



Final decisions and reasons for decisions by delegates of the Secretary to the Department of Health

25 January 2017

The date and reasons for the final scheduling decision relating to Codeine have not changed. Corrections have been made in this update to rectify a publishing error.

20 December 2016

(Codeine - ACMS meetings – July/August 2015 and March 2016)

Notice under subsection 42ZCZS of the Therapeutic Goods Regulations 1990 (the Regulations)

The delegate of the Secretary to the Department of Health hereby give notice of delegate's final decisions for amending the *Poisons Standard* (commonly referred to as the *Standard for the Uniform Scheduling of Medicines and Poisons - SUSMP*) under subsection 42ZCZS the Therapeutic Goods Regulations 1990 (the Regulations). This notice also provides the reasons for the decision and the date of effect (implementation date) of the decision.

The delegate's final decision and reasons relate to the scheduling of codeine considered by:

- the July/August 2015 meeting of the Advisory Committee on Medicines Scheduling (ACMS#15); and
- the March 2016 meeting of the Advisory Committee on Medicines Scheduling (ACMS#17).

Scheduling proposals referred to the expert advisory committees.

Pre-meeting public notice

July/August 2015 ACMS#15

On 1 April 2015, under subsection 42ZCZK of the *Therapeutic Goods Regulations 1990* (the Regulations), the delegate published a [pre-meeting public notice](#) on the TGA website which specified the proposed amendments to the current Poisons Standard and invited public comment. The proposed amendments referred to the ACMS by the medicines scheduling delegate for codeine were:

- To delete the Schedule 3 entry for codeine, and re-schedule the current Schedule 3 codeine entry to Schedule 4 due to potential issues of morbidity, toxicity and dependence.

- Consideration may be given as to whether all current Schedule 3 preparations should be re-scheduled to Schedule 4, or whether any re-scheduling to Schedule 4 should only apply to combination analgesic products containing codeine.
- Consideration may be given as to whether the Schedule 2 entry for codeine should also be amended.

The pre-meeting consultation period was open for public comment for 20 business days and closed on 7 May 2015.

In accordance with subsection 42ZCZL of the Regulations redacted versions of public submissions received in response to this invitation were published on 15 December 2015 at: [Public submissions on scheduling matters](#).

Interim decision

July/August 2015 ACMS#15

On 1 October 2015, in accordance with subsection 42ZCZN of the Regulations, the delegate made an interim decision on an application and under subsection 42ZCZP of the Regulations, the [delegate's interim decision](#) and the reasons for the decision were published on TGA website. Further submissions were also invited from the applicants and parties who made valid pre-meeting submissions. The invitation to make submissions was open for 10 business days and closed on 15 October 2015.

Redacted versions of public submissions received in response to these invitations were published on 15 December 2015 at: [Public submissions on scheduling matters](#).

Additional consultation period

In order to give due consideration to the submissions received in the interim decision public consultation period and to seek further advice from the ACMS at its March 2016 meeting, the medicines scheduling delegate on 18 November 2015 deferred a [final decision](#) on the proposed codeine re-scheduling.

The TGA then sought further advice and public comment on several options for codeine re-scheduling via an [additional consultation period](#) that was open from 10 December 2015 through 29 January 2016.

Edited versions of valid public submissions received in response to the additional consultation period were published on 20 December 2016 at [Public submissions on scheduling matters](#).

Final decision

In accordance with subsection 42ZCZR of the Regulations, the delegate having made an interim decision on an application, has made a final decision confirming the interim decision after consideration of all submissions.

Publishing of the amendments to the Poisons Standard

The amendments to the Schedules, Appendices or other parts of the *Poisons Standard* are published electronically on ComLaw as amendments to the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) prior to the date of effect (implementation date) of the final decisions. Further information, including links to the *Poisons Standard* on ComLaw, is available at [SUSMP](#).

Glossary

Abbreviation	Name
AAN	Australian Approved Name
AC	Active constituent
ACCC	Australian Competition and Consumer Commission
ACCM	Advisory Committee on Complementary Medicines (formerly Complementary Medicine Evaluation Committee [CMEC])
ACNM	Advisory Committee on Non-prescription Medicines (formerly Medicines Evaluation Committee [MEC])
ACPM	Advisory Committee on Prescription Medicines (formerly Australian Drug Evaluation Committee [ADEC])
ACSOM	Advisory Committee on the Safety of Medicines (formerly Adverse Drug Reactions Advisory Committee [ADRAC])
ADEC	Australian Drug Evaluation Committee (now Advisory Committee on Prescription Medicines [ACPM])
ADI	Acceptable daily intake
ADRAC	Adverse Drug Reactions Advisory Committee (now Advisory Committee on the Safety of Medicines [ACSOM])
AHMAC	Australian Health Ministers' Advisory Council
APVMA	Australian Pesticides and Veterinary Medicines Authority
AQIS	Australian Quarantine and Inspection Service
ARfD	Acute reference dose
ASCC	Australian Safety and Compensation Council
ASMI	Australian Self-Medication Industry
ARTG	Australian Register of Therapeutic Goods

Abbreviation	Name
CAS	Chemical Abstract Service
CHC	Complementary Healthcare Council of Australia
CMEC	Complementary Medicine Evaluation Committee (now Advisory Committee on Complementary Medicines [ACCM])
CMI	Consumer Medicine Information
COAG	Councils of Australian Governments
CRC	Child-resistant closure
CTFAA	Cosmetic, Toiletry & Fragrance Association of Australia
CWP	Codeine Working Party
DAP	Drafting Advisory Panel
ECRP	Existing Chemicals Review Program
EPA	Environmental Protection Authority
ERMA	Environmental Risk Management Authority (New Zealand)
FAISD	First Aid Instructions and Safety Directions
FDA	Food and Drug Administration (United States)
FOI	Freedom of Information Act 1982
FSANZ	Food Standards Australia New Zealand
GHS	Globally Harmonised System of Classification and Labelling of Chemicals
GIT	Gastro-intestinal tract
GP	General practitioner
HCN	Health Communication Network

Abbreviation	Name
IMAP	Inventory Multi-tiered Assessment Prioritisation
INN	International Non-proprietary Name
ISO	International Standards Organization
LC ₅₀	The concentration of a substance that produces death in 50 per cent of a population of experimental organisms. Usually expressed as mg per litre (mg/L) as a concentration in air.
LD ₅₀	The concentration of a substance that produces death in 50 per cent of a population of experimental organisms. Usually expressed as milligrams per kilogram (mg/kg) of body weight.
LOAEL	Lowest observed adverse effect level
LOEL	Lowest observed effect level
MCC	Medicines Classification Committee (New Zealand)
MEC	Medicines Evaluation Committee (now Advisory Committee on Non-prescription Medicines [ACNM])
MOH	Ministry of Health (New Zealand)
NCCTG	National Coordinating Committee on Therapeutic Goods
NDPSC	National Drugs and Poisons Schedule Committee
NHMRC	National Health and Medical Research Council
NICNAS	National Industrial Chemicals Notification & Assessment Scheme
NOAEL	No observed adverse effect level
NOEL	No observable effect level
NOHSC	National Occupational Health & Safety Commission
OCM	Office of Complementary Medicines
OCS	Office of Chemical Safety (formerly Office of Chemical Safety and Environmental Health [OCSEH])

Abbreviation	Name
OCSEH	Office of Chemical Safety and Environmental Health (now Office of Chemical Safety [OCS])
ODA	Office of Devices Authorisation
OMA	Office of Medicines Authorisation (formerly Office of Prescription and Non-prescription Medicines)
OOS	Out of session
OTC	Over-the-counter
PACIA	Plastics and Chemicals Industries Association
PAR	Prescription animal remedy
PBAC	Pharmaceutical Benefits Advisory Committee
PEC	Priority existing chemical
PGA	Pharmaceutical Guild of Australia
PHARM	Pharmaceutical Health and Rational Use of Medicines
PI	Product Information
PIC	Poisons Information Centre
PSA	Pharmaceutical Society of Australia
QCPP	Quality Care Pharmacy Program
QUM	Quality Use of Medicines
RFI	Restricted flow insert
SCCNFP	Scientific Committee on Cosmetic and Non-Food Products
SCCP	Scientific Committee on Consumer Products
STANZHA	States and Territories and New Zealand Health Authorities

Abbreviation	Name
SUSDP	Standard for the Uniform Scheduling of Drugs and Poisons
SUSMP	Standard for the Uniform Scheduling of Medicines and Poisons
SVT	First aid for the solvent prevails
TCM	Traditional Chinese medicine
TGA	Therapeutic Goods Administration
TGC	Therapeutic Goods Committee
TGO	Therapeutic Goods Order
TTHWP	Trans-Tasman Harmonisation Working Party
TTMRA	Trans-Tasman Mutual Recognition Agreement
WHO	World Health Organization
WP	Working party
WS	Warning statement

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Part A - Final decisions on matters referred to an expert advisory committee

1. Scheduling proposals referred to the July/August 2015 and March 2016 meeting of the Advisory Committee on Medicines Scheduling (ACMS# 15 and ACMS#17)

Summary of delegate's final decisions

Substance	Final decision
Codeine	<p>Schedule 8 - Amend Entry</p> <p>CODEINE except when included in Schedule 4.</p> <p>Schedule 4 - Amend Entry</p> <p>CODEINE when compounded with one or more other therapeutically active substances:</p> <ul style="list-style-type: none"> a) in divided preparations containing 30 mg or less of codeine per dosage unit; or b) in undivided preparations containing 1 per cent or less of codeine. <p>Schedule 3 - Delete Entry</p> <p>Schedule 2 - Delete Entry</p> <p>Implementation date: 1 February 2018.</p>

Codeine

Delegate's scheduling proposal

The medicines scheduling delegate (the delegate) referred the following scheduling proposal for consideration by the Advisory Committee on Medicines Scheduling (ACMS) at the July/August 2015 meeting:

- Proposal to delete the Schedule 3 entry for codeine, and re-schedule all current Schedule 3 codeine to Schedule 4 due to issues including morbidity, toxicity and dependence.
- Consideration could include whether all current Schedule 3 preparations should be re-scheduled to Schedule 4, or whether any re-scheduling to Schedule 4 should only apply to combination analgesic products containing codeine.
- Consideration could include whether the Schedule 2 entry for codeine should also be amended.

Substance summary

Codeine or its salts, especially the phosphate, are given orally in the form of linctuses for the relief of cough, and as tablets for the relief of mild to moderate pain, often with a non-opioid analgesic such as aspirin, ibuprofen, or paracetamol. The phosphate is also given by intramuscular injection, in doses

similar to those used orally, for the relief of pain; the intravenous, subcutaneous, and rectal routes have also been used.

For the relief of pain codeine phosphate may be given in doses of 30 to 60 mg every 4 hours to a usual maximum of 240 mg daily.

To allay non-productive cough codeine phosphate may be given in doses of 15 to 30 mg three or four times daily.

Codeine phosphate is also used as tablets or in mixtures for the symptomatic relief of acute diarrhoea in doses of 15 to 60 mg given three to four times daily.

Other codeine salts used include the hydrochloride, sulfate, camsilate, and hydrobromide. Codeine polistirex (a codeine and sulfonate diethenylbenzene-ethenylbenzene copolymer complex) is used in modified-release preparation.

Current scheduling status

CODEINE is currently listed in Schedules 8, 4, 3 and 2 as follows:

Schedule 8

CODEINE **except** when included in Schedule 2, 3 or 4.

Schedule 4

CODEINE when compounded with one or more other therapeutically active substances:

- a) in divided preparations containing 30 mg or less of codeine per dosage unit; or
- b) in undivided preparations containing 1 per cent or less of codeine,
except when included in Schedule 2 or 3.

Schedule 3

CODEINE when:

- a) not combined with any other opiate substance;
- b) compounded with one or more other therapeutically active substances, of which not more than one is an analgesic substance:
 - i) in divided preparations containing 12 mg or less of codeine per dosage unit; or
 - ii) in undivided preparations containing 0.25 per cent or less of codeine;
- c) labelled with a recommended daily dose not exceeding 100 mg of codeine; and
- d) in packs containing not more than 5 days' of supply at the maximum dose recommended on the label,

except when included in Schedule 2.

Schedule 2

CODEINE in preparations for the treatment of coughs and colds when:

- a) not combined with any other opiate substance;
- b) compounded with one or more other therapeutically active substances, of which at least one is phenylephrine and not more than one is an analgesic substance:
 - i) in divided preparations containing 10 mg or less of codeine per dosage unit; or

- ii) in undivided preparations containing 0.25 per cent or less of codeine;
- c) labelled with a recommended daily dose not exceeding 60 mg of codeine; and
- d) in packs containing not more than 6 days' supply at the maximum dose recommended on the label.

Scheduling history

National Drugs and Poisons Schedule Committee: June 2008

The NDPSC agreed to form a Codeine Working Party to review the availability of all OTC combination analgesics containing codeine. This followed concerns raised at previous NDPSC meetings (June 2005, October 2005 and June 2007) of abuse of codeine from a codeine-ibuprofen combination analgesic product (by cutting a bi-layer tablet in half to access the codeine, or separating codeine from the product by simple dissolution in water).

National Drugs and Poisons Schedule Committee: February 2009

The NDPSC considered a report from the Codeine Working Party, together with findings from an evaluation of OTC codeine-containing analgesics, and agreed to foreshadow a proposal to re-schedule all OTC codeine to Schedule 3 (with suggestions to limit the maximum daily dose to 100 mg codeine, limit the maximum pack size to 5 days' supply, restrict divided preparations to 12 mg of codeine per dosage unit and restrict undivided preparations to 0.25% codeine). In addition, a member proposed to maintain a Schedule 2 entry for codeine + phenylephrine, if all other OTC codeine was included in Schedule 3. The NDPSC foreshadowed a proposal to include all OTC codeine (and not just analgesics) to encourage public comment.

National Drugs and Poisons Schedule Committee: June 2009

The NDPSC agreed that the current scheduling of OTC codeine combinations for coughs and colds remained appropriate (but with a pack size limit of 5 days' supply), and that all OTC combination analgesics containing codeine should be re-scheduled from Schedule 2 to Schedule 3 (with the maximum daily dose limited to 100 mg, the duration of treatment limited to 5 days, divided preparations restricted to 12 mg of codeine per dosage unit and undivided preparations restricted to 0.25% codeine) and that Schedule 3 codeine should not be included in Appendix H. The implementation date was to be 1 May 2010.

National Drugs and Poisons Schedule Committee: October 2009

Following consideration of June 2009 post-meeting submissions and further discussion, the NDPSC agreed to amend the pack size limit for Schedule 2 cough and cold preparations to a maximum of 6 days' supply. The NDPSC also confirmed the June 2009 resolution regarding the Schedule 3 entry for all OTC combination analgesics containing codeine. The implementation date remained as 1 May 2010. An editorial amendment was made to the Schedule 3 entry at the February 2010 NDPSC meeting.

Delegates Final Decision: September 2011 - Advisory Committee on Medicines Scheduling: July 2011

The scheduling of codeine was considered as a part of the cold and cough preparation review, which looked at the use of these preparations for the treatment of children aged 2 to 12 years. Taking into consideration the committee's recommendation, the delegate decided that there should be no change to the scheduling of codeine in cold and cough preparations.

Pre-meeting (July/August 2015) public submissions

The TGA received 60 public submissions prior to the July/August 2015 ACMS meeting. Twenty-nine (29) submissions supported the proposal, twenty-five (25) submissions opposed the proposal and six (6) submissions did not state whether they supported the proposal or not.

The main points in support were:

- Reduce the potential for harm – particularly in paracetamol/ibuprofen products (complications due to overdose);
- Reduce the potential for abuse;
- Prevent ease of access to an opioid, meaning patients seek other low risk medications/further medical advice;
- Numerous studies/clinical evidence shows misuse/abuse and significant risk to public health;
- Not currently possible for pharmacists to monitor and control safe use of low dose codeine.
- Low dose codeine not efficacious.

The main points opposed were:

- Increase in bookings to see GP – cost prohibitive.
- Unable to see GP on demand – potential increase at hospital emergency departments.
- Issue for those in rural areas being able to access medication if it becomes Schedule 4.
- Increase price of medication containing codeine.
- Prefer a national, real time monitoring system.
- Lower quality of life for those with chronic pain.
- Research suggests codeine is affective for acute pain which meets the claim of short term relief.
- In 2010, the NDPSC found the Schedule 2 entry for codeine appropriate.

Summary of ACMS advice to the delegate – July/August 2015

The ACMS advised the deletion of the current Schedule 2 and 3 entries for codeine and amendment of the current Schedule 4 and 8 entries to reflect this change.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the delegate included: a) the risks and benefits of the use of the substance; b) the purposes for which a substance is to be used and the extent of use of a substance; c) the toxicity of the substance; d) the dosage, formulation, labelling, packaging and presentation of a substance; e) the potential for abuse of a substance; and f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the advice comprised the following:

- Risks of medication misadventure through polymorphic metabolism, deliberate misuse/abuse combined with the relative lack of efficacy compared to safer products.
- OTC intended for management of acute self-limiting pain, however, there is inappropriate use for chronic pain.
- Purpose is questioned since benefit is low.
- OTC sales data are incomplete.
- Codeine shares the properties of other opioid analgesics and is potentially capable of producing dependence and, in overdose, respiratory depression and reduced level of consciousness.
- Changing the labelling and decreasing the pack size will not adequately address the problem of misuse and dependence.

- Increasing amount of evidence for harm from abuse.
- Misuse of OTC codeine products including deaths resulting from hepatic injury, gastrointestinal perforations, hypokalaemia and respiratory depression.
- Genetic influence on codeine's action complicates risk and benefit decisions, and leads to questions regarding the role of codeine in clinical practice.
- To adequately determine the clinical needs an appropriately qualified practitioner to assess risk.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal
- Public submissions received
- The evaluation report (not publicly available)
- ACMS advice;
- Section 52E of the *Therapeutic Goods Act 1989*;
- [Scheduling Policy Framework](#) (SPF 2015)
- Other relevant information.

Delegate's interim decision – 1 October 2015

The delegate's [interim decision](#) was to delete the current Schedule 2 and 3 entries for codeine and amend the current Schedule 4 and 8 entries to reflect this change.

The proposed implementation date was 1 June 2016. This date will allow time for education of consumers, pharmacists and medical practitioners regarding pain management and alternative analgesia available. It is noted that comments made during the interim decision consultation period will be taken into consideration in any final decision on implementation date.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the delegate included: a) the risks and benefits of the use of the substance; b) the purposes for which a substance is to be used and the extent of use of a substance; c) the toxicity of the substance; d) the dosage, formulation, labelling, packaging and presentation of a substance; e) the potential for abuse of a substance; and f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the decision comprised the following:

- Risks of medication misadventure through polymorphic metabolism, deliberate misuse/abuse combined with the relative lack of efficacy compared to safer products.
- The risk/benefit profile for codeine in doses of 8 mg – 15 mg per dosing unit in combination with other analgesics is unfavourable. There is also a lack of evidence of any benefit of codeine over placebo in the relief of cough, making the risk/benefit profile for this indication unfavourable also. Codeine demonstrates marked variability in its transformation to morphine in different individuals, with the potential for very severe toxicity in ultra-rapid metabolisers.
- OTC intended for management of acute self-limiting pain, however, there is inappropriate use for chronic pain
- Purpose is questioned since benefit is low.

- The purposes for which codeine is intended to be used are for Schedule 2 products for the “treatment of coughs and colds” and for Schedule 3 products for the “temporary relief of strong pain and discomfort associated with a number of different medical conditions.”
- Codeine shares the properties of other opioid analgesics and is potentially capable of producing dependence and, in overdose, respiratory depression and reduced level of consciousness.
- Codeine, as a prodrug, causes its direct toxicity primarily through its biotransformation into morphine. The metabolic polymorphism discussed above leads to major variability within the population in terms of the extent and rapidity of this conversion to morphine. Ultra-rapid metabolisers, who have an accelerated rate and higher extent of conversion, are exposed to morphine concentrations that are many-fold higher than those reached in poor metabolisers. This variant is found in up to 10% of Caucasians, and higher proportions of populations of North African, Oceanic and Middle Eastern origin. Very few individuals are aware of their own metaboliser status, and it would thus be very difficult to protect ultra-rapid metabolisers by way of warnings. High concentrations of morphine in the plasma can lead to serious sedation and respiratory depression, and potentially to death.
- The potential for severe adverse effects at “usual” doses in ultra-rapid metabolisers is such that codeine appears to be an unsuitable candidate for OTC availability, with either Schedule 2 or Schedule 3 scheduling. This conclusion applies equally well to the products intended for treating coughs and colds, and those intended for the treatment of pain.
- Changing the labelling and decreasing the pack size will not adequately address the problem of misuse and dependence.
- Current labelling and packaging include insufficient warnings, and that there should be clear warning labels stating the risks of addiction and dependence, the risks of harm from the paracetamol or ibuprofen, and the risk of death. Access to codeine in Australia is inconsistent, in that the total amount of codeine available in a pack of Panadeine Extra® (40 tablets containing 15 mg each) is the same quantity as that available in a pack of codeine phosphate (20 tablets containing 30 mg each), which is included in Schedule 8 and recognised to have potential for abuse or addiction.
- Some sources, including the Panadeine® product information, suggest or imply that before taking codeine a person should know their CYP4502D6 status, and this in turn means that no person should be able to self-administer codeine that has been obtained OTC. It is argued that the benefit of medical supervision that would be obtained with a re-scheduling to Schedule 4 includes the ability of the prescriber to discuss with the patient the risks of excessive opiate effect, and provide advice about actions to take if this occurs. This argument applies equally well to products currently available in both Schedule 2 and Schedule 3.
- Increasing amount of evidence for harm from abuse
- Codeine is emerging as an increasingly commonly used drug of abuse internationally and in Australia. Data from the national opioid pharmacotherapy statistics in 2013 showed that codeine was the opioid drug of dependence for 1,038 clients receiving opioid substitution pharmacotherapy. The actual number was likely to be higher than this because of missing data. Another recently published study of 902 people who inject illicit drugs found that about one third had misused OTC codeine during the preceding six months.
- Misuse of OTC codeine products including deaths resulting from hepatic injury, gastrointestinal perforations, hypokalaemia and respiratory depression.
- Genetic influence on codeine’s action complicates risk and benefit decisions, and leads to questions regarding the role of codeine in clinical practice.

- An appropriately qualified practitioner needs to assess the risk before making the decision that codeine will be used.
- A recently released combination of two non-opioid analgesics (ibuprofen plus paracetamol) appears to be more effective than the codeine-containing analgesics (CCAs), with a number needed to treat (NNT) of 1.5. This combination would fill any gap left by the unavailability of CCAs over the counter, giving consumers access to a more effective analgesic without requiring a prescription and without the risks of the marked variability in pharmacokinetics or abuse potential that are associated with codeine.
- Potential unintended consequences and disadvantages of a decision to re-schedule CCAs to Schedule 4 need to be considered. One would be a reduction in the availability of analgesics for moderate to severe pain, although the evidence suggests that the addition of codeine adds only a minor additional analgesic effect over and above that of the ibuprofen or paracetamol in the combination product. The recent introduction of a paracetamol/ibuprofen combination may fill this niche more effectively than the CCAs have done, without the disadvantages of codeine. A reduction in the availability of a drug known as an antitussive agent, despite the lack of evidence available to support this, would also occur, but significant actual disadvantages are unlikely to occur. No other potential disadvantages to the community are readily identified.
- The major impact on public health of the proposed amendment would be a reduction in the risk to those individuals who, unbeknownst to themselves, have a rapid metaboliser phenotype of CYP4502D6 and are therefore at significant risk of excessive morphine concentrations following ingestion of usually recommended doses of codeine for any indication.
- Codeine is an opioid which must be metabolised by CYP2D6 to its active metabolite, morphine, for its analgesic effect. Different genetic groups show significant variations in metabolism of codeine. Of particular concern are “ultra-rapid” metabolisers, where the accelerated metabolism of codeine to morphine results in an increased risk of morphine toxicity and adverse events.
- The function of the enzyme carrying out that transformation is genetically controlled and highly variable between individuals because of the existence of multiple forms of the relevant gene; the difference in exposure to morphine following a standard dose of codeine can be up to 45-fold higher in ultra-rapid metabolisers compared with poor metabolisers.
- Ultra-rapid metabolisers are therefore at risk of morphine overdose, with potentially fatal consequences, following “usual” doses of codeine.
- Individuals rarely know their metaboliser status, and testing is not readily available.
- All other opioids are at least Schedule 4.
- The approved indication for the Schedule 3 codeine products is for the “temporary relief of strong pain and discomfort associated with a number of different medical conditions”. It is noted that there is significant use of Schedule 3 codeine products for longer term relief of chronic pain and a number of public submissions by consumers have noted that this is how they use it.
- The management of chronic pain would be better achieved by having medical practitioner input with appropriate advice on non-medicine treatments and appropriate medicinal treatment for the chronic pain, rather than self-treating with long term CCAs.
- The presence of codeine in OTC combination analgesics contributes to severe adverse outcomes associated with overdosage of the paracetamol or ibuprofen component, because the development of dependence on codeine leads to overuse of the combination. Anecdotally some abusers of OTC codeine products are consuming 30 to 70 tablets/capsules per day of the CCAs.

- In Europe codeine is not an OTC medicine (i.e. is a prescription only medicine at least) in 13 countries being Austria, Belgium, Croatia, the Czech Republic, Finland, Germany, Greece, Italy, Luxembourg, Portugal, Slovakia, Spain and Sweden.
- Codeine is also a Prescription Medicine in the USA, Hong Kong, Iceland, India, Japan, the Maldives, Romania, Russia, and the United Arab Emirates.
- There is no evidence that low dose codeine combination analgesics provide any additional analgesia over optimal dosing of paracetamol, aspirin or ibuprofen.
- In February 2009 NDPSC decided that:
 - Based on the currently available information from Australia, the evaluator concluded that there was potential for significant harm from OTC combination analgesics containing codeine (CACC) and even death, and it was not possible to accurately estimate the associated risk, although the following were reasonably assumed:
 - the proportion of all users that abuse OTC CACC is low.
 - the risk of harm among all users of OTC CACC is low.
 - the risk of harm among abusers of OTC CACC is high.
 - Central consideration in allowing OTC supply of codeine combinations was that the benefits outweighed the risks and therefore asserted that the insufficient data on efficacy may mean that the benefits no longer outweighed the risks. While agreeing that efficacy remains important to any case justifying OTC supply of codeine, the Committee noted the Codeine Working Party advice that there was not sufficient information available to the Members at this time to resolve the question of codeine efficacy at $\leq 30\text{mg}$.
- The NDPSC re-scheduled OTC codeine-containing combination analgesics to Schedule 3 in 2010, with the aim of increasing surveillance of codeine medication usage by pharmacists to ensure quality use of medicines, as it was recognised that there is a potential for harm if used inappropriately. The Schedule 3 entry included limits on the maximum daily dose and pack size, and restrictions on the quantities of codeine in divided (and undivided) preparations.
- Re-scheduling to Schedule 3 has not achieved the required reduction in harm to affected individuals. Since the re-scheduling of codeine from 2010 there hasn't been the reduction in risk that might have occurred.
- Codeine is increasingly a drug of abuse in Australia, and some individuals have developed severe adverse effects from the high doses of paracetamol and ibuprofen that accompany the use of large numbers of tablets in a codeine-dependent person. A pack of CCA available under Schedule 3 contains the same total dose of codeine as a pack of codeine available only under Schedule 8.
- Since OTC CCAs were re-scheduled to Schedule 3 in 2010, industry and pharmacy organisations have not been able to fully address concerns regarding codeine dependence.
- Codeine in the unit doses present in OTC products provides very little additional analgesic effect over and above that provided by the accompanying drug in the combination. It is also noted that there are new combination products with paracetamol and ibuprofen which are more efficacious than low dose CCAs.
- CCAs do not meet the criteria required for Schedule 3, particularly that they are not “substantially safe in use but require professional advice or counselling by a pharmacist”, and cannot be said to “not require close medical management.” Rather, it would be more appropriate for CCAs to be prescribed so that consumers can be warned about the potential risks and adverse effects can be more closely monitored.

- Concurrently the Advisory Committee on the Safety of Medicines (ACSOM) has recently considered the risks of codeine use in children, and codeine use in persons who are ultra-rapid metabolisers of codeine. Excerpts from the meeting statement from ACSOM 28 state:
 - ACSOM agreed that the risks of respiratory depression and possible death in the context of ultra-rapid metabolism associated with codeine outweigh the benefits of codeine for all indications in children under the age of 12 years.
 - As it is not possible to identify in advance the subgroup of children who are at increased risk of toxicity (e.g. through being an ultra-rapid metaboliser), the committee's advice relates to the risks for all children under the age of 12.
 - ACSOM also agreed that the risks associated with codeine outweigh the benefits of codeine for analgesia in children under the age of 18 years who have undergone tonsillectomy or adenoidectomy for sleep apnoea, for the same reasons as for children under the age of 12 years, as above. This is consistent with the United States Food and Drug Administration (US FDA) position that codeine use after adenotonsillectomy is contraindicated. The committee also noted that there have been a number of adverse event cases observed that are not clearly explained but may relate to sleep apnoea.
 - ACSOM also agreed that the risks to breastfed infants associated with ultra-rapid metabolism of codeine by their mothers outweigh the benefits of codeine for any indication by breastfeeding mothers.
 - As a mother's knowledge of her own experience with codeine (and indirectly, metaboliser status) does not predict the infant's response, breastfeeding should be a contraindication for codeine.
 - ACSOM noted the following contraindications which were recommended in the TGA's safety review to be included in the codeine Product Information - use in children under the age of 12 for any reason; use in people of any age known to be ultra-rapid metabolisers; use in children younger than 18 years of age who have undergone adenotonsillectomy for obstructive sleep apnoea; and use by breastfeeding mothers.
 - The committee noted that the OTC availability of codeine-containing medicines supported a general perception in the community that codeine is safe. Therefore, communication of the contraindications by label changes alone was not likely to achieve the desired outcome of risk reduction. Additional measures including education and the possible re-scheduling of codeine-containing medicines also needed to be considered. The committee supported consistency and harmonisation in labelling across all codeine-containing medicines, especially regarding advice to breastfeeding mothers.
 - Activities to reduce the use of codeine cannot occur in isolation from consideration of alternative pain management strategies. Pain management strategies that do not include codeine needed to be carefully defined and their implementation carefully considered. For example, direct administration of morphine could be considered as an alternative and the issues of analgesic polypharmacy and escalation up the 'pain ladder' also require consideration in the development of any pain management strategies that omit codeine.
- It should be noted that the following factors for a Schedule 3 medicine in the Scheduling Policy Framework (SPF) are not met:
 - Codeine does not meet the SPF scheduling factors for inclusion in Schedule 3. In particular, criterion 2 is not satisfied – i.e. "The use of the medicine at established therapeutic dosages is not expected to produce dependency. Where there is a risk of misuse, abuse or illicit use identified, the risk can be minimised through monitoring by a pharmacist."

- Codeine containing analgesics should now be included in Schedule 4 because codeine meets the factors in the Scheduling Policy Framework required for Schedule 4, and particularly the following factors:
 - In particular, use at established therapeutic dosage levels may produce dependency (criterion 3).
 - Codeine also meets SPF Schedule 4 criterion 1 (diagnosis, management or monitoring of chronic pain conditions requires medical or dental intervention before use and, although OTC codeine products are intended for short-term use, many consumers use them for chronic pain without medical intervention) and criterion 7 (its use has contributed to, or is likely to contribute to, communal harm).
- Other issues:
 - Codeine alone is ineffective as an analgesic in doses <60 mg (number needed to treat (NNT) to achieve one patient obtaining a 50% pain relief response is 12).
 - Combination analgesics containing codeine plus paracetamol or codeine plus ibuprofen show minimal analgesic benefit compared to the simple analgesics (paracetamol or ibuprofen) alone.
 - In up to 10% of the population (poor metabolisers), it is ineffective but can still cause harmful effects.
 - In up to 4-10% of the population (ultra-rapid metabolisers), it can cause life-threatening toxicity
 - If codeine is to remain in use as an analgesic, then the patient's metaboliser status needs to be ascertained prior to prescription or dispensing; however this is not practical
- It was suggested that there were options to try and minimise the abuse related to CCAs by either expanding Project Stop or real-time monitoring of CCA use.
- Project Stop relates to the monitoring of sales of pseudoephedrine and is a police related activity to prevent diversion of pseudoephedrine as a precursor for illegal methamphetamine manufacture.
- The Project Stop website states its role as:
 - Project STOP is an initiative of the Pharmacy Guild of Australia to address the problem of precursor diversion through Australian Community Pharmacies. The most common precursor sourced through the community pharmacy channel is pseudoephedrine which can be used in the illegal manufacture of methamphetamines.
 - Project STOP is an online tool which provides decision support to pharmacists who need to establish whether requests for products containing pseudoephedrine are legitimate. It also assists pharmacists in meeting their state regulatory recording requirements where they exist.
- Despite the risks of abuse identified when CCAs were up-scheduled in 2010 there has been no initiative to include CCAs into Project Stop prior to the application to up-schedule codeine to Schedule 4.
- Real-time monitoring of medicines is not currently in place in any jurisdiction other than Tasmania where it is restricted to Schedule 8 medicines. There is no formal implementation of real-time monitoring across Australia and whether its implementation would it is unsure whether it would ever come down to Schedule 3 medicines.
- In both Project Stop and real-time monitoring the onus on prevention of supplying CCAs would fall on pharmacists when dealing directly with consumers.
- Another option considered was decreasing the pack size of CCAs from the current limit of five days with a recommended daily dose not exceeding 100 mg of codeine to a pack size limit of three days'

supply as has occurred in the United Kingdom. However decreasing the available pack sizes of OTC codeine products might help reduce the incidence of new users becoming dependent on codeine, but is unlikely to be effective for those who are already dependent.

- A number of the pre-meeting submissions considered it unduly burdensome to require consumers to obtain a prescription for supply of codeine combination analgesics. However, pharmacists can recommend alternate pain relief products, such as a paracetamol-ibuprofen combination, or consumers could obtain a prescription (to have on hand when needed for acute pain) if they visit a general practitioner for any reason.
- To be consistent with the interim decision to remove the Schedule 3 entry for codeine and for the issues around codeine in the 12 and under population as recommended by ACSOM the Schedule 2 entry should also be deleted.
- There are alternative OTC analgesic products for short-term pain relief.
- The ACMS recommendation and reasons.

Schedule Entry – Interim decision

Schedule 8 – Amendment

CODEINE **except** when included in Schedule 2, ~~3 or~~ 4.

Schedule 4 – Amendment

CODEINE when compounded with one or more other therapeutically active substances:

- a) in divided preparations containing 30 mg or less of codeine per dosage unit; or
- b) in undivided preparations containing 1 per cent or less of codeine,
except when included in Schedule 2 or 3.

Schedule 3 – Delete Entry

~~CODEINE when:~~

- ~~a) not combined with any other opiate substance;~~
- ~~b) compounded with one or more other therapeutically active substances, of which not more than one is an analgesic substance:~~
 - ~~i) in divided preparations containing 12 mg or less of codeine per dosage unit; or~~
 - ~~ii) in undivided preparations containing 0.25 per cent or less of codeine;~~
- ~~c) labelled with a recommended daily dose not exceeding 100 mg of codeine; and~~
- ~~d) in packs containing not more than 5 days' of supply at the maximum dose recommended on the label,~~

~~**except when included in Schedule 2.**~~

Schedule 2 – Delete Entry

~~CODEINE in preparations for the treatment of coughs and colds when:~~

- ~~a) not combined with any other opiate substance;~~
- ~~b) compounded with one or more other therapeutically active substances, of which at least one is phenylephrine and not more than one is an analgesic substance;~~

- ~~i) in divided preparations containing 10 mg or less of codeine per dosage unit; or~~
- ~~ii) in undivided preparations containing 0.25 per cent or less of codeine;~~
- ~~e) labelled with a recommended daily dose not exceeding 60 mg of codeine; and~~
- ~~d) in packs containing not more than 6 days' supply at the maximum dose recommended on the label.~~

Additional information considered by the delegate after the interim decision

TGA Safety Reviews

The TGA has undertaken or commissioned three separate reviews over the past seven years that have included the efficacy and/or safety of codeine. All reviews have been published on the TGA website.

Safety and efficacy of registered OTC cough and cold medicines for children aged 2-12 years (TGA, 2012)¹

Between 2009 and 2012, the TGA carried out a comprehensive review of the medical literature relating to the safety and efficacy of OTC medicines containing various substances for the symptomatic treatment of cough and cold in children aged less than 12 years. Codeine was considered as part of this review due to its purported antitussive activity.

The TGA concluded that there was a lack of evidence to support the efficacy of OTC cough and cold medicines in children under 12 years of age, although there was no immediate safety risk associated with their use in adults. Further, the potential risks of adverse reactions in children under 12 years of age were high relative to the limited benefits. This conclusion was supported by adverse reactions recorded in children under the age of 12, which included deaths associated with respiratory depression.

Safety review on codeine use in children and ultra-rapid metabolisers (TGA, October 2015)²

The TGA's second safety review of codeine use considered the use of codeine-containing products in children and breastfeeding mothers in the context of genetically determined ultra-rapid metabolism of codeine to morphine. Children who metabolise codeine to morphine ultra-rapidly are at a higher risk of accidental morphine overdose, which can lead to respiratory compromise and death due to their immature airway anatomy. Codeine that has been metabolised to morphine can also be ingested by infants through breast milk, causing risk of respiratory depression to infants of ultra-rapid metaboliser mothers who take codeine.

Internationally, deaths have been reported in children with ultra-rapid metabolism who were given codeine, as well as in breast-fed infants of mothers who are ultra-rapid metabolisers of codeine. The final recommendations of the safety review (amongst others) included the contraindication of the use of codeine in children younger than 12 years of age for any indication, and in children 12-18 years post adenotonsillectomy.

The review recommendations were supported by the TGA's Advisory Committee on the Safety of Medicines at their meeting on 10 July 2015, noting that the OTC availability of codeine containing medicines supported a general community perception that codeine is safe and that there would need to be consumer education and possible up-scheduling, to achieve the desired outcome of risk reduction.

¹ [OTC cough and cold medicines for children - Final outcomes of TGA review](#)

² [Safety review: Codeine use in children and ultra-rapid metabolisers](#)

Investigating the efficacy and safety of OTC codeine containing combination analgesics for pain and codeine based antitussives (March 2016; George Institute review)³

The aim of this systematic review was to determine the efficacy and safety of OTC codeine combination analgesics for the treatment of any pain condition, or as an antitussive. Three trials compared combination codeine medicines with appropriate single ingredient comparators, two of which reported no statistically significant difference in analgesia, with one trial reporting a marked increase in analgesia attributable to codeine activity.

Public submissions on the interim decision – 15 October 2015

After the interim decision was published on 1 October 2015, One hundred and twenty-seven (127) public submissions were received prior to the deadline of 15 October 2015.

Fourteen (14) submissions supported the decision, with reasons being:

- Have seen the impact and consequences that OTC codeine dependence has on people;
- Adding low dose codeine to non-opioid analgesics provides little additional analgesic benefit;
- Dependence on OTC codeine analgesics is a significant concern and can cause serious, sometimes life-threatening adverse effects due to the combination with paracetamol or NSAIDs;
- Evidence now demonstrates that under current arrangements (Schedule 3 Pharmacist Medicine) there is a substantial level of harm from the easy and widespread availability of these opioid medicines.

One hundred and thirteen (113) submissions opposed the delegate's interim decision. Some of the main points are provided below:

- A large majority of people who use codeine containing products do so safely and effectively;
- Re-scheduling will make pain relief medicines more expensive and more difficult to obtain;
- Cost to Medicare/Pharmaceutical Benefits Scheme;
- Issues with access to/cost associated with seeing GPs;
- Restriction of codeine to prescription only will not mitigate the risk of misuse or abuse;
- Pharmacists are accessible and suitably qualified to implement an effective risk mitigation strategy to address concerns of misuse or abuse;
- Consideration should be given to consumers who are unable to take paracetamol/ibuprofen alternatives;
- There is no evidence to suggest cough and flu preparations are subject to abuse/misuse;
- There should be the implementation of a national system of real time recording and reporting of the prescribing and dispensing of particular medicines.

The above de-identified [submissions](#) (60 plus 127) are available to the public on the TGA website.

Public submissions - additional consultation period

In order to give due consideration to the submissions received in the interim decision public consultation period and to seek further advice from the ACMS at its March 2016 meeting, the

³ CA Shaheed, CG Maher and A McLachlan. 'Investigating the efficacy and safety of over-the-counter codeine containing combination analgesics for pain and codeine based antitussives.' <https://www.tga.gov.au/alert/review-efficacy-and-safety-over-counter-codeine-combination-medicines>. 21 March 2016. (this report is also referred to as the 'George Institute Report')

medicines scheduling delegate on 18 November 2015 deferred a [final decision](#) on the proposed codeine re-scheduling.

The TGA then sought further advice and public comment on several options for codeine re-scheduling via an [additional consultation period](#) that was open from 10 December 2015 through 29 January 2016. The scheduling options included:

Schedule 2 (cough and cold medicine preparations):

- a. Proposal to amend the Schedule 2 entry to reduce the pack size to not more than 3 days' supply and include a label warning that codeine can cause addiction, OR
- b. Proposal to up-schedule the Schedule 2 entry to Schedule 3 and reduce the pack size to not more than 3 days' supply and include a label warning that codeine can cause addiction, OR
- c. Retain the interim decision to up-schedule to Schedule 4.

Schedule 3 (including, but not limited to codeine-containing analgesics):

- a. Proposal to amend the Schedule 3 entry to reduce the pack size to not more than 3 days' supply and include a label warning that codeine can cause addiction, OR
- b. Retain the interim decision to up-schedule to Schedule 4.

The medicines scheduling delegate outlined a provision of the re-scheduling options listed above, that they were not precluded from considering alternative scheduling options.

The TGA received 49 public submissions from this additional consultation. Roughly equal numbers of submissions were received either for or against the interim decision. Many submissions were copies of previous submissions. These were included in the overall information considered at the March 2016 ACMS meeting. Redacted versions of these submissions will be included on the TGA website at [Public submissions on scheduling matters](#) in due course.

Of these submissions, the stated positions on the proposed scheduling options (for Schedule 2 or Schedule 3) were as follows:

Schedule 2 (a): Six submissions supported and fifteen submissions opposed.

Schedule 2 (b): Four submissions supported and fifteen submissions opposed and one submission was opposed, but willing to accept.

Schedule 2 (c): One submission supported and no submission was opposed.

Schedule 3 (a): Fourteen submissions supported and fourteen submissions opposed.

Schedule 3 (b): One submission supported and three submissions opposed.

ACMS meeting advice – March 2016

The ACMS advice to the delegate in March 2016 was consistent with the previous advice provided in July/August 2015, that the interim decision:

- to up-schedule the current Schedule 3 entries for codeine to Schedule 4 be retained, with an implementation date of 1 February 2017.
- to up-schedule the current Schedule 2 entries for codeine to Schedule 4 be retained, with an implementation date of 1 October 2017.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the Committee included: (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the

dosage, formulation, labelling, packaging and presentation of a substance; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The reasons for the advice were:

- The risks of medication misadventure through polymorphic metabolism, deliberate misuse/abuse combined with the relative lack of efficacy compared to safer products.
- Opioid analgesic capable of producing dependence and, in overdose, respiratory depression and death.
- Moderate potential for abuse of the substance.
- Harms detailed to the committee following the misuse of OTC codeine products including deaths resulting from hepatic injury, gastrointestinal perforations, hypokalaemia and respiratory depression.
- Members considered the need to introduce controls on access to codeine analgesic products as soon as possible as these products are being abused now with harm to individuals now. Members also considered the need for access to codeine-containing cold and flu medications (with lower codeine content) during the flu season. While it was noted there is much less abuse/addiction risk of those products, the codeine in these preparations is present as an analgesic and thus such products should be scheduled consistent with other analgesic codeine-containing products.

Regulation Impact Statement (RIS) and KPMG modelling report

Given the sensitivity of the interim decision and the implications for both the public and industry, a Regulation Impact Statement (RIS) (available on TGA website) has been completed that reviews the significant public health concerns with use of codeine, the scheduling options available, and the regulatory impacts associated with the scheduling options.

The RIS is further supported by an independent KPMG report that modelled the economic, social and regulatory impacts and net benefit to society for all the scheduling options. This modelling found that a net benefit to society could be achieved only when all OTC codeine products are up-scheduled to Schedule 4.

The key finding of the KPMG modelling is that Scenario 4, which aligns with the interim decision, is the only scenario resulting in a net economic benefit to society, estimated to be \$5.2 billion over 10 years (Table 1).

Table 1: Summary of costs and benefits for regulatory scenarios from 2017-2026 (\$ million)

Element	Scenario 2	Scenario 3	Scenario 4
	Reduce pack size and include warning label for Schedule 2 and Schedule 3	Schedule 2 up-scheduled to Schedule 3 and reduce pack size and include warning label for Schedule 3	Interim decision Schedule 2 and Schedule 3 up-scheduled to Schedule 4
Regulatory costs (not discounted, \$M)	(\$1.80)	(\$102.70)	(\$124.50)
Economic costs (7% discount \$M)	(\$430.57)	(\$424.36)	(\$265.90)
Economic benefits (7% discount \$M)	0	0	\$5,597.12
Net benefit (\$M)	(\$432.37)	(\$527.06)	\$5,206.72

This estimated net benefit to society for Scenario 4 (the interim decision) is a consequence of:

- prevention of accidental deaths from accidental or deliberative codeine overdose
- improved quality of life years (QALY), resulting from adoption of more effective treatment options for moderate pain
- net financial savings to consumers through lower cost OTC medicine alternatives
- prevention of adverse events related to unintentional overdose of paracetamol or ibuprofen (which is combined with codeine in many products)
- reduced dependence and reduced risk of dependency.

Importantly, even when the assumptions for costs are maximised and those for benefits are minimised, the estimated net economic benefit to society remained positive.

The health benefits estimated for Scenario 4 include gains in QALY due to the exploration of alternative, more effective treatment pathways that would not have previously been explored as well as the prevention of deaths.

The number of deaths prevented per year for Scenario 4 is conservatively estimated at five, with each death prevented valued at \$4.2 million.

A gain in QALY is estimated to be \$1,651 million (in 2017) and a gain (present value) of \$4,399 million over the period of 2017-26.

Preferred scheduling scenario as required by the RIS

Scenario 4, consisting of up-scheduling codeine in Schedules 2 and 3 to Schedule 4, is estimated to deliver significant protection to public health and safety as a result of positive changes in consumer behaviour, raise awareness of codeine dependency and increase exploration of alternative therapeutic and treatment pathways for pain management. Scenario 4 also delivers an estimated net positive benefit to society of \$5,206.72 million over a 10-year period.

MedsASSIST

The delegate considered the latest MedsASSIST data and the progress of real time monitoring program (RTM). Since the introduction of MedsASSIST in February 2016, and as of 23 November 2016, approximately 68% (3810)⁴ of pharmacies across Australia have adopted the monitoring system, with over 2.7 million OTC codeine transactions recorded. An overview of the MedsASSIST data:

- 62% (June 2016), 65% (September 2016) and 68% (November 2016)⁴ of all pharmacies are using MedsASSIST across various geographical locations (both city and rural pharmacies).⁵
- Between July and September 2016 there was a 38% increase in the number of transactions recorded per pharmacy with only a 3% increase in the number of pharmacies participating in the program. Despite the increase in the number of transactions between July-September (38%), no increase in the level of denial was recorded.
- Between 8 February and 6 September 2016 (7 months), over 2.6 million transactions were recorded. During this period:
 - Over 97% of transactions were for a Schedule 3 combination analgesic product; the remaining were for Schedule 2 cold and flu products.
 - Approximately 2% of transactions were denied.
 - Approximately 0.06% of transactions were made under duress in pharmacies (following a real or perceived threat to the safety of pharmacy staff).
 - 66% of patients requested a codeine product once, while 12% requested a codeine product more than three times
- The most recent November 2016 figures suggest the number of recorded transactions has risen to 4 million transactions since March 2016.⁶ During this period 86% of consumers who had made five or more purchases were recommended to seek medical advice with regards to managing pain, abuse and misuse.
- Where a unique ID appears more than 3 times (within 7 months), it is likely that the person is dependent on codeine and therefore at risk of serious morbidity. As of September 2016, this number is 153,037 individuals.⁵ It is also noted that this number does not include the 35% of pharmacies who were not participating in the MedsASSIST program, and that codeine-dependent consumers are likely to seek out these pharmacies to obtain a supply of codeine products.
- For the July 2016 period, there were a significant number of occasions when a consumer was denied a codeine product by a particular pharmacy, but the data also highlighted that shopping at a second pharmacy subsequently allowed the individual to access codeine. One example provided to TGA during the consultation process showed that an individual received 660 tablets over the period despite their purchasing behaviour being tracked in MedsASSIST. This brings into doubt whether MedsASSIST is actually deterring consumers with codeine-dependence problems from accessing codeine, with the data suggesting that consumers with addiction problems will change their behaviour in order to source codeine. Some GPs and specialists have expressed concerns around the effectiveness of RTM.⁷

⁴ Guild calls for codeine monitoring laws. Posted online 23 Nov 2016, Pharma In Focus 23, Issue date 21-27 Nov. <http://www.pharmainfocus.com.au/news.asp?newsid=11384>

⁵ Figures from June 2016 and September 2016 were provided to the TGA by the PGA directly.

⁶ Pharmacy points to success of codeine monitoring. Posted online 23 Nov 2016, PharmaDispatch. No. 16 <https://pharmadispatch.com/news/pharmacy-points-to-success-of-codeine-monitoring>.

⁷ Codeine monitoring 'too hard'. Posted online 11 Nov 2016, Pharma in focus, 7-13 Nov 2016.

- Of note is that the MedsASSIST sales data from March to July 2016 represents only 10% of the total sales in 2015 when compared to IMS data. This lower than expected coverage could be a consequence of the 65% coverage of pharmacies generally, the rate of uptake over these five months, or it could be the result of patients selecting to go to pharmacies that did not use MedsASSIST.
- Given the instances of ‘*pharmacy shopping*’ to source codeine,⁸ questions have been raised whether the patient use of codeine is best monitored by GPs noting their ability to better diagnose, treat and manage patients in relation to chronic pain. GPs are familiar with the treatment options available for their patient, and can refer patients to pain management specialists or clinics for greater oversight and intervention, a formal referral system that is not available for pharmacists.
- While MedsASSIST aims to provide pharmacists with a purchasing history for codeine-containing medicines, reservations were expressed relating to the limited ability of pharmacists to actively engage with ‘challenging’ patients to manage the use of codeine in OTC medicines, noting that the pharmacy environment does not usually allow for private conversations in the way that doctors’ rooms do.
- States and territories would need to agree to support MedsASSIST with mandatory reporting; such changes require uniform adoption at the jurisdiction level and changes to relevant jurisdiction legislation, which would take time.

There is no provision in the *Therapeutic Goods Act*, Regulations (Part 6, Division 3A) or the [SPF](#) that allows for a real-time monitoring (RTM) system to be mandated as part of the delegate’s scheduling decision. However, for the purpose of attempting to minimise the abuse and misuse of codeine-containing medicines, it is possible that a mandated RTM could be considered by the commonwealth, state and territory governments.

The Self Medication Association of South Africa (SMASA), the Community Pharmacy Sector and the Pharmacy Society of South Africa (PSSA), launched the real-time monitoring system known as the Codeine Care Initiative (<http://selfcare247.co.za/247-codeine-care-initiative/>) in 2013. In November 2016, an update on this initiative was provided to the TGA by SMASA. One key point that came out of this update was that the program was limited by a lack of universal adoption throughout the country. This was largely driven by operational limitations, as not all public hospitals have access to computerised record keeping.⁹ This appears to be the only RTM program associated with codeine identified globally.

If Australia was to mandate a RTM program for codeine, this would be inconsistent with Australia’s national scheduling framework, as no such RTM programs currently exist for Schedule 4 (prescription medicines) or Schedule 8 (controlled drugs) medicines despite the higher risks associated with these medicines.

International regulations for codeine

There is wide variability in the way codeine-containing medicines are regulated internationally (USFDA, Europe, Asia, United Kingdom). There is growing evidence to suggest that countries with less strict regulations around codeine availability generally see more abuse and misuse of the low-dose OTC codeine medicines.^{10, 11, 12, 13} In Australia, a recent 2016 study indicates that the use of opioid

⁸ Fitzpatrick, L 2016 ‘Is codeine too easy to get in Australia? These young addicts think so’ Vice. Posted online 5 May 2016. Accessed 25/11/2016: http://www.vice.com/en_au/read/pharmaceutical-opioid-addiction-in-australia.

⁹ Personal communication, D Bayever

¹⁰ Razzaghi, E.M., Rahimi, A., Hosseni, M., and Madani, S. 1998-1999, ‘Rapid situation assessment (RSA) of drug abuse in Iran (1998-1999)’, Prevention Department, State Welfare Organization, Ministry of Health, I.R. of Iran and United Nations International Drug Control Program

¹¹ Paul, A., ‘MDs seeing stream of opioid overdoses’, Winnipeg Free Press, Posted on 17/11/2016. Accessed on 24/11/2016: <http://www.winnipegfreepress.com/local/mds-seeing-stream-of-opioid-overdoses-401671245.html>

¹² Gornall, J, ‘Addicted to over-the-counter opium: Few realise codeine headache pills come from the same source as heroin - and evidence reveals more and more are getting hooked, Daily Mail Australia, Posted online 19/09/2016. Accessed 24/11/2016:

analgesics increased considerably over a decade (2001-2013), with Australia showing some of the most significant increases in opioid consumption for pain management behind Germany, North America, Austria and Gibraltar.¹⁴ While the reasons behind this increase were not specifically identified in the study, authors speculated that physical availability, practical accessibility and affordability could be main driving factors. This suggestion is not unreasonable given that Australia is in the minority of countries to sell codeine-containing medicines OTC.¹⁵

Additional publicly available literature

In a 2016 study by Mill and co-workers,¹⁶ the number of patients hospitalised due to serious adverse effects relating to misuse of OTC codeine-containing analgesics, and the related cost of hospitalisation, was determined for one South Australian hospital over a 5-year period. There were 99 admissions related to OTC codeine-containing analgesic (pertaining to 30 individual patients), with most relating to GI morbidities secondary to ibuprofen/codeine misuse. Patients consumed a mean of 28 codeine-containing tablets per day, over a mean duration of 606 days prior to admission. The mean cost per hospital admission was \$10,183.

Implementation timeframe

The delegate considered the feedback received from the public submissions as well as the targeted consultations with industry during the development of the RIS to understand the minimum and ideal timeframes connected with codeine re-scheduling. The delegate noted the critical importance of implementation timeframes in enabling businesses to reposition themselves with this decision. It was further noted that sponsors indicated a reasonable end-to-end implementation timeframe would, at a minimum, be between 18 to 24 months, but that this was at odds with the protection of public health and safety. The delegate was informed that:

- Pharmacies generally hold between 1 to 2 -months' worth of stock.
- Most manufacturers do not hold large amounts of produced stock but make to order, with some bulk material purchases turning over every 9 months.
- Shelf life of OTC codeine products is generally 24 months.
- The minimum timeframe to comply with an up-scheduling decision appears to be 9 to 12 months.

Delegate's considerations

The delegate considered the following in regards to this proposal:

- Scheduling proposal
- ACMS advice and other independent expert
- Public submissions received
- The evaluation report (not publicly available)

<http://www.dailymail.co.uk/femail/article-2424740/Addicted-counter-opium-Few-realise-codeine-headache-pills-come-source-heroin-evidence-reveals-more-getting-hooked.html>

¹³ A 100-a-day, over-the-counter addiction, Stuff Nation. Posted online 18/09/2016. Accessed 24/11/2016: <http://www.stuff.co.nz/stuff-nation/assignments/the-reality-of-dealing-with-addiction/10509686/A-100-a-day-over-the-counter-addiction>

¹⁴ Berterame et al, Use of and barriers to access to opioid analgesics: a worldwide, regional, and national study, Lancet 2016; 387: 1644–56

¹⁵ Fitzpatrick, L 2016 'Is codeine too easy to get in Australia? These young addicts think so' Vice. Posted online 5 May 2016. Accessed 25/11/2016: http://www.vice.com/en_au/read/pharmaceutical-opioid-addiction-in-australia.

¹⁶ Mill D, Johnson J, Cook V, Monaghan E and Hotham E (2016), Abstract presented at Australian Professional Society on Alcohol and Other Drugs (APSAD), Sydney Conference. Abstract available here https://www.eiseverywhere.com/file_uploads/a5e36f68887d8c77c1a487a94559925b_20_DeannaMill.pdf

- TGA safety reports (publicly available on TGA Website)
- Regulatory Impact Statement for Codeine and KPMG Economic modelling report
- Section 52E of the *Therapeutic Goods Act 1989*
- [Scheduling Policy Framework](#) (SPF 2015)
- Other relevant information.

Delegate's final decision

The delegate has confirmed the interim decision as no evidence has been received to alter the interim decision. The delegate's final decision is to delete the Schedule 2 and Schedule 3 entries for codeine and amend the Schedule 4 and 8 entries to reflect the entry deletions from Schedules 2 and 3.

The Schedule entries for codeine are as follows:

Schedule 8 – Amend Entry

CODEINE except when included in Schedule 4.

Schedule 4 – Amend Entry

CODEINE when compounded with one or more other therapeutically active substances:

- a) in divided preparations containing 30 mg or less of codeine per dosage unit; or
- b) in undivided preparations containing 1 per cent or less of codeine.

Schedule 3 – Delete Entry

Schedule 2 – Delete Entry

The implementation date is **1 February 2018**.

The matters under subsection 52E (1) of the *Therapeutic Goods Act 1989* considered relevant by the delegate included: a) the risks and benefits of the use of the substance; b) the purposes for which a substance is to be used and the extent of use of a substance; c) the toxicity of the substance; d) the dosage, formulation, labelling, packaging and presentation of a substance; e) the potential for abuse of a substance; and f) any other matters that the Secretary considers necessary to protect public health.

The following reasons from the interim decision remain:

- Risks of medication misadventure through polymorphic metabolism, deliberate misuse/abuse combined with the relative lack of efficacy compared to safer products.
- The risk/benefit profile for codeine in doses of 8 mg – 15 mg per dosing unit in combination with other analgesics is unfavourable. There is also a lack of evidence of any benefit of codeine over placebo in the relief of cough, making the risk/benefit profile for this indication unfavourable also. Codeine demonstrates marked variability in its transformation to morphine in different individuals, with the potential for very severe toxicity in ultra-rapid metabolisers.
- OTC codeine is intended for management of acute self-limiting pain, however, there is inappropriate use for chronic pain.
- The clinical purpose of low dose codeine medicines is questioned since benefit is low and risks of dependence are high.
- The purposes for which codeine is intended to be used are for Schedule 2 products the “treatment of coughs and colds” and for Schedule 3 products the “temporary relief of strong pain and discomfort associated with a number of different medical conditions.”

- Codeine shares the properties of other opioid analgesics and is potentially capable of producing dependence and, in overdose, respiratory depression and reduced level of consciousness.
- Codeine, as a prodrug, causes its direct toxicity primarily through its biotransformation into morphine. The metabolic polymorphism discussed above leads to major variability within the population in terms of the extent and rapidity of this conversion to morphine. Ultra-rapid metabolisers, who have an accelerated rate and higher extent of conversion, are exposed to morphine concentrations that are many-fold higher than those reached in poor metabolisers. This variant is found in up to 10% of Caucasians, and higher proportions of populations of North African, Oceanic and Middle Eastern origin. Very few individuals are aware of their own metaboliser status, and it would thus be very difficult to protect ultra-rapid metabolisers by way of warnings. High concentrations of morphine in the plasma can lead to serious sedation and respiratory depression, and potentially to death.
- The potential for severe adverse effects at “usual” doses in ultra-rapid metabolisers is such that codeine appears to be an unsuitable candidate for OTC availability, with either Schedule 2 or Schedule 3 scheduling. This conclusion applies equally well to the products intended for treating coughs and colds, and those intended for the treatment of pain.

Changes in labelling and packaging

- Changing the labelling and decreasing the pack size will not adequately address the problem of misuse and dependence.
- Current labelling and packaging include insufficient warnings, and that there should be clear warning labels stating the risks of addiction and dependence, the risks of harm from the paracetamol or ibuprofen, and the risk of death. Access to codeine in Australia is inconsistent, in that the total amount of codeine available in a pack of Panadeine Extra® (40 tablets containing 15 mg of codeine phosphate each) is the same quantity as that available in a pack of codeine phosphate (20 tablets containing 30 mg each), which is included in Schedule 8 and recognised to have potential for abuse or addiction.
- Some sources, including the Panadeine® product information, suggest or imply that before taking codeine a person should know their CYP4502D6 status, and this in turn means that no person should be able to self-administer codeine that has been obtained OTC. It is argued that the benefit of medical supervision that would be obtained with a re-scheduling to Schedule 4 includes the ability of the prescriber to discuss with the patient the risks of excessive opiate effect, and provide advice about actions to take if this occurs. This argument applies equally well to products currently available in both Schedule 2 and Schedule 3.

Increasing amount of evidence for harm from abuse

- Codeine is emerging as an increasingly commonly used drug of abuse internationally and in Australia. Data from the National Opioid Pharmacotherapy Statistics in 2013¹⁷ showed that codeine was the opioid drug of dependence for 1,038 clients receiving opioid substitution pharmacotherapy. The actual number was likely to be higher than this because of missing data. Another recently published study of 902 people¹⁸ who inject illicit drugs found that about one third had misused OTC codeine during the preceding six months.
- Misuse of OTC codeine products including deaths resulting from hepatic injury, gastrointestinal perforations, hypokalaemia and respiratory depression.

¹⁷ Australian Institute of Health and Welfare 2014. National opioid pharmacotherapy statistics 2013. Drug treatment series no. 23. Cat. no. HSE 147. Canberra: AIHW.

¹⁸ Arora, S., Roxburgh, A., Bruno, R., Nielsen, S. and Burns, L. (2013), A cross-sectional analysis of over-the-counter codeine use among an Australian sample of people who regularly inject drugs. *Drug Alcohol Rev*, 32: 574–581. doi:10.1111/dar.12059

- Genetic influence on codeine’s action complicates risk and benefit decisions, and leads to questions regarding the role of codeine in clinical practice.
- An appropriately qualified practitioner needs to assess the risk before making the decision that codeine will be used.
- A recently released combination of two non-opioid analgesics (ibuprofen plus paracetamol) appears to be more effective than the codeine-containing analgesics (CCAs), with a number needed to treat (NNT) of 1.5. This combination would fill any gap left by the unavailability of CCAs over the counter, giving consumers access to a more effective analgesic without requiring a prescription and without the risks of the marked variability in pharmacokinetics or abuse potential that are associated with codeine.
- Potential unintended consequences and disadvantages of a decision to re-schedule CCAs to Schedule 4 need to be considered. One would be a reduction in the availability of analgesics for moderate to severe pain, although the evidence suggests that the addition of codeine adds only a minor additional analgesic effect over and above that of the ibuprofen or paracetamol in the combination product. The recent introduction of a paracetamol/ibuprofen combination may fill this niche more effectively than the CCAs have done, without the disadvantages of codeine. A reduction in the availability of a drug known as an antitussive agent, despite the lack of evidence available to support this, would also occur, but significant actual disadvantages are unlikely to occur. No other potential disadvantages to the community are readily identified.
- The major impact on public health of the proposed amendment would be a reduction in the risk to those individuals who, unbeknownst to themselves, have a rapid metaboliser phenotype of CYP4502D6 and are therefore at significant risk of excessive morphine concentrations following ingestion of usually recommended doses of codeine for any indication.
- Codeine is an opioid which must be metabolised by CYP2D6 to its active metabolite, morphine, for its analgesic effect. Different genetic groups show significant variations in metabolism of codeine. Of particular concern are “ultra-rapid” metabolisers, where the accelerated metabolism of codeine to morphine results in an increased risk of morphine toxicity and adverse events.
- The function of the enzyme carrying out that transformation is genetically controlled and highly variable between individuals because of the existence of multiple forms of the relevant gene; the difference in exposure to morphine following a standard dose of codeine can be up to 45-fold higher in ultra-rapid metabolisers compared with poor metabolisers.
- Ultra-rapid metabolisers are therefore at risk of morphine overdose, with potentially fatal consequences, following “usual” doses of codeine.
- Individuals rarely know their metaboliser status, and testing is not readily available.
- All other opioids are at least Schedule 4.
- The approved indication for the Schedule 3 codeine products is for the “temporary relief of strong pain and discomfort associated with a number of different medical conditions”. It is noted that there is significant use of Schedule 3 codeine products for longer term relief of chronic pain and a number of public submissions by consumers have noted that this is how they use it.
- The management of chronic pain would be better achieved by having medical practitioner input with appropriate advice on non-medicine treatments and appropriate medicinal treatment for the chronic pain, rather than self-treating with long term CCAs.
- The presence of codeine in OTC combination analgesics contributes to severe adverse outcomes associated with overdosage of the paracetamol or ibuprofen component, because the development of dependence on codeine leads to overuse of the combination. Anecdotally some abusers of OTC codeine products are consuming 30 to 70 tablets/capsules per day of the CCAs.

- In Europe codeine is not an OTC medicine (i.e. is a prescription only medicine at least) in 13 countries being Austria, Belgium, Croatia, the Czech Republic, Finland, Germany, Greece, Italy, Luxembourg, Portugal, Slovakia, Spain and Sweden.
- Codeine is also a Prescription Medicine in the USA, Hong Kong, Iceland, India, Japan, the Maldives, Romania, Russia, and the United Arab Emirates.
- There is no evidence that low dose codeine combination analgesics provide any additional analgesia over optimal dosing of paracetamol, aspirin or ibuprofen. It is also noted that there are new combination products with paracetamol and ibuprofen which are more efficacious than low dose CCAs.

Outcomes of previous re-scheduling considerations

- In February 2009 NDPSC decided that:
 - Based on the currently available information from Australia, the evaluator concluded that there was potential for significant harm from OTC combination analgesics containing codeine (CACC) and even death, and it was not possible to accurately estimate the associated risk, although the following were reasonably assumed:
 - the proportion of all users that abuse OTC CACC is low.
 - the risk of harm among all users of OTC CACC is low.
 - the risk of harm among abusers of OTC CACC is high.
 - Central consideration in allowing OTC supply of codeine combinations was that the benefits outweighed the risks and therefore asserted that the insufficient data on efficacy may mean that the benefits no longer outweighed the risks. While agreeing that efficacy remains important to any case justifying OTC supply of codeine, the Committee noted the Codeine Working Party advice that there was not sufficient information available to the Members at this time to resolve the question of codeine efficacy at ≤ 30 mg.
- The NDPSC re-scheduled OTC codeine-containing combination analgesics to Schedule 3 in 2010, with the aim of increasing surveillance of codeine medication usage by pharmacists to ensure quality use of medicines, as it was recognised that there is a potential for harm if used inappropriately. The Schedule 3 entry included limits on the maximum daily dose and pack size, and restrictions on the quantities of codeine in divided (and undivided) preparations.
- Re-scheduling to Schedule 3 has not achieved the required reduction in harm to affected individuals. Since the re-scheduling of codeine from 2010 there hasn't been the reduction in risk that might have occurred.
- Codeine is increasingly a drug of abuse in Australia, and some individuals have developed severe adverse effects from the high doses of paracetamol and ibuprofen that accompany the use of large numbers of tablets in a codeine-dependent person. A pack of CCA available under Schedule 3 contains the same total dose of codeine as a pack of codeine available only under Schedule 8.
- Since OTC CCAs were re-scheduled to Schedule 3 in 2010, industry and pharmacy organisations have not been able to fully address concerns regarding codeine dependence.

Advice of the Advisory Committee on the Safety of Medicines (ACSOM)

- ACSOM has considered the risks of codeine use in children, and codeine use in persons who are ultra-rapid metabolisers of codeine. Excerpts from the meeting statement from ACSOM 28 state:
 - ACSOM agreed that the risks of respiratory depression and possible death in the context of ultra-rapid metabolism associated with codeine outweigh the benefits of codeine for all indications in children under the age of 12 years.

- As it is not possible to identify in advance the subgroup of children who are at increased risk of toxicity (e.g. through being an ultra- rapid metaboliser), the committee’s advice relates to the risks for all children under the age of 12.
- ACSOM also agreed that the risks associated with codeine outweigh the benefits of codeine for analgesia in children under the age of 18 years who have undergone tonsillectomy or adenoidectomy for sleep apnoea, for the same reasons as for children under the age of 12 years, as above. This is consistent with the United States Food and Drug Administration (US FDA) position that codeine use after adenotonsillectomy is contraindicated. The committee also noted that there have been a number of adverse event cases observed that are not clearly explained but may relate to sleep apnoea.
- ACSOM also agreed that the risks to breastfed infants associated with ultra-rapid metabolism of codeine by their mothers outweigh the benefits of codeine for any indication by breastfeeding mothers.
- As a mother’s knowledge of her own experience with codeine (and indirectly, metaboliser status) does not predict the infant’s response, breastfeeding should be a contraindication for codeine.
- ACSOM noted the following contraindications which were recommended in the TGA’s safety review to be included in the codeine Product Information - use in children under the age of 12 for any reason; use in people of any age known to be ultra-rapid metabolisers; use in children younger than 18 years of age who have undergone adenotonsillectomy for obstructive sleep apnoea; and use by breastfeeding mothers.
- The committee noted that the OTC availability of codeine-containing medicines supported a general perception in the community that codeine is safe. Therefore, communication of the contraindications by label changes alone was not likely to achieve the desired outcome of risk reduction. Additional measures including education and the possible re-scheduling of codeine-containing medicines also needed to be considered. The committee supported consistency and harmonisation in labelling across all codeine-containing medicines, especially regarding advice to breastfeeding mothers.
- Activities to reduce the use of codeine cannot occur in isolation from consideration of alternative pain management strategies. Pain management strategies that do not include codeine needed to be carefully defined and their implementation carefully considered. For example, direct administration of morphine could be considered as an alternative and the issues of analgesic polypharmacy and escalation up the ‘pain ladder’ also require consideration in the development of any pain management strategies that omit codeine.
- CCAs do not meet the criteria required for Schedule 3, particularly that they are not “substantially safe in use but require professional advice or counselling by a pharmacist”, and cannot be said to “not require close medical management.” Rather, it would be more appropriate for CCAs to be prescribed so that consumers can be warned about the potential risks and adverse effects can be more closely monitored.
- The delegate notes that the following factors for a Schedule 3 medicine in the Scheduling Policy Framework (SPF) are not met:
 - Codeine does not meet the SPF scheduling factors for inclusion in Schedule 3. In particular, criterion 2 is not satisfied – i.e. “The use of the medicine at established therapeutic dosages is not expected to produce dependency. Where there is a risk of misuse, abuse or illicit use identified, the risk can be minimised through monitoring by a pharmacist.”
- Codeine containing analgesics should now be included in Schedule 4 because codeine meets the factors in the Scheduling Policy Framework required for Schedule 4, and particularly the following factors:

- In particular, use at established therapeutic dosage levels may produce dependency (criterion 3).
- Codeine also meets SPF Schedule 4 criterion 1 (diagnosis, management or monitoring of chronic pain conditions requires medical or dental intervention before use and, although OTC codeine products are intended for short-term use, many consumers use them for chronic pain without medical intervention) and criterion 7 (its use has contributed to, or is likely to contribute to, communal harm).
- Other issues:
 - Codeine alone is ineffective as an analgesic in doses <60 mg (number needed to treat (NNT) to achieve one patient obtaining a 50% pain relief response is 12).
 - Combination analgesics containing codeine plus paracetamol or codeine plus ibuprofen show minimal analgesic benefit compared to the simple analgesics (paracetamol or ibuprofen) alone.
 - In up to 10% of the population (poor metabolisers), it is ineffective but can still cause harmful effects.
 - In up to 4-10% of the population (ultra-rapid metabolisers), it can cause life-threatening toxicity
 - If codeine is to remain in use as an analgesic, then the patient's metaboliser status needs to be ascertained prior to prescription or dispensing; however this is not practical

Real time monitoring program

- It was suggested that there were options to try and minimise the abuse related to CCAs by either expanding Project Stop or real-time monitoring of CCA use.
- Project Stop relates to the monitoring of sales of pseudoephedrine and is a police related activity to prevent diversion of pseudoephedrine as a precursor for illegal methamphetamine manufacture.
- The Project Stop website states its role as:
 - Project STOP is an initiative of the Pharmacy Guild of Australia to address the problem of precursor diversion through Australian Community Pharmacies. The most common precursor sourced through the community pharmacy channel is pseudoephedrine which can be used in the illegal manufacture of methamphetamines.
 - Project STOP is an online tool which provides decision support to pharmacists who need to establish whether requests for products containing pseudoephedrine are legitimate. It also assists pharmacists in meeting their state regulatory recording requirements where they exist.
- The Pharmacy Guild instigated MedsASSIST as a Real Time Monitoring (RTM) program and information about it is included above. It is noted that only up to 68% of pharmacies have been involved, leaving nearly a third outside the RTM program. The information provided has demonstrated that there is still significant long-term use of CCAs by many individuals. The sales of CCAs in pharmacies not using MedsASSIST is not known; and despite the annual sales of 21 million packs reported by industry, MedsASSIST has only reported 2.7 million packs of CCAs sold over a six-month period.
- A recording and monitoring system is not consistent with an OTC medicine (Schedule 2 and Schedule 3 substances), which as classified, should not have risk profiles that require monitoring. The implementation of the Electronic Recording and Reporting of Controlled Drugs (ERRCD), as a nationally consistent recording system for capturing all transactions, will only involve Schedule 8 medicines in line with mandated state and territory requirements. As such it does not even include Schedule 4 opioids or benzodiazepines, so there is an incongruity with having a RTM for OTC products.

- It is noted that the Self Medication Association of South Africa (SMASA), the Community Pharmacy Sector and the Pharmacy Society of South Africa (PSSA), launched a real-time monitoring system known as the Codeine Care Initiative (<http://selfcare247.co.za/247-codeine-care-initiative/>) in 2013. In November 2016, an update on this initiative was provided to the TGA by SMASA. One key point that came out of this update was that the program was limited by a lack of universal adoption throughout the country. This was largely driven by operational limitations, as not all public hospitals have access to computerised record keeping.¹⁹ This appears to be the only RTM program associated with codeine identified globally.
- One option considered was to decrease the pack size of CCAs from the current limit, which is five days and a recommended daily dose not exceeding 100 mg of codeine, to a pack size limit of three days, as has occurred in the United Kingdom. Although decreasing the available pack sizes of OTC codeine products might help reduce the incidence of new users becoming dependent on codeine, it is unlikely to be effective for those who are already dependent. A personal communication with the Medicines and Healthcare products Regulatory Agency (MHRA) in early 2016 indicated that there had been a drop in sales of OTC codeine combination analgesics in the UK post these regulatory reforms; however, literature suggests that the UK has actually observed an increase in overall opioid use for pain management over the 2011-2013 period.²⁰
- In oral pain relief OTC preparations, codeine phosphate (usually 8 mg per dosing unit) is often combined with a non-opioid analgesic such as aspirin, ibuprofen or paracetamol. The approved indication for Schedule 3 codeine products is for the *'temporary relief of strong pain and discomfort associated with a number of different medical conditions'*. However there is significant use of Schedule 3 codeine products for long term relief of chronic pain and a number of public submissions by consumers have noted that this is how they use it.

Clinical use and Therapeutic Guidelines

- Opioid analgesics are generally not considered suitable for a first-line therapy to treat chronic non-cancer pain, nor are they appropriate for long-term use.²¹ Instead, clinical therapeutic guidelines for analgesia²² and proponents of up-scheduling state that the management of chronic non-cancer pain would be better achieved via medical practitioner evaluation and advice with regards to appropriate pharmacological and non-pharmacological treatments.
- The Australian Therapeutic Guidelines for acute pain management²³ do not include the use of codeine for mild acute pain and when it is introduced in the treatment of moderate pain it is at a dosage of *"30 to 60 mg orally, 6 –hourly as necessary"*, which is at dosages aligned to the Schedule 4 levels and not the Schedule 3 codeine dose levels. It also notes that *"there is evidence that a lower dose of codeine, less than 30 mg 6-hourly, is no more effective than simple analgesia"*. The other opioids mentioned for moderate acute pain are tramadol and oxycodone immediate release, neither of which is available OTC. This is important as the indication for CCAs is for short term relief of pain with a restriction to 5-day pack sizes.

¹⁹ Personal communication, D Bayever

²⁰ Berterame, S. *et al.* 2016 'Use of and barriers to access to opioid analgesics: a worldwide, regional, and national study.' *The Lancet* 387 (10028), 1644-1656.

²¹ Opioid prescription in chronic pain conditions: Guidelines for South Australian general practitioners (GPs). These guidelines were produced by Drug & Alcohol Services South Australia, the Flinders Medical Centre Pain Management Unit, and the Royal Adelaide Hospital Pain Management Unit with funding under the Ministerial Council on Drug Strategy Cost Shared Funding Model. 2008. www.dassa.sa.gov.au/goto/ddu, accessed on 21 September 2016.

²² Therapeutic Guidelines Ltd (eTG July 2016 edition): Analgesic, <https://tgldcdp.tg.org.au/viewTopic?topicfile=pain-clinical-assessment>, accessed on 21 September 2016.

²³ Therapeutic Guidelines Ltd (eTG November 2016 edition): Analgesic>Acute pain: a general approach https://tgldcdp.tg.org.au/viewTopic?topicfile=acute-pain-general-approach#toc_d1e191

- The Australian Therapeutic Guidelines for analgesics for chronic nonmalignant pain management²⁴ states that “opioids work well in acute pain, but their role in chronic non-malignant pain management is limited....evidence for long-term benefit is lacking.” It also states that “Experience suggest that opioids work in only one in three patients and that they reduce pain intensity by 30-50% at best”. It is notable this is talking about all opioids of which the majority are far stronger than low dose codeine. The suggested dosing recommendations for opioids used first line in the treatment of chronic pain do not include codeine at any dose.
- The WHO “Cancer pain relief (SECOND EDITION) With a guide to opioid availability²⁵” identifies codeine as an “opioid for mild and moderate pain” and notes:

“Codeine by mouth

Codeine may be given by mouth in doses of 30-120 mg every four hours. Above this dose, adverse effects tend to increase disproportionately to pain relief. The adverse effects of codeine are essentially those common to all opioids (see page 27).”

- Again it is noted these doses are not in line with the current Schedule 3 doses so do not support low dose codeine in cancer pain relief.
- It is noted that low dose codeine is a poor analgesic with unpredictable efficacy and with risks associated with appropriate use. There is no literature data to support analgesic efficacy of combination medicines containing 8 or 15 mg codeine with paracetamol. Efficacy was only examined in combination analgesics where the amount of codeine is greater than that currently allowed in Schedule 3.
- With respect to Schedule 2 codeine containing products - these are only currently available for the treatment of coughs and colds and the codeine has been indicated for its alleged antitussive properties. A recently published Comprehensive Evidence-Based Review on European Antitussives²⁶ looked at the efficacy of antitussive drugs and noted re codeine:

Codeine is often considered the archetypal antitussive, yet there is little evidence that it has any intrinsic activity of its own. In man, codeine acts as a prodrug, being converted to morphine in the liver by the enzyme cytochrome P450 2D6.[26] Morphine has been used for centuries in the treatment of cough and indeed has been demonstrated to have efficacy in randomised controlled trials (RCTs). Experience in chronic cough suggests that morphine is only efficacious in about a third to half of patients, others having no effective relief of the symptom. Whether this is also true in the acute bronchitis and cough in common cold is unknown.

Despite its widespread use, there is very little clinical evidence supporting significant antitussive activity for orally administered codeine. In some studies, it has been reported to have no effect on cough challenge or on the sensation of urge to cough, whereas others have reported a small but significant effect.[27] In two well-designed studies investigating cough due to URTIs, codeine 30 mg, followed by 4 days of dosing four times a day, had no effect greater than placebo syrup, either on an objective initial cough recording or on a subsequent self-reported cough.[28] In the second study, oral codeine (50 mg) was compared with placebo syrup in 82 participants in a parallel group design using all three measures of cough assessment; again, no effect greater than that of placebo was observed.[29]

24 Therapeutic Guidelines Ltd (eTG November 2016 edition): Analgesic>Chronic pain: pharmacological management https://tgldcdp.tg.org.au/viewTopic?etgAccess=true&guidelinePage=Analgesic&topicfile=chronic-pain-pharmacological-management&guidelineName=Analgesic§ionId=toc_d1e75#toc_d1e75

25 Cancer pain relief : with a guide to opioid availability - 2nd ed. World Health Organization Geneva 1996 <http://apps.who.int/iris/bitstream/10665/37896/1/9241544821.pdf>

26 Morice A, Kardos P. Comprehensive evidence-based review on European antitussives. BMJ Open Resp Res 2016;3:e000137. doi:10.1136/bmjresp-2016-000137

The cytochrome system which converts the prodrug codeine to morphine is highly polymorphic.[26] Some patients are fast metabolisers converting the majority of codeine to morphine at first pass through the liver.[26] In others, the slow metabolisers, very little codeine is converted. Thus, when prescribing codeine to an individual patient who has not previously used the drug, it is impossible to predict the degree of opiate effects or indeed side effects. Both overdosing or underdosing occurs in an unpredictable fashion. The European Medicines Agency has restricted the use of codeine in children for precisely this reason while the FDA are currently reviewing the use of codeine cough-and-cold medicines in children.[30,31] Children who are fast metabolisers were observed to have dangerous levels of sedation and suppression of respiration.[26] We believe that this is not just a problem in the young and that the dangers of codeine far outweigh the limited evidence of efficacy in clinical studies. (underlined emphasis)

- It is also noted that Schedule 2 codeine containing products could also be readily accessed and should not be left available for abuse with the Schedule 3 CCAs being up-scheduled.
- The dependence on opioid analgesics is a significant concern in Australia and it is noted that OTC codeine has contributed to this by the generally unmonitored access.
- It is noted that there has been an increase in codeine-related deaths in Australia over the period 2000-13 from 3.5 deaths per million to 8.7 deaths per million.

Reasons for the final decision additional to those provided from the interim decision

The delegate's reasons for their decision are based on considerations of the Scheduling Factors from AHMAC Scheduling Policy Framework (SPF) and legislative considerations in Section 52E(1) of the Therapeutic Goods Act 1989 as outlined below.

Consideration of the Scheduling Factors from AHMAC Scheduling Policy Framework (SPF)

Under the SPF cascading principle a substance “*is first assessed using the factors for Schedule 8. If the factors for Schedule 8 are not applicable, the substance is assessed against the Schedule 4 factors and if not applicable, against the Schedule 3 factors, and if not applicable, against the Schedule 2 factors.*”

For the purposes of codeine re-scheduling and consideration of the current indications for Schedule 3 and Schedule 2 products, the cascade will begin with **Schedule 4 factors**:

- 1. The ailments or symptoms that the substance is used for require medical, veterinary or dental intervention:** Diagnosis, management or monitoring of the medical condition is such that it requires medical, veterinary or dental intervention before the substance is used.

Although short term ailments/symptoms can be self-managed it is obvious from consumer submissions and MedsASSIST data that these CCA products are being used in significant amounts long-term for ailments/symptoms which could be better managed by a medical intervention and more appropriate management.

Although the majority of the population might be using the Schedule 3 products for short term use there is still a significant proportion of the population using them long term who would benefit from further medical management.

- 2. The use of the substance requires adjunctive therapy or evaluation:** Adjunctive therapy could include other medicines, non-pharmacological measures, or specialised medicine delivery devices. Evaluation could include laboratory tests or additional clinical assessments.

N/A

- 3. The use of the substance at established therapeutic dosage levels may produce dependency but has a moderate propensity for misuse, abuse or illicit use:** *Control of access and duration of therapy by a medical, veterinary or dental practitioner is required.*

Evidence exists that even when using the Schedule 3 products within their dosing instructions they can produce dependency. The long term use as occurs with a significant proportion of the population leads to dependency. There is evidence of dependency and reports of the use of up to 75 dosage units per day in some cases.

- 4. The seriousness, severity and frequency of adverse effects are such that monitoring or intervention by a medical, veterinary or dental practitioner is required to minimise the risk of using the substance.**

There has not been intervention by a medical practitioner when use of the Schedule 3 CCAs has been excessive and adverse effects are only noted when patients are admitted with the adverse effects predominantly due to the NSAID component, such as gastrointestinal bleeds, or liver damage due to the paracetamol component. Even with the recent use of MedsASSIST it appears that although it might encourage the pharmacist to recommend the patient goes to their medical practitioner it has not stopped ongoing supply of Schedule 3 CCAs to patients.

- 5. The margin of safety between the therapeutic and toxic dose of the substance is such that it requires medical, veterinary or dental intervention to minimise the risk of using the substance.**

N/A

- 6. The seriousness or severity and frequency of the interactions of the substance (medicine-medicine, medicine-food, or medicine-disease) are such that monitoring or intervention is required by a medical, veterinary or dental practitioner.**

N/A

- 7. The use of the substance has contributed to, or is likely to contribute to, communal harm:** For example the development of resistant strains of microorganisms. Appropriate use, and/or the decision to continue treatment, requires evaluation by a medical, veterinary or dental practitioner.

There is documentation of communal harm from the misuse of the CCAs as documented in submissions by consumers relating to either their own harm or that of their relatives, as well as from addiction medicine specialist submissions.

- 8. The experience of the use of the substance under normal clinical conditions is limited:** Unexpected effects of the substance may only become evident after widespread use. Close monitoring of the patient is required by a medical, veterinary or dental practitioner to monitor for unanticipated effects.

N/A

From the above information, the delegate considers that low dose codeine products align with SPF factors associated with Schedule 4 in view of their history of use.

Looking at the **Schedule 3 factors**:

- 1. The medicine is substantially safe with pharmacist intervention to ensure the quality use of the medicine. There may be potential for harm if used inappropriately.** *The consumer can identify the ailments or symptoms that may be treated by the medicine but counselling and verification by a pharmacist is required before use. Pharmacist-consumer dialogue is necessary to reinforce and/or expand on aspects of the safe use of the medicine.*

Although the majority of patients would seem to be covered by this criteria it is well documented that there has not been quality use of CCAs where their indication is only for short term use, however patients have been allowed to be continually supplied with Schedule 3 CCAs as noted in MedsASSIST data. There is definitely harm occurring when used inappropriately.

2. **The use of the medicine at established therapeutic dosages is not expected to produce dependency. Where there is a risk of misuse, abuse or illicit use identified, the risk can be minimised through monitoring by a pharmacist.**

It is recognised that dependency can occur with established therapeutic dosages and this is exaggerated by the continual use of Schedule 3 CCAs by a significant proportion of patients.

3. **The risk profile of the medicine is well defined and the risk factors for adverse effects and interactions are known, identifiable and manageable by a pharmacist.**

Noting the risks of dependency and inappropriate long term use for chronic pain that has been occurring for some time and has continued with the use of MedsASSIST, it appears that the risks are not being well managed by pharmacists. What is occurring in the third of pharmacies where MedsASSIST is not being used is unknown.

4. **Where the medicine is intended for recurrent or subsequent treatment of a chronic condition, pharmacist intervention is required to monitor safe use of the medicine following recommendation by a medical practitioner or a pharmacist. *The consumer may not be able to self-monitor the safe ongoing use of the medicine. The condition does not require medical diagnosis or only requires initial medical diagnosis, and the consumer does not require close medical management.***

Noting that Schedule 3 CCAs are not indicated for long term use then this is not relevant, noting that even with the use of MedsASSIST pharmacists are allowing chronic use despite the known risks.

5. **The use of the medicine at established therapeutic dosage levels may mask the symptoms or delay diagnosis of a serious condition. *Pharmacist-consumer dialogue is required to detect the risk of masking a serious disease or compromising medical management of a disease, and to deal with it appropriately.***

From the evidence it does not appear that the pharmacist-consumer dialogue has restricted the long term use of CCAs and ensured that consumers with chronic pain are having their chronic pain diagnosed and managed appropriately with both non-medicine and appropriate medicine management.

From the information above, the delegate considers that Schedule 3 CCAs do not satisfy the majority of criteria for a Schedule 3 medicine.

Under the legislative considerations in Section 52E(1) of the Therapeutic Goods Act 1989

52E(1) Considerations	Reasons
a) – the risks and benefits of the use of a substance	<p>RISKS: Public health concern: As a prodrug codeine causes direct toxicity primarily through its biotransformation into morphine. Metabolic polymorphism leads to major variability within the population in terms of the extent and speed of this conversion to morphine.. High morphine plasma concentrations can lead to deep sedation, respiratory depression and death. This potential for severe adverse effects at therapeutic doses in ultra-rapid metabolisers suggests that codeine is an unsuitable OTC candidate.</p> <p>There is substantial published evidence for the involvement of codeine in cases of drug toxicity, contributing to both accidental and intentional deaths, many of which can be attributed to the misuse of combination codeine medicines. This, in combination with the limited data supporting the incremental effectiveness of codeine associated with codeine combination products, results in a negative risk/benefit analysis.</p> <p>There is also a greater risk of medication misadventure with codeine’s relative lack of efficacy compared to safer products. From an efficacy prespective, there is no evidence</p>

	<p>that low-dose codeine combination analgesics provide any additional pain relief over optimal dosing of paracetamol, aspirin or ibuprofen.</p> <p>The availability of codeine-containing medicines in Schedules 2 and 3 is inconsistent with the known risk of developing codeine dependence associated with these medicines. Codeine dependency is a major public health concern that, in some cases, requires opioid substitution therapy with methadone or similar drugs to overcome dependence. The intentional misuse and abuse of codeine leads to the ingestion of excessive doses of the companion drugs (usually paracetamol or NSAIDs) resulting in morbidity and/or death.</p> <p>BENEFITS: There are little demonstrated benefits for low dose codeine in products currently available as Schedule 2 or Schedule 3.</p> <p>From this the overall benefit risk is negative for OTC codeine.</p>
b) – the purposes for which a substance is to be used and the extent of use of a substance	<p>The approved indication for Schedule 3 codeine products is for the <i>‘temporary relief of strong pain and discomfort associated with a number of different medical conditions’</i>. However there is significant use of Schedule 3 codeine products for long term relief of chronic pain and a number of public submissions by consumers have noted that this is how they use it. Rather than self-treating with long term OTC codeine-containing analgesics, the management of chronic pain would be better achieved through medical practitioner input, with advice on appropriate non-pharmacological treatments and alternative pharmacological treatments.</p> <p>Opioid analgesics are generally not considered suitable for a first-line therapy to treat chronic non-cancer pain, nor are they appropriate for long-term use. Instead, clinical therapeutic guidelines for analgesia and proponents of up-scheduling state that the management of chronic non-cancer pain would be better achieved via medical practitioner evaluation and advice with regards to appropriate pharmacological and non-pharmacological treatments.</p> <p>The approved indication for Schedule 2 codeine products is <i>“for the treatment of coughs and colds”</i> and there is little evidence of the efficacy of codeine for this indication with identified risks.</p>
c) – the toxicity of a substance	<p>Public health concern: In addition to genetic polymorphism of codeine metabolism that may lead to unexpectedly high levels of morphine in some patients, codeine shares the properties of other opioid analgesics (which are included in Schedule 4 or Schedule 8) and is potentially capable of producing dependence and, in overdose, respiratory depression and reduced level of consciousness.</p>
d) – the dosage, formulation, labelling, packaging and presentation of a substance	<p>Although the approved indication for Schedule 3 codeine products is for the <i>temporary relief of strong pain and discomfort associated with a number of different medical conditions</i>, the medical literature and consumer submissions received in 2015 indicate that the use of Schedule 3 codeine products for long term relief of chronic pain is significant. The previous decrease in pack sizes has not reduced the chronic use and reducing the pack size further would not prevent chronic use of OTC codeine as it would only require consumers to attend a pharmacy more often.</p>
e) – the potential for abuse of a substance	<p>Public health concern: Codeine is a commonly used drug of abuse, both internationally and in Australia. The presence of codeine in OTC combination analgesics and the development of codeine dependence contributes to severe adverse health outcomes associated with the overdose of other active constituents, such as paracetamol or ibuprofen. There is substantial evidence of harm from abuse or misuse of codeine-containing medicines, including deaths.</p>
f) – any other matters that the	<p>See above under SPF Factors.</p>

<p>Secretary considers necessary to protect public health</p>	<p>International alignment: UK: Warnings on the Summary of product characteristics (SmPC), Patient Information Leaflet (PIL) and label reflect the importance of not taking the medicines for more than three days continuously without medical review, and to warn about the risks of addiction and headache from overuse. The PIL and labels state that products containing codeine can cause addiction if used continuously for more than three days.</p> <p>The potential role of RTM was considered, however the non-compulsory nature for non-Schedule 8 products such as is being rolled out under ERRCD does not provide apocopate protection to public health.</p> <p>There are significant inconsistencies in the restrictions on codeine availability between Schedules 2, 3, 4 and 8.</p> <ul style="list-style-type: none"> • Codeine is available OTC as a Schedule 3 medicine (Pharmacist Only) in packs of up to 40 tablets (e.g. Panadeine Extra®) containing 15 mg each, totalling 600 mg codeine (in combination with paracetamol) per pack. • Paradoxically, the same total pack quantity of 600 mg codeine (single active ingredient) is also available as a Schedule 8 (Controlled Drug) medicine in packs of 20 tablets containing 30 mg each. A Schedule 8 substance is recognised to have potential for abuse or addiction. • Similarly, an even higher quantity of 1500 mg codeine per pack is available as a Schedule 4 medicine (Prescription Only) in packs of up to 50 tablets (e.g. Panadeine Extra®) containing 30 mg each (in combination with paracetamol) per pack. <p>Economic and regulatory costs or savings are not necessarily considered by the delegate under the Scheduling Policy Framework (SPF) and the scheduling regulatory framework as specified in Therapeutic Goods legislation.</p>
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In summary, when looking at the issue from a whole of population perspective, although there are some parts of the population that would benefit from accessing Schedule 3 codeine containing products, the risk to the whole population is such that up-scheduling all codeine containing products to at least Schedule 4 is appropriate and outweighs the limited benefits.

Reasons for the 1 February 2018 implementation date include:

The delegate considered the feedback received within the public submissions and targeted consultations during the development of the RIS to understand the minimum and ideal timeframes connected with different change processes. The delegate noted the critical importance of implementation timeframes in enabling business to reposition themselves with this decision. Further noted that sponsors indicated a reasonable end-to-end implementation timeframe would, at a minimum, be between 18 to 24 months, but that this was at odds with the protection of public health and safety. The delegate was informed that:

- Pharmacies generally hold between 1 to 2 -month worth of stock.
- Most manufacturers do not hold large amounts of produced stock but make to order, with some bulk material purchases turning over every 9 months.
- Shelf life of codeine products is 24 months.
- The minimum timeframes to comply with an up-scheduling decision appears to be around 9 months.

In view of this an implementation date of 1 February 2018 allows sufficient time for an education program for doctors, pharmacists and consumers to occur to minimise the effect on individual patients and allow more appropriate medicines to be prescribed or dispensed to patients. It allows time for

pharmaceutical companies to deal with their current codeine containing products affected by the up-scheduling.