Public Submissions on the Proposed Amendments to the Poisons Standard

Notice under subsections 42ZCZL 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 public submission on the proposed amendments to the Poisons Standard (commonly referred to as the *Standard for the Uniform Scheduling of Medicines and Poisons* - SUSMP). These submissions were considered by the Advisory Committee on Medicines Scheduling (ACMS) #11 (March 2014 meetings).

In accordance with the requirements of subsection 42ZCZL 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), issued by the National Coordinating Committee on Therapeutic Goods. The SPF is accessible at www.tga.gov.au/industry/scheduling-spf.htm.

Discrete submissions have been grouped by substance.

List of Submissions

Substance	**Total number of public submissions**
Doclofenac	2 submissions
Naproxen	4 submissions
Perampanel	1 submission
Sodium Oxybate	11 submissions

Eleven Submissions on Sodium Oxybate, eight personal submissions have not been included.

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19 February 2014

The Secretary
Scheduling Secretariat
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Dear Sir or Madam,

Re: Invitation for public comment –ACMS Meeting, March 2014
ASMI Comment

We refer to the notice inviting public comment under Regulation 42ZCZK of the Therapeutic Goods Regulations and would like to provide comment on the scheduling proposal that is to be considered by the ACMS at its March 2014 meeting. The comments submitted below address matters raised in s.52E of the *Therapeutic Goods Act 1989*. Thank you for providing the opportunity to comment.

ASMI (Australian Self Medication Industry) is the peak body representing companies involved in the manufacture and distribution of consumer health care products (non-prescription medicines) in Australia. ASMI also represents related businesses providing support services to manufacturers, including advertising, public relations, legal, statistical and regulatory consultants.

ASMI provides the following comments in relation to one of the agenda items for the ACMS meeting.

Substance	**Proposal**
Diclofenac	Proposal to amend the current Schedule 2 diclofenac entry to exempt dermal use preparations containing 2 per cent or less of diclofenac from scheduling. This would be more closely harmonised with its New Zealand medicine classification.

Comment:

ASMI supports efforts to harmonise Australian and New Zealand medicines schedules, particularly with the commitment made towards the joint agency, ANZTPA. We therefore support the above proposal to amend the current Schedule 2 diclofenac entry to exempt dermal use preparations containing 2% or less of diclofenac from scheduling.

Topical diclofenac has a favourable safety profile and provides a useful addition to the variety of therapeutic options available for short term relief of soft tissue injury, musculoskeletal injury/pain and osteoarthritis. ASMI does not believe that the proposed scheduling amendment has any negative implications for consumer safety.

Harmonisation assists sponsors by allowing aligned product details, labelling and distribution channels across both markets. It also minimises consumer confusion.

As an industry representative, ASMI is a key stakeholder in scheduling matters and appreciates the opportunity to comment on the scheduling proposals to be considered at the ACMS March 2014 meeting.

ASMI is keen to provide further input as required. We look forward to the Delegate's interim decisions.

Yours sincerely,

The Pharmacy Guild of Australia

Advisory Committee for Medicines Scheduling

Meeting March 2014

Comments by the Pharmacy Guild of Australia to the proposed amendments referred by the delegate for scheduling advice

Closing date for submission – 20 February 2014

[redacted]

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BESTPRACTICE CERTIFICATION ISO9001 QUALITY MANAGEMENT SYSTEM

Background

The Pharmacy Guild of Australia (Guild) welcomes the opportunity to comment on proposed amendments to the Standard for the Uniform Scheduling of Medicines and poisons (SUSMP) being considered by the Advisory Committee on Medicines Scheduling (ACMS) at its meeting of March 2014.

The Guild is an employers' organisation servicing the needs of independent community pharmacies. It strives to promote, maintain and support community pharmacies as the most appropriate primary providers of health care to the community through optimum therapeutic use of medicines, medicines management and related services.

Community Pharmacists provide professional advice about the safe use of medicines for optimal effect and are supported by a team of pharmacy assistant who are trained to ask questions in order to assist the pharmacist and assess if and when the pharmacist should be consulted

Further information can be found in Appendix 1.

Comments on Proposed Amendments

The Guild has considered the proposed amendments to the SUSMP of relevance to community pharmacy, with particular reference to Section 52E(1) of the Therapeutic Goods Act 1989. We provide comments for the following proposed amendments in line with the rationale for our position provided above and in Appendix 1:

- **3.2** Proposal to amend the Schedule 2 diclofenac entry to exempt dermal use preparations containing 2 per cent or less of diclofenac from scheduling. This would be more closely harmonised with its New Zealand medicine classification.

The Guild has concerns with the proposal in its current form as it poses a risk to public health. Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) used for musculo-skeletal pain and inflammation. The adverse events associated from systemic NSAID therapy (oral or rectal) led to the development of topical formulations for local use with reduced adverse effects.

Products containing 1% diclofenac (equivalent to 1.16% diclofenac diethylammonium) are exempt from scheduling, irrespective of quantity. This proposal would double the strength of diclofenac that is exempt from scheduling.

Key Points

1. Generating confusion amongst consumers by listing different strengths under a scheduling exemption
2. Safety profile of NSAIDs warrants supply of stronger topical preparations to be managed through the pharmacy sector.
3. The inclusion of warnings and directions on packs does not surmount the issues associated with poor consumer health literacy without the opportunity for counselling.
4. Appropriate scheduling must be based on best available evidence reflecting Quality Use of Medicines with harmonisation with another countries' regulatory classifications very much a secondary consideration.

(a) Risks and benefits of the use of a substance

- All NSAIDs have a similar capacity to cause renal impairment, congestive heart failure, hypertension and oedema.[1]
- NSAIDs are associated with significant cardiovascular risks, with ibuprofen associated with the highest risk of stroke, followed by diclofenac. Diclofenac also has the highest risk of cardiovascular death.[2]
- While evidence-based reviews show 1% topical diclofenac to be an effective and well tolerated treatment in painful and inflammatory conditions for short-term use, further research is recommended. [3]
- Stronger topical preparations will cause greater systemic exposure, even with proper use. Inappropriate use such as greater frequency or larger areas of application risk even greater systemic exposure.
- Chronic sustained systemic exposure to NSAIDs, particularly in patients over 65 years of age is of concern owing to documented increased risk of gastrointestinal and cardiovascular events.[4]
- Older patients are more at risk of NSAID-related adverse effects and their need for NSAID therapy should be assessed carefully. [5] The choice of a short-acting drug is especially important in patients with impaired renal function.
- This proposal would result in different strengths of diclofenac being available for general sale, without access to a trained health professional. As a result a consumer not only has to determine whether the product is suitable for them, they also have to select what strength. Current guidelines (eTGs) suggest that the lowest effective dose of NSAID should be used for the shortest period of time.[6]
    - Pharmacist counseling and advice is important in this instance as some consumers have a tendency to take more than the recommended dose, particularly with analgesics when pain control is not optimal. Surveys in the

USA showed that 6% to 13% of non-prescription ibuprofen users exceed the recommended daily dose of 1200mg and up to 1% have reported taking more than 3200mg daily.[7]

- With 1% topical diclofenac already available for general sale, it is questionable what benefit would be achieved from having a 2% strength available, and it is highly doubtful it would outweigh the various risks that have been highlighted above.

i) Polypharmacy with other NSAIDS

Concomitant administration of diclofenac gel with oral NSAIDs or aspirin may result in increased adverse NSAID effects.[8] With the unrestricted availability of aspirin and ibuprofen, there is a potential for people to combine these with topical diclofenac use, increasing the risk of systemic adverse effects. Guidelines for prescribing indicate only one non-aspirin NSAID should be used at any time. [9] The elderly will be particularly at risk and prevalence the incidence of osteoarthritis in this age group, there is a strong likelihood that they may use topical NSAID preparations as well as oral NSAIDs; particularly with targeted marketing campaigns.

ii) Advisory labels

Although advisory labels would outline to consumers the key differences with extended formulations and recommended dosages, the Guild has consistently argued that risk cannot be addressed by warning labels alone. A survey of 1000 people conducted in Northern Ireland identified only 80% of participants always or often read the instructions on non-prescription medicine packages and that 3.4% rarely or never read the information. Coupled with participants that only sometimes read the manufacturer's information, 10% of the people would be at risk of misusing these medicines.[10] As such, the Guild believes, pharmacist oversight is essential in ensuring this product is suitable for individual patients, increase patient education regarding the key differences with varying strengths of diclofenac and hence increase the likelihood the medicine will be taken correctly and safely.

(b) Harmonisation with New Zealand classification of diclofenac

The Guild notes the proposal mentions the fact this change to the scheduling of diclofenac would be more closely reflect New Zealand's medicine classification. As stated in our submission to the proposed joint regulatory scheme under ANZTPA, the Guild supports harmonisation in principle providing that less restrictive scheduling of

medicines is not automatically adopted. Rather the determining principle for harmonisation between Australia and New Zealand should be what is considered to be the most appropriate schedule.

In the case of diclofenac, the classifications in New Zealand are far less restrictive than in Australia, irrespective of the current scheduling proposal. As such, the Guild feels the proposal to increase scheduling exemption for diclofenac from 1 per cent to 2 per cent, potentially represents the 'thin edge of the wedge' and further down-scheduling proposals for diclofenac will follow. In fact in New Zealand, there are no sale restrictions on the supply of diclofenac for external use, regardless of strength or quantity. This obviously increases the risk to patients as not only is the amount of diclofenac available for purchase without the oversight of a healthcare professional considerably larger, consumers also have to select which strength and formulation of diclofenac is the most suitable. For example, consumers in New Zealand must determine independent of advice from a health professional whether a gel product containing 1 per cent diclofenac or a spray product containing 4 per cent diclofenac is the appropriate product for their condition. The various risks associated with such an approach have already been raised under the risks and benefits section above.

The Guild would therefore not support Australia's scheduling of diclofenac being relaxed simply to reflect New Zealand's medicine classification. Appropriate scheduling must be based on best available evidence reflecting Quality Use of Medicines with harmonisation very much a secondary consideration.

Recommendation and Conclusion

The Guild does not support the proposal to amend the Schedule 2 diclofenac entry to exempt dermal use preparations containing 2 per cent or less of diclofenac from scheduling and believes the current scheduling is appropriate.

Diclofenac and other commonly available NSAIDs are associated with increased cardiovascular risks. Even with the use of topical preparations, these risks are increased with stronger products, inappropriate use such as more frequent application or application to larger areas, or concomitant use with oral NSAIDs or aspirin. In addition, having two different strengths of diclofenac available for general sale is likely to confuse customers and could lead them to take more than the recommended dose or more than what is required to alleviate symptoms. Finally, the determining principle for harmonisation between Australia and New Zealand should be what is considered to be the most appropriate schedule based on best available evidence reflecting Quality Use of Medicines with harmonisation very much a secondary consideration.

Appendix 1

Quality Use of Medicines

Quality Use of Medicines (QUM) is one of the central objectives of Australia's National Medicines Policy[11]. The Guild believes that QUM is best supported by the supply of medicines through a pharmacy where there is access to professional support and advice from a pharmacist, with assistance provided from trained pharmacy assistants.

It should be noted that community pharmacy maintains a high standard of patient care with the Quality Care Pharmacy Program (QCPP) which is recognised as the Australian Standard[12] for service provision within the community pharmacy sector. By contrast, there are no controls or quality assurance processes in place for the supply of medicines outside of the pharmacy sector.

The QCPP is a quality assurance program aimed at raising the standards of pharmacy services, ensuring community pharmacies provide a uniform approach when delivering professional services and customer care. QCPP accreditation has been shown to support continuous improvement in the supply of medicines.[13]

As of 30 June 2013, approximately 92 per cent of Australian community pharmacies are QCPP accredited. As part of QCPP, it is a requirement that all pharmacy assistants involved in the supply of non-prescription medicines must be appropriately trained by an external training provider. This training includes initial and refresher training in supplying non-prescription medicines and teaches the use of protocols such as 'Ask, Assess, Advise'[14] in order to triage patient requests and refer to the pharmacist when appropriate.

Through the QCPP, the Guild conducts a Standards Maintenance Assessment (SMA) program, commonly referred to as the 'Mystery Shopper' program. Since its inception, the objectives of the SMA program have been aligned with the National Medicines Policy. As part of the SMA program, QCPP accredited pharmacies are assessed to measure the pharmacy's performance in the supply of non-prescription medicines, specifically Pharmacy Medicines (Schedule 2 or S2) and Pharmacist Only Medicines (Schedule 3 or S3). They are provided with feedback and benchmarked as part of a continuous improvement process. Analyses of SMA data to date have demonstrated continued improvement in the supply of non-prescription medicines through the pharmacy sector.[15]

Consumer access and advice

Medicines are not normal products of commerce, having the potential to do significant harm if used incorrectly or inappropriately. Consumers need and want advice on the correct and proper use of medicines and this is best achieved with supply through the pharmacy sector.

The use of and access to medicines in Australia is changing, with the population ageing and consumers contributing more and more to the cost of medicines.[16] It is essential to protect the most vulnerable consumer groups, particularly children, the elderly, those from poorer socio-economic backgrounds or those who do not speak or understand English well. Providing consumer access to information via hand-outs or labelling is not enough. Facilitating access to professional advice for the prescribing and supply of medicines is the best way to maintain safe and cost-effective access to medicines.

The high incidence of polypharmacy warrants health professional advice on the use of medicines. A recent random cross-sectional survey of Australians aged 50 years and over reports that 87% of the respondents used a medicine in the previous 24 hours, with a mean of 4.6 medicines per participant. Over 43 per cent of participants reported use of five or more medicines in the previous 24 hours and almost 11 per cent reported using ten or more medicines.[17]

With regards to non-prescription medicines, a research project[18] from the Fourth Community Pharmacy Agreement demonstrated that 80% of the interviewed consumers wanted advice to always be available at the time of purchase and the majority of people do not have issues with accessing non-prescription medicines from community pharmacies.

Reference Sources:

[1] NPS RADAR August 2005; Elevenated cardiovascular risk with NSAIDs

[2] S Trelle, S Reichenbach, S Wandel et al; Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis; BMJ 2011; 342:c7086 doi:10.1136/bmj.c7086

[3] J.Zacher, R.Altman, N.Bellamy et al; Topical diclofenac and its role in pain and inflammation: an evidence-based review; Current medical research and opinion; 2008; Vol 24, No 4; pp 925-950

[4] Safety of diclofenac topical solution compared with oral diclofenac for treatment of osteoarthritis of the knee in patients aged ≥65 years; 30th Annual Scientific Meeting of the American Pain Society; 19 May 2011

[5] ETG online – Diclofeanc http://online.tg.org.au/complete/desktop/index.htm

[6] Therapeutic Guidelines-ETP Online- NSAIDS online.tg.org.au

[7] http://www.fda.gov/ohrms/dockets/ac/02/briefing/3882B2_02_McNeil-NSAID.htm#_Toc18761792

[8] Voltaren gel Prescribing Information; September 2009; http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm193047.htm

[9] ETG online – Diclofeanc http://online.tg.org.au/complete/desktop/index.htm

[10] M Wazaify, E Shields, CM Hughes et al; Societal perspectives on OTC medicines; Family Practice 2005; 22:170-176

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

[12] Australian Standard® AS 85000-2011 Quality care Pharmacy Standard – quality management system for pharmacies in Australia

[13] Chapman J, An Evaluation of the Quality Care Pharmacy Program Part 5; Pharmacy Guild of Australia; 2005

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

[15] Quality Improvement in Pharmacy – NCCTG Interim Report October 2011; prepared by the Pharmacy Guild of Australia in conjunction with the Australian College of Pharmacy

[16] Australians paying for medicines – new research; AHHA 13/09/2011; http://ahha.asn.au/news/australians-paying-more-medicines-new-research

[17] Morgan TK, Williamson M, Pirotta M; A national census of medicines use: a 24-hour snapshot of Australians aged 50 years and older; MJA 2012; 196(1):50-53

[18] Consumer perception on supply of and access to Pharmacy Medicines; Healthcare Management Advisors; March 2010

Bayer HealthCare

11 December 2013

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Dear Sir Madam,

Re: Invitation for public comment –ACMS Meeting March 2014

We refer to the notice inviting public comment under Regulation 42ZCZK of the Therapeutic Goods Regulations 1990 and would like to take this opportunity to draw the attention to the pharmacokinetic profile of the modified release naproxen sodium 660 mg dosage form.

The following summary of data in Table 1, Figure 1 highlights the following:

1 Dose dependent kinetics of naproxen from modified release (ER) dosage forms containing 600 mg, 750 mg and 1000 mg.

Table 1: Summary of Pharmacokinetics of naproxen sodium from IR and ER dosage forms[1]

Ref	No of subjects	Age (years)	Naproxen dose (mg)	Cmax (mg/L)	Tmax (h)	AUC (mg/L.h)
2	11	19-25	250 bid X 5 days	74.9	1.4	1248
[redacted]						
3	18	20-45	750 ER once daily X 6 days	76.3	4.5	1313
4	18	18-42	250 qid X 7 days	99.5	0.89	1640
			500 bid X 7 days	101.8	5.00	1560
			1000 ER once daily X 7 days	110.7	1.36	1580

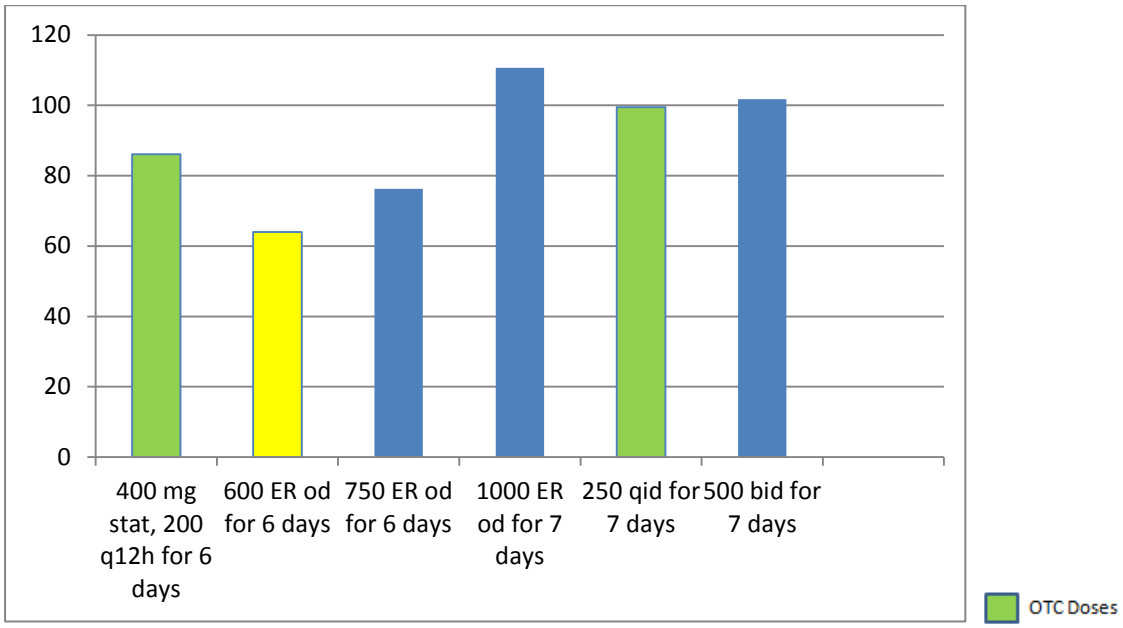
bid=twice daily; qid=four times daily

2. Steady state peak mean plasma levels (Cmax) with the 600 mg ER dosage forms are relatively lower when compared with the IR dosage forms at OTC dosages (Figure 1) of:

- 400 mg in the morning followed by 200 mg in 12 hours; or
- 250 mg four times a day.

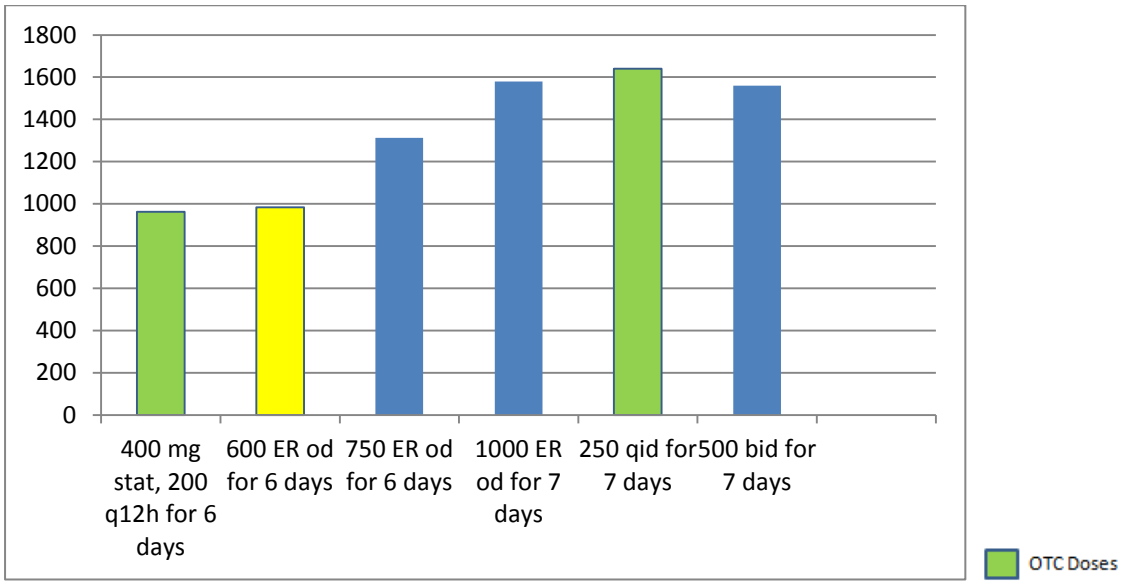
[1] Kelly JG, Kinney CD, Mulligan S, et al. Pharmacokinetic properties and clinical efficacy of once-daily sustained-release naproxen. Eur J Clin Pharmacol 1989; 36: 383-8

Figure 1 Steady state mean maximum plasma levels (Cmax mg/L) of naproxen



3. In terms of the extent of absorption (bioavailability) measured by AUC (mg/L.h), there were no differences between the IR dosage forms when given at OTC doses and the 600 mg ER product (Figure 2).

Figure 2 Steady state bioavailability (AUC mg/L.h) of naproxen



The steady state mean peak plasma level with the modified release naproxen sodium 600 mg dosage form are no higher when compared to the recommended OTC dosage regimens of the S2 naproxen 200 mg or 250 mg dosage forms and this serves to support that that the scheduling proposal for an S2 would be appropriate for the naproxen modified release dosage form.

Again, we wish to reiterate the use of extended-release products offers some potential advantages in patient convenience/compliance, sustained blood levels leading to better therapeutic outcomes and lower peak plasma levels and attenuation of adverse effects[2].

[redacted]

Yours faithfully,

[redacted]

[2] Sansom LN. Extended-release products. Aust Prescr 1999;22:88-90

Eur J Clin Pharmacol (1989) 36: 383–388

European Journal of Clinical Pharmacology

Pharmacokinetic properties and clinical efficacy of once-daily sustained-release naproxen

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Summary. The pharmacokinetics and clinical efficacy of a once-daily sustained-release formulation of naproxen (sodium salt) have been compared with those of conventional-release agents.

In a single dose pharmacokinetic study, the rate of absorption of the sustained-release preparation was less than that of a conventional-release preparation but the extent of absorption was the same. As is the case with conventional-release naproxen, food decreased the rate but not the extent of absorption of the sustained-release formulation.

On multiple dose administration for 7 days, the AUC and average concentrations of the sustained release preparation (1 g daily) were the same as those for conventional release preparations of naproxen sodium (250 mg four times daily) and naproxen free acid (500 mg daily). The conventional-release sodium salt was absorbed more quickly with no differences in bioavailability. A double-blind clinical comparison in patients with osteoarthritis showed the sustained-release preparation (1 g daily) to be equivalent in efficacy to conventional naproxen capsules (500 mg twice daily) but to have a significantly lower incidence of gastrointestinal side-effects.

The results suggest that sustained-release naproxen sodium has potential for use as a once-daily treatment for inflammatory disease.

Key words: naproxen; sustained-release formulation, pharmacokinetics, bioavailability, efficacy, tolerability

Naproxen, ((+) −2 −(6-methoxy-2-naphthyl) propionic acid), is a propionic acid derivative with analgesic and antiinflammatory properties and is widely used in the treatment of rheumatic and other inflammatory diseases. The half-life of naproxen in man is around 13 h [1]. Typical daily doses are in the range 0.5–1 g in two or three divided doses. The efficacy of naproxen is related to its plasma concentrations [2]. The development of a once-daily, sustained-release form of naproxen has several potential benefits. Once daily dosing is convenient, would minimize fluctuations in plasma concentrations and administered in the evening would produce pre-dose plasma concentrations the following morning higher than those following conventional drug administration.

The present work describes studies conducted with a once-daily sustained-release naproxen preparation. Its single- and multiple-dose pharmacokinetics were investigated and compared to those of conventional formulations. The effect of food on the pharmacokinetics of the sustained release preparation was also examined. The efficacy and tolerability of the sustained-release preparation were compared to conventional naproxen in a double-blind clinical study in patients with osteoarthritis.

Materials and methods

Drug materials

The sustained-release formulation was in a compressed microparticulate tablet form with rapid disintegration of the primary tablet matrix. This disintegration ensured wide dispersion of the sustained-release microparticles, confirmed during a study with a barium sulphate loaded preparation. The preparation contained the sodium salt of naproxen, (500 mg) as did the 250 mg conventional release preparation. The 500 mg conventional-release preparation used in the pharmacokinetic studies contained naproxen free acid. In the clinical study, capsules containing naproxen free acid 250 mg and an identical placebo were used together with a placebo for the sustained-release preparation.

Single-dose study

Twelve healthy male volunteer subjects participated in this study. Subjects were aged 18 to 42 years and weighed 58 to 78.5 kg. No subject was obese and 7 were smokers. The study was of an un-

Table 1. Pharmacokinetic summary, single-dose study (SEM) (Ranges are shown in brackets)

	C_{max} ($\mu g \cdot ml^{-1}$)	t_{max} (h)	$t_{1/2}$ (h)	Beta (h^{-1})	AUC ($\mu g \cdot ml^{-1} \cdot h$)	AUC inf. ($\mu g \cdot ml^{-1} \cdot h$)	f (rel) %
Conventional (fasting)	71.0 (2.7) (47.5-87.9)	1.58 (0.21) (0.5-3)	15.5 (1.1) (12.0-25.7)	0.047 (0.003) (0.027-0.058)	925.0 (44.6) (658-1167)	1033.0 (48.8) (753-1306)	100
Sustained-release (fasting)	40.8 (2.7) (30.5-59.4)	5.08 (0.33) (3-6)	15.3 (0.8) (12.7-22.8)	0.046 (0.002) (0.03-0.054)	967.7 (45.2) (716-1242)	1118.7 (61.2) (816-1549)	110.3 (7.6)
Sustained-release (fed)	38.2 (3.4) (19.1-56.1)	10.33 (2.78) (4-36)	19.1 (2.2) (13.0-38.4)	0.040 (0.003) (0.018-0.053)	961.7 (53.8) (643-1247)	1156.1 (79.4) (803-1743)	113.2 (7.8)

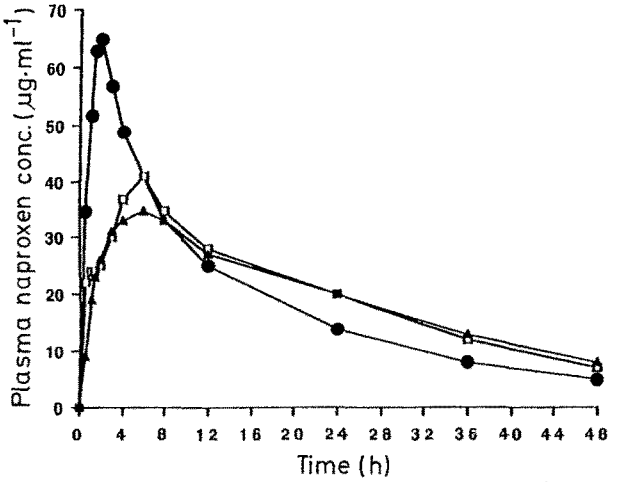

Fig. 1. Mean plasma naproxen concentrations ($\mu g \cdot ml^{-1}$). Single dose study; n = 12; ● conventional (fasting); □ sustained-release (fasting); ▲ sustained-release (fed)

blinded single-dose, three period cross-over design. Participants arrived at the study site on the evening prior to drug administration. On one occasion, participants fasted from the previous evening (for at least 11 h) and received a single 500-mg dose of a conventional-release naproxen preparation. On another occasion participants, again fasting, received a single-dose of the sustained-release formulation containing naproxen 500 mg. In each of the above cases food was served 2 h after naproxen administration with a return to a conventional diet afterwards. On a third occasion the sustained-release preparation was administered 30 min after a substantial fried breakfast. The order of the treatments was randomized. Blood specimens for assay of plasma naproxen concentrations were obtained before and at the following times after administration of the preparations: 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36 and 48 h. At least 7 days separated each administration.

Multiple-dose study

Eighteen healthy male volunteers, aged 18 to 42 years and weighing 58.5 to 90 kg participated in the study. None were obese and 15 were smokers. The study was of an unblinded, multiple-dose, three way design. Each treatment period lasted for 7 days with a minimum of 7 days between the end of one period and the beginning of the next. Participants arrived at the study site on the evening prior to each first dose. Subjects were always fasting prior to the morning doses. Subjects received the following treatments, in random order: Naproxen 500 mg conventional-release, every 12 h for 7 days; naproxen 250 mg conventional-release every 6 h for 7 days; naproxen 1.0 g as the sustained-release preparation (2 × 500 mg tablets) every morning for 7 days. All medications were administered with 150 mg of cold water. Blood specimens for assay of plasma naproxen concentrations were obtained before each morning dose and at the following times relative to the Day 7 morning dose, 0.5, 1, 2, 4, 6, 6.5, 7, 8, 10, 12, 12.5, 13, 14, 16, 18, 18.5, 19, 20, 22 and 24 h

Clinical study

Forty patients were enrolled into a ten-week-long randomized, double-blind, double-dummy cross-over study comparing the sustained-release preparation with conventional naproxen. Their average age was 63.5 years (range 33-81 years). There were 22 females and 18 males. Patients had a diagnosis of osteoarthritis confirmed clinically and radiologically. Previous anti-inflammatory drugs were discontinued for 7 days before the beginning of the study. Patients were randomly assigned to one of two groups. One group received (on a double-blind basis) 2 *tablets* of the sustained-release preparation (1 g) daily together with two placebo capsules twice daily. The other group received 2 *capsules* each containing naproxen 250 mg twice daily and two sustained-release placebo tablets once-daily. Each treatment period lasted for 4 weeks. There was a 1-week washout period and thereafter patients crossed to the alternate treament. The sustained-release preparation (or placebo) was taken in the morning (09.00 h). The conventional capsules were taken in the morning and in the evening (21.00 h), 12 h later. Each patient was supplied with 56 paracetamol tablets (500 mg each) and in the event of additional analgesia requirements were recommended to take 2 tablets up to 4 times daily. Clinical assessments were made before entry to the study and before, after two weeks and at the end of each treatment period. The overall degree of pain was assessed by the patient on a visual analogue scale. Pain on standing, while walking, at night and on passive motions were each graded on a 4 point verbal rating scale as none, mild, moderate or severe. At the end of each treatment period a global assessment of response to the treatment was made and graded on a four point scale as poor, moderate, good or excellent. At the end of the study, patients were asked which treatment period, if any they preferred. Adverse effects were recorded at each visit based upon spontaneous statements made by the patient and by indirect questioning. At the end of each treatment period a questionnaire was completed asking specifically about gastro-intestinal side effects. Unconsumed medication was returned and quantified at the end of each treatment period.

Plasma naproxen concentrations

Plasma naproxen concentrations were measured by high performance liquid chromatography. To 1 ml aliquots of plasma were added 100 μg ibuprofen internal standard followed by 1.5 ml acetonitrile. This mixture was left for 5 min and centrifuged. The clear supernatant was filtered and aliquots injected on to a 15 cm × 4.6 mm column packed with Spherisorb 5 ODS1. The mobile phase was a mixture of 175 ml acetonitrile and 325 ml of a 2 mg · ml^{-1} aqueous solution of disodium hydrogen phosphate. The pH was adjusted to 4.5 with phosphoric acid and the mixture was filtered and degassed before use. The mobile phase flow rate was 1.2 ml · min^{-1} at ambient temperature. Detection was by UV absorbance at 235 nm. Typical retention times were 3.8 min and 4.7 min for naproxen and internal standard respectively. Coefficients of variation at 50 μg · ml^{-1} were 1.6% (intra) and 2.4% (inter). The limit of quantitation was 2 μg · ml^{-1} for the present work. The assay was linear up to at least 140 μg · ml^{-1} naproxen in plasma. There were no endogenous plasma interfering peaks in the chromatography and caffeine did not interfere with the assay.

Numerical methods

Values of AUC were calculated by the trapezoidal rule. The elimination constant (beta) was calculated from the slope of the terminal portion of the log concentration-time curves and the half-life calculated as 0.693/beta. Relative bioavailability values were calculated as the ratios of the appropriate AUC values. During the multiple-dose pharmacokinetic study, average plasma concentrations at steady-state (Caverage) were calculated as AUC/24. A two-way analysis of variance (ANOVA) appropriate to the final balance of the study was used to assess differences between values for plasma concentrations at each sampling time, AUC, peak concentrations (C_{max}) and times-to-peak (t_{max}). Ordinal information was assessed using the Wilcoxon Signed Rank test. Patients' preference for one or other treatment was compared using a Chi-Square test. Pain scores on the visual analogue scale were analysed using two way analysis of variance (ANOVA).

Ethical aspects

Studies were approved by the Institutional Ethical Committee and all participants gave written informed consent to the studies.

Results

Single-dose study

Figure 1 shows the mean plasma concentrations of naproxen in the 12 participants in the single-dose study. The major pharmacokinetic findings are shown in Table 1. Plasma concentrations after administration of the sustained-release formulation showed typical differences from those after the conventional-release preparation. Peak concentrations were lower, times-to-peak were greater and post-peak declines in plasma concentrations were slower following the sustained-release formulation. Plasma concentrations of naproxen were significantly

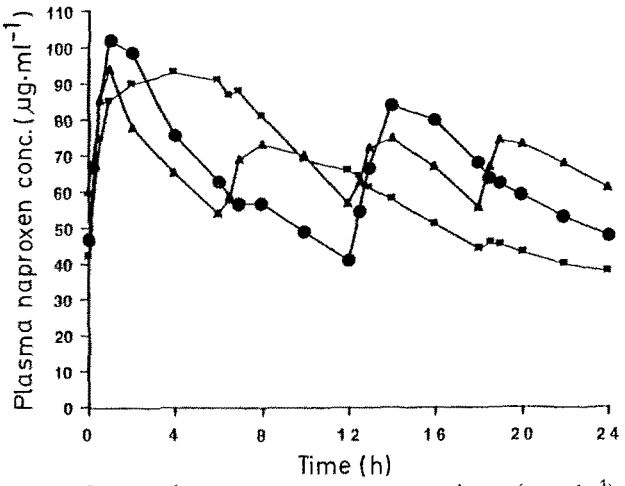

Fig. 2. Mean plasma naproxen concentrations (μg · ml^{-1}). Multiple dose study; $n = 18$; conventional (500 mg × 2 daily, ●); sustained-release (1 g daily, ■); conventional (250 mg × 4 daily, ▲)

Table 2. Mean plasma concentrations of naproxen (SEM) before the breakfast-time dose of the 3 preparations

Days	2	3	4	5	6	7
Sustained-release (1 g daily)	34.9 (2.3)	40.0 (2.2)	38.9 (2.3)	40.2 (2.0)	40.0 (2.0)	42.4 (2.8)
Conventional (500 mg twice daily)	44.1 (2.0)	47.3 (1.8)	45.2 (2.3)	49.3 (2.3)	47.4 (1.8)	47.0 (1.8)
Conventional (250 mg four times daily)	58.8 (2.5)	60.1 (2.3)	63.8 (2.5)	60.6 (2.1)	60.8 (2.6)	59.8 (2.2)

($p < 0.05$) greater following the conventional formulation at 0.5–4 h. From 6 to 12 h there were no significant differences between the formulations. From 24–48 h plasma concentrations were significantly higher following the sustained-release formulation. These differences between the conventional- and sustained-release formulations applied whether the sustained-release formulation was administered to fasting or fed subjects. Plasma concentrations obtained with the sustained-release formulation on the two occasions were significantly different at 0.5 h when plasma concentrations were higher when subjects were fasting. There were no significant differences at any other times.

Values of AUC and AUC infinity were closely similar on the three occasions. Relative bioavailability calculated as the ratio of AUC infinity values and giving the conventional formulation a value of 100, was 110.3% and 113.2% following administration of the sustained-release formulation to fasting and fed participants respectively. Values of half-life were not significantly different on the three occasions except that values after administration of the

Table 3. Pharmacokinetic study, multiple-dose study (SEM) (Ranges are shown in brackets)

	C_{max} ($\mu g \cdot ml^{-1}$)	t_{max} (h)	Caverage ($\mu g \cdot ml^{-1}$)	$t_{1/2}$ (h)	Beta (h^{-1})	AUC ($\mu g \cdot ml^{-1} \cdot h$)
Sustained-release (1 g daily)	101.8 (3.7) (81.1-131)	5.00 (0.70) (2-12.5)	65.0 (1.7) (55.9-82)	17.9 (2.5) (6.2-49.3)	0.049 (0.005) (0.014-0.111)	1560 (39.9) (1340-1967)
Conventional (500 mg twice daily)	110.7 (3.6) (90.2-139)	1.36 (0.14) (0.5-2)	65.9 (1.8) (52.2-79.4)	13.6 (2.1) (6.4-37.8)	0.065 (0.006) (0.018-0.108)	1580 (43.7) (1275-1870)
Conventional (250 mg four times daily	99.5 (2.8) (80.8-122)	0.89 (0.05) (0.5-1)	68.4 (1.8) (55.9-82)	13.0 (2.4) (5.6-35.9)	0.069 (0.009) (0.019-0.123)	1640.6 (44.0) (1381-2101)

Table 4. Mean (SEM) pain measurements, visual analogue scale (0-10, proportional to pain) before, during and after 4 weeks treatment with each preparation ($n = 36$)

	Baseline	Pre-treatment	2 weeks treatment	4 weeks treatment	1 week after treatment
Conventional	5.40 (0.37)	5.35 (0.39)	4.08 (0.42)	3.59 (0.38)	5.13 (0.37)
Sustained-release	5.08 (0.40)	5.35 (0.39)	3.53 (0.38)	3.47 (0.37)	5.13 (0.37)

sustained-release preparation to fed participants tended to be longer. Times-to-peak showed clear differences. The range of values for the conventional formulation was 0.5-3 h with most values (9/12) in the range 1-2 h. When the sustained-release preparation was administered to fasting participants, times-to-peak were always longer with 6 h as the commonest value (7/12). Following administration of the sustained-release formulation to fed participants, the times-to-peak were even longer with most values in the range 6-8 h although 2 subjects had considerably longer times-to-peak of 24 and 36 h. These reflected a commonly observed and prolonged "plateau" in plasma concentrations in the general region of 20-30 $\mu g \cdot ml^{-1}$ observed on both fasting and fed days. They did not represent a steadily rising concentrations but rather oscillations around this plateau. The differences in times-to-peak between conventional and sustained-release (fasting) and between sustained-release (fasting) and sustained-release (fed) were significant (Wilcoxon test).

Multiple-dose study

Figure 2 shows plasma concentrations of naproxen on the final day of the multiple-dose study. Table 2 shows the mean values of plasma naproxen concentrations before the breakfast-time dose on Days 2-7 of the study. These pre-morning dose concentrations related to the time since the last dose. The 250-mg dose had last been given 6 h previously, the 500-mg dose had been given 12 h previously and the 1-g dose (sustained) had been given 24 h previously.

Plasma concentrations for the 250-mg dose (four times daily) were higher than for the 500-mg dose (twice daily) which were in turn higher than for the 1-g dose (once daily). On the final dosing day, plasma concentrations of naproxen after administration of the sustained-release formulation showed the same characteristics as those observed after single-dose administration. Average times-to-peak were 5 h for the sustained-release formulation and 1.36 and 0.89 h for the conventional preparations given twice and four times daily respectively. These latter refer to the dose which gave the highest concentration of the final dosing day, not necessarily to the first dose of that day. Table 3 summarizes these and other pharmacokinetic findings. Of note are the Caverage concentrations and the values of AUC. Both of these parameters were very similar for all three preparations. Values of apparent half-life and beta in this study should be viewed with caution since they were calculated on the basis of the last study day, representing 24 h for the sustained-release preparation but only 12 h and 6 h for the twice daily and four times daily conventional-preparations. In the case of the latter, insufficient data points in the descending part of the curve meant that half-life could not be estimated in 6 subjects and half-life data for this preparation refers to 12 subjects only.

Clinical study

Four patients did not complete the study. One dropped out for reasons unconnected with the study. Two dropped out while receiving conventional naproxen sodium. One of these suffered acute gastritis and one complained of a "facial rash and puffiness". One dropped out while receiving the sus-

tained-release preparation, complaining of fluid retention. These patients were not included in any statistical evaluations.

Both treatment were effective. Table 4 shows the results of the visual analogue recording of pain (on a scale of 1–10). Pre-treatment values were the same. Following two weeks of treatment the pain scores had significantly fallen with further small but insignificant falls at 4 weeks. One week after the end of treatment, pain scores had risen again. The treatments were not significantly different on the bases of these visual analogue records.

Verbal pain scores were calculated by giving the four subjective values least to greater pain, a score of 1 to 4. These were then summed up for the four individual assessments (standing, walking, night and passive, see Methods) on a particular visit. The average pre-treatment values were 9.82 (0.45) and 9.79 (0.47) for the conventional and sustained-release reparations respectively, falling to 7.84 (0.46) and 7.87 (0.37) respectively after the second week of treatment and to 7.21 (0.35) and 7.30 (0.37) after the fourth week of treatment. Again there was no significant difference between the preparations. The preference at the end of the study, based upon pain relief, was similar for both preparations with the majority of physicians and patients scoring both medications as moderate/good. Percentages of returned paracetamol tablets were not significantly different.

Adverse effects were recorded in two different ways. At each visit, any comments made by the patients were recorded together with the result of indirect questioning by the physician. On this basis a total of 27 side-effects were noted in a total of 12 patients receiving conventional naproxen against a total of 17 side-effects in 9 patients receiving the sustained-release preparation. Of these a total of 19 gastrointestinal complaints were made by patients while receiving conventional-release naproxen against 10 complaints while receiving the sustained-release preparation. The direct questions posed by the questionnaire elicited more responses. Upon specific questioning at the end of each treatment, 30 complaints of adverse gastrointestinal effects during the treatment period were made by a total of 13 patients receiving conventional naproxen. There were significantly less (Wilcoxon test) complaints (12 complaints in 7 patients) in the case of the sustained-release preparation. The commonest complaints in all cases related to indigestion, heartburn, dyspepsia, nausea and vomiting. Thus, while the two preparations were equally scored in respect of efficacy, the sustained-release preparation demonstrated better tolerability.

Discussion

Two of the studies reported here have examined the pharmacokinetics of a once-daily sustained-release formulation of naproxen and have related its pharmacokinetic profiles to that of conventional agents. The effect of food on the pharmacokinetics of the sustained-release formulation was also examined. The rate of absorption of the sustained-release preparation was less than that of conventional-release naproxen and this was demonstrable in both studies by the prolonged times-to-peak. The extent of absorption, assessed by measurements of AUC was very similar for all the preparations, demonstrating that bioavailability of naproxen was not reduced by its incorporation in a sustained-release system.

Previous work [3] has suggested that, for conventional-release naproxen, absorption tends to be more rapid in fasting people but that the extent of absorption is not impaired. The present single-dose study showed clearly that this also happens for a sustained-release preparation with a significant increase in t_{max} but no change in C_{max} or AUC.

Examination of the data from the final day's treatment for the multiple-dose study, gives a useful indication of how the sustained-release preparation would behave in clinical use. The relatively long time-to-peak contrasts with those observed for the two conventional release preparations. One of the conventional-release preparations was the sodium salt of naproxen and the other was the acid. The free acid form of naproxen was administered as 500 mg twice daily. The sodium salt reference material was administered four times daily. The results from the final day's administration suggested that the time-to-peak was earlier for the sodium salt (0.89 h compared to 1.36 h for the acid). These results are in agreement with those of Sevelius et al. [4] who found naproxen sodium to be more rapidly absorbed than the acid form but, as we have observed, with no change in bioavailability. It should be noted that the comparative pharmacokinetic studies were performed in relatively young subjects. Naproxen, however, may be administered to patients of greatly varying ages and, in particular, many patients with inflammatory disease requiring such treatment will be elderly. In further multiple-dose studies, not reported here, we have found the bioavailability of the sustained-release preparation to be the same as that of conventional naproxen in elderly subjects.

In the clinical study, the sustained-release preparation at a dose of 1 g daily was compared with conventional-release naproxen 500 mg twice daily. Naproxen free acid was chosen here since this is the conventionally used form. No difference in efficacy

would be expected however, between the sodium salt and the free acid at similar plasma concentrations of naproxen. The similar clinical efficacies of the once-daily preparation and the twice-daily preparation was a reasonable finding since the pharmacokinetic studies indicated that the once-daily preparation had the same bioavailability as a similar daily dose of either naproxen sodium or free acid. While the efficacy of the two preparations was the same tolerability was notably different. Total spontaneous complaints and specific gastrointestinal complaints were markedly fewer when patients were receiving the sustained-release preparation. While definitive reasons for this would require further study, a possible explanation might lie in the nature of the sustained-release preparation. This was a rapidly disintegrating tablet matrix leading to wide dispersion of sustained-release microparticles, responsible for the pharmacokinetic characteristics. This dispersion was evident using barium sulphate-loaded test formulations with radiological examination. A conventional tablet and indeed a slowly disintegrating sustained-release preparation might result in local to high concentrations of naproxen with the consequent risk of localized lesions.

A sustained-release naproxen preparation such as the present one has a potential role in clinical practice. The AUC and average plasma concentrations were similar to those of conventional-release preparations given in the same doses. However, once-daily administration offers convenience for the patient. Administration in the morning produces concentrations which remain high throughout the day and next morning are still sufficiently high to have a useful role in preventing or reducing morning stiffness and pain. The formulation results in a much lower incidence of gastrointestinal side-effects suggesting that this might be applicable to other drugs which produce such effects.

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Received: October 10, 1988
accepted in revised form: January 30, 1989

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19 December 2013

The Secretary
Scheduling Secretariat
GPO Box 9848
Canberra ACT 2601

Dear Sir or Madam,

Invitation for public comment – ACMS meeting, March 2014
Notice inviting public submissions under Reg 42ZCZK of the Therapeutic Goods Regulations 1990
Naproxen – Proposal to amend the Schedule 2 entry to include a modified release dosage form of 600mg or less naproxen

We refer to the notice inviting public comment under Regulation 42ZCZK of the Therapeutic Goods Regulations and would like to provide comment on the scheduling proposals that are to be considered by the ACMS at the March 2014 meeting.

ASMI (Australian Self Medication Industry) is the peak body representing companies involved in the manufacture and distribution of consumer health care products (non-prescription medicines) in Australia. ASMI also represents related businesses providing support services to manufacturers, including advertising, public relations, legal, statistical and regulatory consultants.

ASMI appreciates the opportunity to provide public comment in relation to the above proposal. We wish to address relevant matters under section 52E of the Therapeutic Goods Act 1989, as applicable to the proposal to amend the Schedule 2 entry for naproxen.

Introduction

Naproxen is currently available as a Schedule 2 medicine in divided preparations containing 250mg or less of naproxen per dosage unit in packs of 30 or less dosage units. The recommended dose of the S2 naproxen products is 2 tablets naproxen sodium (550mg, equivalent to 500mg naproxen) as a first dose, followed by one tablet (275mg, equivalent to 250mg naproxen) every 6 to 8 hours. The total daily dose is 1375 mg naproxen sodium, equivalent to 1250mg naproxen.

ASMI supports the amendment of the Schedule 2 entry to include provision for a modified release form of naproxen, as outlined in the ACMS invitation for public comment –

Naproxen in a modified release dosage form of 600mg or less of naproxen per dosage unit in packs of 16 or less dosage units when not labelled for the treatment of children under 12 years of age.

Naproxen is a non-steroidal anti-inflammatory with a long history of use in Australia as a Schedule 2 medicine. It has a favourable safety profile, is well tolerated and has low potential for harm from inappropriate use or intentional misuse.

Scheduling criteria

The product strength of 600mg is specific to the modified release formulation, and the once a day dosage of the proposed product results in a much lower daily dose of naproxen compared to the maximum allowable dose for Schedule 2 medicines. It is highly unlikely that the formulation or dosage differences and the difference in pack size will have a negative impact on the scheduling criteria, as outlined below.

<u>The medicine is used for minor ailments that are easily recognizable by the consumer and unlikely to be confused with more serious conditions.</u>
Consumers are familiar with OTC use of naproxen and other non-steroidal anti-inflammatories for temporary relief of pain and inflammation associated with muscular aches and pains, osteoarthritis, headache, dental pain and period pain. The modified release dosage form will present no difference in this respect.

<u>The use of the medicine is substantially safe for short term treatment and the potential for harm from inappropriate use is low.</u>
Naproxen has been available for many years as a Schedule 2 medicine, which is an acknowledgement that the medicine is substantially safe for short term use. It has already been demonstrated to have a low risk of inappropriate use or misuse.

ASMI understands that the modified release tablet formulation of naproxen provides an immediate-release component as well as a prolonged-release component equivalent to a total naproxen dose of 600mg per day. This total daily dose is substantially lower than the current recommended daily dose of naproxen in Schedule 2 products (1250mg). It is reasonable to expect that the lower daily dose of naproxen may result in a comparable if not lower risk of cardiovascular and gastrointestinal adverse events.

<u>The use of the medicine at established therapeutic dosage levels is unlikely to produce dependency and the medicine is unlikely to be misused, abused or illicitly used.</u>
Naproxen in Schedule 2 has already been demonstrated to have low potential for abuse or misuse and is not subject to illicit use. The modified release dosage form in the proposed dose and pack size is similarly not expected to be subject to misuse or abuse.

<u>The risk profile of the medicine is well defined and the risk factors can be identified and managed by a consumer through appropriate packaging and labelling.</u>
Naproxen has a long history of use of in Australia, has a well-documented safety profile and is well tolerated. Risk factors have been well defined and the TGA has defined appropriate warnings and precautionary statements in RASML, indicating that there has already been acceptance that the risks are well defined and manageable through labelling and packaging.

Allowing for the modified release format in Schedule 2 will not alter the risks or change the way that any risks can be managed. It would be anticipated that product labelling should highlight the extended release nature of the formulation so that consumers can easily differentiate between the immediate release and modified release formulations.

Some other substances in Schedule 2, such as paracetamol and guaiphenesin, allow for both immediate release and extended release formulations within the same schedule. This is an acknowledgement that formulation differences can easily be managed through packaging and clear labelling, together with advice from a pharmacist or pharmacy assistant when needed.

The use of the medicine at established therapeutic dosage levels is not likely to mask the symptoms or delay diagnosis of a serious condition.
The indications / uses of the modified release formulation are expected to be consistent with the immediate release formulation, as being suitable for short term, temporary relief. Consumers are advised through appropriate labelling to consult a healthcare professional if symptoms persist.

Schedule 2 includes other non-steroidal anti-inflammatories and it is well recognised that these medicines as a class do not mask the symptoms or delay diagnosis of a serious medical condition when used as directed.

Conclusion

ASMI believes that the relevant factors specified in Section 52E have been demonstrated for naproxen as the proposed modified release tablet formulation with a single daily dose of naproxen of 600mg, which is substantially lower than the current recommended total daily dose for the immediate release formulation.

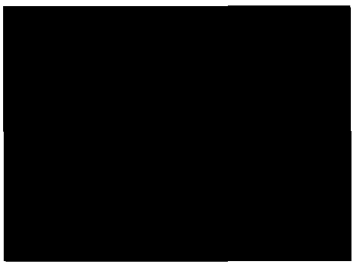
The formulation differences between the immediate release and modified release products are unlikely to impact on any of the criteria specified as part of Section 52E, namely:

52E(1)(a) – Risks and benefits
52E(1)(b) – Purposes for which a substance is to be used and the extent of use of a substance
52E(1)(c) – The toxicity of the substance
52E(1)(d) – Dosage, formulation, labelling, packaging and presentation
52E(1)(e) – Potential for abuse of the substance

Naproxen has a long history of safe use in Australia as a Schedule 2 medicine. It has a well-documented safety profile, consistent with other non-steroidal anti-inflammatory medicines and low potential for abuse or misuse. The convenience and lower daily dose can provide an additional, useful alternative product for consumers. Availability in the pharmacy environment offers consumers easy accessibility to pharmacists' professional advice.

A modified release product would provide a useful alternative to existing Schedule 2 non-steroidal anti-inflammatory products and the once daily dosage is advantegeous for compliance and consumer acceptability.

ASMI therefore supports the proposal for amendment of the Schedule 2 entry for naproxen to allow for a modified release product as described above, consistent with the Schedule 2 entry criteria as well as other non-steroidal anti-inflammatory medicines.



Pharmaceutical Society of Australia

Submission

March 2014 meeting of the Advisory Committee on Medicines Scheduling

DEC
2013

Purpose

The Pharmaceutical Society of Australia (PSA) makes this submission in relation to the proposal on naproxen referred by the Delegate for scheduling advice to the March 2014 meeting of the Advisory Committee on Medicines Scheduling. The proposal is:

> *…to amend the Schedule 2 entry for naproxen to include a modified release dosage form of 600 mg or less of naproxen per dosage unit in packs of 16 or less dosage units when not labelled for the treatment of children under 12 years of age.*

Recommendation

PSA recommends that naproxen in a modified release dosage form of 600 mg or less per dosage unit in packs of 16 dosage units or less when not labelled for the treatment of children under 12 years of age, be included in Schedule 3.

Specific comments

Scheduling and use

Naproxen is widely available and is used for its anti-inflammatory, analgesic and antipyretic properties. It is available as an over-the-counter (OTC) medicine in many countries including New Zealand, USA, Canada and the UK.

The uses of naproxen across all strengths include: headache, sinus pain, cold and flu symptoms, acute and chronic inflammatory pain, dysmenorrhoea, gout, acute migraine, rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, palliative care.

In Australia, the current Schedule 2 entry for naproxen is:

> *…in divided preparations containing 250 mg or less of naproxen per dosage unit in packs of 30 or less dosage units.*

Naproxen is also available in divided preparations in higher strengths as a Prescription Medicine (Schedule 4), containing per dosage unit 375 mg, 500 mg, 750 mg or 1000 mg. The two highest

doses are formulated as sustained release preparations and are generally administered as 750 to 1000 mg once a day.

The reported absorption profile[1] suggests that the lowest plasma naproxen concentrations attained are equivalent between a once a day dose of a 750 mg or 1000 mg sustained release formulation and a 375 mg or 500 mg twice daily dose of a standard immediate release tablet formulation.

PSA notes that naproxen (500 mg) is also available in a modified release tablet form in combination with esomeprazole (20 mg). This must be taken into consideration in the assessment of impact of any scheduling change arising from this proposal.

Balancing risks and benefits

Precautions most relevant to OTC naproxen products include: gastric ulcers and disorders, asthma, prolonged use, persistent symptoms and use in pregnancy. Previously reported[2] risks of major cardiovascular events with non-steroidal anti-inflammatory drugs (NSAIDs) appear to be associated with use at high frequency or dose and not with moderate use.

The standard dose recommendation is for a total daily dose to not exceed 1250 mg of naproxen. However, consumer factors must be carefully assessed and responses monitored with the aim of using the lowest effective dose for the shortest possible duration so that optimal therapy can be achieved while minimising possible harm. The potential for NSAIDs to cause gastrointestinal side effects or exacerbate co-existing diseases is important, particularly so for the elderly population group as the effect of these medicines can be amplified.[3]

Potential duplication of therapy is also a key consideration, not just with the elderly but also for the broader population due to the availability of naproxen and other NSAIDs in many products and forms, and across both prescription and non-prescription medicine categories.

As mentioned above naproxen is included in Schedule 4 when in a:

- modified release dosage form; or
- standard immediate release divided dosage form containing more than 250 mg per dosage unit.

The proposed amendment to Schedule 2 naproxen therefore encapsulates two significant changes — the maximum unit dose quantity is more than double the existing upper limit and the inclusion of a new (modified release) dose form which has the effect of extending the duration of the pharmacological action.

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1 Information on *Proxen SR*, *Anaprox* and *Naprosyn SR* published in eMIMS, Apr 2013.

2 Chan AT, Manson JE, Albert CM et al. Nonsteroidal anti-inflammatory drugs, acetaminophen, and the rosk of cardiovascular events. Circulation, 113: 1578–87 (2006).

3 National Prescribing Service Limited. Ageing-related changes affecting medicines use. Aug 2013. At: *www.nps.org.au/conditions-and-topics/topics/ages-life-stages/for-individuals/older-people-and-medicines/for-health-professionals/ageing-related-changes#references*.

An additional consideration is that modified dose forms are generally more difficult to manage in overdose cases. With naproxen in particular, there is no specific antidote and a high risk of consequential adverse gastrointestinal outcomes such as bleeding and perforation.

Overall, in the absence of market experience as a non-prescription medicine in this dose form and strength, PSA believes a measured transition in any rescheduling is warranted.

Intervention by pharmacists

While standard dosing instructions and warning statements relevant to the active ingredient and dose form will be required and included on the labelling and packaging of any product, pharmacists and other health professionals know that consumer factors are critical elements that impact on the achievement of optimal therapy outcomes. Although self-management of minor ailments is supported, PSA would contend that intervention by pharmacists and provision of advice which is tailored to the consumer in the context of their presenting health care needs is key to enhancing the benefits derived from medicine use.

Promoting optimal use

Where several medication therapy options are available to consumers, pharmacists will have a core role in assisting with the selection of the most appropriate option. A wide range of prescription and non-prescription products are available in the analgesic and/or NSAID class of medicines.

Although modified release dosage form products may have a therapeutic advantage in some situations PSA believes it should not be used as first line, for example, if the consumer has not tried other options. Pharmacists will have the opportunity to reinforce the message that the lowest effective dose should be used and only for a short duration.

Minimising adverse outcomes

Analgesics, including NSAIDs, are a key group of medicines implicated in adverse events. All NSAIDs increase vascular and gastrointestinal risks but the profile of risks vary for each NSAID. Naproxen is not thought to significantly increase major vascular events[4] but is considered to have moderately high risk of upper gastrointestinal complications associated with its use.[5] Indeed, evidence-based advice[6] suggests NSAIDs should be avoided in older people.

Looking at the use of medicines in the broadest sense, many adverse events ought to be preventable. The expertise of pharmacists should be utilised to detect or prevent medicine-

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4 Coxib and traditional NSAID Trialists' (CNT) Collaboration. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet, 382: 769–79 (2013).

5 Castellsague J, Riera-Guardia N, Calingaert B et al. Individual NSAIDs and upper gastrointestinal complications. A systematic review and meta-analysis of observational studies (the SOS project). Drug Saf, 35: 1127–46 (2012).

6 National Prescribing Service Limited. Medicines to avoid in older people. Aug 2013. At: *www.nps.org.au/conditions-and-topics/topics/ages-life-stages/for-individuals/older-people-and-medicines/for-health-professionals/inappropriate-prescribing/medicines-to-avoid*.

related problems and assist in selecting a therapeutic option which is appropriate for the individual consumer.

The impact of health literacy

The importance of health literacy on medicine use is widely known and has been a part of Australia's national health goals and targets for several decades. Health literacy is reported to impact on the level of understanding of dosing instructions and warning statements, correct medication management decisions, adherence to agreed treatment schedules, and correct use of therapeutic devices. Lower health literacy levels can impact on adverse events, health outcomes and health care costs.

A study in 2006 showed that 59% of Australian adults (15–74 years) had health literacy skill levels which were lower than 'adequate' (Level 3). The people with lower level health literacy skills had difficulty with tasks such as locating information on a bottle of medicine about the maximum number of days the medicine could be taken.[7]

It is known that health literacy can also decline with age.[7] This is important in the context of older people being more likely to have chronic health conditions including, for example, osteoarthritis where long-term use of analgesics is common.

Although the proposed daily dose of naproxen in this rescheduling application is not stated, a single daily dose seems likely given the modified release formulation. This would make it possible for a 16-dose pack size to provide for continuous therapy for over two weeks. The use of naproxen in such circumstances is not a preferable option.

These factors reinforce why intervention by pharmacists is important in ensuring medicines are used safely and optimally. Pharmacists and other health care providers are recognised as having a role in addressing health literacy in a coordinated way in Australia.[8]

Overall, the issues presented above clearly present Schedule 3 as the most appropriate classification and arrangement for the purposes of the current rescheduling proposal for naproxen. This will enable the consumer to be informed about therapy options and to receive advice that is tailored to their health needs and circumstances. Other factors (e.g. environmental, social) can also be taken into account. The need for monitoring of symptoms and therapy outcomes and possible triggers for medical intervention can also be emphasised. Pharmacists will also be aware that a consumer's understanding of health information and their health needs and preferences may evolve and be different from one health episode to the next.

Summary

The proposed availability of a new modified release dose form of naproxen must be considered in the context of other similar products already being used by consumers and broader implications around health literacy and quality use of medicines. Overall PSA believes that Schedule 3, with the benefits of pharmacist intervention, is the most appropriate entry in the Poisons Standard for

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7 Australian Bureau of Statistics. Australian social trends. Health literacy. Canberra: ABS; 2009.

8 Australian Commission on Safety and Quality in Health Care. Consumers, the health system and health literacy: Taking action to improve safety and quality. Consultation paper. Sydney: ACSQHC; 2013.

naproxen 600 mg in a modified release dosage form and is likely to deliver safer and better health outcomes for consumers.

The Pharmacy Guild of Australia

Advisory Committee for Medicines Scheduling

Meeting of 18 March 2014

Comments by the Pharmacy Guild of Australia to the proposed amendments referred by the delegate for scheduling advice

Closing date for submission – 19 December 2013

[redacted]

Comments on Proposed Amendments

The Guild has considered the proposed amendments to the SUSMP of relevance to community pharmacy, with particular reference to Section 52E(1) of the Therapeutic Goods Act 1989. We provide comments for the following proposed amendments in line with the rationale for our position provided above:

- Proposal to amend the Schedule 2 entry for Naproxen to include a modified release dosage form of 600 mg or less of naproxen per dosage unit in packs of 16 or less dosage units when not labelled for the treatment of children under 12 years of age.

1. **Naproxen – Proposal to amend the Schedule 2 entry for Naproxen to include a modified release dosage form of 600mg or less of naproxen per dosage unit in packs of 16 or less dosage units when not labelled for the treatment of children under 12 years of age**

   The Guild has concerns with the proposal in its current form. The proposal more than doubles the amount of naproxen that is available to consumers that can be purchased without the direct oversight of a health professional. Naproxen is a non-steroidal anti-inflammatory drug (NSAID) and while they are effective in relieving pain, fever and inflammation, they have well established side effects. These side effects include raised liver enzymes, diarrhoea, headache, dizziness, salt and fluid retention and high blood pressure.[9] In addition, dyspepsia, GI ulceration and bleeding or also common side effects.[10]

   The Guild is concerned that a Schedule 2 entry for a stronger naproxen product poses a public risk. Pharmacist counseling and advice is important in this instance as some consumers have a tendency to take more than the recommended dose, particularly with analgesics when pain control is not optimal. Surveys in the USA showed that 6% to 13% of non-prescription ibuprofen users exceed the recommended daily dose of 1200mg and up to 1% have reported taking more than 3200mg daily.[11]

   In addition, owing to the fact that unlike other OTC NSAIDs which have to be taken every 4-8 hours, the extended release formulation only needs to be taken once a day. As a result consumers who regularly take NSAIDs for pain relief may be inclined to inadvertently take more than recommended dosage if they switch to the extended release formulation if they mistakenly believe they need to take this product every 4-8 hours as it is typically the case for standard NSAIDs. Although advisory labels would outline to consumers the key differences with extended formulations and recommended dosages, the Guild has consistently argued that risk cannot be addressed by warning labels alone. A survey of 1000 people conducted in

Northern Ireland identified only 80% of participants always or often read the instructions on non-prescription medicine packages and that 3.4% rarely or never read the information. Coupled with participants that only sometimes read the manufacturer's information, 10% of the people would be at risk of misusing these medicines.[12] As such, the Guild believes if this medicine is to be down-scheduled, pharmacist oversight is essential in ensuring this product is suitable for individual patients, increase patient education regarding the key differences from other NSAIDs hence and increase the likelihood the medicine will be taken correctly.

Current guidelines (eTGs) suggest that the lowest effective dose of NSAID should be used for the shortest period of time.[13] Product Information from other forms of sustained release naproxen suggest that SR tablets are not intended for patients requiring short-term treatment for acute indications. Considering that the most likely consumers of this product are patients with rheumatoid arthiritis, osteoarthritis and other chronic inflammatory conditions, there is a risk that consumers could be taking this medication long term without monitoring by a health professional.

Dosage in special populations: elderly; renal impairment

It is generally considered in therapeutic guidelines that the choice of a shorter-acting drug is especially important in the older patient and in patients with impaired renal function due to the risk of accumulation and increased risk of significant adverse effects.[14]The Guild proposes the inclusion of SR naproxen in Schedule 3 where a pharmacist can use their clinical judgement as to the appropriateness of this medicine for the individual patient.

Research indicates that patients older than 65 years of age should take no more than 220mg every 12 hours unless directed to do so by a physician. [15] The proposal in its current form would enable a person over the age of 65 to access significantly more than the recommended dosage of naproxen without the direct oversight of a health professional. Considering the most common side effects of naproxen are gastro-intestinal irritation, headache, vertigo and depression[16] the Guild believes this proposal would pose a particular risk to this subset of the population.

Schedule Classification of other NSAIDS

The scheduling classification of naproxen, NSAIDS and paracetamol is shown in the table on the following page:

Schedule classification of other NSAIDS (Sourced from SUSMP)

Substance	Schedule 2	Schedule 3	Schedule 4
Iburprofen	In preparations for oral use when labelled with a recommended daily dose of 1200mg or less of ibuprofen: a) In liquid preparations when sold in the manufacturer's original pack containing 8 grams of less of ibuprofen b) In divided preparations, each containing 200mg or less of ibuprofen, in packs of not more than 100 dosage units except when i) As the only therapeutically active constituent (other than phenylephrine or when combined with an effervescent agent); ii) Packed in blister or strip packaging or in a container with child-restraint closure; iii) In a primary pack containing not more than 25 dosage units; iv) Compliant with the requirements of the RASML v) Not labelled for the treatment 6 years of age or less, and vi) Not labelled for the treatment of children under 12 years of age when combined phenylephrine	In divided preparations, each containing 400mg or less of ibuprofen in a primary pack containing not more than 50 dosage units when labelled: a) With a recommended daily dose of 1200mg of less of ibuprofen; and b) Not for the treatment of children under 12 years of age	Except: a) When included in or expressly excluded from Schedule 2 or 3, or b) In preparations for dermal use
Diclofenac	When: a) In divided preparations for oral use containing 12.5 mg or less of diclofenac per dosage unit in a pack containing 20 or less dosage units and labelled with a recommended daily dose of 75 mg or less of diclofenac; b) In preparations for dermal use containing 4 per cent or less of diclofenac except in preparations for dermal use containing 1 per cent or less of diclofenac or for the treatment of solar keratosis; or c) In transdermal preparations for topical use containing 140mg or less of diclofenac	In divided preparations for oral use containing 25 mg or less of diclofenac per dosage unit in a pack containing 30 or less dosage unit except when included in Schedule 2.	Except a) When included in Schedule 2 or 3; or b) In preparations for dermal use unless: i) For the treatment of solar keratosis ii) Containing more than 4 per cent of diclofenac

Substance	Schedule 2	Schedule 3	Schedule 4
Naproxen	In divided preparations containing 250mg or less of naporoxen per dosage unit in packs of 30 or less dosage units		Except when included in Schedule 2
Other similar pain relief medicines			
Paracetamol	For therapeutic use except: a) When included in Schedule 4; b) In individually wrapped powders or sachets each containing 1000mg or less of paracetamol as the only therapeutically active constituent (other than phenylephrine and/or guiaphenesinor when combined with effervescent agents) when: i. Enclosed in a primary pack that contains not more than 12 such powders or sachets of granules ii. Compliant with the requirements of the RASML iii. Not labelled for the treatment of children under 12 years of age when combined c) In tablets or capsules each containing 500mg or less of paracetamol as the only therapeutically active constituent (other than phenylephrine and/or guaphensin or when combined with effervescent agents) when: i. Packed in blister or strip packaging or in a container with a child-resistant closure; ii. In a primary pack containing not more than 25 tablets or capsules iii. Compliant with the requirements of the RASML iv. Not labelled for the treatment of children 6 years of age or less; and v. Not labelled for the treatment of children under 12 years of age when combined with phenylephrine and/or guaiphenesin	When combined with ibuprofen in a primary pack containing 30 dosage units or less	a) When combined with aspirin or salicylamide or any derivative of these substances except when separately specified in these Schedules b) When combined with ibuprofen in a primary pack containing more than 30 dosage units c) In slow release tablets or capsules containing more than 665mg of paracetamol d) In non-slow release tablets or capsules containing more than 500mg of paracetamol e) In individually wrapped powders or sachets of granules each containing more than 1000mg of paracetamol; or f) For injection

Commentary on NSAID Scheduling table

Naproxen is the only NSAID listed in the table that currently does not have a Schedule 3 listing. All other NSAIDS have tiered classifications across Schedule 2, 3 and 4. The determination for these scheduling categorisations is based predominantly on the strength and dosage recommendation of the product. It is noted the maximum dose of ibuprofen in an individual dose form that can be supplied as a Schedule 3 medicine is 400mg and 200mg as a Schedule 2 medicine. For paracetamol, the maximum dosage available as a Schedule 2 medicine is 500mg. The proposal for Naproxen would allow a significantly higher dosage of Naproxen to be available as a Schedule 2 Medicine, particularly when compared to Ibuprofen. Considering the risk profile for Naproxen is similar or perhaps greater than ibuprofen[17], the proposal to include a modified release dosage form of 600mg or less of naproxen per dosage unit in Schedule 2 appears to be inconsistent with the scheduling classification of other NSAIDS.

Availability through non-pharmacy outlets

In addition, the Guild is concerned with the potential availability of Naproxen 600mg as a Schedule 2 product through licensed non-pharmacy retail outlets in rural/remote areas. Jurisdictions license non-pharmacy outlets to supply Schedule 2 medicines in locations in which there is no pharmacy within a specified distance (from 10km in Tasmania[18] to 40km in the Northern Territory[19]). In such circumstances, there is no training for any of the retail staff and there is no access to health professional advice. Knowing that people living in rural and remote areas have generally older populations, higher levels of health risk and higher rates of chronic disease,[20,21] the risks described above are thus significantly intensified. Even though the population may be small, the safety of people in these locations still remains an important priority. People in rural/remote areas will not be disadvantaged with regards to access to a non-prescription anti-inflammatory as naproxen 250mg products remain readily available.

<u>Recommendation</u>

The Guild does not support the proposal to amend the Schedule 2 entry for Naproxen. Instead, the Guild proposes a new Schedule 3 entry for Naproxen to incorporate a modified release dosage form of 600mg or less of naproxen per dosage unit in packs of 16 or less dosage unit when not labelled for the treatment of children under 12 years of age. In relation to listing under Appendix H, the Guild would be open to supporting such a proposal.

Contact person:

[redacted]

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[17] Henry, D., Lim, L. L., Rodriguez, L. A. G., Gutthann, S. P., Carson, J. L., Griffin, M., ... & Fries, J. T. (1996). Variability in risk of gastrointestinal complications with individual non-steroidal anti-inflammatory drugs: results of a collaborative meta-analysis. *Bmj*, *312*(7046), 1563-1566.

[18] Tasmanian Poisons Act 1971 (s.27)

[19] Northern Territory Poisons and Dangerous Drugs Act (s.24)

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[21] AIHW – Rural Health; http://www.aihw.gov.au/rural-health/

commercial eyes pty ltd

The Secretary
Medicines & Poisons Scheduling
Office of Chemical Safety (MDP 88)
GPO Box 9848
Canberra ACT 2601

19th February 2014

Dear Sir / Madam

Re: Proposed amendment referred by the delegate for scheduling advice for consideration by the Advisory Committee on Medicines Scheduling (ACMS) relating to perampanel – proposal for a new Schedule 8 entry and possible inclusion in Appendix D, Item 1.

The TGA Delegate has referred the above new chemical entity for scheduling to the Advisory Committee on Medicine Scheduling (ACMS), meeting of 3 March 2014. Eisai Australia Pty Ltd, the sponsor of the application for registration in Australia, wish to make a submission to the ACMS for consideration of perampanel in schedule 4 of the Poisons standard.

Eisai submits that the extensive research and development program, with data to support several years of safe treatment of epilepsy in the clinical setting, does not indicate concern regarding the potential risk of abuse and dependency with perampanel and therefore that the drug should be included in Schedule 4 of the Poisons Standard, consistent with the scheduling status of other Anti Epileptic Drugs (AEDs) – lacosamide, pregabalin and retigabine. This is also consistent with the scheduling status in Europe, Canada and Switzerland where perampanel is registered. The recent EMA Pharmacovigilance Risk Assessment Committee (PRAC) report of 6 Feb 2014 (covering the PSUR Period 23 January 2013 to 22 July 2013) concluded that **"that there is insufficient evidence for an association between Fycompa use and drug abuse, dependency and withdrawal".**

A detailed discussion of the data to support this position follows.

[redacted]

Eisai Position on the Abuse Potential and Scheduling Status of Perampanel

The development program of perampanel has incorporated a detailed assessment of abuse liability in nonclinical and in clinical studies, as well as in post-marketing pharmacovigilance activities.

The overall nonclinical and clinical data for perampanel do not support more restrictive scheduling than the last 3 approved AEDs lacosamide, pregabalin, and retigabine.

Risks of dependency and abuse/misuse are already identified as potential risks in the risk management plan (RMP), which include the EU Post Approval Safety Study (PASS) 402 and routine pharmacovigilance. Support of the Eisai position is summarized below. Additional details can be found in the attached 8-Factor Analysis.

Nonclinical Studies

Perampanel acts via selective noncompetitive inhibition of AMPA-type glutamate receptor activity. The affinity of perampanel for an unidentified allosteric site, confirmed by the lack of competition for the binding of labeled AMPA, excludes the possibility of structural determinants in common with drugs of abuse acting through subtypes of the glutamate receptor. This has been confirmed by binding data showing that perampanel did not bind to the PCP receptor. This body of results means that perampanel does not interact with the NMDA receptor or other molecular targets of interest, even at concentrations much higher than those observed clinically. Perampanel also showed no (or very low) binding to other abuse-related molecular targets.

To further evaluate the potential effects of perampanel on various GABA receptor subunits, electrophysiological assays were conducted to profile perampanel for positive-allosteric activities on the GABAA α1β3γ2, GABAA α2β3γ2, GABAA α 3β3γ2, and GABAA α5β3γ2 ion channels. Perampanel did not have significant positive-allosteric effects on GABA evoked currents in any of the cell lines tested.

Currently known drugs of abuse do not act via the alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. Moreover, nonclinical studies assessing the effects of other AMPA receptor antagonists have not shown these drugs to have significant abuse potential or to potentiate the effects of other drugs of abuse. Rather, studies have shown these drugs to reduce the effects of drugs of abuse, including cocaine and alcohol. The effects of noncompetitive AMPA antagonists do not generalize to NMDA antagonists, and vice versa. A review of the literature suggests that AMPA antagonists do not potentiate the effects of other drugs of abuse, but rather reduce at least some of the effects related to abuse.

A physical dependence liability study was conducted in rats to determine the ability of

perampanel to produce physical withdrawal signs after 4 weeks of administration. The findings noted in the perampanel groups were considered to be withdrawal signs indicative of development of physical dependence. However, severe withdrawal signs, such as convulsions observed as a withdrawal sign of barbiturate dependence in rats (Tagashira et

al. 1978), were not observed in perampanel-treated rats under the conditions of this study, even if the half-life of perampanel in rats is only 1.8 hrs vs, the 25-105 hrs in humans.

In an intravenous (i.v.) self-administration study of perampanel in monkeys, two of the four monkeys tested (50%), trained with phenobarbital, reached the criteria established to demonstrate a positive reinforcing effect. The effect size was lower than the one with phenobarbital, as both drugs have CNS depressant effects, there might have been a non-specific component in the outcome.

Overall Extent of Exposure in Clinical Studies

In the pool of the double-blind Phase 3 studies consisting of the 1480 subjects who were randomly assigned to a treatment group and received at least one dose of study drug, 1264 (85.4%) completed therapy in one of the three studies. The completion rates were comparable in the placebo group (88.7%) and the perampanel 2-, 4-, and 8-mg/day groups (85.6%, 91.9%, and 85.2%, respectively) but somewhat lower in the 12-mg/day group (75.7%). The most common primary reasons for discontinuation in all treatment groups were AEs and subject choice.

As of January 22, 2014, there have been an estimated 5,683 unique exposures to perampanel for a duration up to 6 years.

Risk of Dependency and Abuse

In a Phase 1 study to assess the safety and tolerability of single perampanel doses up to 36 mg in recreational polydrug abusers (Study E2007-A001-023), there were elevations in 'drug liking' and 'good drug effects'. The 28-mg dose was associated with the highest peak of 'drug liking' and 'good drug effects', and these subjective effects did not appear to decline extensively over time. An important caveat is that this study was not designed with the intent of meeting criteria for a well-controlled human abuse liability study as it did not include proper controls to allow for appropriate interpretation of the findings. Rather, it was designed primarily as a safety and tolerability study, which included some measures of abuse liability, and was used to guide the dose selection for the well-controlled study described below.

In a subsequent human abuse potential study (Study E2007-A001-024), perampanel produced elevations in scores indicative of positive subjective effects that were lower than those produced by ketamine, a US FDA Schedule III drug and Schedule 8 drug in Australia, had a slower onset of effect, and also produced negative effects that were persistent, in some cases as long as 48 hours after administration. Perampanel did produce positive effects that were comparable to the positive control drug, alprazolam, a US Schedule IV drug and Schedule 8 drug in Australia, both in magnitude of effect, onset of action, and duration of effect. Again, however, perampanel also produced negative effects that were higher than alprazolam, and which lasted longer. On the 'take drug again' visual analog scale, measuring the subject's desire to take the drug again, all doses of perampanel produced numerically lower scores than 1.5 and 3 mg alprazolam, and most of the differences were statistically significant. All doses of perampanel produced peak scores significantly lower than ketamine. This measure may be deemed important because one of

the measures cited in the US FDA guidance documents as being “most directly related to likelihood of abuse” is “determining the subjects’ disposition to take the drug again.”

Further, the majority of subjects dosed with perampanel answered “no” to the question “Would you take this drug again”, more so than when dosed with alprazolam or ketamine. Finally, on the drug identification questionnaire, perampanel was most often identified as a benzodiazepine. This would suggest that the abuse potential of perampanel is no greater than benzodiazepines, and probably even less given perampanel’s profile of negative effects (drug disliking effects).

Data from Phase 1 clinical studies in healthy volunteers and Phase 2 and 3 clinical studies in subjects with epilepsy were programmatically searched and clinically reviewed, to identify TEAEs that may be suggestive of abuse potential, according to criteria set by the Controlled Substance Staff of the US FDA. The majority of these reports did not occur until after many days, weeks, months, or even years of taking the drug on a daily basis, which would not be a pattern seen with any prototypic drug of abuse. This indicates that there is little risk of abuse among the patient population, or among others who might be exposed to the drug, with the possible exception of sedative abusers.

Based on Phase 3 clinical studies, perampanel is generally well tolerated across a range of therapeutic doses up to 12 mg. In clinical studies, the most commonly reported AEs at higher doses were dizziness, somnolence/sedation, fatigue and headache, irritability, and symptoms related to coordination; there was a clear relationship between the time of onset of these AEs and the occurrence of peak plasma concentrations (C_{max}). Most AEs were mild in severity and resolved without sequelae. During Phase 3 clinical trials, there have been reports of overdose and accidental overdose; most of them were due to incorrect dose administration requiring re-education of the subjects on the proper doses. There were 15 instances of accidental overdose (three in Study E2007-G000-304, four in Study E2007-G000-306, three in Study E2007-G000-305 and one in Study E2007-G000-307), one intentional overdose and one attempted suicide (both in Study E2007-G000-307). The event most frequently associated with overdose was dizziness, which was reported as an overdose-associated treatment-emergent adverse event (TEAE) in a total of 8 (0.8%) of the 1038 subjects who received perampanel in the double-blind, Phase 3 studies.

Most of the cases of overdose resulted in an increase in the rate and severity of AEs, but did not put the subject at significant risk. Only five overdose cases resulted in serious AEs requiring hospitalization, and in each case, the symptoms resolved. Even extremely high doses of perampanel (i.e., at least 200 mg in one case) did not result in a fatal overdose. This is reassuring, because abusers will typically use higher-than-recommended amounts of a drug to achieve the desired subjective effect. In this case, the subject used over 16 times the maximum tablet dose that will be marketed (12 mg). One would not predict many abusers would take amounts this high or higher.

In the definitive human abuse liability study, perampanel doses of 8 mg to 36 mg were not related to any medically significant safety or tolerability issues, although the higher doses were associated with a greater proportion of moderate versus mild AEs.

Withdrawal

In the withdrawal study in rats, withdrawal signs indicative of development of low to mild physical dependence were reported. It is important to note that it is likely that the mild withdrawal signs seen in rodents would be less likely in humans based on the differences in the pharmacokinetics of the drug (approximately 1.8 hrs in rodents vs. 24-105 hrs in humans).

In a Phase 2 study of subjects with refractory partial seizures in which doses up to 12 mg were administered (Study 207), no patterns of withdrawal symptoms emerged after up to 424 weeks of perampanel during the 4-week Follow-up Period after cessation of use without tapering. In studies of Parkinson's disease using doses up to 4 mg as adjunctive therapy to dopaminergic drugs, there was no evidence of withdrawal by passive collections of AEs, including a study (Study 205) in which the drug was administered for 48 months.

In Phase 3 clinical studies of epilepsy in which doses up to 12 mg were administered, withdrawal data were proactively collected using a questionnaire consisting of withdrawal symptoms commonly seen after chronic use of sedatives, alcohol, and opioids. At the cut-off date of March 3, 2013, the number of subjects with Withdrawal Questionnaire data has increased two-fold, from 269 to 531. Based on the results of Withdrawal Questionnaire data analysis, no new symptoms appear to occur upon withdrawal from perampanel. The majority of subjects rated all symptoms as 'none' at all post-baseline assessments. These results were similar to those observed at the time of the MAA submission.

Moreover, the TEAE and SAE profile during the Follow-up Period of the Phase 3 double-blind studies and OLE Study 307 did not reveal any events different than those previously reported that would be considered new safety signals.

In conclusion, with available data thus far, there has been no evidence of emergent withdrawal symptoms in these studies where perampanel dosing ended without tapering. In view of the significant amount of new data now available and lack of new safety signals, we conclude that there are no noteworthy dependence effects associated with perampanel. It should be noted that approval of perampanel in the EU back in July 2012 does not have restrictive labeling language related to abuse potential.

Risk-Management Plan and other Post-Approval Requirements

Perampanel has been approved in over 36 countries. In all of them, except US, and including EU, Canada, and Switzerland, perampanel is not a controlled substance, and it is in the same prescribing class as pregabalin, lacosamide and retigabine. In US, perampanel is a Schedule III controlled substance, as ketamine, while the other AEDs mentioned above are in Schedule V, and benzodiazepines, as alprazolam, are in Schedule IV.

In addition to routine pharmacovigilance, Eisai is fulfilling the following requests from Regulatory Authorities:

- The Risk Management Plan for perampanel contains a Post-Approval Safety Study requested by the EMA including assessment of the potential for drug abuse and dependence.
- A physical dependence study in partial onset seizure subjects has been requested by the US FDA.

Post-Marketing Experience

As of February 2014, perampanel has been approved in over 36 countries, including the United States, the European Union, Switzerland, and Canada, with an estimated total exposure of 1,394,000 patient-days.

A search was performed for events coded to the Standard MedDRA Query (SMQ) for drug abuse and dependence, SMQ for drug withdrawal, and the Primary Term (PT) of euphoric mood. Cumulatively, there has been 1 report of an overdose in a 25 year old female who took 10 tablets of perampanel (dosage unknown) along with 4 g of levetiracetam, and 1.6 g of ibuprofen, and experienced vomiting. In addition, there were 3 reports of drug withdrawal convulsions following discontinuation of perampanel (all reports were of patients on an 8 mg dose).

In addition a search was performed for events in patients with a medical history coded to the Higher Level Term of substance-related disorders or drug and chemical abuse. Cumulatively, there were 2 reports; 1 report in a patient with a history of alcohol abuse and 1 report in a patient with history of substance abuse. The events reported in these cases included dizziness, nausea, and impulse-control disorder.

Overall, the post-marketing data do not show a signal for abuse and dependence, and the safety profile of perampanel remains unchanged compared to the one in the clinical development experience.

Discussion

The pharmacological activity profile of perampanel as observed in nonclinical pharmacological studies and pharmacodynamic evaluations in humans are not indicative of significant abuse or dependence liability.

- Perampanel is structurally and pharmacologically distinct from any other substance of abuse. Of the three in vivo studies to assess abuse liability, perampanel:
    - was negative in the drug discrimination test in rodents trained with diazepam and ketamine,
    - was positive in the reinforcement study in 2 out of 4 monkeys trained on phenobarbital, but with an effect size lower than the barbiturate
    - displayed signs of physical dependence (withdrawal) in rodents, where it has a very short half-life (1.9 hrs) compared to humans (24-105 hrs)

- In the definitive human abuse potential study, there were dose-related elevations in several measures of Drug Liking relative to placebo, indicating that perampanel may have some level of abuse potential. However, this abuse potential was lower than the comparison drug, US Schedule III and Australia Schedule 8 ketamine and, in many measures, lower than the other comparison drug, US Schedule IV and Australia Schedule 8 alprazolam:
    - Perampanel produced elevations in scores indicative of positive subjective effects that were lower than those produced by ketamine, had a slower onset of effect, and produced negative effects that were persistent, in some cases as long as 48 hours after administration. All doses of perampanel produced peak cores significantly lower than ketamine on the Take Drug Again scale.
    - Perampanel did produce positive effects comparable to the positive control drug, alprazolam, both in magnitude of effect, onset of action, and duration of effect. Again however, perampanel produced negative effects that were higher than alprazolam, and which lasted longer.
    - On the Take Drug Again visual analog scale, all doses of perampanel produced numerically lower scores than 1.5 and 3 mg alprazolam, and most of the differences were statistically significant. This measure may be deemed important because one of the measures cited in the US FDA guidance documents as being "most directly related to likelihood of abuse" is "determining the subjects' disposition to take the drug again."
    - These overall results of the definitive abuse liability study indicate that the abuse potential of perampanel is no greater than benzodiazepines, and probably less, based on the profile of negative effects.

- Clinically, perampanel has been tested in almost 6,000 subjects for a duration of up to 6 years. Overdose, diversion, and adverse events suggestive of abuse potential have been monitored and no signals have been detected. A withdrawal questionnaire, agreed with the Controlled Substances Staff of the US FDA has been used in all Phase 3 Epilepsy studies, and has not suggested differences between perampanel and placebo.
- Perampanel has been approved in over 36 countries including EU, USA, Canada, and Switzerland, and marketed to date in 15 of them, for an estimate exposure of almost 1.4M patient days. No signals of abuse and dependence have been detected, with an overall safety profile similar to what observed in the clinical program.

The long half-life of the drug suggests that if there were withdrawal symptoms, and if one were to occur after abrupt cessation following chronic use, it would be relatively weak in intensity and substantially delayed in onset from drug administration compared to a drug with a short half-life. For example, heroin (a short-acting opioid) produces a withdrawal syndrome that has onset within 8 hours, is fairly brief (5 to 10 days), but quite intense. In contrast, methadone (a long-acting opioid) withdrawal is slower in onset and lasts longer, but is much less intense than the withdrawal seen after cessation from a short-acting opioid (O'Brien B,. 2006, Kleber, 1981).

Because the abuse potential of perampanel appears to be weak, it is unlikely that drug abusers would engage in complex manipulation of the formulation. A series of studies conducted to assess the tamperability of the drug product suggests that the most simple extraction methods for injection (i.e., crushing the tablet and extracting in water) would not be viable due to the low solubility of the drug. While the drug can be solubilized in other solvents (e.g., 1N HCl, alcohol, acetone), it is unlikely that the practice would become widespread due to the hazardous nature of these solvents, and the fact that additional steps would be required to make the solution suitable for injection. These studies also suggest that smoking of the product would also not be a viable option, due to low recovery of the active drug during heating.

Perampanel will only be available by prescription to a population of patients diagnosed with epilepsy. Patients with epilepsy are not expected to be at particularly high risk for recreational abuse of the drug and this is expected to limit the availability of perampanel to inappropriate populations of diverters and abusers.

The potential for adverse drug-drug interactions is low. There is a potential for pharmacodynamic interactions between perampanel and other drugs causing sedative effects (e.g., sedatives, hypnotics, and alcohol). Caution should be exercised when using alcohol and/or these medications in addition to perampanel, and this is stated in the proposed perampanel labeling.

Overall, it is unlikely that perampanel is associated with a major risk to public health related to its abuse. Perampanel, the starting material, intermediates, and major metabolites are not viable chemical precursors to any known controlled substance.

All data taken together indicate that the overall profile of perampanel is comparable to other approved AEDs, including pregabalin, retigabine, and lacosamide.

In summary, considering the overall profile of perampanel in polydrug users in Studies 023 and 024, which included dose-dependent negative effects and unwillingness to try the drug again, it is highly unlikely that perampanel would have abuse liability in current and previous drug abusers.

An updated comprehensive abuse potential evaluation report (CTD M5.3.5.3.3) concluded that it is unlikely that perampanel is associated with significant risk to public health from drug abuse.

Conclusion

The extensive research and development program for perampanel, with data supporting several years of safe treatment of epilepsy in clinical setting, does not indicate concern regarding the potential risk of abuse and dependency with perampanel. The position of Eisai is that the scheduling class should be no more restrictive than the one for the recently approved AEDs lacosamide, pregabalin and retigabine. Risks of dependency and abuse/misuse are already identified as potential risks in the Risk Management Plan.

Abuse Potential Evaluation Report:

Perampanel

Version: FINAL, revised per CSS comments
Date: November 8, 2011

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[redacted]

December 4, 2013

[redacted]

Dear Sir/Madam

Re: Proposal to include sodium oxybate for human therapeutic use in Schedule 8

We are writing to support the proposal to include sodium oxybate as a Schedule 8 drug. We are the treating physicians of a young man who is only 18 years of age and who suffers from uncontrolled, disabling narcolepsy/cataplexy since the age of 13yo. He has trialled all currently available medications at their maximum doses without good effect. Currently he is on very large doses of stimulants (Dexamphetamine and Modafinil) for narcolepsy and significant doses of an anti-depressant, Clomipramine, for cataplexy. Despite this, he continues to suffer from excessive daytime sleepiness, sleep attacks, episodes of cataplexy (sudden loss of muscle tone), fragmented sleep, and features of REM behaviour disorder. This has caused a decline in his academic performance culminating in his failing to attend his HSC exams. Currently he is struggling to complete one unit at University. He struggles with memory and concentration and learning because of the narcolepsy. This is in a child who was previously at the top of his class.

The frequent episodes of cataplexy followed by prolonged periods of sleep paralysis have severely impacted his social life and social integration. He now suffers from significant anxiety. This chronic and highly disabling condition has caused a dramatic impact on his quality of life which is well known to occur in children with under-treated narcolepsy. He spends many hours of the day sleeping after unpredictable sleep attacks. On waking, he may spend up to an hour in a state of sleep paralysis – awake but unable to move his body. This occurs several times a day.

Sodium Oxybate (Xyrem) is an FDA-approved medication that reduces attacks of muscle weakness (cataplexy) and improves daytime sleepiness in patients with narcolepsy. Not just the FDA but the European Medicines Agency has also authorized its use in narcolepsy with cataplexy. In fact, the European guidelines have recommended Modafinil and Sodium Oxybate as *first line agents* in the treatment of narcolepsy/cataplexy. A recent meta-analysis has confirmed its efficacy and safety in adults (Alshaikh, 2012). Efficacy and tolerability in children was also demonstrated in a recent retrospective review (Lecendreux, 2012). As you are aware, **in Australia it remains a schedule 9 drug and is not available**.

We would be very grateful if you could consider this case and other similar cases around Australia in deciding whether Sodium oxybate can become a schedule 8 drug. At the moment,

this medication is the only hope that we can offer our young patient and his family for improved quality of life.

REFERENCES

1. Alshaikh M, Tricco A, Tashkandi M, Mamdani M, Straus S, BaHammam A. Sodium oxybate for Narcolepsy with Cataplexy: Systematic Review and Meta-Analysis. Journal of Clinical Sleep Medicine 2012;8(4):451-458.

2. Lecendreux M, Poli F, Oudiette et al. Tolerance and Efficacy of Sodium Oxybate in Childhood Narcolepsy with Cataplexy: A retrospective Study. Sleep 2012;35(5):709-711.

AUSTRALASIAN SLEEP ASSOCIATION SUBMISSION REGARDING THE PROPOSALTO INCLUDE SODIUM OXYBATE AS A SCHEDULE 8 MEDICATION FOR HUMAN THERAPEUTIC USE IN NARCOLEPSY

The Australasian Sleep Association (ASA) is the peak body in Australasia representing sleep medicine physicians. The vision of the ASA is to live in a community that recognizes the importance of good sleep to health, public safety, productivity and quality of life. A key mission of the ASA is to lead and promote sleep health and sleep science across Australia. The ASA strongly supports the proposal to include sodium oxybate in Schedule 8 of the poisons standard.

The key recommendations of the ASA regarding this submission are:

1. Sodium oxybate is effective and safe in the treatment of narcolepsy when used within the confines of a strict regulatory framework, and its use is supported by international treatment guidelines for this condition.
2. Some patients with narcolepsy remain inadequately treated despite optimal doses of currently available agents, or are unable to tolerate these agents, with resultant impact on their quality of life and productivity. In many other countries the availability of sodium oxybate for this sub-group of patients can be very beneficial for their overall quality of life. The ASA supports the access of Australian patients to sodium oxybate in this situation.
3. The ASA has provided a position statement outlining how sodium oxybate should be used in narcolepsy, to help guide sleep physicians in the use of sodium oxybate in narcolepsy.

Included in this submission are the following attachments:

1. ASA position statement and guidelines on the use of sodium oxybate in narcolepsy. This incorporates the rationale for the availability of sodium oxybate for Australian patients.
2. Documentation of the clinical experience in using sodium oxybate from Dr Dev Banerjee, Staff Specialist in Sleep Medicine at St Vincent's Hospital Sydney. Dr Banerjee had over 10 years' experience using sodium oxybate while working as a sleep physician in the UK, in one of the largest narcolepsy clinics in the NHS.

AUSTRALASIAN SLEEP ASSOCIATION

[redacted]

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[redacted]

[redacted]

6th Dec 2013

The Secretary
Scheduling Secretariat
GPO Box 9848
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Email: SMP@health.gov.au

Dear Sir/Madam

Re: Proposal to include sodium oxybate for human therapeutic use in Schedule 8

I am writing to support the proposal to include sodium oxybate as a Schedule 8 drug.

I have been specifically asked by the Australasian Sleep Association (ASA) to convey my experience in using Sodium Oxybate. I am currently working as a Staff Specialist in Sleep Medicine at the Woolcock Institute of Medical Research University of Sydney and at the Thoracic and Sleep Medicine Department, St Vincent's Hospital Darlinghurst, Sydney. Prior to this I was Head of the Sleep Medicine department at the Birmingham Heartlands Hospital, Heart of England NHS Foundation Trust, UK for ten years. My role in moving to Sydney was to continue to support the development of Sleep Medicine clinical services and academia in Sydney. Whilst in Birmingham, I ran one of the largest Narcolepsy clinic in the UK, after St Thomas Hospital London, Papworth Hospital Cambridge, and the South Tees Middlesborough in the UK. The clinic looked after 110 patients with typical, atypical and severe complex narcolepsy, with and without cataplexy. As head of department I also had the responsibility of looking after eight patients using sodium oxybate over the last six years, and therefore I regard myself as having good experience in using this drug.

My views on sodium oxybate are very positive. This relates to the clinical improvement patients benefited from, but also that I experienced no issues regarding safety, governance, abuse, and no major side effects when used correctly, particularly when delivered under the close supervision by the clinician with controlled prescribing processes.

As I have had close clinical encounters with patients using sodium oxybate, plus by virtue that sodium oxybate is not available in Australia, I am privileged to be asked to provide information on patient experiences and being possibly the only Royal College of Australasian Physicians Sleep Medicine speciality accredited staff specialist working in Australia that has had this experience. Some examples of patients from my UK clinic:

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[redacted]

[redacted]

SUMMARY

The above cases therefore highlight how sodium oxybate can transform lives. Having much experience with working with funding bodies, my reassurances to them were that only a distinct few at the extremely severe end of the clinical spectrum would require sodium oxybate, and that sodium oxybate would not be first choice therapy. In my case, I had 8 patients out of 110 on sodium oxybate.

My experience with sodium oxybate has shown me that when the assessment for sodium oxybate is carried out by accredited sleep physicians, with experience in the pharmacotherapy of narcolepsy and with thorough education of the patient on the side effects and administration of the drug, that sodium oxybate is a very useful drug to use in exceptional circumstances. The case of exceptionality in my view is severe symptoms that have a major impact on quality of life, health and potential contribution to society (ie not relying on disability benefits) despite first and second line of therapy. Exceptionality is also seen in cases whereby extremely large doses of first and second line medication are intolerable and cause severe side effectives. I therefore anticipate that these are the kind of patients that may require sodium oxybate if it became available in Australia.

Therefore I fully support the application for sodium oxybate as a schedule 8 drug and I would be very happy to advise and assist on this matter in view of my successful experience in using this drug in the UK.

[redacted]

[redacted]

[redacted]

[redacted]

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16th December, 2013

Re: Public Comment Submission for the
Proposal to include sodium oxybate for human therapeutic use in
Schedule 8 and in Appendix D Item 1.

Dear Sir / Madam,

In response to the notice inviting public submissions under Regulation 42ZCZK of the Therapeutic Goods Regulations 1990 regarding the 'proposal to include sodium oxybate for human therapeutic use in Schedule 8 an in Appendix D Item 1', I would like to provide the following comments relevant to section 52E of the Therapeutic Goods Act 1989 which support this amendment.

I represent Narcolepsy Support Australia (NSA), a not for profit charity made up of narcolepsy sufferers and their families, which has an active online community of 500 plus members.

In 2002, Sodium Oxybate (Xyrem) was legislated in the USA and later in Europe, UK and Canada for the treatment of cataplexy in narcolepsy with an expanded indication for the treatment of excessive daytime sleepiness (EDS) in narcolepsy.

It is our belief that it is time for Australia to follow suit and make Sodium Oxybate, the most effective and up to date treatment for narcolepsy with cataplexy and EDS in narcolepsy, available to Australian narcolepsy sufferers .

In particular, we believe the time is right as earlier this year Australia voted in support of the United Nations decision to transfer GHB from Schedule IV to Schedule II of the United Nations Convention on Psychotropic Substances 1971 effective late 2013, which makes Sodium Oxybate (Xyrem) eligible under the criteria required for a Schedule 8 Substance for the first time in Australia.

a) **The risks and benefits of the use of a substance:**
The current treatments available in Australia to treat narcolepsy are largely outdated and ineffective in treating the multiple symptoms of narcolepsy. Consequently, narcolepsy sufferers have an extremely poor quality of life and cannot enjoy many of the activities that mainstream society takes for granted

like driving a car or having a career. NSA members are well informed about the risks and benefits of Xyrem (Sodium Oxybate) and much discussion has taken place on our closed online community regarding this substance. The overwhelming response is that based on the results seen in the USA and UK in significantly decreasing the number and frequency of cataplexy attacks, improvements in daytime sleepiness and the reduction in night time waking, that the benefits of Xyrem (Sodium Oxybate) far outweigh its risks.

b) **The purposes for which the substance is to be used and the extent of use of a substance:**
We fully support the use of sodium oxybate for human therapeutic use in Schedule 8, so that it can be made available on prescription from Sleep Physicians for the treatment of Narcolepsy with Cataplexy and EDS in Narcolepsy as it is currently available in the USA, UK, Canada and Europe. Currently, there is no drug available in Australia that treats all symptoms of narcolepsy as effectively as Sodium Oxybate (Xyrem).

c) **The toxicity of a substance:**
Clinical trials have proven that Xyrem (Sodium Oxybate) is safe and effective in treating Narcolepsy with Cataplexy and EDS in Narcolepsy when prescribed within the active dose range and when administered during night-time hours. It has effectively been used in the treatment of narcolepsy in the USA since 2002 and also in the UK, Europe and Canada.

d) **The potential for abuse of a substance**
We understand that Sodium Oxybate the sodium salt gamma hydroxybutyrate (GHB) which has the potential for abuse. However, in the USA and UK this has been minimised through the use of a Controlled Distribution System which we would support to be implemented in Australia.

There is no cure for narcolepsy; therefore treatment relies on the management of symptoms through medicine with therapeutic benefits. However, there are no drugs actually licensed for the treatment of narcolepsy with cataplexy.

In conclusion, NSA fully supports the proposed amendment for sodium oxybate for human therapeutic use in Schedule 8.