EDITED SUBMISSIONS RECEIVED IN RESPONSE TO THE NOTICE INVITING FURTHER SUBMISSIONS IN RELATION TO DELEGATES' INTERIM DECISIONS ON RECOMMENDATIONS FROM THE:

Advisory Committee on Chemicals Scheduling – 21 June 2011 (ACCS#2); and
Advisory Committee on Medicines Scheduling – 22 June 2011 (ACMS#3).

Regulation 42ZCZQ, Therapeutic Goods Regulations 1990 (the Regulations)

A delegate of the Secretary of the Department of Health and Ageing publishes herein all public submissions made in response to the invitation contained in the August 2011 Reasons for delegate's interim decisions (accessible at www.tga.gov.au/industry/scheduling-decisions-interim.htm).

The call for further submissions (as required under subsection 42ZCZP of the Regulations), invited comments on the delegates' interim decisions from the applicant and parties who made a valid submission in response to the original invitation for submissions (published on 13 April 2011 at www.tga.gov.au/newsroom/consult-scheduling-acmcs.htm).

In accordance with the requirements of subsection 42ZCZQ of the Regulations these further submissions have been edited to remove information that a delegate considers to be confidential.

As advised in the notice inviting public submissions, it was up to the person making the submission to highlight any information which they wished to request be considered as confidential. Material claimed to be commercial-in-confidence was then considered against the guidelines for the use and release of confidential information set out in Chapter 6 of the Scheduling Policy Framework (SPF), issued by the National Coordinating Committee on Therapeutic Goods i.e. a request for material to be confidential did not automatically classify that material as confidential. The SPF is accessible at www.tga.gov.au/industry/scheduling-spf.htm.

Discrete submissions are grouped by item. However, where submissions relate to multiple items, these are separately grouped.

LIST OF SUBMISSIONS

1. SUBMISSIONS ON INTERIM DECISIONS ARISING FROM RECOMMENDATIONS BY ACCS#2

Item	Number of submissions
1.2 Saflufenacil	1
1.4 Naphthalene	1

2. SUBMISSIONS ON INTERIM DECISIONS ARISING FROM RECOMMENDATIONS BY ACMS#3

Item	Number of submissions
2.1.1 Loperamide	1
2.1.3 Orphenadrine and paracetamol combination	1

1.2 Saflufenacil - Submission 1 of 1

[redacted]

5 September 2011

The Secretary
Scheduling Secretatiat
GPO Box 9848
Canberra ACT 2601
Australia
e-mail submission

[redacted]

Subject: Interim decisions & reasons for decisions by delegates of the secretary to the department of health and ageing. August 2011 invitation for further submissions - Saflufenacil

Dear Secretary,

[redacted] supports the delegate's decision from the June 2011 Advisory Committee on Chemical Scheduling (ACCS) regarding saflufenacil, a new chemical currently under evaluation by the Australian Pesticide and Ve[redacted]ines Authority for use as a herbicide. As the applicant for saflufenacil [redacted] would like to affirm our support for the following proposal made by the delegate.

Schedule 5 – New entry

SAFLUFENACIL in water dispersible granule preparations.

Schedule 7 – Amendment

SAFLUFENACIL – Amend entry to read:

SAFLUFENACIL **except** when included in Schedule 5.

Thank you for your consideration of this information.

[redacted]

[redacted]

[redacted]

1.4 Naphthalene - Submission 1 of 1

[redacted]

7 September 2011

The Secretary
Scheduling Secretariat
GPO Box 9848
CANBERRA ACT 2601

Email: SMP@health.gov.au

Dear Sir/Madam

Public Comment Submission to the Delegate's Interim Decision under subsection 42ZCZP of the Therapeutic Goods Regulations 1990

We refer to the notice published on 24 August 2011 of the Delegate's interim decisions under subsection 42ZCZP of the *Therapeutic Goods Regulations 1990*, inviting public submissions, with respect to certain substances, addressing a matter raised in section 52E of the *Therapeutic Goods Act 1989.*

[redacted] provided comments on **naphthalene** for consideration at the 2nd meeting of the ACCS in June 2011.

[redacted] has reviewed the Interim Decisions & Reasons for Decisions by the Delegate of the Secretary to the Department of Health and Ageing. [redacted] wishes to take the opportunity provided by the Delegate's Interim Decision notice to make a further submission on naphthalene. The submission is attached.

We look forward to further advice from the ACCS. Should the Committee require any additional information from [redacted] at this stage please do not hesitate to contact me on [redacted].

Yours faithfully

[redacted]

[redacted]

[redacted]

[redacted]

1.4 Naphthalene

[redacted] congratulates the ACCS for the pragmatic consideration of naphthalene as an impurity in hydrocarbon solvents. Naphthalene is an unavoidable impurity in a number of hydrocarbon solvents and the risk posed by the naphthalene impurity in solvents can be better managed through the scheduling controls of hydrocarbon solvents, rather than through the scheduling controls for naphthalene.

[redacted] therefore fully supports the interim decision to exempt naphthalene from scheduling when present as impurity in hydrocarbon solvents. We understand that the risk controls in place for hydrocarbon solvents will also be effective for any naphthalene as impurity in hydrocarbon solvents.

We seek clarification on the reasons behind the decision to add naphthalene flakes to paragraphs 17, 28 and 29.

With the addition of the word "flake" to paragraph 17, 28 and 29 of the Poisons Standard, naphthalene flakes will be required to be provided in a device that:

(1) In normal use, prevents removal or ingestion of its contents; and
(2) Is incapable of reacting with the poison; and
(3) Is sufficiently strong to withstand the ordinary risks of handling, storage or transport; and
(4) Has the word "POSION" and the approved name of the poison embossed or indelibly printed on it.

During the ACCS considerations, it is our understanding that the Committee reached a view that the hazards and risks associated with naphthalene flakes were consistent with other naphthalene forms, therefore leading to the suggestion that naphthalene flakes be added to paragraphs 17, 28 and 29 of the SUSMP.

The inhalation risk of naphthalene flakes is unlikely to change whether they are provided in free flake form or in an enclosed device – naphthalene only works by releasing vapours.

We would therefore assume that the decision to only allow flakes to be supplied in an enclosed device is based on the consideration that picking up and/or sucking on an enclosed device containing naphthalene flakes is likely to deliver a lower dose of naphthalene than picking up and/or ingesting free flake forms of naphthalene.

Clarification on the reasons behind the ACCS consideration and the interim decision will aid industry in planning the necessary risk mitigation measures that best address the risk concerns.

We also seek clarification on the practical application of the proposed new scheduling requirements for naphthalene in flake form.

Naphthalene flakes are much smaller in size than naphthalene balls, discs and blocks, and therefore cannot be provided in "cages". The only possible option is to consider a see-through "sachet" like enclosure where vapours of naphthalene can escape, but the flakes themselves are contained. We seek clarification whether these individual sachets are acceptable and also need to have the word "POISON" and "naphthalene" embossed or indelibly printed on them. We do not believe that these additional labeling requirements are imposed internationally.

[redacted]

7 September 2011

Comments by [redacted] on the Delegate's Interim Decisions – August 2011

Interim Decision

LOPERAMIDE – Schedule 2 Amendment

LOPERAMIDE in divided preparations for oral use in packs of 20 dosage units or less except in preparations containing 2 mg or less of loperamide per dosage unit, in a primary pack containing 8 dosage units or less.

[redacted] position

[redacted] does not support the interim decision to exempt small packs of 8 dosage units or less of loperamide from scheduling. We believe that access to professional advice should be facilitated, particularly for more vulnerable population groups, and this is better managed by retaining a minimum Schedule 2 listing for loperamide.

Contact person:

[redacted]

[redacted]

Background

At a meeting on 22 June 2011, the Australian Committee for Medicines Scheduling (ACMS) recommended an exemption from scheduling for loperamide in packs containing 8 dosage units or less. Subject to final ratification, the delegate has agreed with the recommendations with an implementation date of 1 May 2012.

Key Points

a. There is no identified need to exempt loperamide from scheduling.

b. Mitigation of safety issues relies significantly on effective labelling and packaging.

c. The grocery sector lacks quality assurance processes for provision of medicines.

Comments

The primary arguments provided in the Delegate's reasons for the interim decision (Interim Decision) for supporting the recommendation of a scheduling exemption for loperamide are:

- loperamide is used for symptom control rather than treating an underlying condition
- limiting open availability to small packs and using effective labelling will address safety issues and ensure appropriate use
- loperamide is relatively safer that other medicines which are exempt from scheduling, such as ibuprofen, aspirin and paracetamol
- loperamide is readily available in other countries
- an exemption would harmonise with New Zealand scheduling

[redacted] considers that the reasons provided in the Interim Decision do not sufficiently justify supporting a scheduling exemption for loperamide and we provide the following information to support our case.

1. There is no identified need to exempt loperamide from scheduling

1.1 In neither the application nor the discussion has it been shown that the Australian public are being disadvantaged by loperamide being a S2 medicine and restricted to sale in pharmacies or licenced premises in regions in which a pharmacy is not within close proximity.

In its submission, the applicant 'asserted that withholding treatment of symptoms with loperamide in the absence of warning signs would be unnecessary and would exacerbate the distress of the disorder'. [redacted] rejects the implication that access is being denied or delayed from the pharmacy sector. Results from a research project[1] conducted under the Fourth Community Pharmacy Agreement (Fourth Agreement) showed that the most common reason for non-purchase of an S2 medicine did not relate to access but to the consumer not wanting to use medicines or treatments, or not believing medicines were required.

Community pharmacies typically have extended trading hours with access 7 days a week. Community pharmacies are located in built-up areas for easy access and in fact, frail and debilitated people would have greater access through pharmacy with additional services such as home delivery and account arrangements. Community pharmacies also maintain arrangements for emergency after-hours needs. We doubt that a person waking up in the middle of the night with diarrhoea is going to rush out to purchase a pack of loperamide from their nearest 'convenience store', if it is indeed open.

1.2 One of the main reasons for requesting an exemption appears to be 'it is done in other countries, therefore it should be done in Australia'. This reasoning is fraught with issues and should not be used as precedence for scheduling decisions. Most of these countries do not have as effective a scheduling system as Australia, with two over-the-counter (OTC) categories. In other countries, there is usually either one or nil OTC categories.

1.3 The 'Risks and benefits' analysis of the 'Evaluation report' identified the beneficial use of loperamide for self-medication of acute diarrhoea by travellers, but this is unlikely to be a reason for immediate access in Australia as travellers purchase diarrhoea medicines to include in their travel kit when going overseas rather than for immediate use. There is a greater risk that travellers going overseas may rely solely on loperamide as the diarrhoea treatment for their travel kit when it is important for them to also have antimicrobial therapy available for treatment when dysentery (passage of blood stools) or high fever may be a complication, particularly if going to remote areas in countries with limited access to quality-assured prescription medicines. 'Traveller's diarrhoea is common and all travellers should have a clear understanding of what to do in the event of illness'.[2] 'Antisecretory agents [such as loperamide] are not advised where there is fever or bloody diarrhoea. Instead, an antibiotic should be used with extra fluids as first line therapy.'[3]

A European study identified that a proportion of Europeans feel that it is sufficient to include loperamide alone in the travel kit for routine treatment of travellers' diarrhoea.[4] We do not want Australian travellers relying solely on a small pack of loperamide in their travel kit to manage gastroenterological emergencies when travelling overseas. This may be the case for travellers who don't have access to pharmacist advice when purchasing loperamide.

Reports from [redacted] indicate that in the pharmacy setting, travellers requesting anti-diarrhoea medicine for their travel kit tend to seek advice for additional health related matters, such as:

- immunisation
- other travel medicines e.g. antibiotics for dysentery and oral rehydration therapy
- water purification needs
- first aid supplies (including sterile products)
- identification of medicines for passing through customs

1.4 We note that the Interim Decision identifies the consideration given by members of the ACMS to harmonising with New Zealand. Considering the recent recommencement of regulatory harmonisation between Australia and New

Zealand, this attitude is premature. This is a political decision and time is needed to reassess the scheduling and safety arrangements in both countries. Discrepancies will be highlighted and can be reconsidered in either country.

When Medsafe agreed to exempt loperamide from scheduling in New Zealand (April 2010), the decision was based on matters of relevance to New Zealand. Likewise, scheduling decisions in Australia should be based on matters of relevance to Australia. We are concerned that a decision at this time that is (partly) based on harmonisation may make it difficult to rescind if the need arises when harmonisation is fully considered. If harmonisation is so important, in the interests of public safety it may be more appropriate for New Zealand to consider up-scheduling agents such as loperamide to harmonise with Australia.

2. Mitigation of safety issues relies significantly on effective labelling and packaging

2.1 We note the Interim Decision suggests the ACMS identified the overall benefit of access to small packs of loperamide outweighed the potential risks. Although we could not identify in the Interim Decision the benefits recognised by the ACMS, we noted considerable discussion about the potential risks and how these could be mitigated by labelling and/or pack inserts, including:

- Use in pregnancy
- Use in lactation
- Use in higher risk age groups (children and the elderly)
- Duration of treatment
- Use when complications are present (e.g. bloody diarrhoea, fever)
- Appropriate spacing of dosing

With all these concerns, it was also noted that the applicant had not included a draft pack label for consideration and stated that the labelling and packaging lay with the Therapeutic Goods Administration (TGA) and would be addressed separately to scheduling. The effectiveness of the labelling recommendations in mitigating safety concerns is a key consideration to this scheduling decision and we do not believe it sufficient to support the scheduling exemption and to just communicate the evaluator's labelling recommendations to another area within the TGA.

[redacted] concern is the significant amount of cautionary labelling required to address the safety concerns identified above. We note with interest the conditions for general sale of loperamide in Britain (Appendix A). It appears that in Britain, a pack insert is required with considerable detail on when a doctor should be consulted before taking loperamide. Unfortunately, to get to such information, the patient will need to have purchased the product and then taken the time to read the information; a very unlikely scenario when feeling particularly unwell. Availability through the pharmacy sector provides access to this information irrespective of purchasing the product, and may also facilitate prompter medical attention for the more serious conditions.

2.2 The ability to read and understand medicine labels in order to understand how to use a medicine and to be aware of safety issues and cautionary advice has long been a recognised problem in Australia and other parts of the World, particularly

for people with vision impairment. Important factors in effective labelling include format-font type, point size, letter compression, line spacing-on readability, comprehensibility, and usefulness to consumers.[5]

In a submission to the Therapeutic Goods Administration (TGA), the Consumers' Health Forum (CHF) indicated that 'advisory statements need to be printed in a font size and design which ensures they are easily recognised and read by consumers. Many consumers report difficulty reading information on medicines labels. Small font size of the print on labels is an ongoing problem for many consumers, such as older people and people with vision impairment, who are most often at risk of medicine-related adverse events themselves, or as carers of children, spouses or family members.'[6] The submission also counselled that 'advisory statements should not take the place of effective communication between a consumer and a health professional.'

At a CHF Workshop[7] in December 2010 on packaging and labelling of medicines, consumer advocates highlighted that medicines packaging and labelling alone did not address Quality Use of Medicines (QUM) issues and 'needs to complement and integrate with other consumer health information and education tools.' While consumers advocated the need for medicines to have readable and understandable instructions and the need for the 'labelling best practice guidelines'[8] to be mandatory, industry representatives indicated the impact of increasing the font size on packaging to be impractical. As an example, a packet of Panadol® was presented with a font size of all type increased to a 14 point sized font, making the packet three times larger than normal. Sponsors will not support such changes and [redacted] suggests they will generally label packs to the minimum requirements without consideration to factors affecting readability.

The final report[9] from the TGA's 'Review to improve the transparency of the Therapeutic Goods Administration' (June 2011) also highlighted labelling issues and the responsibility for regulation and monitoring.

Irrespective of the promises made by sponsors, [redacted] does not believe that labelling is sufficiently effective to ensure that all consumers understand how to use loperamide and the safety cautions associated with its use. Availability through the grocery sector with packets that meet all the labelling recommendations will still leave the most at-risk population groups (the elderly, the young, illiterate, non-English speaking background, poorly educated) vulnerable to misadventure. Retaining loperamide as a S2 medicine provides an opportunity for health professional interaction for all people, in particular those most vulnerable to misadventure.

2.3 The effectiveness of labelling to address QUM concerns relies on the information being read and understood. In its report on improving medication safety[10], the Australian Council for Safety and Quality in Health Care (ACSQHC) highlighted that difficulty in understanding medicine labels can lead to misadventure, providing the following examples of misunderstanding from a survey of 100 older consumers:

- The instruction 'take one tablet every 6 hours, 1 hour before food (four tablets per day on an empty stomach)' was correctly interpreted by 16% and misunderstood by 84%.

- The simple instruction 'take one tablet twice a day' was misunderstood by 17% of consumers.

The CHF Workshop in December 2010 also identified an issue with instructions on medicines labels being ambiguous and unclear, making it difficult for consumers, particularly for non-English speaking backgrounds, to understand how to take their medicines. Interestingly, the example provided as causing difficulty for consumers from non-English speaking backgrounds was the instruction 'take one tablet twice a day'. A clearer instruction suggested was 'take one tablet in the morning and another one in the evening.'

Although consumers want clearer, less ambiguous instructions on their medicines, there are no requisite processes to address this issue and therefore, [redacted] does not feel that labelling alone mitigates safety concerns. Scheduling should reflect the need to access health professional advice and we believe S2 is a more appropriate schedule for loperamide.

2.4 In our initial submission, we raised concerns about the lack of health literacy in Australia, notably:

- A survey[11] conducted by the Australian Bureau of Statistics (ABS) identified 46% of Australians aged 15 to 74 years as not having sufficient literacy skills to meet the complex demands of everyday work and life, and that on the health scale, 60% attained scores below the minimum requirement to meet everyday needs.
- The ABS survey also identified that only 36% and 38% of people whose language was not English attained scores at or above the level that demonstrated sufficient prose and document literacy respectively to meet everyday needs.

With these types of figures, we remain concerned that labelling and packaging alone will not sufficiently address the safety issues that have been identified. The Fourth Agreement research project[12] showed that two-thirds of purchasers of S2 medicines sought pharmacy advice with their purchase and that nearly 30% identified the need for advice.

2.5 With such a high reliance on appropriate labelling to mitigate safety concerns, there is the potential for convenience stores and supermarkets to cover important information with price ticketing and other adhesive labels. This occurred when ibuprofen first became available through the grocery sector in small packs. The grocery sector has no regard to labelling and medicine safety issues and there are no quality assurance mechanisms in place to ensure important information is not covered.

2.6 We note the applicant enlisted the aid of three gastroenterologists to provide expert comment to support exempting loperamide from scheduling, arguing that loperamide is safer than other products exempt from scheduling such as paracetamol, aspirin or ibuprofen and that as 'loperamide is already available in a general sales environment through the internet, the restriction of the location of physical sales was less relevant'.

The arguments presented in these brief submissions did not demonstrate a public benefit for exempting loperamide from scheduling and the comments relate more to the efficacy of the scheduling system rather than the scheduling of loperamide. While [redacted] shares the safety concerns for paracetamol, aspirin and

ibuprofen, it is essential that scheduling decisions are not based on precedence. Scheduling decisions should not depend on the comparisons of the side-effect or safety profile of loperamide with that perceived for other agents from completely different drug classes. Decisions should be based on the impact of referral delays or delays to more appropriate treatments for the given complaint, that being 'acute diarrhoea' for loperamide. With the benefit of hind-sight, scheduling exemptions for these other medicines may no longer be supported should they be reconsidered.

[redacted] is very disappointed with the attitude of such distinguished health professionals to also concede that internet sales set precedence for open supply. The availability of medicines over the internet is problematic and there are professional requirements in the form of professional guidelines and standards[13,14,15] for the supply of S2 medicines from Australian pharmacies, managed through the Pharmacy Board of Australia. There are no such requirements for the supply of medicines through the grocery sector.

[redacted] is also concerned at the recognition provided by the ACMS to the expert opinion of only three gastroenterologists as provided by the applicant. 'Expert opinion' can usually be found to support either side of an argument, as seen in the 1970s and 1980s when tobacco lobbyists produced 'experts' downplaying the ill-effect of cigarette smoking. It is expected that the applicant would only provide evidence to support their application and [redacted] would be interested to know if the Gastroenterological Society of Australia fully supports this proposal.

3. The grocery sector lacks quality assurance processes for provision of medicines

3.1 QUM is one of the central objectives of Australia's National Medicines Policy[16]. There are no controls or quality assurance processes in place for the supply of medicines through the grocery channel. There is no health care intervention to question patients about the condition, their health or medication history or what treatments they may have already tried. Availability of medicines through the grocery sector relies completely on effective labelling and packaging and as identified in the 'Applicant's response to the Evaluation Report', this will be managed only as much as needed. The applicant identified that pack inserts are not mandatory and that packaging and labelling will be managed by the TGA separately to the scheduling decision. While there are guidelines for best-practice labelling, these are not mandatory and we feel the minimum standards for medicines labelling are not sufficient to address these safety concerns.

3.2 [redacted] is also concerned with the lack of control in the grocery sector for the quantity that can be purchased. Limiting pack size is only a gesture and provides no quality control. People can purchase as many packs of an item as they like as often as they like. While it may be unlikely that people would purchase large amounts of loperamide for intentional misuse or abuse, [redacted] remains concerned that people with conditions that require or would benefit from medical intervention may delay seeing their doctor because advice is only being provided via information on the pack – and people need to both read and understand the advice on the label for it to have any effect.

3.3 Maintaining loperamide as a S2 product provides an opportunity for intervention to address situations of greater risk. The Fourth Agreement research project

reported that purchasers of S2 medicines were generally very satisfied with the level of pharmacy advice provided and approximately 80% of purchasers want advice to always be available for S2 products in the future, even if not sought with every purchase.

3.4 Pharmacy assistants must undertake mandatory training for handling requests for S2 and S3 medicines, learning protocols such as 'Ask, Assess, Advise'[17], 'WHAT-STOP-GO'[18] or 'CARER'[19] to ensure the public is appropriately supported when purchasing S2 or S3 medicines.

3.5 Through its Quality Care Pharmacy Program (QCPP), the Guild conducts a Standards Maintenance Assessment (SMA) program, formerly known as a Mystery Shopper program. As part of this program, QCPP accredited pharmacies are assessed to measure the pharmacy's performance in the supply of S2 and S3 medicines. They are provided with feedback and benchmarked as part of a continuous improvement process. As of 30 June 2011, approximately 98% of the total number of community pharmacies in Australia are registered with QCPP and approximately 93% are accredited or in the process of becoming accredited.

A number of scenarios for direct-product-requests (DPR) for loperamide (similar to purchasing through the grocery sector), have been used for these assessments. Although the scenarios are prepared to suggest the patient may have 'food poisoning', as part of a DPR assessment, the 'mystery shopper' cannot provide such information unless prompted by questioning from pharmacy personnel.

Although there is no mandatory requirement for providing counselling or advice with the purchase of S2 products, 75% of mystery shopper requests for loperamide elicited questioning on who was the patient. This type of questioning assists in identifying at-risk patients such as children, the elderly or pregnant or lactating women. In addition, with 60% of the interactions, questions were asked about symptoms, assisting in identifying problematic symptoms such as bloody stools or fever. In over 33% of the interactions, unprompted advice was provided. The longitudinal analysis of loperamide mystery-shopper interventions also indicates an ongoing improvement over time. This is not unexpected considering the greater demand for pharmacy assistant training as part of QCPP.

This demonstrates that pharmacy delivers over and above the regulatory requirements for the provision of S2 medicines.

Conclusion

Medicines are not normal commercial products that should be freely available without quality control arrangements. Although the majority of diarrhoea cases in Australia may be uncomplicated, the public have not been disadvantaged by accessing loperamide through the pharmacy sector. In fact, this has provided an opportunity for greater and more prompt intervention in more complicated situations.

[redacted] does not support the Delegate's interim decision to exempt loperamide from scheduling and strongly suggests that inclusion within Schedule 2 remains appropriate.

Appendix A – Conditions for General Sale of loperamide in Britain

LOPERAMIDE HYDROCHLORIDE

Conditions for GSL supply

Product will be P unless the following conditions are met:

Max strength: 2mg
For the symptomatic treatment of acute diarrhoea, in adults and children 12 years and over. For the symptomatic treatment of acute episodes of diarrhoea associated with irritable bowel syndrome in adults aged 18 years and over following initial diagnosis by a doctor.
Max dose : 4mg, Max daily dose : 12mg
Max pack : 6 tabs or caps

Additional product information requirements

The first line of treatment in acute diarrhoea is the prevention or treatment of fluid and electrolyte depletion. This is of particular importance in frail and elderly patients.

<u>For acute diarrhoea</u>
If symptoms persist for more than 24 hours, consult your doctor.

<u>For acute episodes of diarrhoea associated with irritable bowel syndrome</u>
Warnings to be included in the leaflet:

Only take Imodium to treat acute episodes of diarrhoea associated with irritable bowel syndrome if your doctor has previously diagnosed IBS.

If any of the following now apply, do not use the product without first consulting your doctor, even if you know you have IBS:

- If you are 40 years or over and it is some time since your last attack of IBS or the symptoms are different this time
- If you have recently passed blood from the bowel
- If you suffer from severe constipation
- If you are feeling sick or vomiting
- If you have lost your appetite or lost weight
- If you have difficulty or pain passing urine
- If you have a fever
- If you have recently travelled abroad

Consult your doctor if you develop new symptoms, or if your symptoms worsen, or if your symptoms have not improved over two weeks.

Reference Sources:

[1]Consumer perceptions of supply and access to consumer medicines: http://www.guild.org.au/sites/The_Guild/tab-Pharmacy_Services_and_Programs/Research_and_Development/Fourth%20Agreement/Consumer%20perceptions%20of%20supply%20of%20and%20access%20to%20consumer%20medicines.page

[2] Traveller's diarrhoea; Bob Kass Australian Family Physician; Vol 34 (4): 213-304; www racgp.org.au

[3] Ibid

[4] HL DuPont, CD Ericsson, MJG Farthing et al; Expert Review of the Evidence Base for self-Therapy of Travelers' Diarrhea; Journal of Travel Medicine 2009; Vol 16 (Issue 3): 161-171

[5] Guidelines for Prescription Labelling and Consumer Medication Information for People with Vision Loss; American Society of Consultant Pharmacists Foundation and American Foundation for the Blind

[6] CHF Submission on the TGA Consultation Document: Consolidated Advisory Statement Requirements for Medicine Labels; Sept 2006; https://www.chf.org.au/pdfs/sub/sub-402-tga-medicine-labels.pdf

[7] Community Quality use of medicines and Diagnostics Project; Achieving Best Practice in the Packaging and Labelling of medicines: Report from the National Consumer Workshop; January 2011

[8] Best practice guideline on prescription medicine labeling; http://www.tga.gov.au/industry/labelling-pm-best-practice.htm

[9] http://www.tga.gov.au/pdf/consult/review-tga-transparency-1101-final-report.pdf

[10] ACSQHC Second National Report on patient Safety Improving Medication safety; July 2002; http://www.health.gov.au/internet/safety/publishing nsf/Content/F0FD7442D1F2F8DDCA2571C6000894FF/$File/med_saf_rept.pdf

[11] ABS 4228.0 – Adult Literacy and life Skills Survey, Summary Results, Australia, 2006 (Reissue); www.abs.org.au

[12] Op cit (Consumer perceptions of supply and access to consumer medicines)

[13] Pharmacy Guidelines for dispensing of medicines – Internet, mail-order dispensing and other indirect supply of medicines; http://www.pharmacyboard.gov.au/Codes-Guidelines.aspx

[14] Pharmacy guidelines on practice-specific issues – Supply of s2 and S3 medicines; http://www.pharmacyboard.gov.au/Codes-Guidelines.aspx

[15] PSA professional Practice Standards Version 4 2010; Standard 6 – Indirect Pharmacy Services; www.psa.org.au

[16] http://www.health.gov.au/internet/main/publishing nsf/Content/National+Medicines+Policy-1

[17] http://www.guild.org.au/Guild_Training/Pharmacy+Assistants+Training/A+Career+in+Pharmacy/Ask+Assess+Advise.page

[18]Standards for the provision of Pharmacy medicines and Pharmacist Only Medicines in Community Pharmacy: http://www.psa.org.au/site.php?id=1121

[19] ibid

[redacted]

2.1.3 Orphenadrine and paracetamol combination - Submission 1 of 1

[redacted]

[redacted]

7 September 2011

The Secretary
Medicines and Poisons Scheduling Secretariat (MDP88)
GPO Box 9848
CANBERRA ACT 2601
e-mail SMP@health.gov.au Facsimile 02-6289 2650

Re: Proposed amendments to the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) for rescheduling orphenadrine from Schedule 4 to Schedule 3 when combined with paracetamol and with certain conditions.

Dear Secretary,

In response to the Delegate's Interim Decision and reasons regarding the above proposed SUSMP amendments, [redacted] thanks the Committee and the Delegate for their deliberations.

[redacted] requests the following matters be considered in support of approving the rescheduling of orphenadrine+paracetamol combination.

Longstanding Heritage of Efficacy and Safety

1. There is solid evidence from credible independent sources including published studies provided as part of the rescheduling application and extensive global post–market surveillance safety data that demonstrates orphenadrine + paracetamol in the proposed dosing regimen and pack size is both effective and safe in the treatment of musculoskeletal pain. The body of evidence also shows an acceptable benefit:risk profile for the orphenadrine+paracetamol combination, which meets the need observed by the Committee for a Schedule 3 medicine of this type i.e. a combination of a skeletal muscle relaxant with an analgesic.

Acceptable Pharmacokinetics

2. The orphenadrine+paracetamol combination has more compatible pharmacokinetics than other existing Schedule 3 medicines, which is noted in the Delegate's reasons for interim decisions, August 2011, pg 92.
[redacted] agrees with this observation and, given more than 30 years global evidence of safe use of the orphenadrine + paracetamol medicine, it can be concluded that the combination is suitable for Schedule 3 inclusion.

Other factors supporting the combination as Schedule 3

The Evaluator states "*The rationale for this combination in terms of pharmacodynamics was reasonable*" and the "*safety of the combination was comparable to that of other anticholinergic medicines, and orphenadrine caused the usual range of adverse effects including dry mouth, palpitations, urinary retention, constipation, and confusion and dizziness in elderly people*".

[redacted] considers these statements supportive of Schedule 3 inclusion and that pharmacist intervention would be sufficient to mitigate any potential risk as a Schedule 3 medicine.

Widespread Use

3. Contrary to a Member's assertion that there appeared to be limited demand or desire for orphenadrine which was not a highly prescribed substance despite all its years as Schedule 4, there is widespread global experience as evidenced by the millions of patient days reported in the PSURs. As [redacted] and the previous sponsor did not actively promote this product (for many years) until recently this would explain why prescribing has not been higher in Australia.

Proven Efficacy

4. [redacted] note the comment regarding modest evidence for efficacy of the combination and of orphenadrine itself in mild, acute musculoskeletal injury.

The TGA approved the Schedule 4 product and, as part, indicated a positive efficacy finding.

There is clear and available evidence of efficacy and real-time ongoing global use of the medicine.

Supporting the efficacy of the combination is the Evaluator's published generally positive comment and conclusion that the indication "relief of pain associated with skeletal muscle spasm" was suitable for Schedule 3 OTC treatment in that it could be diagnosed by consumers and appropriate treatment could be purchased with the assistance of a pharmacist.

Additionally, the evaluator stated "Orphenadrine in this dosing regimen had been shown to be effective (albeit in a small number of studies) and safe in the treatment of musculoskeletal pain, and would be suitable for availability as a Schedule 3 medicine".

This commentary by the Evaluator subsequently reviewed by the Committee seems completely at odds with the Interim Decision to retain the current scheduling arrangement.

Norgesic tablets were registered in Australia on 14 December 1979. Given the 32 years availability, it is reasonable to conclude that the product provides an efficacious outcome to patients for the indicated use.

Additionally, as stated in the original application, Norgesic tablets containing orphenadrine citrate 35mg and paracetamol 450mg (same formulation as available in Australia) are currently marketed in up to 64 countries including Finland, Sweden, Austria, South Africa, Philippines, Hong Kong, Malaysia, Taiwan, Singapore and Thailand.
Significantly, Orphenadrine 100 mg tablets have been granted Over The Counter classification in Canada[2]. (Refer embedded Attachment 2)

Proven Safety

5. The evaluator and committee noted concerns regarding dosing and other related safety aspects.

[redacted] refers to the evaluator's positive comments that in terms of safety "The PSURs and ADRAC reports were reassuring in that the number of reports of adverse effects was a very small proportion of the number of people who were likely to have consumed orphenadrine".

Several Members also noted that orphenadrine had CNS effects and that muscle relaxants must be used with caution due to their potential for misuse.

Orphenadrine (as the hydrochloride salt) has been used for many years for the treatment of Parkinsons Disease in elderly patients, at doses far higher than the recommended dose of the proposed combination without an increase in reported adverse effects.
As with many other OTC medicines, older consumers are more vulnerable to adverse effects, and it would be at the pharmacist's discretion whether or not the orphenadrine+paracetamol

combination was deemed an appropriate product for a specific individual as he/she would for any other Schedule 3 medicine.

Pharmacists are well used to advising consumers on the safe and appropriate use of medicines with anticholinergic activity and they would assess the elderly at the point of sale of the medicine.

[redacted] reiterates that intervention by the healthcare professional is the key aspect to mitigating potential risk and the pharmacist is best positioned to do this effectively.

No Evidence of Substance Abuse – US FDA Reports

6. Members noted that there existed US FDA reports of associations of orphenadrine with substance abuse.

Publicly available documents from the US FDA on substance abuse do not attribute dependency or abuse to an orphenadrine + paracetamol combination such as proposed in this rescheduling application.

[redacted] asserts that whilst the US FDA reports might discuss association of orphenadrine, real world studies and global post-market experience do not correlate or support the USFDA reports. The plethora of post-market surveillance data and long-standing clinical studies do not support or correlate to any abuse issue with orphenadrine.

[redacted] also emphasises that in the US, the availability of orphenadrine products to a consumer is significantly different in terms of formulation, dose strengths and pack size from that proposed for the orphenadrine+paracetamol combination as a Schedule 3 medicine in Australia.

The proposed small blister pack size of orphenadrine 35 mg and paracetamol 450 mg contained in primary blister strips, when taken at the recommended dose, is not consistent with dependency and does not correlate at all with the availability and control of the product in the USA. The muscle relaxant component in the combination is present at a relatively low dose (35mg) in combination with paracetamol and the medicine is presented in a small pack size of 4 days supply.

Published studies conducted with higher strength 100 mg orphenadrine product clearly identify a lack of dependence. This is consistent with the findings presented in [redacted] rescheduling submission by Bakris et al. (1982)[1] who, in a double blind randomised study comparing diazepam 5mg TID and 100mg orphenadrine BD for periods up to 6 months in the treatment of muscle contraction headache, reported that **"a comparison of effective dosage schedules reveals orphenadrine citrate to be clearly more convenient and void of any psychological or physical dependence."**

Specifically, in the ***Summary of evaluation of applicant's specific claims against section 52E*** the Evaluator reports as follows :

(e) Potential for misuse/abuse

- *There was little, if any, evidence of abuse potential of orphenadrine.*

Additionally, global post market surveillance from over 45 years in market does not indicate any trend or signal indicator of specific abuse of orphenadrine.

Education and Counselling

Availability of the orphenadrine+paracetamol combination as a Schedule 3 medicine would require the direct intervention of a pharmacist at the point of sale. This involves determining suitability of use, education and counselling; and will be supported by a PSA (Pharmaceutical Society of Australia) developed protocol, as previously stated in the application.

Opportunity for abuse of the medicine, should that exist, would be minimised by the requirement for a pharmacist to assess the clinical need and suitability of the product for the consumer before supply.

Toxicity aspects

7. A Member noted that the toxicity of six tablets of the combination could be significant in children.

However the proposed combination, supplied under the judgement and care of a pharmacist, available in the proposed small pack size significantly reduces the risk to children of ingesting the quantity noted by the Member. This is particularly so when compared with the unrestricted availability of paracetamol in supermarkets in 24s packs, at a greater strength, available in seemingly unlimited quantity and at prices a child could afford and without the intervention of a healthcare professional. The combination presents no greater risk of toxicity than other current Schedule 3 medicines were 6 tablets to be consumed at once by a child.

Need for a Schedule 3 medicine of this type

8. A number of Members agreed that "*there may be a need for a Schedule 3 medicine of this type"* (i.e. a combination of a skeletal muscle relaxant with an analgesic), yet felt orphenadrine+paracetamol did not appropriately fulfil this need.

[redacted] asserts there is a need for a Schedule 3 medicine of this type i.e. a combination of a skeletal muscle relaxant with an analgesic and in that, concurs with the Committee.

Respectfully, [redacted] disagrees with the Committee "feeling" that orphenadrine+paracetamol did not appropriately fulfil this need particularly given these facts that the combnation is:

- the only product containing a skeletal muscle relaxant and low level analgesic AND
- an alternative option to benzodiazepines AND
- codeine and opioid free AND
- NSAID free.

[redacted] is strongly committed to providing a well established, proven, effective and safe Schedule 3 medicine of this type i.e. a combination of a skeletal muscle relaxant with an analgesic, and asserts that orphenadrine+paracetamol combination fully and appropriately fulfils this need.

[redacted] requests, in respect of the relevant matters under section 52E(1) of the Therapeutic Goods Act 1989 including (a) risks and benefits; (b) the purpose and extent of use; (c) toxicity; and (e) potential for abuse – that has already been noted in the original evaluation report by the Delegate as "*There was little, if any, evidence of abuse potential of orphenadrine."*, that this response be duly considered in support of the rescheduling of orphenadrine and paracetamol combination as proposed for Schedule 3 status.

Yours sincerely

[redacted]

[redacted]

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2. Health Canada, Drug Product Database Online Query, Accessed 7 Sept 2011.

Attachments

1. Bakris G., et al. An effective alternative for muscle contraction headaches. Orphenadrine citrate. *Illinois Medical Journal* February 1982.

2. Health Canada, Drug Product Database Online Query, Accessed 7 Sept 2011

An Effective Alternative For Muscle Contraction Headaches

Orphenadrine Citrate

By George L. Bakris, M.A., M.D., George P. Mulopulos, M.D., Subhash Tiwari, M.D., and Cory Franklin, M.D./Chicago

A prospective, randomized study, comparing the efficacy of diazepam to orphenadrine citrate for relief of muscle contraction headaches, was conducted. Symptomatic improvement of 38 female outpatients was assessed by patient response to drugs at intervals of one week, one month, and six months. Both drugs showed equal efficacy for headache alleviation regardless of duration. After a six month trial, 79% of the diazepam group and 74% of the orphenadrine group reported a decreased incidence of symptom exacerbation. Hence, orphenadrine citrate, with its minimal side effects and comparable effectiveness, may be a preferred alternative to diazepam for symptomatic control of muscle contraction headaches.

Muscle contraction headache (MCH), a bilateral, diffuse pain extending over the cranium with common occipital-nuchal localization, is associated with muscle spasm, anxiety and depression.[1] It affects 80% of the adult population and three-fourths of its victims are women.[2]

The chronic management of this symptom has resulted in a plethora of effective prophylactic medications. In recent years, some authors[3,4] have claimed diazepam to be the drug of choice for alleviating MCH. However, this anxiolytic has been associated with psychological and physical dependence, abuse, and withdrawal psychosis.[5]

We feel these anxiolytic attributes are unacceptable and necessitate the use of an alternative agent. Orphenadrine citrate, a central skeletal muscle relaxant, has been shown to possess significant activity for relieving MCH.[6,7] The purpose of this prospective study is to compare the two agents regarding their efficacy for treatment of muscle contraction headaches.

Materials and Methods

In a random, prospective study, 38 Caucasian females, newly diagnosed as having muscle contraction headache of varying duration, were treated at a public outpatient clinic. All patients described a chronic, constant, headache pain with localization in the occipital-nuchal area, which altered their daily activities and was unresponsive to both aspirin and acetaminophen. Patients with a history of arthritides, neurologic diseases, seizure disorders or migrainous phenomena as well as those receiving other analgesics, tranquilizers, sedatives or anti-inflammatory agents, were excluded from the study. Patients were randomly assigned to two groups. The diazepam group received 5mg. every 8 hours whereas the orphenadrine group received 100mg. every 12 hours. Patients were randomly given unlabeled containers of pills, which stated the number and fre-

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Table 1

Summary of Headache Response to Drugs

	Medication		
	Diazepam	*Orphenadrine citrate*	*P*
1) **Duration of muscle contraction headaches prior to treatment (months):**			
Mean SD	10 ± 1.4	9 ± 1.3	NS
Range	6-14	6-12	
2) **Median Age**	41	38	
3) **% Improvement**			
One week	90(17/19)	95(18/19)	NS
One month	79(15/19)	84(16/19)	NS
Six months	79(15/19)	74(14/19)	NS

quency with which the pills were to be taken. An assistant dispensed and refilled all medications as prescribed by the protocol. Follow-up visits were conducted at one week, one month, and six month intervals. At these periods patients were asked if headache symptoms had improved and what side effects they experienced. A positive response was defined as alleviation of headache symptoms so that pain did not interfere with daily activities. Slight improvement of persistent pain constituted unresponsiveness to medication if it interfered with daily activities.

The point-biserial correlation (t) and chi-square (X^2) tests were used to assess statistical significance of nominal data. The results were considered significant when ($P<0.05$).

Results

Eighty-three female patients were evaluated; thirty-eight (46%) met the criteria for study. The age of the entire group was 38 ± 1.2 (mean ± SEM) with a range from 21 to 59 years.

After one week of medication, three people dropped out of the study, reporting no significant benefit from treatment.

Table 1 summarizes the data. Neither group demonstrated a significant difference between mean duration of headache symptoms prior to treatment and symptom alleviation. In addition, no significant difference was observed in drug effectiveness for symptom relief after one week, one month, and six month periods.

Table 2 lists the most common side effects observed with both drugs. Other commonly reported adverse effects of these drugs, *i.e.* tolerance and withdrawal insomnia with diazepam and constipation with gastrointestinal upset with orphenadrine citrate, were not reported by our population.

Table 2

A Summary of Side Effects Observed in 38 Female Patients with Muscle Contraction Headaches

	Total No. (%)	
	Diazepam	Orphenadrine citrate
Drowsiness	18(95)	0
Weight gain	4(21)	0
Skin rash	1(5)	0
Dry mouth	0	19(100)
Dizziness	0	2(11)

Comment

Diazepam and orphenadrine citrate have demonstrated efficacy for treatment of muscle contraction headaches.[3,4,6,7] Our data give further support to these findings. Headache duration prior to therapy was not a factor in symptom improvement. In addition, no significant difference in effectiveness over a six month period was observed in either group. These data reveal both drugs possess equal efficacy for alleviation of muscle contraction headaches.

Many other drugs[8] have been utilized for relief of MCH, although most are not used for long term treatment or prophylaxis. The more popular classes of analgesics and narcotics do not possess anti-anxiety or muscle-relaxant properties.[9] Furthermore, long term use of these agents can lead to nephropathy, gastrointestinal complications, hemorrhagic diatheses and addiction.[10] Barbiturates in therapeutic doses have no muscle-relaxant properties and can result in physical dependence, drug interference by enzyme induction, and increased risk of suicide.[11] Benzodiazepines, notably diazepam, possess both direct anti-anxiety and indirect muscle-relaxant properties, attributes which quell most cases of MCH. Unfortunately, prolonged use of this drug has demonstrated a potential for addiction.[12]

Orphenadrine citrate has demonstrated efficacy for treatment of MCH; its relative disuse is unexplained. It acts on the higher levels of the central

nervous system interfering with reflex pathways for pain and skeletal muscle contraction. The resultant effect is spasmolysis of skeletal muscle contraction without reduction in the general muscle tonus.[13]

A comparison of effective dosage schedules reveals orphenadrine citrate to be clearly more convenient and void of any psychological or physical dependence.[14] Furthermore, toxic reactions in humans from gross overdosage have never been reported.[15] Chronic administration of ten times the recommended clinical dose of orphenadrine citrate to dogs and rats produced no toxic effects.[16] In light of these facts and the chronic nature of muscle contraction headache, orphenadrine citrate appears to be an excellent alternative to the commonly prescribed anxiolytics.

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Schedule(s): Select All

5 **Results Found,** 1-5 **are Displayed**

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Status	DIN	Company	Product	Class	PM *	Schedule	# **	A.I. Name ***	Strength
Active	01966162	GRACEWAY PHARMACEUTICALS	NORFLEX INJ LIQ 30MG/ML	Human	No	Ethical	1	ORPHENADRINE CITRATE	30 MG / ML
Active	01966154	GRACEWAY PHARMACEUTICALS	NORFLEX TAB 100MG	Human	No	OTC	1	ORPHENADRINE CITRATE	100 MG
Active	02047535	STERIMAX INC.	ORFENACE TABLET 100MG	Human	No	OTC	1	ORPHENADRINE CITRATE	100 MG
Active	02229731	CYTEX PHARMACEUTICALS INC.	ORPHENADRINE CITRATE INJECTION, USP	Human	No	Ethical	1	ORPHENADRINE CITRATE	30 MG / ML
Active	02243559	SANDOZ CANADA INCORPORATED	SANDOZ ORPHENADRINE	Human	No	OTC	1	ORPHENADRINE CITRATE	100 MG

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