Further Public Submissions on the Proposed Amendments to the Poisons Standard

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

A delegate of the Secretary to the Department of Health publishes herein all valid public submissions made in response to the invitation for further submissions on the interim decisions regarding the proposed amendments to the Poisons Standard. These submissions were considered by the medicines scheduling delegate.

In accordance with the requirements of subsection 42ZCZQ of the Regulations these submissions have had confidential information removed.

Material claimed to be commercial-in-confidence was considered against the guidelines for the use and release of confidential information set out in Chapter 6 of the Scheduling Policy Framework for Medicines and Chemicals (SPF, 2015), issued by the Australian Health Ministers Advisory Council (AHMAC). The SPF is accessible at: https://www.tga.gov.au/publication/ahmac-scheduling-policy-framework-medicines-and-chemicals.
19 February 2015

Medicines Scheduling Secretariat
PO Box 100
Woden ACT 2606

Medicines.Scheduling@tga.gov.au

Dear Sir/Madam

Re: Invitation for public comment – ACMS Meeting February 2015 Naproxen Appendix H

We refer to the notice inviting public comment under Regulation 42ZCZP of the Therapeutic Goods Regulations 1990. We would like to take this opportunity to submit comments.

Notes there were four public submissions received regarding the proposal to include naproxen in Appendix H. Three supported the submission (one with an additional request for pharmacy to input into the development of any promotional material) and one submission which did not support inclusion citing no public benefit would result from advertising.

Naproxen is safe and efficacious when used for the treatment of mild to moderate pain such as back, neck and shoulder pain and osteoarthritis in adults and children over 12 years of age. These ailments are common and self-limiting, readily diagnosed by consumers and can be managed without medical intervention. The use of naproxen is substantially safe for short term treatment and the potential for harm from inappropriate use is low.

The primary aim of scheduling is to determine the level of access consumers should have to medicines. Once the level of appropriate access has been determined through a scheduling decision advertising does not alter the way the medicine is accessed or the level of access. Access to a Schedule 3 medicine requires pharmacist intervention regardless of the medicines advertising status. Schedule 2 naproxen immediate release medicines are already advertisable. Both Schedule 3 and Schedule 2 diclofenac medicines are also already advertisable.

The wider availability of safe, proven and affordable medicines has the potential to make a positive impact on public health by providing consumers with easier, more convenient and faster access to therapeutic products to treat conditions and maintain good health. The current arrangements for advertising of some Schedule 3 medicines disempowers consumers because “they are not allowed to know” about these medicines. They constrain
the ability to make consumers aware of treatments which are available without a prescription. It is difficult to mount a public health benefit argument to support these restrictions, especially in view of the mandatory involvement of a pharmacist in the supply of these products. Consumers will continue to consult GPs for conditions which could be safely managed by pharmacists such as extended pain relief from muscle aches, back, neck and shoulder pain and osteoarthritis. The UK, Canada, New Zealand and the US permit advertising of all non-prescription medicines. Unlike Australia, no exception is made for medicines that are classified as the equivalent of Schedule 3, where such a classifications exists, i.e. in New Zealand and Canada. Although there may be minor country to country differences in which medicines are listed in Schedule 3 type classifications, other comparable markets allow consumer advertising of these medicines.

In the case of extended or modified release formulations of naproxen advertising the availability of this new medicine via a pharmacist would increase consumer awareness of a medicine that may provide a useful long-lasting analgesic alternative that does not require three or more times a day dosing compared to other immediate release analgesics. Advertising will encourage consumers to consult with their pharmacist regarding their pain conditions and if this new modified dosage form is an appropriate treatment for them the pharmacist will recommend it. This will help to expand the professional role of pharmacists in the delivery of primary healthcare in a timely manner and utilise valuable GP resources for the treatment of more serious health conditions.

intends to work with and assist stakeholders to educate all pharmacy staff, including pharmacists about modified release naproxen and to produce a treatment protocol to assist pharmacists in the supply of naproxen.

supports the advertising of Schedule 3 modified release formulations of naproxen and requests that approval is granted for Appendix H listing.

Yours faithfully
19 February 2015

Medicines Scheduling Secretariat
PO Box 100
Woden ACT 2606

Medicines.Scheduling@tga.gov.au

Dear Sir/Madam

Re: Invitation for public comment – ACMS Meeting February 2015 Naproxen Schedule 2

We refer to the notice inviting public comment under Regulation 42ZCZP of the Therapeutic Goods Regulations 1990. We would like to take this opportunity to submit comments regarding the proposal to amend the Schedule 2 naproxen entry to exclude naproxen in a dosage form of 200 mg or less of naproxen per dosage unit in packs of 12 or less dosage units with a maximum recommended daily dose of not more than 600 mg of naproxen, and when not labelled for the treatment of children 12 years of age or less.

Notes there were five public submissions received. One supported the proposal with appropriate wording that is consistent with other OTC medicines such as paracetamol and ibuprofen. Four others opposed any amendment to the Schedule 2 entry for naproxen due to potential risks if the substance is accessible to consumers outside registered pharmacy premises.

Low doses of simple analgesics currently available as open sale for minor aches and pain include:
- aspirin 500 mg in packs of up to 16 dosage units or aspirin 325 mg in packs of up to 25 dosage units;
- paracetamol 500 mg in packs of up to 20 dosage units;
- ibuprofen 200 mg in packs of up to 25 dosage units.

Naproxen is safe and efficacious when used for the treatment of mild to moderate pain such as back, neck and shoulder pain, headache and osteoarthritis in adults and children over 12 years of age. The use of naproxen is substantially safe for short term treatment and the potential for harm from inappropriate use is low.

The risk profile of naproxen and other NSAIDs are well defined with identifiable risk factors. The risks associated with the use of naproxen are no greater than other analgesics such as aspirin, ibuprofen or paracetamol.
- For gastrointestinal disorders, various meta-analyses have shown that the risks at OTC doses are low and comparable to those of ibuprofen or paracetamol.
- For cardiovascular disorders, various meta-analyses have demonstrated that all NSAIDs showed some evidence for an increased risk of cardiovascular death compared with placebo. Naproxen appeared to confer the least risk.
These risks can be effectively managed via appropriate labelling as is currently the case for other unscheduled NSAIDs.

Naproxen in divided preparations containing 250 mg or less of naproxen per dosage unit in packs of up to 30 dosage units has been included in Schedule 2 since 1999 without any known problems of misuse, abuse, illicit use or safety issues. Excluding naproxen from scheduling under limited circumstances (200 mg or less per dosage unit in packs of 12 or less dosage units when not labelled for the treatment of children under 12 years of age) is comparable to other jurisdictions such as the USA and Canada. Naproxen sodium 220 mg has been available widely in drug stores and convenience stores in the USA since 1994 and it's safety at the recommended low OTC doses for up to 10 days has not been a cause for concern.

supports the amendment to exclude naproxen at a lower strength of 200mg or less of naproxen per dosage unit in 12 or less dosage units when not labelled for the treatment of children under 12 years of age from Schedule 2 of the Poison Standard.

Yours faithfully
19th February 2015

The Secretary
Scheduling Secretariat
GPO Box 9848
Canberra ACT 2601

Email: smp@tga.gov.au

Dear Sir/Madam,

Re: Interim Decision on scheduling matters referred to the joint ACCS-ACMS#10 (November 2014): Item 1.2 – Paracetamol/Caffeine

[Redacted text]

has considered the interim decision and public submissions in relation to the requested amendment to the scheduling of paracetamol compounded with caffeine such that it will be exempt from Schedule 2 when supplied in primary packs of not more than 20 tablets/caplets or 10 sachets of powders/granules. We provide here comment for consideration prior to any final decision being made.

The submission provided ample information, supported by current scientific literature and local/global pharmacovigillance data, demonstrating the excellent risk:benefit profile of fixed dose paracetamol/caffeine formulations (when sold in the proposed packs of not more than 20 tablets). This ingredient combination meets all of the criteria for exclusion from Schedule 2 thereby justifying the proposed amendment to exempt it from scheduling.

The reasons for not recommending the revised scheduling comprised the following:

- Potential risk of harm through excessive unintentional use of caffeine
- No strong argument for increasing availability
- Concern of the product being used with other caffeine containing products and concern about the toxicity of the combination in intentional overdose
- Preference for combination analgesics to only be available where professional advice is available
- There was not a supported argument for public health benefit
- Risk of consumer confusion without access to advice
- Risk of consumer confusion regarding their caffeine intake from multiple sources, given that many caffeine-containing products (including food, drinks and dietary supplements, as well as medicinal products) are freely available to consumers.
In addition, the publically submitted oppositions to the proposal cite a number of reasons for retaining paracetamol/caffeine products in Schedule 2; these fall into the following key categories – lack of efficacy, hypothetical potential for risk of harm and potential for medication overuse headache – each of which were adequately addressed with supporting data in our submission.

Apart from the above we note that no other quantitative evidence supporting the interim decision was cited in the published reasons for the delegate’s interim decision. Hence, it can be concluded that this constitutes the sum total of the information available to the ACMS and the delegate upon which to base their recommendation/decision respectively. If the situation is otherwise, all available information should be made public and a further opportunity to comment should be afforded for the delegate’s consideration ahead of the delegate’s final decision.

**Availability of combination products**

The delegate’s interim decision states that there is a “preference for combination analgesics to only be available where professional advice is available”. Firstly, caffeine is not an analgesic but acts as an adjuvant to enhance the efficacy of the single analgesic present, paracetamol. Secondly, such reasoning is contrary to the current scheduling of cold and flu products.

The long-standing evidence base underpinning safety and efficacy of paracetamol/caffeine combinations is no less substantial than is that for analgesics/phenylephrine combinations which have been exempt from scheduling since 2010. We can surmise from this determination that the issue is not combination analgesics per se; rather it is specific to discrimination against caffeine combinations.

**Efficacy data**

Respondents opposing the proposal drew upon data cited in an NPS Medicine Wise Update on Panadol Extra, published in December 2010* to suggest that paracetamol/caffeine products have only a small incremental efficacy benefit over paracetamol alone.

The relevant data are cited in Palmer et al., 2010. In this analysis of eight studies, 8% more patients achieved at least 50% maximum pain relief with the paracetamol/caffeine combination than with paracetamol alone (65% vs 57%, \( P < 0.05 \)).

The NPS document has not been updated since December 2010. It fails to acknowledge more recent research supporting the clinical relevance of this 8% difference. Per the data in our submission, Derry et al., 2012 have published the results of Cochrane Database Systematic Literature Review on the use of caffeine combined with analgesics. In this analysis 7% more patients achieved this efficacy measure with the paracetamol/caffeine combination.

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than with paracetamol alone (67% vs 60%, p < 0.05). **They have concluded that an increase of 5-10% of responders is clinically relevant**.[2]

Derry et al., 2014 (published in December and not available at the time of our original scheduling submission) provides an updated analysis of the 2012 Cochrane Database Systematic Literature Review.[3] In this update, the authors recognise that around 25 additional studies exist with almost 12,500 participants for which data for analysis were not obtainable. However, they note that the majority of the unobtainable data are reported to have similar results as their review. Even if all the known missing data had no beneficial effect, this would not change the overall conclusions of the meta-analysis. This 2014 review concludes that the addition of caffeine to a standard dose of commonly used analgesics **provides a small but important increase in the proportion of participants who experience a good level of pain relief**.

Haag et al., 2011 (also provided in our original submission) describe the evidence base behind the guidelines for the self-medication of migraines and tension-type headaches recommended by the German Society of Neurology, the Austrian Headache Society and the Swiss Headache Society.[4] For tension-type headache the evidence conclusively supports the use of fixed-dose combination paracetamol/caffeine as self-medication of first choice and paracetamol as a remedy of second choice (Table 1):

### Table 1

<table>
<thead>
<tr>
<th>Quality of the scientific evidence</th>
<th>Paracetamol (1000 mg) + caffeine (130 mg)</th>
<th>Paracetamol 1,000 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scientific evidence of efficacy</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Clinical impression of effectiveness</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Clinical impression of tolerability</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Recommendation for self-medications</td>
<td><strong>Drug of first choice</strong></td>
<td><strong>Drug of second choice</strong></td>
</tr>
</tbody>
</table>

Three meta-analyses and evidence-based guidelines provide more than sufficient data to support that the addition of caffeine to paracetamol results in a clinically meaningful increase in pain relief. Clearly, the combination offers an important alternative when paracetamol alone is not effective enough. Thus providing a strong, evidence-based argument for its increasing availability and the public health benefit of its wider availability.

**Hypothetical risk concerns**

Hypothetical concerns have been raised regarding the potential risk of harm through either an excessive unintentional use of caffeine (i.e. taking the product with other caffeine-containing products may lead to an excess in total daily caffeine intake) or toxicity in intentional overdose. Available data negates these concerns.

The average daily adult caffeine consumption is estimated to be 300 mg. Serious toxicities are rarely seen with caffeine excess. If taken at the maximum recommended daily dose of two caplets four times a day, the daily intake of...
caffeine would be 520mg. It is estimated that overdoses in adults require the ingestion of a large quantity, typically in excess of 5 g.[5]

The paracetamol/caffeine product is labelled in a way that clearly and prominently distinguishes its contents from other standard paracetamol products (such as colour, pack size/shape, and clear labelling as to the caffeine content on the front of pack). For example, the active ingredients and their amounts on the front of the pack are double the letter height required of other medicines. In addition, unlike any other standard paracetamol pack, this product contains a clearly labelled caution on the back of pack, which draws the user’s attention to the caffeine content of the product. It reads: “Limit the use of caffeine containing products (including tea and coffee) when taking these caplets. One dose of [Panadol Extra] contains 130mg of caffeine; this is about 2 cups of instant coffee. Caffeine may cause sleeplessness if it is taken up to several hours before going to bed.”

NPS Medicine Watch educates consumers as to the appropriate use of medicines. The paracetamol/caffeine document alerts consumers to the important side effects of paracetamol/caffeine (“The paracetamol and caffeine in Panadol Extra can cause side effects, but these are very rare when it’s used correctly”) and the need to be cognizant of total daily caffeine intake. This information has been readily available to consumers for more than 4 years.

The above information is a clear demonstration that strategies are in place to mitigate any risk of consumer confusion without access to advice or concerns about caffeine intake from multiple sources.

Paracetamol/caffeine products are associated with a very low risk of misuse, abuse or illicit use. The available evidence does not support a pivotal role of caffeine in initiating or sustaining the overuse of analgesics; compulsive drug-seeking behaviour involving caffeine has not been observed.

On the topic of caffeine and headaches, an expert panel, convened by the National Headache Foundation to discuss the published evidence, has surmised that: “Despite the fact that there have been numerous studies conducted on caffeine, there is no compelling evidence that supports the misconception that caffeine is addictive or habit forming for the vast majority of people.”

An analysis of the risks of the combination of paracetamol/caffeine, with a particular focus on hepatotoxicity, found no compelling data to suggest a clinically meaningful increase in hepatotoxicity with the use of this combination.[1] These data have been reiterated in a recent review article addressing the modern pharmacology of paracetamol.[6] These authors conclude: “A critical review of the data has indicated that there is no significant evidence for such toxicity at therapeutic levels and some studies indicate the opposite (i.e. decreased hepatotoxicity).”

Overdoses, intentional or otherwise, with paracetamol/caffeine combination analgesics are extremely uncommon. This combination has been available as an open sale product in major markets around the world for over 20 years.

† Available from: http://www.headaches.org/content/caffeine-and-headache [Accessed 18 Feb 2015]
There have been no deaths reported with the use of paracetamol/caffeine products.[5, 7]

It is of note that one of the respondents opposing the proposed scheduling highlighted data from a recent systematic literature review aimed at identifying high-risk medications. The authors of this review concluded: “Ten drugs or drug classes caused two thirds (72%) of all fatal events, and seven of those drugs or drug classes caused half (47%) of all serious MEs [medication errors]. The serious problems caused by these drugs have apparently not changed over the years when comparing older and newer references, despite of numerous efforts to improve the quality and safety of prescribing in recent years.” [8] Notably, paracetamol combined with caffeine was not cited in this watch list of harmful medicines. Thus, adding to the data supporting the overwhelming safety in use of this product.

The evidence supports the strong benefit-risk profile of paracetamol/caffeine combinations products. Thus providing a strong, evidence-based argument against hypothetical potential risks of harm.

**Medication overuse headache**

Concerns regarding the use of paracetamol/caffeine and increased potential for medication overuse headache appear to stem from the belief that analgesics compounded with other substances are more likely to produce this syndrome and that caffeine withdrawal symptoms may provide an incentive to ingest more caffeine along with the analgesic.

Caffeine coformulated with analgesics has been repeatedly accused of inducing or sustaining analgesic overuse. A detailed analysis of the original publications behind the numerous literature citations shows that the epidemiological studies did not provide any convincing evidence for a role of caffeine in prompting excessive analgesic use.[9] Others have established that caffeine withdrawal is not likely to cause stimulation or sustainment of analgesic intake.[10]

A recent analysis of available studies have shown that opioid analgesics are the only class of medications significantly more likely to be used in patients with chronic daily headache than in those with episodic headache; there is no association between caffeinated analgesics and chronic daily headache.[11]

Extensive and adequate provisions are already in place to alert consumers to the caffeine content of this combination product. These provisions draw attention to the amount of caffeine, total daily intake of caffeine and duration of use of the product. Given the very extensive experience with paracetamol and paracetamol-containing medicines the general public is aware of how these products should be used. The majority of users will comply with the labelling and the risk of inadvertent self-harm is very unlikely given the extensive safety data and known profile of these products. As with all OTC products the labelling instructs the consumer seek medical advice if symptoms persist and to take for only a few days at a time without medical advice.

The evidence, combined with these labeling provisions, effectively negates potential concerns pertaining to an increase in medication overuse headaches.
should the paracetamol/caffeine product be rescheduled from Pharmacy Only to open sales.

**In summary**

The available data support that the fixed dose paracetamol/caffeine combination product provides clinically meaningful efficacy over paracetamol alone; has an excellent safety profile; a very low risk of nephrotoxicity, toxicity in overdose, misuse, abuse or illicit use; and a highly favourable risk:benefit profile.

Since the late 1970s Australia has had an opposing view to those of other regulatory bodies in key markets around the world with regards to the scheduling and risk:benefit profile of fixed dose paracetamol/caffeine products. The interim decision highlights that this view prevails today. This is despite the conclusions of the NDPSC at its 50th Meeting in June 2007 in which it was determined that it would be appropriate to consider whether this product could be exempt from scheduling when market experience had been gained with its use as a Schedule 2 product in Australia.

The data supplied in our submission and that reiterated here adequately addresses each of the reasons cited for not recommending the revised scheduling.

- Evidence of greater efficacy with no increase in safety risk to that of other currently available analgesics in open sale provide a strong argument for increasing availability and underpin the public health benefit of wider access to the product.
- Available data support the safety of paracetamol/caffeine combination when used as directed; there is no evidence to substantiate concerns of potential risks of harm through excessive unintentional use of caffeine or the product being used with other caffeine containing products.
- Overdoses, intentional or otherwise, with paracetamol/caffeine combination analgesics are extremely uncommon; there is no evidence to substantiate increased potential toxicity of the combination in intentional overdose.
- The preference for combination analgesics to only be available where professional advice is available appears to apply only to paracetamol/caffeine products, despite their excellent risk:benefit profile.
- Multiple strategies are in place to mitigate potential risks of consumer confusion without access to advice or concerns about confusion over caffeine intake from multiple sources.

More than ample (>4 years) in-market experience with this product has been gained in Australia with no adverse safety signals. There are no new data suggesting that the risk:benefit profile of the product has changed since the 2007 NDPSC decision. As such, the exemption from scheduling of paracetamol/caffeine formulations (when sold in packs of 10 sachets/20 tablets or less) is warranted and justified by the available evidence.

We trust that the above will be taken into due consideration prior to making your final determinations on this matter so as to reverse the interim decision and
recommend the exemption of paracetamol/caffeine from scheduling, as per the scheduling proposal.

Yours sincerely,

References (available on request)
Further submission in relation to proposed amendments to the Poisons Standard:

**Performance and Image Enhancing Drugs**

Proposal to include new entries for Growth Hormone Releasing Hormones and Analogues, Growth Hormone Secretagogues, Growth Hormone Releasing Peptides and Growth Hormone Variant, as well as new individual entries for CJC-1295, ipamorelin, GHRP-2, GHRP-6, hexarelin and AOD-9604 in Schedule 4 and Appendix D.

February 2015
Confidentiality statement

Proposed amendment referred by the delegate for scheduling advice for consideration by the Advisory Committee on Medicines Scheduling (ACMS):

Performance and Image Enhancing Drugs: Proposal to include new entries for Growth Hormone Releasing Hormones and Analogues, Growth Hormone Secretagogues, Growth Hormone Releasing Peptides and Growth Hormone Variant, as well as new individual entries for CJC-1295, ipamorelin, GHRP-2, GHRP-6, hexarelin and AOD-9604 in Schedule 4 and Appendix D.

Comment

Further to the ‘Reasons for scheduling delegate’s interim decision and invitation for further comment for the ACMS - Interim decisions on matters referred to an expert advisory committee: ACMS February 2015’, is responding in relation to the proposal to include AOD-9604 in Appendix D.

There is a lack of explanation in the published reasons for scheduling as to how inclusion in Appendix D would assist in the control of possession or supply of AOD-9604 over and above the control afforded it by include in Schedule 4.

The reasons provided refer to Performance and Image Enhancing Drugs (PIEDs) as a group and does not address the applicability of each of the “relevant matters under Therapeutic Goods Act 1989 section 52E(1)” in relation specifically to AOD-9604. Supply of the synthesised substance by is controlled by licensing arrangements and have no evidence to suggest that there is supply of their AOD-9604 outside of physician/pharmacy control.

The evidence, noted by the delegate (uncited), that PIEDs are being advertised to attract a number of user markets, that they are being misused, that organised crime are involved in their supply and that they are promoted as safe alternatives to traditional performance enhancing substances such as the anabolic steroids, may apply to other PIEDs under consideration by the delegate but it is not clear from the published reasons that the delegate has evidence that these findings apply to AOD-9604. Noting that AOD-9604 is not human growth hormone and does not stimulate production of IGF1 (insulin-like growth factor 1), therefore should not be associated with the risks applicable to growth hormone.

Based on our understanding of the legislation, unless each of the various states and territories follow through on Appendix D inclusions, either directly or indirectly, the inclusion of AOD-9604 in Appendix D would not be effective. Thus inclusion in Appendix D would not add value to inclusion of AOD-9604 in Schedule 4 but would create a burden for legitimate clinical development in the states and territories which do adopt Appendix D. As a minimum if acted on it would be impossible to interpret, hence non-transparent, without resorting to each State or Territory’s legislation.
We submit that inclusion in Schedule 4, which will limit AOD-9604 to supply by ‘authorised prescribers’ is adequate control of this substance. Inclusion in Appendix D is a step too far with a requirement for further unpredictable and possibly diverse regulatory action by other regulators.
