controlled substance prescriptions from health care providers, usually on a state-wide level [25]. In these systems, providers look up a patient's prescription history for opioids and other controlled substances in a centralised database and assess patient risk for misuse or dependence before recording their new prescription in the database. PDMPs are designed to make opioid prescribing practices safer and prevent patients from obtaining opioid prescriptions from multiple providers inappropriately – often called "doctor shopping". However, not all US states require prescribers to check the PDMP before writing an opioid prescription, some simply report their prescription to the PDMP for record-keeping purposes.

Although there is evidence for reductions in prescribing following implementation of these programmes, the evidence is mixed regarding outcomes for patients [17, 25]. Opioid overdose deaths are often used as a patient outcome measure. Some studies have found decreases in patient mortality alongside reductions in prescribing, but others have found no such reductions, or a switch from licit to illicit overdose deaths [25]. There may also be unintended consequences, such as prescribers finding it difficult to discuss the findings of monitoring programmes with patients, severe adverse effects associated with abrupt cessation of opioids and patients seeking illicit alternatives [26].

#### *3.4.3.2 Australia*

Real-time prescription monitoring programmes are also being implemented in Australia. Since April 2020, all prescribers in the state of Victoria must view patients' prescription histories prior to writing or dispensing a prescription for medicines monitored through the SafeScript system [27].

#### *3.4.3.3 New Zealand*

New Zealand does not currently have real-time prescription monitoring programmes. However, the NZ ePrescription Service (NZePS) is currently being implemented. The NZePS is a secure messaging channel for prescribing and dispensing systems to exchange prescription information electronically [28]. It enables a prescription to be generated by the prescriber, transmitted to the NZePS health information exchange broker, and downloaded electronically at a community pharmacy. The prescriber can note the reason for prescribing and make other comments at the time of prescribing. This will be sent as part of the prescription information passed electronically to the pharmacy. Prescribers can request a notification when a patient's medication has not been dispensed, and pharmacists can send dispensing comments back to the prescriber. Some practice management systems are integrated with NZePS, and the Ministry is working with other providers to integrate their systems.

Controlled drugs cannot be prescribed through NZePS because the Misuse of Drugs legislation requires prescriptions for all Controlled Drugs, including Class C, to be on a paper prescription and signed physically, by the prescriber, in their own handwriting [29]. The only exceptions to this are exempt or partially exempt Class C Controlled Drugs which can be treated in the same way as non-controlled drugs.

Medsafe could discuss with the Ministry the feasibility of using the NZePS (or any other digital health initiatives) for prescription monitoring programmes for opioids.

### 3.5 Communication activities

In order to improve awareness and understanding of opioid regulatory actions in their respective countries, international regulators have developed, supported or promoted a variety of communication activities. Many of these activities involved other government agencies, professional bodies and consumer organisations.

For health care professionals, communication activities included:

- articles in the regulator's drug bulletin describing the changes
- online education modules about pain management and appropriate prescribing
- written resources for use between health care provider and patient
- new or updated prescribing and tapering guidelines and position statements
- online tools to guide the assessment and management of pain
- online screening tools for dependence
- clinical audits for prescribers to review their opioid prescribing
- sponsor-funded continuing education activities.

For consumers these included:

- information about opioids and chronic pain
- links to pain management services
- online resources for the self-management of pain.

Some regulators also developed dedicated web pages describing the regulatory changes for opioids [12], and pages with links to resources for health care professionals and credible information for consumers [30].

In New Zealand, the relevant health care professional bodies are responsible for education of their members, including prescribing and best practice guidelines. Note that following a recommendation from the Medicines Classification Committee in April 2018, Medsafe wrote to New Zealand Medical Association, Royal New Zealand College of General Practitioners, Pharmaceutical Society of New Zealand, Pharmacy Council of New Zealand, Pharmacy Guild of New Zealand, New Zealand Nurses Organisation, Chairs of the District Health Boards, Dental Council and the New Zealand Dental Association regarding the importance of better education and professional development for health professionals regarding acute and chronic pain management, analgesics with the potential for abuse and a reminder of section 24(1) of the Misuse of Drugs Act 1975 [31].

Following any recommendation from the Medicines Adverse Reactions Committee, Medsafe could contact the relevant health care professional bodies and consumer organisations to discuss the best way to promote and educate about the safe use of opioids in New Zealand. We can also publish information on the Medsafe website and in *Prescriber Update*.

## 4 DISCUSSION AND CONCLUSIONS

This paper reviews the possible options to minimise the risk of opioid abuse, misuse and dependence in New Zealand. These include changes to opioid data sheets, enhanced safety monitoring, labelling changes, prescribing restrictions, and communication activities.

Some of the suggested options are outside of Medsafe's regulatory role. However, as discussed, Medsafe could collaborate with other professional bodies and consumer organisations as appropriate to develop and/or implement the Committee's preferred options, within in the limits of our available resources.

## 5 ADVICE SOUGHT

The Committee is asked to advise:

- Which of the suggested options does the Committee prefer to minimise the risk of opioid abuse, misuse and dependence in New Zealand?

## 6 ANNEXES

Annex 1: Australian boxed warnings and opioid class statements

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