Classification of codeine

Information paper for the Medicines Classification Committee

Medsafe
June 2019

CONTENTS

INTRODUCTION

The Medicines Classification Committee (MCC) considers recent changes to scheduling in Australia at every meeting in the interests of harmonisation. In December 2016, Australia decided that from 1 February 2018 medicines containing codeine would no longer be available without a prescription.

The MCC considered whether to harmonise the classification of codeine with Australia at the 57th, 58th and 59th meetings. At the 59th meeting, the MCC made a recommendation that did not fully harmonise with Australia. Instead, the MCC recommended an alternative option:

That, from 31 January 2020, all codeine in combination medicines, both analgesics and those used for cough and colds, should be reclassified to prescription medicines.

That, from 31 January 2020, medicines containing codeine as the only active ingredient should be reclassified from prescription to restricted medicine; for oral use in adults and children over 12 years of age in medicines containing not more than 15 mg per solid dosage unit with a maximum daily dose not exceeding 90 mg of codeine for use as an analgesic and when sold in a pack of not more three days' supply

The Ministers Delegate had requested further information from Medsafe on the MCC's recommendation from the 59th meeting prior to making a decision. No changes to the classification of codeine have been implemented while awaiting further information.

The MCC is expected to make recommendations about medicines which it has been asked to consider and which have undergone consultation. In the case of items for harmonisation, the MCC is expected to recommend on whether to harmonise or not, rather than recommend an alternative option. This approach was agreed upon in 2000 in a policy statement about the Scope of Committee Recommendations.

PURPOSE

This paper will summarise the risks and benefits of harmonising the classification of codeine with Australia and the alternative option recommended by the MCC at the 59th meeting in order to meet the consultation requirements. The scope of this paper includes all products that contain codeine as the only active ingredient, codeine in combination with another active ingredient for pain, and codeine in combination with another active ingredient for cough and cold covering all three classifications (prescription, restricted and pharmacy-only).

Each classification option presented should be considered as mutually exclusive for reasons agreed in the policy statement on the Scope of Committee Recommendations. If the MCC makes a recommendation that is not one of the options outlined below, the recommendation must go out for a consultation again for a future meeting.

Medsafe asks that the MCC consider the following options for the classification of codeine:

A. to retain the status quo
   (codeine when in combination with another active ingredient in cough and cold medicines remains classified as a pharmacy-only medicine, codeine when in combination with another active ingredient for analgesia remains classified as a restricted medicine, all other medicines containing codeine remain classified as prescription medicines)
B. to harmonise with Australia
   (all medicines containing codeine would be classified as prescription medicines)
C. to reclassify codeine as per the recommendation made at the 59th meeting
   (medicines containing codeine as the sole active ingredient ≤15 mg per solid dosage unit in packs of not more than 3 days' supply with a maximum daily dose of not more than 90 mg for oral use in adults and children for analgesia be classified as restricted medicines, all other medicines containing codeine would be classified as prescription medicines).

BACKGROUND INFORMATION

The classification of codeine has been considered extensively by the MCC many times at previous meetings. Recent discussions on the classification of codeine are summarised in Table 1.

Table 1 Recent meetings when the MCC discussed the classification of codeine

Meeting	Date	Comments
55th	3 May 2016	The MCC noted discussions in Australia by the Advisory Committee on Medicines Scheduling (ACMS) on the classification of codeine.
57th	1 November 2017	The MCC reviewed the outcomes of the ACMS and requested that an agenda item on codeine be added to the 58th meeting to consider reclassifying to a more restrictive classification. The ACMS had recommended to up-schedule all codeine products to prescription medicines because it considered that there were safer alternatives available.
58th	16 May 2017	The classification of codeine was added to the agenda for the 58th meeting and included in public consultation. To support this agenda item, Medsafe had prepared a submission on the Reconsideration of the classification of codeine to provide background information and a range of options for the Committee to consider. The MCC recommended that codeine should be reconsidered at the following meeting and requested further information from the sector to address concerns around the supply of codeine without a prescription.
59th	7 November 2017	The MCC recommended that: - all codeine in combination medicines, both analgesics and those used for cough and colds, should be reclassified to prescription medicines - medicines containing codeine as the only active ingredient should be reclassified from prescription to restricted medicines; for oral use in adults and children 12 years of age in medicines containing not more than 15 mg per solid dosage unit with a maximum daily dose not exceeding 90 mg of codeine for use as an analgesic and when sold in a pack of not more than three days' supply. The reasoning for this recommendation can be found in the minutes of the 59th meeting.
60th	26 April 2018	The Committee acknowledged the complexities around the implementation of the recommendations made at the 59th meeting.
61st	2 November 2018	The Committee noted that a paper on the reclassification of codeine was being prepared.

More information on when codeine was discussed at MCC meetings has been summarised in the previous paper on the Reconsideration of the classification of codeine. Background information previously presented to the MCC has not been duplicated in this paper.

The most recent classification change implemented for codeine was made following recommendations made at the 42nd meeting on 3 November 2009. The MCC recommended that codeine in combination products for analgesia should be reclassified from a pharmacy-only medicine to a restricted medicine. Reasons for up-scheduling included the growing concern around the increasingly large pack sizes, the up-scheduling of these medicines in Australia and also regulatory actions taken in the UK and the USA.

TIMEFRAMES FOR IMPLEMENTATION

At the 59th meeting, the MCC had recommended an implementation date of 30 January 2020. The Minister's Delegate requested further information and consultation on the recommendation from the MCC. The proposed implementation date 30 January 2020 is no longer considered a practicable time frame considering that the MCC is only considering this paper at their 63rd meeting in late 2019.

The standard time frame for implementation is four weeks following the publication of the minutes of the meeting (Medsafe, 2019). Table 2 summarises estimated time frames for each option proposed to the MCC following confirmation by the Ministers Delegate.

There are two parts to be considered in timeframes for implementation:

1. when any new level of classification would come into effect and
2. when the labelling of the product is required to be changed by.

The new level of classification would come into effect from the date on which the Gazette notice is published. A Gazette notice is published approximately four weeks after the publication of the minutes.

Products where the classification change is to make the product a prescription medicine, cannot be sold over-the-counter from the date the gazette notice is published. If the classification change is to make a prescription medicine available over-the-counter, then product in a pack that meets the requirements for over-the-counter sale (including labelling) would need to be approved before any over-the-counter sale could be made.

Sponsor companies are allowed three months from the date of notification to update labels at wholesale level and six months for stock at retail level. These time frames are legislative and are described in regulation 15(4) and (5) of the Medicines Regulations 1984.

Medsafe will work with industry, patient groups and health care professionals to discuss what changes may be required and to determine a suitable timeframe for when they can be implemented. This would include any practical expectations.

Feedback from stakeholders on the timeframe for implementation during this consultation process is welcomed. Communication options will be considered if option B) is recommended, including experience from the Australian market.

Table 2 Estimated time frames for each classification option

Option	Timeframes
Option A) retain the status quo	This recommendation could be implemented as per the standard time frames (four weeks following publication of the minutes).
Option B) harmonise with Australia	This recommendation could be implemented as per the standard time frames (four weeks following publication of the minutes).
Option C) to reclassify codeine as per the recommendation made at the 59th meeting	This recommendation would require a change to both the Medicines Regulations and the Misuse of Drugs Regulations. The timeframe for this is uncertain.

PART A: ADMINISTRATIVE INFORMATION

1. Drug substance information

Codeine is an opioid analgesic that is a well-established drug substance that is described in international pharmacopoeia and Martindale. The classification of codeine includes but is not limited to the following:

- Codeine hydrobromide
- Codeine hydrochloride
- Codeine monohydrate
- Codeine N-oxide
- Codeine phosphate
- Codeine phosphate hemihydrate
- Codeine phosphate sesquihydrate

These substances are covered in the codeine entry in Part 2 of Schedule 3 of the Misuse of Drugs Act 1975 (controlled drug Class C2) where the entry is specified to include the isomers, esters, ethers and salts.

2. Affected products

A list of all currently approved products that will be affected by the options proposed for the classification of codeine has been compiled and is supplied as Appendix 1.

Most of the currently approved products are considered well-established in the market and have been approved for distribution for over five years. The registration status 'not available' means that consent for distribution has been granted for this product, but the product is currently unavailable for supply and the data sheets for these products may not have been maintained.

Option B) would affect codeine combination products that are currently available without a prescription. This includes products classified as pharmacy-only and restricted medicines, which would become prescription medicines. Medicines containing codeine as the sole active ingredient would be unaffected by option B) and remain available only on prescription.

Option C) would affect all codeine combination products that can currently be sold as over-the-counter products, and solid unit dose oral products containing 15 mg or less of codeine. All codeine combination products would be reclassified to prescription medicine. This includes products indicated for analgesia and also for relief of cough and cold symptoms. Codeine up to 15 mg in a solid oral dosage form would no longer be a Controlled Drug C2 (and prescription) and products for the treatment of pain in adults and children over 12 years of age with a maximum dose of 90 mg per day and no more than three days' supply (a maximum pack size of 18 tablets) could be approved for sale as restricted medicines.

3. Current classification of codeine

Table 3 Current classification of codeine

Ingredient	Conditions (if any)	Classification
Codeine	Other than a preparation or mixture described in Schedule 3, Part 6	Class C2 Controlled Drug
Codeine	(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	Class C6 Controlled Drug
Codeine	**Except** when specified elsewhere in this schedule	Prescription
Codeine	In medicines for oral use containing not more than 15 milligrams of codeine per solid dosage unit or per dose of liquid with a maximum daily dose not exceeding 100 milligrams of codeine, 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, for use as an analgesic and when sold in a pack of not more than 5 days' supply, approved by the Minister or the Director-General for distribution as a restricted medicine	Restricted
Codeine	In medicines for oral use, containing not more than 15 milligrams of codeine per solid dosage unit or per dose of liquid with a maximum daily dose not exceeding 100 milligrams of codeine, 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, for the treatment of the symptoms of cough and cold and when sold in a pack of not more than 6 days' supply, approved by the Minister or the Director-General for distribution as a pharmacy-only medicine	Pharmacy Only

Codeine is a Class C2 controlled drug except when specified in Schedule 3 Part 6 of the Misuse of Drugs Act 1975. Schedule 3 Part 6 (C6) exempts the following preparations containing codeine from compliance with the requirements of the Act and Regulations. Preparations containing codeine are exempt 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 could constitute a risk to health; and

(ii) containing not more than 100 mg of the substance in each dosage unit and with a concentration of not more than 2.5% in undivided preparations.

Codeine 15 mg is a Class C2 controlled drug, unless it meets the criteria specified to be a Class C6 controlled drug. If so then compliance with the Misuse of Drugs legislation is no longer required and the availability is controlled by the Medicines Regulations 1984.

4. Classification options

The MCC has been asked to consider the following options for the classification of codeine:

A. to retain the status quo
(codeine in combination when in combination with another active ingredient in cough and cold medicines remains classified as a pharmacy-only medicine, codeine when in combination with another active ingredient for analgesia remains classified as a restricted medicine, all other medicines containing codeine remain classified as prescription medicines)

B. to harmonise with Australia
(all medicines containing codeine would be classified as prescription medicines)

C. to reclassify codeine as per the recommendation made at the 59th meeting
(medicines containing codeine as the sole active ingredient ≤15 mg per solid dosage unit in packs of not more than 3 days' supply with a maximum daily dose of not more than 90 mg for oral use in adults and children for analgesia be classified as restricted medicines, all other medicines containing codeine would be classified as prescription medicines).

These three options were identified following the MCC's consideration of the recent changes to the classification of codeine in Australia in the interests of harmonisation. Recent classification changes in Australia are routinely included in the agenda for the MCC. It is expected that with harmonisation issues, that the MCC will recommend to either harmonise or not (option A or B). The reason that the final recommendation should be limited to harmonise or not, is because alternative options have not been described in the agenda, and therefore have not been consulted on.

However, in this situation the MCC has proposed an alternative option (C) for the classification of codeine. This alternative option has been included in this paper to enable public consultation and feedback. Option (C) would mean that the classification of codeine will not be harmonised with Australia. This recommendation would require a longer time frame than usual because it will require changes to the Misuse of Drugs Regulations.

5. Classification of codeine in other countries

The regulatory situation for medicines containing codeine varies in overseas countries. The following table summarises the classification status of medicines containing codeine in Australia, UK, the USA and Canada.

Table 4 Classification of codeine in Australia, UK, the USA and Canada

Country	Classification status	
Australia	• Prescription	Effective from 1 February 2018, all medicines containing codeine were scheduled as prescription only medicines. In April 2019, the TGA reported that there has been significant decrease in the amount of codeine supplied to Australians and their analysis did not support the assertion that patients were switched from low- to high-strength codeine medicines after up-scheduling.
UK	• Prescription • Pharmacy medicines when in combination with non-opioid analgesic (paracetamol, aspirin and ibuprofen)	Codeine-combination products for pharmacy only supply may contain a maximum dose of up to 25.6 mg of codeine phosphate (ie 2 tablets/dose of 12.8mg/tablet) or 20 mg when calculated as base. Oral liquid products for pharmacy only supply may contain codeine for the symptomatic treatment of dry cough in strengths of up to 15 mg/5 mL. In 2010 the MHRA restricted over-the-counter use to 18 years and above.
USA	• Prescription • General sale • The availability of codeine is determined at the state level; in some states it is available without prescription and in other states sale is prohibited without a prescription.	In January 2018, the FDA required a labelling change for prescription opioid cough and cold medicines to limit their use to adults 18 years and older. An extensive review concluded that the risks of slowed or difficult breathing, misuse, abuse, addiction, overdose and death with these medicines outweighed their benefits in patients younger than 18 years of age. This regulatory action was for opioid cough and cold medicines requiring a prescription. However the FDA is also considering regulatory action for codeine cough medicines that are available over-the-counter in a few states.
Canada	• Prescription • Over-the-counter when not more than 8 mg of codeine in solid form, not more than 20 mg codeine per 30 mL in liquid form and if the preparation contains at	In October 2018. Health Canada added a requirement for a mandatory warning sticker and patient information handout to be provided with prescription opioids at the time of sale. Opioid preparations containing low dose codeine in combination with two or more other medicinal ingredients are exempt from

	least two additional medicinal ingredients other than a narcotic.	this requirement because they are not prescription opioids. The sticker contains warnings about the risks of dependence, addiction and overdose. The patient information handout contains broader information on the safe use of opioids as well as associated risks including serious warnings, signs of overdose, possible side effects and information on safe storage and disposal of opioids. In February 2016, all non-prescription codeine was banned in the province of Manitoba.

The following table summarises other countries where codeine containing products are available without a prescription.

Table 5 Other countries where codeine containing products are available without a prescription

Denmark	When in combination with aspirin.
Finland	Mixture of codeine phosphate hemihydrate and guafenesin, oral solution.
Ireland	Supply through pharmacies following consultation with a pharmacist (equivalent to a Restricted classification in New Zealand). Maximum strength 1.5%, maximum dose 20 mg. Advertising to the public is prohibited. Combination with aspirin possible under these restrictions. As of 1 August 2010 codeine-containing over-the-counter medicines in the pharmacy must be stored out of view (ie, in the dispensary) and consultation with a pharmacist is required before purchase.
Japan	Only 13 years of age and over is allowed.
Slovenia	In combination with other analgesics.
Switzerland	Maximum single dose 20 mg codeine phosphate hemihydrate.
The Netherlands	For the relief of tickling cough in adults and children over 12 years of age. Maximum strength 0.39 mg/mL, maximum pack size 200 mL. Codeine tablets and combinations with paracetamol are classified as prescription medicines. Over-the-counter codeine cough medicines may only be sold in a pharmacy. Public advertising is not allowed.

Codeine is classified as a prescription medicine in the following countries:

- Argentina
- Austria
- Belgium
- Chile
- China
- Colombia
- Croatia
- Czech Republic
- France
- Germany
- Greece
- Hungary
- Italy
- Norway
- Portugal
- Spain
- Sweden
- Venezuela

6. Extent of usage in New Zealand

Limited information is available for over-the-counter purchases of codeine combination products for pain relief and cough and cold symptoms. There are no public records kept of over-the-counter sales of codeine containing products.

Prescribed

Information on the extent of usage in New Zealand has therefore mainly been based on data available for codeine and codeine combination products that are supplied on prescription. Data on funded prescriptions dispensed at pharmacies from 2013 to 2017 is publicly available from DataPharm (Ministry of Health, 2018), which extracts information from the Pharmaceutical Collection[1].

Overall, the use of codeine (15 mg, 30 mg and 60 mg) has increased in New Zealand in regard to the number of times codeine has been dispensed, the number of prescriptions, and also the number of people who have been prescribed codeine. Dispensings (the number of times a pharmaceutical product was dispensed from a pharmacy to a named person) increased from 560,657 in 2013 to 670,944 in 2017. The number of people who received a dispensing from the pharmacy at least once during the year also increased from 267,780 in 2013 to 309,988 in 2017. Both dispensings and prescriptions for each strength of codeine also increased from 2013 to 2017 and this is consistent with the overall trend.

There has been an increase in the number of prescriptions dispensed for codeine phosphate 15 mg tablets, and also an increased number of dispensings. Dispensings of codeine 15 mg increased from 128,630 in 2013 to 186,506 in 2017 (an increase of 57,876 dispensings). The number of people who received a dispensing of codeine 15 mg increased from 65,928 to 95,943 in 2017 (an increase of 30,014 people). It is noted that the increased number of dispensings for codeine phosphate 15 mg tablets (57,876) is greater than the increase in the number of people who received a dispensing (30,014).

A small downward trend was observed for dispensings of products containing both paracetamol and codeine. Dispensings reduced from 411,033 in 2013 to 384,721 in 2017. This data does not include the volume of products containing both paracetamol and codeine that were purchased over-the-counter and so are not an accurate reflection of the use due to this limitation.

Although there is a small downward trend for dispensings for products containing both paracetamol and codeine, the number of dispensings remains comparatively high. In 2017, paracetamol with codeine products was the 37th most dispensed medicine (384,721). The number of dispensings was comparable to codeine phosphate 30 mg tablets (442,603), simvastatin 20 mg (389,386) and flucloxacillin 500 mg (367,028).

Alternative products for analgesia were more commonly dispensed than paracetamol with codeine products. The number of dispensings in 2017 for paracetamol 500 mg tablets were 2,303,668 (approximately 6 times more) and ibuprofen 200 mg tablets were 688,455 (approximately 1.7 times more).

A brief comparison between use in New Zealand and England would suggest that codeine is more widely used in New Zealand (NHS Digital, 2019). The use of both codeine 15 mg tablets and codeine 30 mg tablets is higher in New Zealand.

[1] The Pharmaceutical Collection is a data warehouse that contains claim and payment information from pharmacies for subsidised dispensings. Appendix 1 contains further information on DataPharm and the data used to estimate the extent of usage in New Zealand.

Over-the-counter

In the absence of sales data, it is not possible to identify any trends in supply of over-the-counter products containing codeine in combination with another pharmacologically active ingredient. Over-the-counter sales would include all products containing codeine in combination with another pharmacologically active substance, such as ibuprofen for relief of pain, or in cough and cold medicines, which are not funded and so are not captured by the Pharmaceutical Collection.

Electronic opioid harm monitoring system

The MCC has previously discussed the benefits of an electronic opioid harm monitoring system in New Zealand to be able to monitor the usage of opioids in New Zealand. It was also considered as a possible risk-mitigating strategy to retain over-the-counter access to codeine and/or codeine-combination products.

An electronic opioid harm monitoring system has not been developed or investigated any further by Medsafe or the Ministry of Health. A similar system has been implemented in Australia, although, the benefits of such a system remain unclear.

It is not known whether an electronic opioid harm monitoring system will be implemented in New Zealand in the foreseeable future. Therefore it is recommended that the MCC should not consider this as a risk-mitigation strategy when considering the classification of codeine.

7. Labelling and warning statements

Codeine as a single active ingredient is a controlled drug and is required to meet the labelling requirements described by regulation 25 of the Misuse of Drugs Regulations 1977. This includes direction for use and its controlled drug classification statement.

Labelling for codeine combination products when sold as an over-the-counter medicine must meet the requirements of Part 4 of the Medicines Regulations 1984. The Labelling Statements Database contains mandatory warnings required on labels of over-the-counter medicines containing codeine (Table 6).

Labelling for codeine when supplied as an over-the-counter medicine must contain all five statements. Labelling for codeine when supplied as a prescription medicine must also contain the required warning statement about addictiveness. Warnings statements form the Labelling Statements database are not required on the bottle that is dispensed from the pharmacy.

Table 6 Labelling Statements Database

Classification	Statements required
When sold as a restricted medicine, pharmacy-only or general sale medicine	• Do not use for more than 3 days. • Codeine is an addictive substance. • Do not use if you are breastfeeding except on doctor's advice. • This medicine may cause drowsiness. • If affected, do not drive a vehicle or operate machinery.
When sold as a prescription medicine	• Codeine is an addictive substance

PART B: PARAMETERS FOR CONSIDERATION

1. Indications and dose

Codeine is an opioid analgesic that is much less potent as an analgesic than morphine and has relatively mild sedative effects. Codeine is given orally for the relief of cough, and for the relief of mild to moderate pain. This may be in combination with another pharmacologically active ingredient such as paracetamol or ibuprofen (Martindale, 2019).

Indications and dosage information

Codeine 15 mg tablets

Indications and dosage information for codeine 15 mg tablets that have been approved in New Zealand are summarised in the following table.

Indications Codeine phosphate is indicated for: • the relief of mild to moderate pain (including pain associated with terminal illness, post-operative pain, headache), • the relief of symptoms in diarrhoea (except diarrhoea caused by poisoning).
Dose and method of administration Adults: 15 – 60 mg every 4 to 6 hours as required, up to a maximum of 300 mg daily dose. If these doses fail to relieve pain, larger doses rarely succeed and may give rise to restlessness and excitement. Paediatric: Do not use in children aged less than 12 years. The usual paediatric dose is 0.5 mg per kg of body weight, every 4 to 6 hours as needed, up to a maximum of 240 mg in 24 hours. The duration of treatment should not normally exceed 3 days.

Codeine combination product

Indications and dosage information for a codeine combination product for pain relief that has been approved in New Zealand has been summarised in the following table.

Indications Temporary relief of moderate to severe acute pain associated with strong headaches, migraine headaches, dental surgery or toothache, menstrual pain and sports injuries (eg, backaches and muscular pain).
Dosage and method of administration 18 years to adults: two tablets every four to six hours if necessary. Maximum of eight tablets in 24 hours. Do not use in children aged below 18 years. Do not exceed the stated dose or take for more than three days without a doctor's advice.

Codeine in combination products for cough and cold are not required to have an approved data sheet that contain information about their approved indications.

Changes for use in children and adolescents

Codeine is no longer recommended for analgesia in children. This is due to the possibility of inadequate analgesic effect and the potential for toxicity, neither of which can be predicted in routine clinical practice because of the polymorphic drug metabolism to morphine (World Health Organisation, 2012) (Schug , Palmer, Scott, Halliwell, & Trinca, 2015).

The Medicines Adverse Reaction Committee (MARC) recently recommended changes to the age restrictions for codeine-containing products in New Zealand, in line with age restrictions in Europe, the United States and Australia.

The MARC recommended at the 173rd meeting in March 2018 that the use of all codeine-containing medicines should be contraindicated in:

- children aged less than 12 years for all indications
- adolescents aged less than 18 years for pain following surgery to remove tonsils and adenoids
- adolescents aged less than 18 years in whom respiratory function might be compromised
- adolescents aged less than 18 years for cough

More information on the MARC's recommendations is available in the minutes of the 173rd meeting.

2. Consumer benefits

Genetic polymorphism and clinical outcomes

Codeine has little to no analgesic activity until it is metabolised to morphine. Metabolism of codeine to morphine predominantly involves the Cytochrome P450 enzyme CYP2D6. Genetic polymorphism in the *CYP2D6* gene results in significant variation between individuals in the efficiency of codeine metabolism via this pathway. Individuals may be classified as a poor, intermediate, extensive or ultra-rapid metaboliser depending on their particular combination of alleles coding for the CYP2D6 enzyme (Crews, et al., 2014).

The regulatory authority in the UK, the MHRA, has recommended that codeine is contra-indicated in patients of all ages who are known CYP2D6 ultra-metabolisers (MHRA/CHM, 2013). CYP2D6 phenotype testing is not widely available, so it is not possible to routinely assess who will be at risk of morphine toxicity if taking codeine, and who will not benefit from the therapeutic effect. A consumer is unlikely to know whether they are an ultra-metaboliser and therefore unable to make an informed decision on whether the product is appropriate for them.

The limited benefits of analgesia from codeine and codeine-combinations is unfavourable compared to the increased risk of adverse effects. The risk-benefit profile for codeine and codeine-combinations is not comparable to other medicines available for self-selection. The TGA concluded that there is little evidence to support the benefit of low-dose codeine and codeine-combination products and this was supported by a review in 2016 (TGA, 2016).

A systematic review of analgesic use in moderate to severe post-operative pain found that single oral doses alone (60 mg and 90 mg) provided only a low level of pain relief compared to placebo, and did not compare favourably with other commonly used analgesics, and their combination with codeine (Derry, Moore, & McQuay, 2010).

Benefits and risks of self-selection

Two systematic reviews comparing paracetamol-codeine combinations versus paracetamol alone found that paracetamol-codeine combinations resulted in a small increase in analgesic effect (de Craen, Di Giuliu, Lampe-Schoenmeckers, Kessels , & Kleijnen, 1996) (Toms, Derry, Moore , & McQuay, 2009). However, they also found an increased incidence of adverse effects with the paracetamol-codeine combination, particularly with repeated doses. The limited benefit in increased analgesic effect was observed with higher doses of codeine (60 mg) (Toms, Derry, Moore , & McQuay, 2009).

Evidence supporting the use of codeine or codeine combination products over other commonly used analgesics such as NSAIDs or paracetamol is limited. Such use may also be associated with additional

adverse effects. There is potentially a limited area of benefit for codeine-combination products following dental surgery (Derry, Moore, & McQuay, 2010). As codeine and codeine combination products have been available for many years, there have been few studies performed and published.

There is good availability of other alternative options than codeine for pain relief and for the relief of cough and cold symptoms. It is noted that dextromethorphan, a cough suppressant, that is commonly used in cough and cold medicines was recently reclassified to a Restricted medicine.

3. Contraindications and precautions

Codeine is metabolised to morphine predominantly by the Cytochrome P450 enzyme CYP2D6. The genetic polymorphism exhibited in the CYP2D6 gene has resulted in a number of contraindications to codeine.

Codeine and breastfeeding

Codeine is contraindicated in women who are breastfeeding.

Both codeine and morphine are excreted into breast milk. Breastfeeding mothers who are ultra-rapid metabolisers will convert a larger proportion of codeine to morphine. Exposure of the infant to breast milk containing morphine may lead to opioid toxicity in the infant, with the potential for respiratory depression and death. Furthermore, opioid toxicity in the mother (such as somnolence) may compromise her ability to identify signs of opioid toxicity in her infant.

Other contraindications and precautions

Codeine has a long list of contraindications including:

- known hypersensitivity to codeine, other opioids or any component of the tablets
- acute respiratory depression, especially in the presence of cyanosis and excessive bronchial secretion
- obstructive airways disease
- acute alcoholism
- head injuries and conditions in which intracranial pressure is raised
- patients at risk of paralytic ileus
- hepatic failure
- acute asthma attack
- heart failure secondary to chronic lung disease
- diarrhoea associated with pseudomembranous colitis or caused by poisoning
- patients taking monoamine oxidase inhibitors or within fourteen days of stopping such treatment.

Special warnings and precautions for use include:

- recent tonsillectomy, adenoidectomy or throat surgery
- hypothyroidism
- adrenocortical insufficiency (eg, Addison's disease)
- impaired kidney or liver function
- prostatic hypertrophy
- shock/hypotension

- myasthenia gravis
- convulsions / convulsive disorders
- gall bladder disease or gall stones
- recent gastro-intestinal surgery
- urinary tract surgery
- reduced respiratory function or history of asthma
- obstructive bowel disorders – codeine reduces peristalsis, increases tone and segmentation in the bowel and can raise colonic pressure
- patients taking monoamine oxidase inhibitors or within 14 days of stopping such treatment.

The long list of contraindications and precautions highlights the need for careful patient selection when use of this medicine is being considered. The potential for dependence and withdrawal syndrome should also be considered. Codeine has been the subject of deliberate misuse, and there has been a history of this in New Zealand.

Codeine has been scheduled as a Class C controlled drug in New Zealand because the risk of harm to individuals and society due to the misuse of codeine has been considered as moderate, as per section 3A of the Misuse of Drugs Act 1975.

4. Undesirable effects

Codeine is associated with dependence and withdrawal effects. This is well documented in scientific literature. Taking codeine regularly for a long time can lead to dependence and stopping treatment can result in withdrawal symptoms. Prolonged use of high doses of codeine has produced dependence of the morphine type in a very small proportion of users. Codeine produces less euphoria and sedation than morphine and is not a completely satisfactory substitute for morphine in morphine addicts. Regular use of analgesics for headache can result in an overuse syndrome.

Abrupt withdrawal precipitates a withdrawal syndrome. Symptoms may include tremor, insomnia, restlessness, irritability, anxiety, depression, anorexia, nausea, vomiting, diarrhoea, sweating, lacrimation, rhinorrhoea, sneezing, yawning, piloerection, mydriasis, weakness, pyrexia, muscle cramps, dehydration and increase in heart rate, respiratory rate and blood pressure. These effects can also occur in neonates exposed to codeine *in utero.*

Tolerance diminishes rapidly after withdrawal so a previously tolerated dose may prove fatal.

5. Overdose & abuse/misuse potential

Codeine is a significant contributor to patient mortality on review of coronial data. In New Zealand, 46 deaths were recorded in the National Coronial Information System for the period 1 January 2008 to 31 December 2013. Codeine was assessed as the primary contributor for deaths due to pharmaceuticals. Death was considered to be unintentional in 26.4%. Overall, codeine phosphate ranked as the fifth leading death causing substance with a total of 46 deaths in the study period (Fountain, Reith, Tomlin, Smith, & Tilyard, 2019).

6. Communal harm

The classification of codeine as a controlled drug is described in Table 3. The Expert Advisory Committee for Controlled Drugs makes recommendations on the scheduling of controlled drugs based on the risk of harm the drug poses to individuals, or to society, by its misuse.

Codeine has been the subject of deliberate misuse in New Zealand. Codeine-combination products have been purchased to produce demethylated products known as 'home bake' containing variable amounts of morphine. In response to this, pharmacists had voluntarily limited and monitored sales of codeine-combination products in response to this issue. The formulation of codeine-combination products was also changed so that codeine would be less recoverable, and subsequent changes were also made to its classification to restrict the availability of these products.

Internationally, there has been a growing concern around opioid addiction and abuse, particularly by the FDA in the United States. The FDA has recognised opioid addiction and abuse as a public health crisis and has given this public health concern a high priority. The FDA has taken a range of regulatory actions to address this public health crisis such as facilitating appropriate prescribing of opiates, developing treatment of addiction as a disease, improving formulations so that they are harder to manipulate and abuse, and strengthening enforcement activities.

The easy availability both of prescription and over-the-counter codeine is a concern considering New Zealand's past history of abuse and the epidemic that is being identified internationally.

7. Integrated benefit-risk statement

Codeine has been described as a weak opioid analgesic, but this may be an artefact of the polymorphic metabolism. It is predominantly used for the relief of mild to moderate pain.

Codeine is only effective when it is metabolised to morphine in the body. Codeine may therefore be considered a pro-drug for morphine. However, unlike morphine, when codeine is administered it is difficult to know how much morphine the patient will receive due to genetic polymorphism.

Genetic polymorphisms result in some individuals having no benefit from taking codeine while others experience toxic side effects such as respiratory depression and death. Identifying individuals remains difficult because genetic polymorphism testing is not performed routinely in New Zealand.

Whilst over-the-counter medicines may be considered to be lower risk than prescription medicines in terms of adverse reactions, there are still significant risks to consumers due to self-selection. Codeine has many contraindications and it would be impracticable to list all of these on the back of a pack, along with its many warnings and precautions. This can result in drug misuse, overdose and abuse leading to hospitalisations, morbidity and even mortality.

Classifying all medicines containing codeine as prescription medicines would help to ensure that codeine is used appropriately as part of a multi-modal approach to acute or chronic pain management.

Internationally, the regulatory situation for codeine has been highlighted in response to the public health crisis around opioid addiction. It has been recognised that opioid addiction results in serious harm, and despite ongoing efforts, the scope of the opioid crisis continues to grow. Regulatory actions taken overseas include decreasing exposure to opioids and preventing dependence.

New Zealand is mindful of the possibility of an opioid crisis and the current use of codeine containing products in New Zealand compared with overseas countries raises concerns.

Harmonising with Australia on the classification of medicines facilitates access to medicines for New Zealanders.

8. Risk mitigation

Reference has been made earlier in this paper to a suggestion from the MCC that a national monitoring system for codeine use in New Zealand be established. Currently the information on use of codeine and codeine combination products in New Zealand is limited to those supplied on prescription. There is no system currently available to monitor over-the-counter use of codeine containing medicines.

A benefit of reclassifying all medicines containing codeine to a prescription medicine (Option B) is that the use may be monitored using currently established data collection systems.

The costs to set up a system to monitor over-the-counter use of medicines containing codeine is thought to be prohibitive and such a system to be of limited benefit.

Information on previous purchases of codeine containing medicines may give a pharmacist more information about the frequency of purchases from other pharmacies to help identify potential misuse. However, the sharing of information obtained by the pharmacy following an over-the-counter sale is limited by the Health Information Privacy Code 1994. Rule 11 of the Health Information Privacy Code prohibits the disclosure of health information except under very specific circumstances. These may not allow for monitoring or post-market surveillance activities of routine sales of codeine-containing medicines.

Such a system would be of limited benefit for other clinical risk factors such as genetic polymorphism.

Other potential risk mitigation strategies could include prescribing, education and stewardship.

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APPENDIX 1: LIST OF AFFECTED PRODUCTS THAT ARE CURRENTLY APPROVED

Current classification	Brand name	Amount of codeine	Sponsor	Status	Approval date
Prescription	Codeine Phosphate Tablets 15 mg PSM	15 mg	PSM Healthcare Ltd trading as API Consumer Brands	Consent given	31/12/1969
Prescription	Paracetamol + Codeine Tablet Relieve	8 mg (= 5.92 mg codeine)	Mylan New Zealand Limited	Consent given	18/06/2009
Restricted	Ibucode Plus film coated tablet 200mg/12.8mg	12.8 mg	Teva Pharma (New Zealand) Limited	Consent given	15/07/2010
Restricted	Mersyndol Tablet	9.75 mg	Sanofi-aventis New Zealand Limited	Consent given	31/03/1994
Restricted	Nurofen Plus Film coated tablet (monolayer)	12.8 mg	Reckitt Benckiser (New Zealand) Limited	Consent given	13/01/2005
Restricted	Panadeine Caplets Tablet 500mg/8mg (New Formulation)	8 mg	GlaxoSmithKline Consumer Healthcare New Zealand Ltd	Consent given	2/04/2009
Restricted	Panadeine Extra Tablet 500mg/ 15mg	15 mg	GlaxoSmithKline Consumer Healthcare New Zealand Ltd	Consent given	03/03/2005
Restricted	Panadeine Tablet 500mg/8mg	8 mg	GlaxoSmithKline Consumer Healthcare New Zealand Ltd	Consent given	31/12/1969
Restricted	Panafen Plus Film coated tablet 200mg, 12.8mg	12.8 mg	GlaxoSmithKline Consumer Healthcare New Zealand Ltd	Consent given	13/01/2005
Pharmacy Only	Codral Cold & Flu tablet	9.5 mg (= 7 mg codeine)	Johnson & Johnson (New Zealand) Limited	Consent given	27/11/2008
Pharmacy Only	Codral Day & Night Cold & Flu New Formula tablet	9.5 mg	Johnson & Johnson (New Zealand) Limited	Consent given	16/12/2009
Pharmacy Only	Codral Multi Action Cold & Flu New Formula tablet	9.5 mg	Johnson & Johnson (New Zealand) Limited	Consent given	16/12/2009
Pharmacy Only	Codral Multi Action Cold & Flu Tablet New Formula	9.5 mg	Johnson & Johnson (New Zealand) Limited	Consent given	27/01/2011
Prescription	Codeine Phosphate Tablet 15 mg Douglas	15 mg	Douglas Pharmaceuticals Ltd	Not available	25/11/1993
Restricted	Codalgin Tablet 500 mg/8mg	8 mg	Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics	Not available	12/06/2003
Restricted	Mersyndol Caplets Tablets 9.75mg/5mg/450mg	9.75 mg	Sanofi-aventis New Zealand Limited	Not available	31/10/1997
Restricted	Obecalpton Tablet Relieve	8 mg (= 5.92 mg codeine)	Mylan New Zealand Ltd	Not available	7/10/2010

Restricted	Paracode Extra Tablet 500mg/15mg	15 mg	Actavis New Zealand Limited	Not available	05/05/2011
Restricted	Paracode Tablet 500mg/8mg	8 mg (= 5.92 mg codeine)	Actavis New Zealand Limited	Not available	16/07/2009
Restricted	Pharmacist's Own Pain Relief Tablet 500mg/10mg	10 mg	PSM Healthcare Ltd trading as API Consumer Brands	Not available	05/11/2010
Restricted	Pharmacist's Own Pain Relief Plus Tablet 450mg/9.75mg/5mg	9.75 mg	PSM Healthcare Ltd trading as API Consumer Brands	Not available	04/11/2010
Restricted	Your Pharmacy Pain Relief Plus Tablet	9.75 mg	Orion Laboratories (NZ) Ltd	Not available	26/05/2011
Restricted	Your Pharmacy Paracetamol Plus Tablet 500mg/10mg	10mg	Orion Laboratories (NZ) Ltd	Not available	14/04/2011
Pharmacy Only	Arrow Co-codamol Tablet 500mg/8mg	8 mg (=5.92 mg)	Actavis New Zealand Limited	Not available	16/07/2009
Pharmacy Only	Lemsip For Pharmacy Cold & Flu Day & Night Tablet	6 mg	Reckitt Benckiser (New Zealand) Limited	Not available	16/05/2013
Pharmacy Only	Lemsip For Pharmacy Cold & Flu Tablet	6 mg	Reckitt Benckiser (New Zealand) Limited	Not available	16/05/2013
Pharmacy Only	Pharmacist's Own Cold & Flu Relief PE Tablet	6 mg	PSM Healthcare Ltd trading as API Consumer brands	Not available	10/03/2011
Pharmacy Only	Paracotene Effervescent tablet 500mg/8mg	8 mg	Multichem NZ Limited	Not available	08/04/2004
Pharmacy Only	Your Pharmacy Cold & Flu PE Tablet	6 mg	Orion Laboratories (NZ) Ltd	Not available	26/05/2011
Pharmacy Only	Your Pharmacy Day + Night Cold & Flu Relief PE tablet	6 mg	Orion Laboratories (NZ) Ltd	Not available	1/03/2012

APPENDIX 2: FURTHER INFORMATION ON DATAPHARM

DataPharm reports measures for 'Prescriptions' and 'Dispensings'. The key difference between 'Prescriptions' and 'Dispensings' is that 'prescriptions' refer to the number of times a pharmaceutical product was dispensed from a pharmacy to a named person as initial dispensings or all at once (ie, excludes repeat dispensings), whereas 'dispensings' shows the number of times the product was dispensed on all occasions (ie, includes repeat dispensings).

Please refer to the DataPharm: Technical Information for further information about the data source, analytical methods used to produce the summary data and definitions for common terms used.

Paracetamol 500 mg and codeine phosphate 8 mg combination products

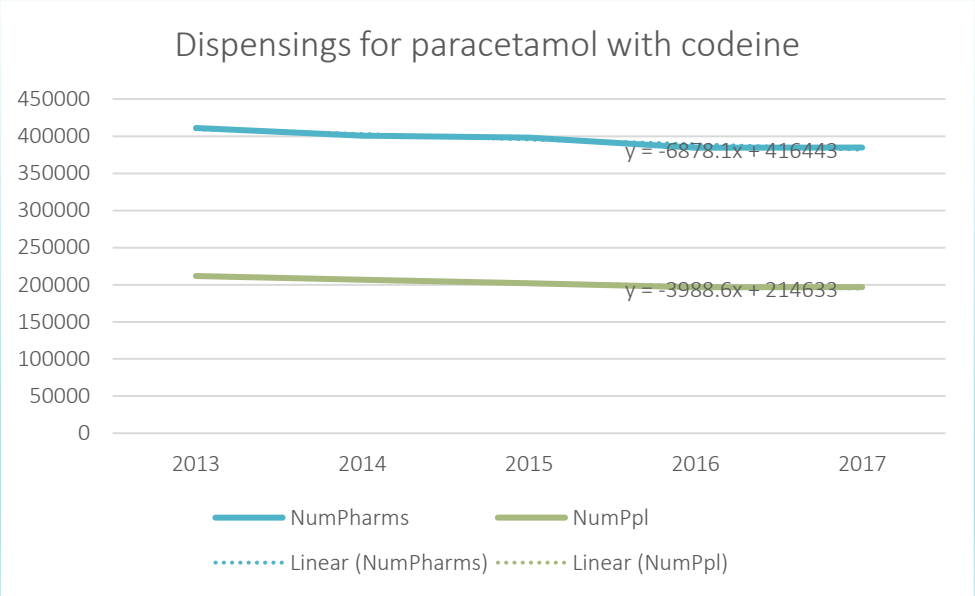

Figure 1 Dispensings for paracetamol with codeine

Table 7 Dispensings for paracetamol with codeine

Year Disp	NumPharms	NumPpl
2013	411,033	211,726
2014	400,648	206,506
2015	391,849	201,779
2016	384,491	196,574
2017	384,721	196,749

Table 8 Prescriptions for paracetamol with codeine

Year Disp	NumPharms	NumPpl
2013	352,128	211,130
2014	341,752	205,943
2015	330,181	201,169
2016	321,008	195,918
2017	319,149	196,090

The dispensings of paracetamol with codeine products was observed to decrease from 2013 to 2017. Both the number of times a product was dispensed and the number of people who received a dispensing of a product decreased, although at different rates. The number of dispensed

pharmaceuticals (NumPharms) had a bigger decrease than the number of people who (NumPpl) who received a dispensing of the pharmaceutical product.

Paracetamol with codeine products were dispensed approximately two times more frequently than codeine phosphate 15 mg tablets. In 2017, there were 384,721 dispensings for paracetamol with codeine compared to 186,506 dispensings for codeine phosphate 15 mg tablets.

Codeine phosphate 15 mg tablets

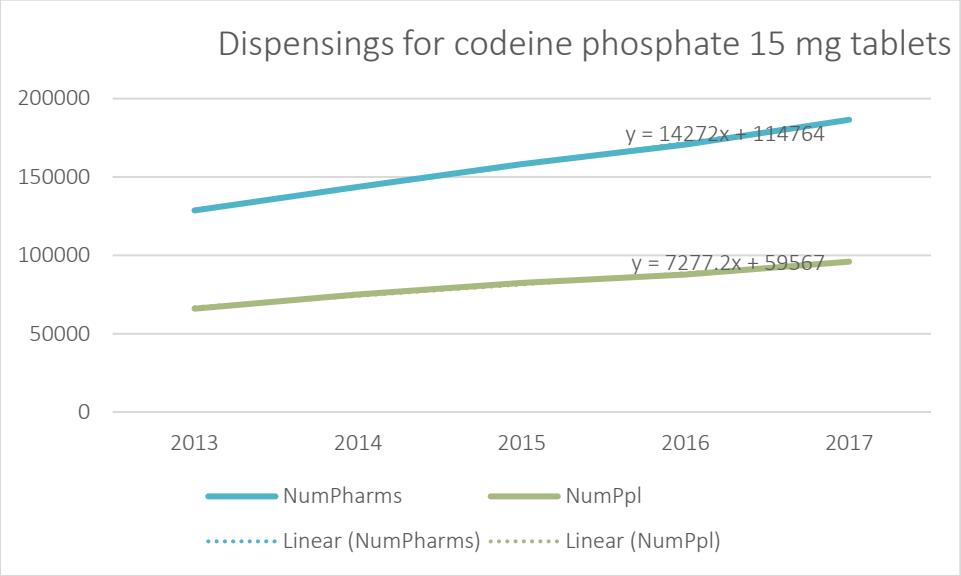

Figure 2 Dispensings for codeine phosphate 15 mg tablets

Table 9 Dispensings for codeine phosphate 15 mg tablets

Year Disp	NumPharms	NumPpl
2013	128,630	65,928
2014	143,751	74,988
2015	158,291	82,405
2016	170,718	87,732
2017	186,506	95,942

Table 10 Prescriptions for codeine phosphate 15 mg tablets

Year Disp	NumPharms	NumPpl
2013	99,406	65,575
2014	111,613	74,593
2015	122,468	81,957
2016	130,226	87,234
2017	142,074	95,364

Dispensings for codeine phosphate 15 mg tablets increased between 2013 and 2017. Both the number of times a product was dispensed and the number of people who received a dispensing of a product increased. The rate of increase for the number of dispensed pharmaceuticals is faster than the number of people who received a dispensing of the pharmaceutical product. The number of prescriptions dispensed had also increased from 99,406 in 2013 to 142,074 in 2017; an increase of 42,668 prescriptions over this period.