Reconsideration of the classification of codeine

Purpose

At the 57th meeting of the Medicines Classification Committee (MCC) it was noted that the Australian Scheduling Committee had 'up-scheduled' codeine to schedule 4 (prescription medicine). This change in classification was in response to on-going concerns regarding harm arising from deliberate misuse.

The MCC requested that Medsafe review the outcome of the Australian Scheduling change and provide advice on the role of codeine in New Zealand. This submission from Medsafe provides information on this topic and provides a range of options for the Committee to consider.

Background

The MCC has previously considered the classification of codeine at many meetings (see Table 1). The most recent classification change for codeine was made at the 42nd meeting on 3 November 2009. At this meeting the Committee recommended changing the classification of analgesic medicines containing codeine in combination with other ingredients to restricted medicines. The Committee noted these recommendations could create the situation where those addicted to codeine may try to seek alternative sources of codeine from cough and cold medicines.

The Committee expressed concerns that people addicted to codeine would seek alternative sources from cough and cold medicines. However, the Committee subsequently decided to allow codeine in cough and cold preparations to remain as pharmacy-only.

It was also recommended that pharmacies voluntarily placed codeine containing medicines out of sight.

Table 1: Summary of MCC discussions on codeine

Meeting	Date	Comments*
1	13 Nov 1984	Abuse of codeine was discussed. The Committee did not consider that a change in the scheduling of codeine was warranted.
2	19 Mar 1985	The Committee did not support the recommendations of the Drugs Advisory Committee that all codeine sales be registered and that the retail pack size be limited to 24 tablets or capsules. The Committee considered that it would be impractical to record every sale of codeine and that desperation in the abusers would lead them to violence against pharmacists and into abuse of more dangerous substances.
3	17 Sep 1985	An update on the abuse of codeine noted that about 20 new patients per month were being treated in Auckland.
4	11 Mar 1986	An update on sales of codeine analgesics was provided.
5	11 Nov 1986	The Committee noted a decreased in sales of codeine analgesics and a decrease in sales of larger pack sizes.
8	6 Dec 1991	One member suggested that all codeine containing medicines be made prescription only. Another member was not supportive of this position and did not agree that this would solve the problem of abuse.

9	28 May 1992	The New Zealand Medical Association (NZMA) requested that sale of over the counter codeine medicines be banned. Members of the Committee disagreed. The Committee agreed that the classification of codeine should remain unchanged. The manufacturer was requested to reformulate Panadeine to make the codeine less readily extractable
10	11 Nov 1992	The Committee considered a response from the manufacturer of Panadeine that they were currently working on the problem.
11	29 Jun 1993	The Committee were updated on actions taken to alleviate the 'homebake problem'.
12	25 Nov 1993	A further update was provided. Companies had been contacted regarding the possibility of making codeine less readily extractable.
13	26 may 1994	A further update was provided to the effect that a formulation from which it was difficult to extract codeine had been found.
18	15 Oct 1997	The classification of codeine in combination with other ingredients was identified as an area for further investigation.
19	20 May 1998	The Committee were told that the only way a change to the classification of codeine could be influenced by a change to the Medicines Regulations by reclassifying all medicines which are controlled drugs under Section C Part VI of the Misuse of Drugs Act 1975. The Committee debated whether the Drugs Advisory Committee should be asked to consider removing codeine from Part VI of Section C, but decided not to. It was noted that the MCC had consistently been of the opinion that it would be unfair to deny genuine users access to a useful product because of its misuse by a minority of the population.
38	14 Dec 2007	This discussion was prompted by the increasing quantities of codeine in pharmacy-only codeine medicine applications to Medsafe. It was noted that since the tighter controls on access to pseudoephedrine that there had been a rise in the abuse of codeine. The Committee recommended further discussion at the next meeting.
39	25 Jun 2008	The Committee agreed that the following action should be taken: • any combination product containing more than 15 milligrams of codeine per dose unit should be reclassified as a prescription medicine immediately: • further consultation should be undertaken prior to the 40th meeting about suitable cut-off points and pack size limits for pharmacy-only and restricted medicine levels of access based on the following proposal:* o **pharmacy-only** combination products should contain 12 milligrams or less of codeine per dose unit with a maximum recommended treatment period of 7 days and an upper pack size limit of 50 dose units. o **restricted medicine** combination products should contain 15 milligrams or less but more than 12 milligrams of codeine per dose unit and an upper pack size limit of 25 dose units. o all combination products containing more than 15 milligrams of codeine per dose unit should be **prescription medicines.** Lower pack size limits for prescription medicine classification would be established

		after upper limits for pharmacy-only and restricted medicines had been finalised. • pharmaceutical companies should be asked to provide package information about rebound headaches and about the potential for addiction. • pharmacy professional bodies and pharmacy marketing groups should be notified that it is inappropriate to display codeine-containing products in dump bins and the Pharmacy Council should be asked to provide guidance to pharmacists about the display of these products.
40	25 Nov 2008	The Committee agreed that a recommendation should be held over until the results of Australian position was known. In the meantime, the current prescription medicine status of codeine in combination products containing more than 15 milligrams of codeine per dose unit should remain.
41	14 May 2009	It was recommended that codeine should be classified as a prescription medicine when in combination products containing more than 15 milligrams of codeine per dose unit. That the two proposals for reclassification of codeine be placed on the agenda of the next meeting of the MCC. The proposals include options to reclassify codeine as either a restricted medicine or pharmacy-only medicine when: • each dose unit contains not more than 15 mg of codeine base • the maximum daily dose is limited to 100 mg of codeine base • the pack size is not more than 5 days' supply.
42	3 Nov 2009	The Committee recommended that codeine in combination products should be reclassified as a restricted medicine when: • each dose unit contains not more than 15 mg of codeine base • the maximum daily dose is limited to 100 mg of codeine base • the pack size is not more than five days' supply • sold in packs approved by the Minister or the Director-General for distribution as a restricted medicine. That the decision to allow cough and cold preparations containing codeine to continue to be available at the pharmacy-only level would be reviewed in 12-18 months time. That Medsafe should write to the Pharmaceutical Society of New Zealand and the Pharmacy Guild regarding the reclassification of codeine in combination products and the recommended reclassification of cough and cold preparations. That Medsafe should be requested to write an article on the reclassification of codeine for General Practitioners in Prescriber Update. That Medsafe require codeine containing products to be labelled with warning statements similar to those required in the United Kingdom – "Do not use for more than 3 days" and "Codeine is an addictive substance". That the requirements for codeine in combination products to be reclassified as a restricted medicine should be inserted into the New Zealand Regulatory Guidelines for Medicines by Medsafe.

43	13 Apr 2010	The Committee recommended that cough and cold preparations containing codeine should be classified as pharmacy-only medicines when: • each dose unit contains not more than 15 mg of codeine base • the maximum daily dose is limited to 100 mg of codeine base • the pack size is not more than six days' supply • sold in a pack approved by the Minister or the Director-General for distribution as a pharmacy-only medicine. That Medsafe should write to the sponsor companies of medicines containing codeine regarding: a. changes to the classification of analgesic medicines and cough and cold preparations containing codeine that would come into effect on 4 October 2010 b. new labelling requirements that would apply to codeine-containing cough and cold preparations from 1 May 2011.
46	15 Nov 2011	The Committee had committed to review the effects of the classification change. The Committee discussed the changes and requested further data
47	1 May 2012	The Committee considered a review from a NZ addiction specialist on codeine misuse and usage data from the manufacturers and the McAvoy publication in the New Zealand Medical Journal (NZMJ, see below). The Committee considered that the reclassification had had the required impact. No further action was needed.
55	3 May 2016	The Committee committed to reviewing the outcomes of the Australian Committee on Medicine Scheduling (ACMS) consideration of codeine.

*The full minutes can be accessed on the Medsafe website

The current classification criteria for codeine containing medicines is shown in Table 2.

Table 2 Current classification of codeine

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

Relevant products

The currently approved medicines containing codeine are included in Tables 3 and 4.

*Table 3 Medicines indicated for the treatment of the symptoms of **coughs and colds** containing codeine*

Brand name	Active ingredients	Sponsor	Status	Approval date	Quantity of codeine
Codral Cold & Flu Tablet, (Pharmacy only)	Codeine; Paracetamol; Phenylephrine	Johnson & Johnson (New Zealand) Limited	Consent given	27/11/2008	Codeine phosphate hemihydrate 9.5 mg
Codral Day & Night Cold & Flu New Formula Tablet, (Pharmacy only)	Chlorphenamine; Codeine; Paracetamol; Phenylephrine	Johnson & Johnson (New Zealand) Limited	Consent given	16/12/2009	Codeine phosphate hemihydrate 9.5 mg
Codral Multi Action Cold & Flu Tablet, New Formula (Pharmacy only)	Chlorphenamine; Codeine; Paracetamol; Phenylephrine	Johnson & Johnson (New Zealand) Limited	Consent given	27/01/2011	Codeine phosphate hemihydrate 9.5 mg
Lemsip For Pharmacy Cold & Flu Tablet, (Pharmacy only)	Codeine; Paracetamol; Phenylephrine	Reckitt Benckiser (New Zealand) Limited	Not available	16/05/2013	Codeine phosphate hemihydrate 6 mg
Lemsip For Pharmacy Cold & Flu Day & Night Tablet, (Pharmacy only)	Chlorphenamine; Codeine; Paracetamol; Phenylephrine	Reckitt Benckiser (New Zealand) Limited	Not available	16/05/2013	Codeine phosphate hemihydrate 6 mg
Pharmacist's Own Cold & Flu Relief PE Tablet, 500mg/6mg/5mg (Pharmacy only)	Codeine; Paracetamol; Phenylephrine	PSM Healthcare Ltd trading as API Consumer Brands	Not available	10/03/2011	Codeine phosphate hemihydrate 6 mg
Your Pharmacy Cold & Flu Relief PE Tablet, (Pharmacy only)	Codeine; Paracetamol; Phenylephrine	Orion Laboratories (NZ) Ltd	Not available	26/05/2011	Codeine phosphate hemihydrate 6 mg
Your Pharmacy Day + Night Cold & Flu Relief PE Tablet, (Pharmacy only)	Chlorphenamine; Codeine; Paracetamol; Phenylephrine	Orion Laboratories (NZ) Ltd	Not available	1/03/2012	Codeine phosphate hemihydrate 6 mg

*Table 4 Medicines indicated for the relief of **pain** containing codeine and available without prescription*

Brand name	Active ingredients	Sponsor	Status	Approval date	Quantity of codeine
Codalgin Tablet, 500mg/8mg (Restricted)	Codeine; Paracetamol	Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics	Not available	12/06/2003	Codeine phosphate hemihydrate 8 mg
Ibucode Plus Film coated tablet, 200mg/12.8mg (Restricted)	Codeine; Ibuprofen	Actavis New Zealand Limited	Consent given	15/07/2010	Codeine phosphate hemihydrate 12.8 mg

Mersyndol Tablet, (Restricted)	Codeine; Doxylamine; Paracetamol	sanofi-aventis new zealand limited	Consent given	31/03/1994	Codeine phosphate hemihydrate 9.75 mg
Mersyndol Caplets Tablet, 9.75mg/5mg/450mg (Restricted)	Codeine; Doxylamine; Paracetamol	sanofi-aventis new zealand limited	Not available	31/10/1997	Codeine phosphate hemihydrate 9.75 mg
Nurofen Plus Film coated tablet, (monolayer) (Restricted)	Codeine; Ibuprofen	Reckitt Benckiser (New Zealand) Limited	Consent given	13/01/2005	Codeine phosphate hemihydrate 12.8 mg
Obecalpton Tablet, Relieve (Restricted)	Codeine; Paracetamol	Mylan New Zealand Ltd	Not available	7/10/2010	Codeine phosphate hemihydrate 8 mg
Panadeine Tablet, 500mg/8mg (Restricted)	Codeine; Paracetamol	GlaxoSmithKline Consumer Healthcare New Zealand Ltd	Consent given	31/12/1969	Codeine phosphate hemihydrate 8 mg
Panadeine Caplets Tablet, 500mg/8mg (New Formulation) (Restricted)	Codeine; Paracetamol	GlaxoSmithKline Consumer Healthcare New Zealand Ltd	Consent given	2/04/2009	Codeine phosphate hemihydrate 8 mg
Panadeine Extra Tablet, 500mg/15mg (Restricted)	Codeine; Paracetamol	GlaxoSmithKline Consumer Healthcare New Zealand Ltd	Consent given	3/03/2005	Codeine phosphate hemihydrate 15 mg
Panafen Plus Film coated tablet, 200mg, 12.8mg (Restricted)	Codeine; Ibuprofen	GlaxoSmithKline Consumer Healthcare New Zealand Ltd	Consent given	13/01/2005	Codeine phosphate hemihydrate 12.8 mg
ParaCode Tablet, 500mg/8mg (Restricted)	Codeine; Paracetamol	Actavis New Zealand Limited	Not available	16/07/2009	Codeine phosphate hemihydrate 8 mg
Paracode Extra Tablet, 500mg/15mg (Restricted)	Codeine; Paracetamol	Actavis New Zealand Limited	Not available	5/05/2011	Codeine phosphate hemihydrate 15 mg
Pharmacist's Own Pain Relief Tablet, 500mg/10mg (Restricted)	Codeine; Paracetamol	PSM Healthcare Ltd trading as API Consumer Brands	Not available	5/11/2010	Codeine phosphate hemihydrate 10 mg
Your Pharmacy Pain Relief Plus Tablet, (Restricted)	Codeine; Doxylamine; Paracetamol	Orion Laboratories (NZ) Ltd	Not available	26/05/2011	Codeine phosphate hemihydrate 9.75 mg
Your Pharmacy Paracetamol Plus Tablet, 500mg/10mg (Restricted)	Codeine; Paracetamol	Orion Laboratories (NZ) Ltd	Not available	14/04/2011	Codeine phosphate hemihydrate 10 mg

Arrow - Co-codamol Tablet, 500mg/8mg nly)	Codeine; Paracetamol	Actavis New Zealand Limited	Not available	16/07/2009	Codeine phosphate hemihydrate 8 mg
Mersyndol Day Strength Caplets Tablet, 9.6mg/500mg	Codeine; Paracetamol	sanofi-aventis new zealand limited	Not available	3/10/1997	Codeine phosphate hemihydrate 9.6 mg
Paracotene Effervescent tablet, 500mg/8mg	Codeine; Paracetamol	Multichem NZ Limited	Not available	8/4/2004	Codeine phosphate hemihydrate 8 mg

Recent international regulatory actions

USA

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. Where codeine can be purchased without a prescription the purchaser's identifying information and details of the sale must be recorded.

The FDA have taken the following actions in response to harms associated with codeine.

2007 Warning regarding the risk of life-threatening side effects in nursing babies whose mothers have taken codeine. (www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm124889.htm).

Comment
This warning is required on the package label for all codeine containing medicines: "Do not use if you are breastfeeding except on doctor's advice".

2012 Warning that codeine use in children after tonsillectomy and/or adenoidectomy may lead to rare but life-threatening adverse events or death. (www.fda.gov/Drugs/DrugSafety/ucm313631.htm).

Comment
This safety concern was discussed by the Medicines Adverse Reactions Committee (MARC) as the December 2012 meeting. The MARC recommended that use of codeine be contraindicated in children under 1 year of age and that warnings regarding this risk be added to the data sheets: www.medsafe.govt.nz/profs/adverse/Minutes152.htm#3.1. The FDA contraindicated codeine containing products for post-operative pain management in children who have undergone tonsillectomy and/or adenoidectomy.

2015 FDA evaluating the potential risks of using codeine cough and cold medicines in children under 18 years. (www.fda.gov/Drugs/DrugSafety/ucm453125.htm).

Comment
This safety concern was discussed at the December 2014 meeting of the MARC. The MARC recommended that the use of codeine-containing medicines for cough and cold in children should be restricted to those aged 12 years and over. www.medsafe.govt.nz/profs/adverse/Minutes160.htm#3.2.4, www.medsafe.govt.nz/safety/EWS/2015/BromhexineOrCodeine.asp. No changes to the classification or label statement database were made.

2016 FDA warns about serious risks and death when combining opioid pain or cough medicines with benzodiazepines (www.fda.gov/Drugs/DrugSafety/ucm518473.htm).

Comment

This issue includes medicines containing codeine. The Committee should also note that there are other opioid containing medicines available without prescription affected by this safety alert (Gees linctus is a pharmacy medicine). The MARC will consider this safety concern at the March meeting.

Canada

2013 Health Canada has reviewed the safety of prescription pain and cough medications containing codeine and is no longer recommending use in children less than 12 years of age. This recommendation is based on very rare cases of serious side effects and deaths in children that have been attributed to codeine, when given directly to a child, or to babies from breast milk (http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2013/33915a-eng.php).

2016 codeine should no longer be used (contraindicated) in patients under 18 years of age to treat pain after surgery to remove tonsils or adenoids, as these patients are more susceptible to the risk of serious breathing problems. Codeine (prescription and non-prescription) is already not recommended for children under the age of 12, for any use (http://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2016/59584a-eng.php).

Europe

2013 European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) reviewed the use of codeine in children for pain relief and recommended.

- Codeine-containing medicines should only be used to treat acute (short-lived) moderate pain in children above 12 years of age, and only if it cannot be relieved by other painkillers such as paracetamol or ibuprofen, because of the risk of respiratory depression associated with codeine use.
- Codeine should not be used at all in children (aged below 18 years) who undergo surgery for the removal of the tonsils or adenoids to treat obstructive sleep apnoea, as these patients are more susceptible to respiratory problems.

The product information of these medicines should carry a warning that children with conditions associated with breathing problems should not use codeine (www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Codeine-containing_medicines/human_referral_prac_000008.jsp&mid=WC0b01ac05805c516f).

2015 PRAC recommended restrictions on the use of codeine-containing medicines for cough and cold in children because of the risk of serious side effects with these medicines, including the risk of breathing problems (www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2015/03/news_detail_002287.jsp&mid=WC0b01ac058004d5c1).

The PRAC recommended specifically that:

- codeine should be contraindicated in children below 12 years. This means it must not be used in this patient group
- use of codeine for cough and cold is not recommended in children and adolescents between 12 and 18 years who have problems with breathing.

All liquid codeine medicines should be available in child-resistant containers to avoid accidental ingestion.

Basis for recent Australian scheduling decision

The ACMS in Australia met on 15 March 2016 to consider the public submissions received following the release of the interim decision. The ACMS also discussed the independent review on the safety and efficacy of low-dose codeine-containing products, which was commissioned by the Therapeutic Goods Administration (TGA)

(www.tga.gov.au/sites/default/files/review-efficacy-and-safety-over-counter-codeine-combination-medicines.pdf;
www.tga.gov.au/media-release/update-proposal-re-scheduling-codeine-products;
www.tga.gov.au/media-release/independent-review-efficacy-and-safety-over-counter-codeine-combination-medicines
www.tga.gov.au/final-decision-re-scheduling-codeine-frequently-asked-questions).

The final decision to 'up-schedule' all codeine containing medicines to prescription was released on 20 December 2016. Medicines containing codeine will be available by prescription only from 1 February 2018.

Specifically, the Australian Standard for the Uniform Scheduling of Medicines and Poisons (the Poisons Standard) will be amended to delete the codeine entries from Schedule 2 (pharmacy only medicines) and Schedule 3 (restricted medicines), leaving only the codeine entries in Schedule 4 (prescription only medicine) and Schedule 8 (controlled drug) on 1 February 2018.

The TGA concluded that:

- there is substantial evidence of harm from the abuse and misuse of low dose codeine-containing medicines
- for most individuals, there is little evidence that low-dose codeine medicines are more effective than alternative medicines without codeine
- the presence of low-dose codeine in widely accessible OTC combination medicines, and the development of tolerance and subsequent dependence on codeine, contributes to severe adverse health outcomes, including liver damage and death
- low-dose codeine-containing medicines are not intended to treat long term conditions; however, public consultation has indicated that this is how most consumers use these medicines
- additionally, some individuals, especially children, experience serious adverse reactions when given codeine, such as difficulty breathing and death

Given these issues, it is clear that alternative regulatory controls are required to drive public health benefits that outweigh the known risks of codeine use.

Scientific information

The analgesic properties of codeine stem from its metabolism in the liver to morphine. This conversion is performed by cytochrome P450 2D6 (CYP2D6). The toxicity of codeine is due to its opioid effects.

CYP2D6 is subject to extensive polymorphism resulting from more than 100 different allelic variants. This translates into a wide spectrum of metabolic capability. Some people known as ultra-rapid metabolisers (1-2% of the population), convert codeine to morphine very quickly and tend to experience the toxic effects of codeine. Other people are intermediate or poor metabolisers (up to 11% of the population) and experience a lack of effect of codeine.

TGA review of the efficacy and safety of codeine containing medicines

The independent review commissioned by the TGA (see link above for full report) investigated the efficacy of codeine containing medicines for pain relief and coughs and colds. To summarise; the analysis included 14 trials involving 788 participants. Ten trials evaluated the efficacy of these medicines for pain and four trials evaluated the effects on cough. None of the trials evaluated long-term use, most were single use studies. The reviewers were able to perform a meta-analysis for studies comparing the efficacy of combination medicines containing codeine with placebo for pain relief.

Efficacy of codeine for pain relief

Pooled results for medicines containing 30 mg or less of codeine given as a single dose (383 participants; 217 taking active treatment, 166 taking placebo) were obtained. The results showed that these medicines were better than placebo for pain relief.

Investigation of the effect of increasing dose did not show a clear increase in effect for higher doses in all the studies.

The authors were unable to perform a meta-analysis of studies comparing combination codeine medicines with a single ingredient medicines containing a non-steroidal anti-inflammatory drug (NSAID) or paracetamol. One systematic review was identified, this review found no statistically significant in pain relief between the combination medicines and NSAID.

Efficacy of codeine for cough

In the four eligible trials (208 participants) comparing codeine combination medicines with placebo two trials evaluated use for chronic cough and two trials looked at acute upper respiratory tract infection. The results were mixed. Two trials reported a reduction in cough symptom severity in both active and placebo groups, one showed a reduction in severity of night time cough but not cough count compared to placebo and one trial found no difference in cough count between treatment and placebo.

Harms of codeine combination medicines

The reviewers noted that evidence from case studies identified that adverse events resulting from the misuse of codeine can be life threatening and even fatal. These effects revolve around renal and biochemical/metabolic impairment. These effects are most likely attributable to the dose of ibuprofen, aspirin or paracetamol ingested to gain the euphoric effects of codeine.

Over 100 deaths in Australia have been attributed to the misuse of combination codeine medicines.

A number of studies reported that codeine-based medicines are purchased from multiple pharmacies among people with problematic codeine use behaviours.

KPMG report

The TGA also asked KPMG to consolidate the results of its regulatory and economic modelling into a standalone report suitable for public release (www.tga.gov.au/publication/economic-modelling-and-financial-quantification-regulatory-impact-proposed-changes-codeine-scheduling). The following key results were demonstrated:

- only rescheduling codeine as a prescription medicines will result in an expected net benefit (compared to the other options).
- the drivers of net benefit are improved quality of life following better treatment pathways, deaths prevented and net financial savings to consumers.
- even under sensitivity analyses that materially reduce benefits and increase costs, a positive net benefit, albeit small remains the projected result of rescheduling to prescription.

New Zealand specific information

As of February 2016, there had only been one adverse reaction report in New Zealand which described abuse or misuse of codeine.

Poisons Centre data was reviewed as it is considered the Poisons Centre is more likely than CARM are to be informed of incidents relating to abuse, misuse and dependence.

Between the beginning of 2011 and the end of 2015, the Poisons Centre received 219 calls where codeine was mentioned as having been taken. In 49 cases, the source of the codeine could be attributed to a non-prescription product.

Patient age ranged from 16 years to 57 years in these 49 cases.

In 14 (/49) cases, it was recorded that codeine had been taken as part of an intentional overdose.

In four (/49) cases, it was recorded that a course of n-acetylcysteine had been started due to high paracetamol blood levels.

In three (/49) cases, codeine was obtained from a cough/cold medicine.

In the remaining cases, the source of the codeine was a combination product with paracetamol (acetaminophen). There were no cases reporting use of an ibuprofen-codeine combination product.

The number of tablets taken, where recorded, ranged from three to 100, and the most commonly reported quantity was ten tablets (in eight of the 49 reports).

It is important to note that there are different reasons why people phone the Poisons Centre for advice. People may have experienced intentional, chronic and/or an accidental overdose. The Poisons Centre note that they are unlikely to be made aware of cases of abuse of codeine.

Medsafe has contacted New Zealand addiction specialists who have indicated that there are persistent problems with the abuse of OTC codeine products.

The Australian independent review included a number of publications documenting harms from codeine in New Zealand (Table 5).

Table 5 New Zealand publications on harms from codeine (taken from the TGA independent report by Shaheed et al

Study	Summary
Robinson GM, Robinson S, McCarthy P, Cameron C. Misuse of over-the-counter codeine-containing analgesics: dependence and other adverse effects. NZ Med J.2010;123:59-64	**Study Type:** Case Report Study **Study Period:** 2009-2010 (2 years) **Country/Setting:** New Zealand, Kenepuru Hospital Detoxification Unit **Cases/Studies involved:** 7 cases **Medication initiated to treat:** unclear **Medication type:** Nurofen Plus **Total daily codeine dose ingested (range):** Nurofen Plus 60-80/day, 48/day, 20/day, up to 72/day, 80/day, up to 120/day, 48/day. Mean dose: ~65 tablets/day; mean codeine dose = 832 mg/day **Daily ibuprofen ingested:** Mean dose 13g ibuprofen / day **Patient Characteristics/ History:** 6 patients had prior or current history of alcohol dependence and 4 had mental health conditions (depression or anxiety and or psychosis). Average duration of use of codeine combination medicines was 22 months. **Reported Harms associated with overuse:** Life threatening: • gastric ulcer (4 patients), • gastrointestinal bleeding (3), • hepatotoxicity (1), • inflammatory bowel conditions (2). **Considerations:** Other long term complications possibly attributed to the NSAID included: gastric ulcer and haemorrhage, anaemia, gastrectomy, ileal resection, inflammatory bowel disease with gastric bypass and colectomy.
McAvoy BR, Dobbin MDH, Tobin CL. Over-the-counter codeine analgesic misuse and harm: characteristics of cases in Australia and New Zealand. N Z Med J. 2011; 124(1346):29-33	**Study Type:** Cross-sectional study of clients presenting to a regional, open-access detoxification clinic covering the Greater Auckland area between 1 January and 31 March 2010. **Study Period:** Over a 12-week period at the beginning of 2010 **Country/Setting:** New Zealand (Greater Auckland Area) **Cases/Studies involved:** 15 cases **Medication initiated to treat:** Unclear **Medication type:** OTC codeine-ibuprofen average 49 per day for average 27 months **Total daily codeine dose ingested:** 627 mg /day **Total daily ibuprofen ingested (range):** 9.8 g **Patient Characteristics/ History:** 53% reported alcohol or other drug use, 93% had mental health conditions. Average use of codeine combination medicines was 27 months. **Reported Harms associated with overuse:** Life threatening: • GI Bleeding/dyspepsia (53%) • Renal Tubular acidosis (7%) • Hospitalisations (66%) **Management Strategies:** detoxification
Evans C, Chalmers-Watson TA, Gearry RB.	**Study Type:** Case report Study **Study Period:** Not specified

Combination NSAID-codeine preparations and gastrointestinal toxicity. N Z Med J 2010;123:92-93.	**Country/Setting:** Otago, New Zealand **Cases/Studies involved:** 1 case **Medication initiated to treat:** back pain **Medication type:** Nurofen Plus (ibuprofen + codeine) **Total daily codeine dose ingested (range):** > 100 tablets /day (1280 mg /day) **Total daily ibuprofen ingested (range):** 20 g /day **Patient Characteristics/ History:** presented to ED with anaemia, exertional dyspnoea and lower leg oedema. Had a history of epigastric pain for one year that was worse on eating. **Reported Harms associated with overuse:** Life threatening: • Acute pyloric ulcer with oedema and stenosis • Post bulbar duodenitis with erosions **Management Strategies:** Balloon dilatation of pyloric stenosis later required. Counselling and treatment for addiction. Switched to codeine phosphate. **Considerations:** This is one of four cases presenting to the service in 2 years with significant GI pathology as a result of gross overuse of combination ibuprofen/codeine products.

Discussion

Table 6 outlines some of the possible options the Committee should consider.

Table 6 Classification options for codeine containing medicines

	Possible changes	**Concerns**	**Possible pros and cons***
1	Status quo.	Accessibility.	Codeine remains easily accessible to those requiring stronger pain relief or for severe cough. The available efficacy data do not indicate an advantage of codeine containing medicines over other available medicines.
		Abuse and misuse.	The current scale of abuse or misuse of codeine containing medicines is unclear, but this will continue to be a risk with the status quo.
		Information for healthcare professionals and consumers.	Data sheets are not required for pharmacy medicines. No additional warning statements would be required on the labels for consumers.
		Use in children.	Recommendations by the MARC and international concerns would not be addressed.
2	Current classification statements amended to restrict pack size, age of use, add other warnings to improve safe use.	Accessibility.	Codeine remains easily accessible to those requiring stronger pain relief or for severe cough. However, the available efficacy data do not indicate an advantage of codeine

			containing medicines over other available medicines. Decreasing pack sizes may increase the financial cost of treatment.
		Abuse and misuse.	The current scale of abuse or misuse of codeine containing medicines is unclear. Decreasing the pack size may not address these concerns as it does not prevent multiple purchases.
		Information for healthcare professionals and consumers.	Data sheets are not required for pharmacy medicines. More information for consumers would be provided on the packaging.
		Use in children.	Recommendations by the MARC and international concerns should be addressed.
3	Change the classification of codeine for cough and colds to restricted medicine, keep the classification of codeine in combined analgesics as restricted medicine.	Accessibility.	Accessibility to codeine is maintained, but with the input of pharmacists.
		Abuse and misuse.	The current scale of abuse or misuse of codeine containing medicines is unclear. There is currently no mechanism in place to prevent multiple purchases from different pharmacies.
		Information for healthcare professionals and consumers.	Data sheets are required for restricted medicines. Information needs are addressed for healthcare professionals but not consumers.
		Use in children.	Recommendations by the MARC and international concerns not addressed, although pharmacists should be able to manage this.
4	Change the classification of codeine for cough and colds to restricted medicine, keep the classification of codeine in combined analgesics as restricted and amend the statements to restrict the pack size, age of use and add other warnings to improve safe use.	Accessibility.	Accessibility to codeine is maintained but with the input of pharmacists. Decreasing pack sizes may increase the financial cost of treatment.
		Abuse and misuse.	The current scale of abuse or misuse of codeine containing medicines is unclear. There is currently no mechanism in place to prevent multiple purchases from different pharmacies.
		Information for healthcare professionals and consumers.	Data sheets are required for restricted medicines. Information needs are addressed for healthcare professionals. Additional warnings on the package provides more information for consumers.
		Use in children.	Recommendations by the MARC and international concerns should be addressed and managed by pharmacists.

5	Change the classification for all codeine containing medicines to prescription only	Accessibility.	Accessibility is reduced. Consumer choice is reduced and financial cost is increased. There may be an increased burden on GPs. There are alternative medicines available without prescription for the same indications.
		Abuse and misuse.	GPs may be able to monitor abuse and misuse better and can refer patients for treatment.
		Information for healthcare professionals and consumers.	Data sheets are required for prescription medicines. Information for consumers is provided by the prescriber.
		Use in children.	Recommendations by the MARC and international concerns should be addressed.

*Medsafe expects that consultation will better establish the pros and cons of each option in New Zealand

The Committee should also note that there is another opiate available as a pharmacy medicine (Gee's Linctus) used to treat coughs.