Australian Government
Department of Health
Therapeutic Goods Administration

Ratified Record of the 15th meeting of the Advisory Committee on Medicines Scheduling

04 August 2015

TRIM Reference no.

TGA Health Safety Regulation

Contents

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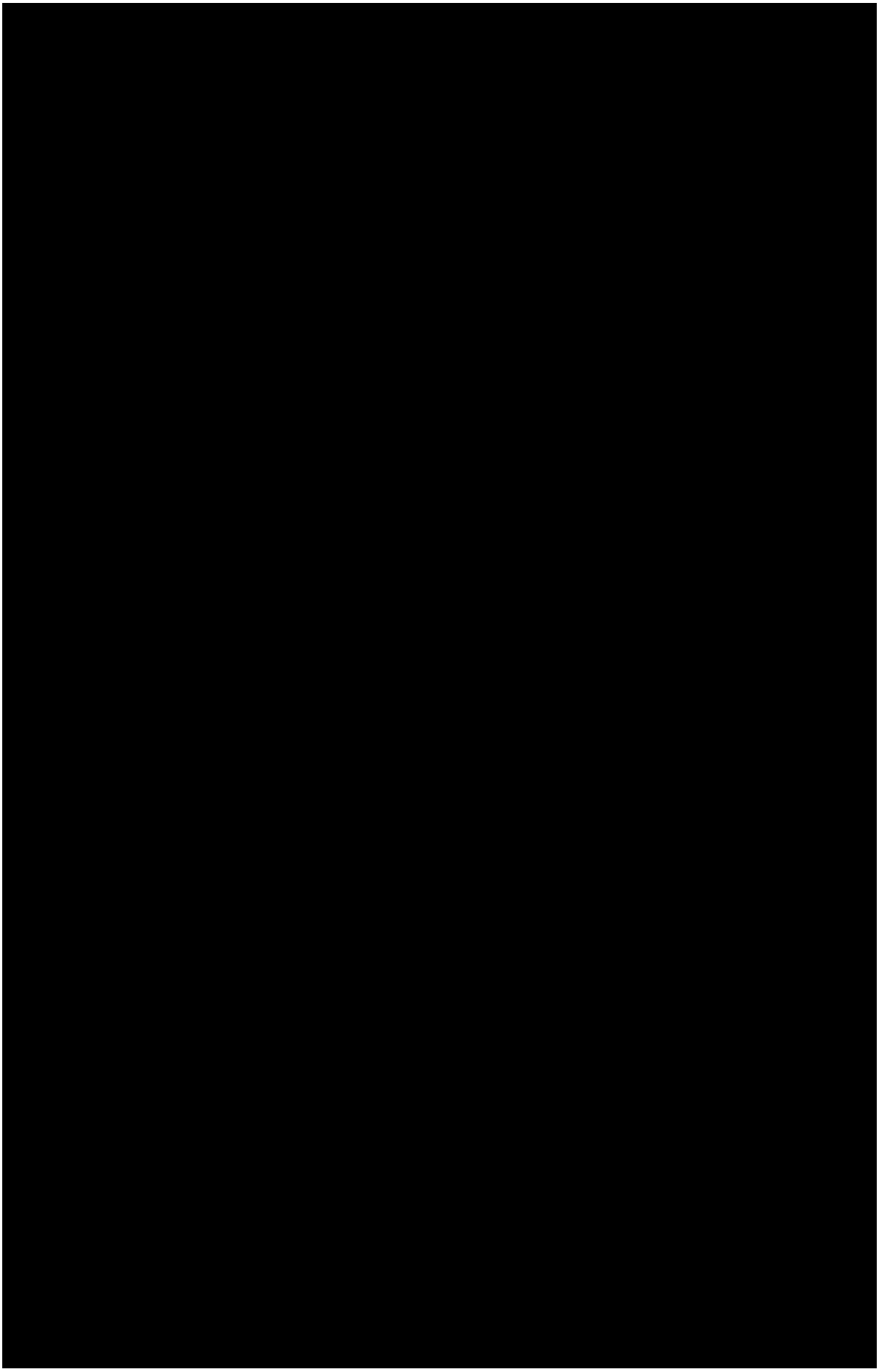

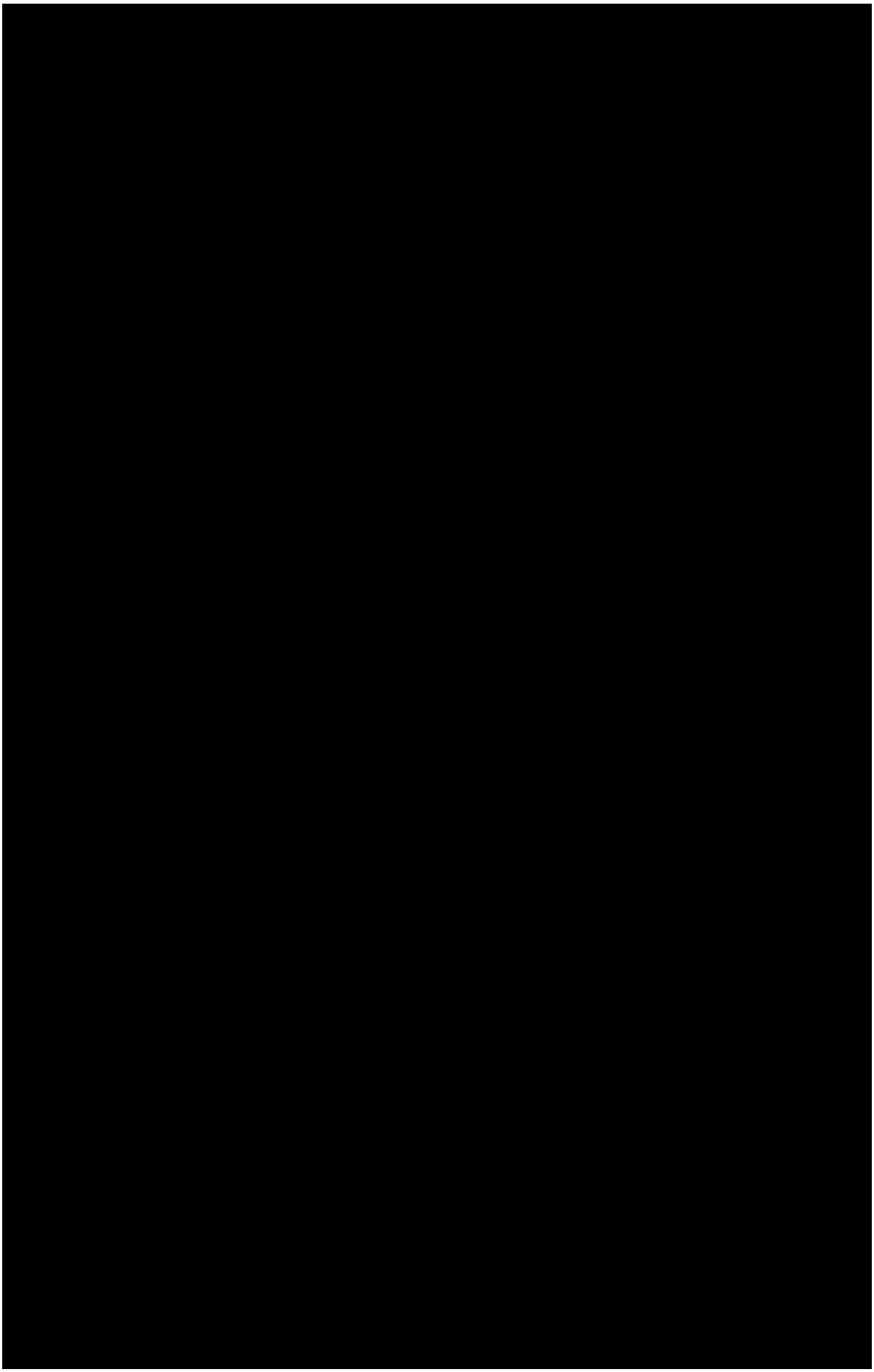

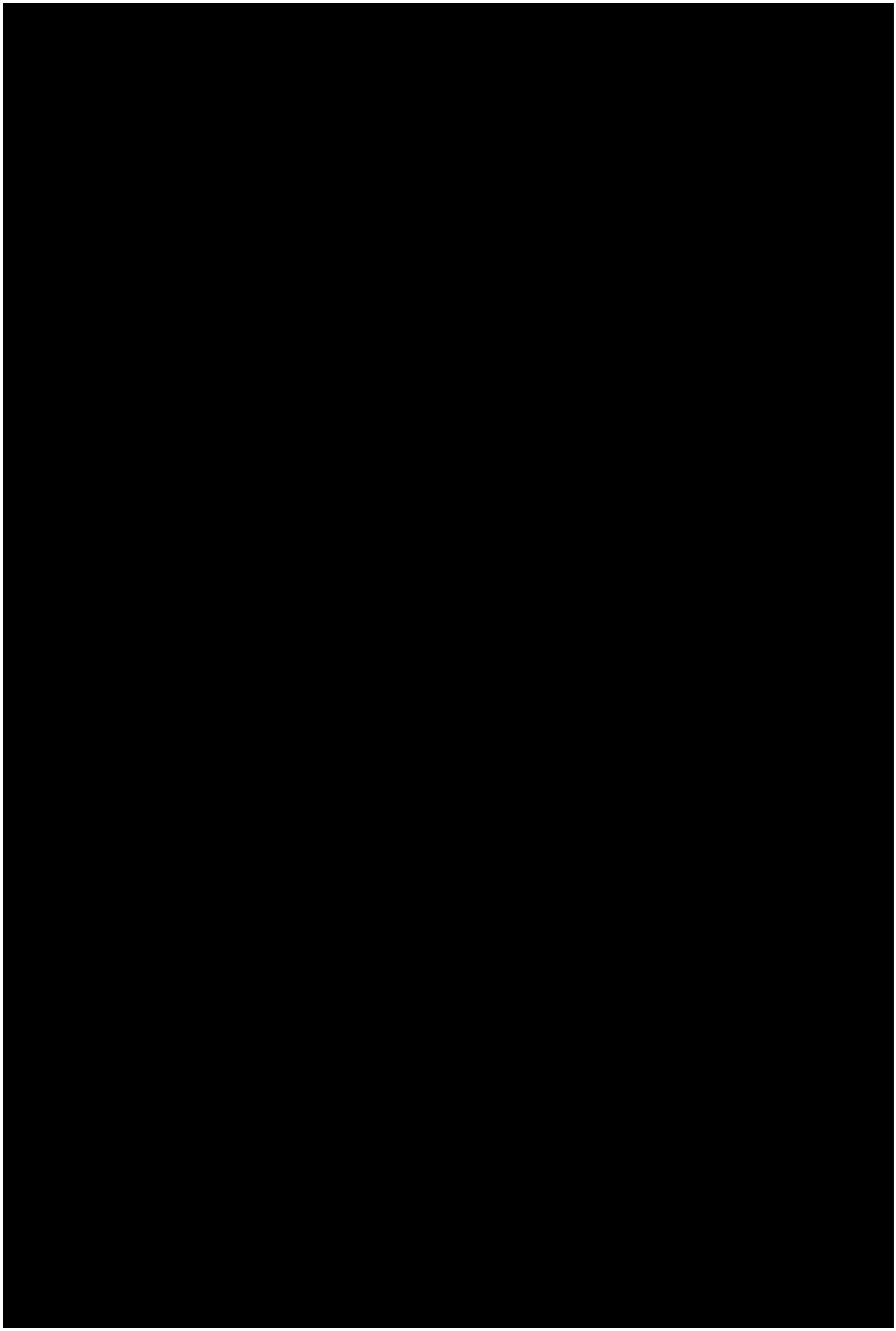

2. Proposed changes to the Poisons Standard

2.1 Codeine

Scheduling proposal

Proposal to delete the Schedule 3 entry for codeine, and reschedule 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 rescheduled to Schedule 4, or whether any rescheduling 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.

Application type

General Application

Rescheduling

Applicant

[redacted] Pain Management Unit, Royal Adelaide Hospital

[redacted]

Date applications received: February 2015

Summary of reasons why the applicant has applied for scheduling

[redacted] Application

- Codeine needs to be metabolised by the cytochrome P450 enzyme system to the active analgesic morphine. The level of analgesia from codeine varies considerably from person to person, from no analgesia to potentially toxic effects – this response is unpredictable, as cytochrome P450 2D6 (CYP2D6) status is unknown in most patients.
- Up to 10% of the Australian population are "poor metabolisers" of codeine – in these people, codeine is ineffective as an analgesic, but can still cause adverse effects.
- Up to 4-10% of the Australian population (including up to 30% of North African descent and up to 20% of Middle Eastern descent) are "ultra-rapid" metabolisers of codeine, and are at high risk of harm with codeine compound analgesics. The much faster metabolism of codeine to morphine means that opioid toxicity, including life threatening respiratory depression, may occur at "usual" therapeutic doses, and there are reports of significant harms (including death) in these individuals, even with use of modest / usual dosages of codeine combination medication. Additionally, such patients may become dependent on codeine and overuse codeine combination analgesics.
- Compound analgesics containing codeine plus paracetamol or ibuprofen show minimal additional analgesic benefit compared with paracetamol or ibuprofen alone. Most of the over-the-counter (OTC) preparations contain considerably less codeine than doses studied in clinical trials, and the applicant has questioned whether low dose OTC codeine combination products can provide meaningful analgesia.
- The National Drugs and Poisons Schedule Committee (NDPSC) rescheduled 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.
- Rescheduling to Schedule 3 has not achieved the required reduction in harm to affected individuals and the applicant is not aware of any formal study examining the benefits and harms from the switch to Schedule 3. Although inclusion in Schedule 3 may have initially decreased abuse of codeine-containing combination analgesics, numbers of patients presenting to drug and alcohol services in South Australia for codeine detoxification have continued to grow since 2011.

[redacted] Application

- Excessive use of OTC combination analgesics containing codeine (CACC) due to development of dependence on codeine has led to many reports of severe adverse outcomes including death associated with the paracetamol or ibuprofen component. Codeine dependence via

excessive CACC use, and the toxicity of the other analgesic component of CACCs, incurs significant costs to the healthcare system. Economic costs and costs in terms of human suffering and disability due to paracetamol overdose, NSAID toxicity or codeine dependence are high.

- Codeine 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.
- Data to support the efficacy of codeine in low doses (OTC doses of 8-15 mg codeine or codeine phosphate) are lacking. References state that there is no evidence that low dose codeine combination analgesics provide any additional analgesia over optimal dosing of paracetamol, aspirin or ibuprofen.
- Options to minimise overuse of CACCs include rescheduling to Schedule 4, real time monitoring and recording, increased written and verbal consumer education and advice, reduced pack size and removal from the market altogether.
- On the basis of lack of proven efficacy, known morbidity and toxicity and increasing role in opioid dependence, all low dose codeine (8-15 mg codeine or codeine phosphate) should be rescheduled from Schedule 3 to Schedule 4.

Advice sought by Delegate

1. What are the benefits and risks of up-scheduling combination analgesics containing codeine that are currently in Schedule 3 to Schedule 4?
2. If rescheduling of the Schedule 3 combination analgesics containing codeine is supported, should the Schedule 3 entry be deleted entirely, or should the Schedule 3 entry be amended to retain combination codeine-containing products other than products indicated for analgesia?

   The current Schedule 3 entry for codeine applies to combination analgesics and also to some other codeine combinations (the schedule entry specifies codeine when compounded with one or more other therapeutically active substances, of which not more than one is an analgesic substance). In addition to the Schedule 3 combination analgesic products containing codeine (plus paracetamol, ibuprofen or aspirin), a number of other combination codeine-containing Schedule 3 products (that are not indicated primarily for analgesia) are registered for supply in Australia. These include cold and flu products (containing codeine, paracetamol and other actives, such as pseudoephedrine), cough medicines (containing codeine and other actives) or anti-diarrhoeal preparations (containing codeine and other actives) – the cough medicines and anti-diarrhoeal product do not contain another substance with analgesic effects.

   a. If the Schedule 3 combination analgesic products containing codeine are rescheduled to Schedule 4, should some or all of these other Schedule 3 codeine combination products remain in Schedule 3 or should they be rescheduled to Schedule 4?
   b. If it is considered that any of the current Schedule 3 codeine combination products should remain in Schedule 3, should any changes be made to the current maximum quantity of codeine per dosage unit in divided preparations (12 mg) or the maximum percentage of codeine in undivided preparations (0.25%), and/or to the maximum recommended daily dose (100 mg) and/or to the maximum pack size (not more than 5 days' of supply at the maximum dose recommended on the label)?
3. Should the Schedule 2 entry for codeine be amended?
4. If it is recommended for codeine to be rescheduled what is an appropriate implementation date?

Evaluation

CONCLUSIONS

The evidence provided has persuaded this evaluator that codeine-containing combination analgesics (CCAs) do not meet the Scheduling Policy Framework (SPF) 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.

Similar conclusions apply to the use of codeine-containing combinations for the treatment of coughs and colds. Again, a more appropriate scheduling would be Schedule 4, allowing close medical supervision and advice. Given the lack of any evidence from randomised controlled trials that codeine has any effect on cough, a better outcome still would be withdrawal of codeine-containing cough and cold medicines from sale.

RECOMMENDATION

Taking all of the above considerations into account, it is RECOMMENDED that codeine in a dose of less than 30 mg per dosing unit or less than 0.25% of codeine in undivided preparations and when combined with other analgesics be rescheduled from Schedule 3 to Schedule 4, AND that codeine in a dose of 10 mg or less per dosage unit or in undivided preparations containing 0.25% or less of codeine be rescheduled from Schedule 2 to Schedule 4.

One of the applicants provided a response to the evaluation – that applicant supported the conclusions and recommendations of the evaluation. The other applicant did not provide a response.

Public pre-meeting submissions

60 submissions were received.

29 submissions supported amending the scheduling of codeine, to delete the Schedule 3 entry for codeine and reschedule all current Schedule 3 codeine to Schedule 4. Main points:

- Reduce the potential for harm – particularly in combination products containing codeine plus paracetamol or ibuprofen (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.

25 submissions opposed the rescheduling proposal. Main points:

- Increase in bookings to see a general practitioner (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 effective for acute pain requiring short term relief;

- In 2010, the NDPSC found the Schedule 2 entry for codeine appropriate.

Six submissions did not state whether or not they supported the rescheduling proposal.

Main discussion points

Efficacy of codeine in OTC products:

- Codeine has questionable efficacy, although data are mostly from single dose studies in the treatment of acute post-operative pain (appropriate for evaluating efficacy in acute, but not chronic, pain).
- Benefits of OTC doses of codeine for pain relief are generally low, but there are efficacy benefits in some individuals, and most consumers use OTC codeine responsibly. Many of the patient-based pre-meeting submissions that reported deriving significant benefit with codeine-containing compound analgesics related to relief of chronic or recurrent pain, which is generally outside the OTC indications for codeine.
- Many consumers who over-use OTC codeine products do not see themselves as drug-dependent, but consider that they have a problem with pain. There are three types of pain – codeine can be effective in nociceptive pain, but is not very effective in neuropathic pain, and is ineffective in neuroplastic pain.
- Data were not presented in support of a clinical benefit of codeine in diarrhoea preparations, but the constipating effect of codeine is accepted.
- Good quality data to support a benefit of codeine as an antitussive at the doses included in cough and cold medication were absent/limited. It was noted, in response to concerns that removal of OTC codeine would increase numbers of patients requesting prescriptions from general practitioners, that many OTC cough and cold preparations do not contain codeine.

Risks with OTC availability of codeine-containing products:

- Risks include dependence, and/or severe toxicity at usual doses (largely in children). The incidence of severe respiratory depression is higher in ultra-rapid metabolisers of codeine. Deaths have been reported in young children given codeine post-operatively and in babies of breastfeeding mothers given codeine. The proportion of users at risk from codeine is poorly defined.
- In addition to the wide inter-individual variability in response to codeine (due to genetic differences in its metabolism to morphine via CYP2D6), there may be interactions between codeine and other drugs that affect CYP2D6 activity.
- Addiction is a complicated issue, as it is influenced by biopsychosocial factors. Data indicate that many people became addicted to codeine after using OTC products to treat acute pain, and many of these were not aware of the risk when they started taking codeine. Further, 17% of about 800 respondents to a Turning Point survey fulfilled criteria for OTC codeine dependence.
- Otherwise, the data do not make clear what proportion of the patients who abuse OTC codeine to maintain an opioid addiction do so simply due to ease of access. A link between genotype and risk of addiction is proposed but not confirmed.
- Conditions in pharmacies, including a lack of privacy for taking sufficient history regarding pain and drug use, limit the ability of pharmacists to identify consumers who abuse codeine.
- Reports of drug abuse or dependence recorded in the TGA's Database of adverse event notifications (DAEN) represent the tip of an iceberg, since well-known adverse effects are not generally reported.

Implications of rescheduling OTC codeine to prescription status:

- Much of the reported morbidity and mortality with OTC codeine combination products is due to ibuprofen. Rescheduling ibuprofen-codeine combination analgesics specifically may increase abuse of paracetamol-codeine products, which could lead to other problems, such as liver damage due to paracetamol.
- Additionally, Schedule 2 and 3 codeine-containing cough and cold medicines are currently not or minimally abused, but this may change if combination analgesics are up-scheduled.
- If OTC codeine-containing products are rescheduled to Schedule 4, should rescheduling of other OTC opioids be considered in the future (e.g. dihydrocodeine, dextromethorphan, pholcodine)?

Other control options:

- Real time monitoring could enhance the ability of pharmacists and prescribers to identify "medicine shoppers" of OTC codeine products. However, currently, real time monitoring is only intended to monitor prescription and supply of Schedule 8 medicines, and real-time access to the monitoring system is only available in Tasmania. Additionally, OTC availability of a substance that requires real time monitoring does not seem appropriate.
- Monitoring supply of codeine using a "Project Stop" system is also not feasible (Project Stop" has a different purpose, as it was developed solely as a means of policing the supply of pseudoephedrine to curb its diversion to manufacture amphetamines).
- In many countries, codeine is not available OTC.
- Some codeine-containing products are available OTC in the United Kingdom (UK). The UK requires that the labels of OTC products include a prominent warning that codeine can cause addiction, and restricting use to three days, on the front of the pack. Some Australian sponsors have voluntarily included similar label warnings.

Other issues raised by members:

- International conventions allow for OTC availability of codeine when compounded (so the codeine cannot be readily extracted). The current concerns primarily relate to harm to drug users from other components in codeine combination products.
- Since OTC codeine combination analgesics were rescheduled to Schedule 3 in 2010, industry and pharmacy have not been able to address concerns regarding codeine dependence. Additionally, no regulatory action appears to have been taken in response to the NDPSC recommendation that TGA review the efficacy of OTC codeine combination analgesics.
- Pharmacists have recently recommended inclusion (per APF23) of a Cautionary and Advisory label on OTC codeine containing analgesics, stating that the products is for 3 days' use and may cause addiction. Given the recent nature of these measures, their impact cannot yet be assessed.'
- The wide use of OTC codeine combination analgesics to manage chronic pain indicates that treatment of chronic pain is poor, and pharmacological treatment is not necessarily the best option. Education of pharmacists and consumers regarding pain management is poor. Pharmacists are not able to manage chronic pain well, and rescheduling to Schedule 4 should encourage consumers to seek medical advice.
- Although Schedule 3 codeine products cannot be advertised to consumers, organisations such as the National Prescribing Service (NPS) can provide consumer education.
- 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.

- Implications of rescheduling include the different regulatory processes for prescription and OTC medicines, with longer evaluation timeframes and higher costs associated with TGA's prescription medicines approval processes, and concerns regarding whether sponsors would continue to supply lower dose codeine combinations as prescription medicines. Additionally, many of the current OTC codeine products are manufactured in Australia.

Scheduling Policy Framework (SPF) considerations:

- Codeine does not meet the SPF scheduling factors for inclusion in Schedule 3. In particular, criterion 2 is not satisfied – ie. *"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 meets SPF criteria for inclusion in Schedule 4. 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).

Scheduling recommendations:

- A number of members considered that all Schedule 2 and 3 codeine should be rescheduled to Schedule 4, primarily due to lack of efficacy data, and also to risk of abuse and ease of access.
- An alternative view was that a study could be conducted (e.g. sponsored by industry and pharmacy) to investigate harms from codeine since the 2010 scheduling changes prior to any rescheduling decision. The following steps could also be implemented: real time reporting; enhanced label warnings (re dependence, lack of efficacy in slow metabolisers, duration of use); consumer education re harms; inclusion of paracetamol/ibuprofen combinations in Appendix H (to allow promotion of alternate effective analgesics); and States/Territories to ensure compliance with existing laws regarding supply of Schedule 3 codeine.
- Other members noted the difficulties in obtaining good data on codeine dependence, but agreed that concerns had not changed appreciably since the 2010 scheduling changes. Codeine dependence should be addressed now, as anecdotal evidence shows sufficiently severe harms from OTC codeine products, and products that may cause dependence should only be available on prescription.
- 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 majority of members supported deletion of the current Schedule 2 and 3 entries for codeine, with corresponding amendments to the Schedule 4 and 8 entries. All codeine combination products would therefore be Schedule 4 or 8.
- Some members instead considered that the Schedule 3 entry for codeine should be amended to reduce the number of days' supply from five to three days. This should be accompanied by education of pharmacists and consumers regarding pain management. Scheduling could be reconsidered if no improvement was seen within 24 months.
- One member's view was that the current scheduling of codeine remains appropriate (and non-scheduling means should be undertaken to address issues of dependence and inappropriate use).

Implementation date:

- An implementation date of 1 June 2016 was recommended. This would allow time for education of health professionals and consumers regarding pain management.
- Members noted that post-meeting comments could be taken into consideration in any final decision on implementation date.

Recommendation and implementation date

The committee recommended 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.

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 a
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;~~
~~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.~~

The committee recommended an implementation date of 1 June 2016.

52E Table

52E(1) Considerations	*Reasons*
a – the risks and benefits of the use of a substance	Risks of medication misadventure through polymorphic metabolism, deliberate misuse/abuse combined with the relative lack of efficacy compared to safer products.
b – the purposes for which a substance is to be used and the extent of use of a substance	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.
c – the toxicity of a substance	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.
d – the dosage, formulation, labelling, packaging and presentation of a substance	Changing the labelling and decreasing the pack size will not adequately address the problem of misuse and dependence.
e – the potential for abuse of a substance	Increasing amount of evidence for harm from abuse
f – any other matters that the Secretary considers necessary to protect public health	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.