PUBLIC SUBMISSIONS ON THE PROPOSED AMENDMENTS TO THE POISONS STANDARD

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

A delegate of the Secretary of the Department of Health and Ageing publishes herein all valid public submissions made in response to the invitation for public submission on the proposed amendments to the Poisons Standard. These submissions were considered by the the Advisory Committee on Chemicals Scheduling (ACCS) #7, the Advisory Committee on Medicines Scheduling (ACMS) #8 and the joint ACCS-ACMS #5 (March 2013 meetings).

In accordance with the requirements of subsection 42ZCZL of the Regulations these submissions have had the 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 (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. A number of applicants provided submissions that related to multiple substances. These submissions on multiple items have been separately grouped.

LIST OF SUBMISSIONS

Substance	Total number of public submissions
Diclofenac	4 submissions (all 4 submissions under 'submissions on multiple substances')
Nabiximols	8 submissions (2 submissions under 'submissions on multiple substances)
Hydrocortisone and Hydrocortisone acetate	4 submissions (3 submissions under 'submissions on multiple substances')
Lisdexamfetamine	1 submission under 'submissions on multiple substances
Oseltamivir	4 submissions (all 4 submissions under 'submissions on multiple substances')
Benzodiazepines	70 submissions (4 submissions under 'submissions on multiple substances')
Adrenaline, Bupicacaine and Lignocaine	5 submissions (2 submissions under 'submissions on multiple substances')
Tylosin	5 submissions (2 submissions under 'submissions on multiple substances)
Terminology – Part 1 Interpretation: Advice on inclusion of terms, such as synthetic, analogue and derivative, to the Part 1, Introduction in order to better define these terms, their intent and purpose	3 submissions

SUBMISSIONS ON MULTIPLE SUBSTANCES

One submission was on benzodiazepines, diclofenac, hydrocortisone and hydrocortisone acetate, nabiximols, oseltamivir, lisdexamfetamine, tylosin, adrenaline and lignocaine.

One submission was on diclofenac and oseltamivir.

One submission was on benzodiazepines, diclofenac, hydrocortisone and hydrocortisone acetate, nabiximols and oseltamivir.

One submission was on benzodiazepines, diclofenac, hydrocortisone and hydrocortisone acetate and oseltamivir.

One submission was on benzodiazepines, tylosin, adrenaline, bupivacaine and lignocaine.

Proposed amendments to the poisons standard referred by the delegate for scheduling advice

1. Proposed amendments referred by the delegate for scheduling advice for consideration by the Advisory Committee on Medicines Scheduling (ACMS)	
Substance/s	**Scheduling proposal**
Benzodiazepines	Proposal to reschedule benzodiazepines from Schedule 4 to Schedule 8. Comment- Agree with Recommendation to change benzodiazepines to Schedule. Benzo's add to the CNS depressant burden on especially the elderly. Have no significant benefit.
Diclofenac	Proposal to exempt from scheduling for diclofenac when presented as a 140 mg or less diclofenac transdermal drug delivery system. Comment- Disagree with the Recommendation to exempt 140 mg or less diclofenac. Potential for NSAID interactions.
Hydrocortisone and hydrocortisone acetate	Proposal to reschedule preparations containing 1 per cent or less hydrocortisone and hydrocortisone acetate when combined with antifungal substances for dermal use from Schedule 3 to Schedule 2. Comment- Disagree with the rescheduling. Hydrocortisone acetate side effect profile is best regulated by restricting access, requiring some professional advice and regulation.
Nabiximols	Proposal to reschedule nabiximols from Paragraph 3 of the Appendix D to Paragraph 1 of the Appendix D. Comment- Agree Novel cannabinoid formulation Nabiximols should be rescheduled, Paragraph 1 of Appendix D.
Oseltamivir	Proposal to reschedule oseltamivir for the treatment and prevention of influenza type A and type B from Schedule 4 to Schedule 3. Comment-Disagree Oseltamivir Tamiflu should remain schedule 4
Lisdexamfetamine	Proposal to include lisdexamfetamine in Schedule 8. Comment-Agree L-lysine-D-amphetamine should be included in Schedule 8

2. Proposed amendments referred by the delegate for scheduling advice for consideration by the joint meeting of the Advisory Committee on Chemicals Scheduling (ACCS) & the Advisory Committee on Medicines Scheduling (ACMS).	
Substance/s	**Scheduling proposal**

2. Proposed amendments received by the deadline for scheduling advice for consideration by the joint meeting of the Advisory Committee on Chemicals Scheduling (ACCS) & the Advisory Committee on Medicines Scheduling (ACMS)	
Substance/s	**Scheduling proposal**
Adrenaline, bupivacaine and lignocaine	Proposal to reschedule a veterinary preparation containing adrenaline, bupivacaine and lignocaine from Schedule 4 to Schedule 6. Comment- Agree that adrenaline and lignocaine should be rescheduled
Tylosin	Proposal to reschedule tylosin from Schedule 5 to Schedule 4. Comment- Agree Tylosin should be rescheduled as schedule 4.

ACMS Public Comment

I thank you for the opportunity to comment on the rescheduling, each has its own unique features that require careful consideration before any change is made.

I commend some changes and urge caution on some.

Yours faithfully

[redacted]

13/01/2013

Confidential

[redacted]

Sub[redacted]ces

17 January 2013

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

Re: Notice inviting public submissions under Regulation 42ZCZK of the Therapeutic Goods Regulations 1990

Dear Secretary

NPS appreciates the opportunity to comment on the proposed amendments to the poisons standard referred by the delegate for scheduling advice. We support changes to improve quality use of medicines however the process must be transparent and required information readily available. In preparing the response to this submission we had great difficulty ascertaining the information needed to respond to all of the proposed changes. For example we would have liked to comment on the proposed scheduling changes to diclofenac but were unable to obtain the necessary further information.

In regards to oseltamivir, while recognising the rescheduling of it to Schedule 3 has the potential to improve the timeliness of access for use in influenza A and influenza B infections, there are a number of concerns which may outweigh any benefit.

The following should be considered:

- The diagnosis of influenza relies on history and examination and there is no highly reliable rapid test currently available for influenza. Moreover oseltamivir has shown a lack of efficacy if given late in the infection or if circulating strains are resistant. As such and coupled with the added commercial pressures pharmacists experience there is the potential for it to be provided for illnesses where it has no effect and there is questionable indication.
- At present there is little evidence directly linking oseltamivir use with the development of resistance. However easier accessibility may promote more liberal use and potentially lead to increasing oseltamivir resistance.
- There have been significant potential adverse effects reported e.g. neuropsychiatric symptoms in Japanese children. Clinical monitoring of patients and referral to a GP would need to be considered in this setting.
- This schedule change would set a precedent for other systemic antimicrobials to be rescheduled which may contribute to increasing the antimicrobial resistance problem more generally.

We would be happy to discuss these issues further if required.

[redacted]

[redacted]

The Pharmacy
Guild of Australia

Advisory Committee for Medicines Scheduling

Meeting of 20-21 March 2013

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

Closing date for submission – 17 January 2013

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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 2013.

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.

Quality Use of Medicines

Quality Use of Medicines (QUM) is one of the central objectives of Australia's National Medicines Policy[1]. 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[2] 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 uniformed approach when delivering professional services and customer care. QCPP accreditation has been shown to support continuous improvement in the supply of medicines.[3]

As of 31 December 2012, approximately 98% of Australian community pharmacies are registered with QCPP and approximately 92% are accredited or in the process of becoming 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'[4] 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.[5]

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.[6] 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% of participants reported use of five or more medicines in the previous 24 hours and almost 11% reported using 10 or more medicines.[7]

With regards to non-prescription medicines, a research project[8] 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.

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:

- Reschedule benzodiazepines from Schedule 4 (S4) to Schedule 8 (S8).
- Exempt from scheduling diclofenac when presented as a 140mg or less diclofenac transdermal medicine delivery system.
- Reschedule oseltamivir for the treatment and influenza type A and type B from Schedule 4 (S4) to Schedule 3 (S3)
- Reschedule nabiximols from Paragraph 3 of the Appendix D to Paragraph 1 of the Appendix D.
- Reschedule preparations containing 1 per cent or less hydrocortisone and hydrocortisone acetate when combined with antifungal substances for dermal use from Schedule 3 (S3) to Schedule 2 (S2).

1. Benzodiazepines – Proposal to reschedule benzodiazepines from Schedule 4 (S4) to Schedule 8 (S8).

The Guild has concerns with this scheduling proposal. Owing to the number of benzodiazepines products dispensed (5.3 million under the PBS, year ending June 2012[9]), a reschedule to S8 would create enormous administrative problems. Jurisdictional health departments would struggle to effectively manage the sheer volume of information that they would receive in order to meet the requirements associated with the schedule change.

There would also be a host of additional financial costs that would impact numerous parts of the medicine supply chain. It would increase costs for wholesalers, pharmacies, aged care facilities and the Commonwealth through increased medicine dispensing fees.

Pharmacies must store S8 medicines in a medicine-safe that meets jurisdictional legislative requirements. Such medicine safes have a limited storage capacity and with more products being restricted to S8, pharmacies must assess and resolve any storage issue. Replacing a safe or installing an additional one can be costly, and some pharmacies may not have the space for such measures without a significant refit of the dispensary. The proposed change is likely to have a similar impact on the pharmacy wholesaler sector as well. Sectors such as acute care and aged care will also be significantly impacted with facilities requiring extra security for the storage of the additional S8 medicines as well as the administrative burden for staff in storing, handling, administering and recording benzodiazepines as an S8 medicine. Another unintended consequence will be the impact on the use of the National Residential Medication Chart[10] as a prescription to streamline prescribing, supplying and claiming medicines for aged care residents.

The Guild's analysis of the Medicare database from July 2011 to June 2012 shows over 5 million subsidised benzodiazepine prescriptions dispensed under the Pharmaceutical Benefits Scheme (PBS) and Repatriation Schedule of Pharmaceutical Benefits (RPBS) – see *Attachment A*. If these numbers remained the same, the additional 'Dangerous Medicine Fee' of $2.71 per item for dispensing subsidised Controlled Medicines would cost the PBS/RPBS an additional $14.5 million per year.[11] While there may be an expectation of a smaller number of benzodiazepines being prescribed and dispensed, the PBS/RPBS may still be impacted if prescribers use alternative subsidised medicines that are more expensive.

In addition, the Guild has concerns this rescheduling would have a detrimental impact on patient access due to differences in jurisdictional requirements for prescribing and supply of Controlled Medicines. Benzodiazepines are subsidised under the PBS for longer term use for conditions such as myoclonic epilepsy (nitrazepam), epilepsy (clonazepam), late-stage malignant neoplasia (nitrazepam, oxazepam, temazepam), palliative care where anxiety is a problem (diazepam, oxazepam) or insomnia is a problem (nitrazepam, temazepam), terminal disease or refractory phobic or anxiety states (bromazepam). They are also subsidised for long term use in people receiving long-term nursing care on account of disability, age, infirmity or other conditions in hospitals, nursing homes or residential facilities with benzodiazepine dependence (diazepam, nitrazepam, oxazepam, temazepam).[12]

Legitimate patients and their carers and providers living in border towns or travelling interstate are most likely to be impacted. In addition, there would be an administrative and access impact on hospitals and clinics regarding the use of the short-acting benzodiazepine midazolam for conscious sedation for short surgical procedures. [Note – the use of midazolam is not listed in the table at Attachment A as it is not subsidised under the PBS].

Furthermore, it is questionable whether this change would address problems with misuse and abuse. Intentional abusers of benzodiazepines usually have other substance abuse problems[13], and in a study that interviewed intravenous drug users, almost three in five thought a reduction in benzodiazepine availability would not affect them because they did not use the medicines or only used them occasionally or legitimately.[14] Reports also suggest efforts to reduce the supply of illicit pharmaceuticals could lead to unintended consequences such as increased crime to finance the higher illicit costs of less available pharmaceuticals and the substitution of more problematic products such as alcohol, methamphetamine or other analgesics.[15] The same reports have concluded a health system response to pharmaceutical misuse is probably a preferable option to a law enforcement or criminal justice system response.[16]

In order to address the concerns regarding doctor and pharmacy shopping as well as abuse and misuse, the Guild suggests the following options:

- Real time reporting
- Smaller PBS quantities
- Promotion of benzodiazepine contracts/staged supply, and
- Alternative options to manage sleep/anxiety disorders

Real time reporting

Real-time reporting (RTR) systems are a much more sophisticated/specific tool to address misuse, alerting the relevant agencies who monitor the problem and providing clinicians with an effective decision support tool. The use of RTR could be considered as part of the proposed Appendix N (notifiable medicines) of the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP), which was described in the draft Scheduling Policy Framework released by the National Co-ordinating Committee on Therapeutic Goods in 2009.

The Guild understands that benefits have been identified in Tasmania as the RTR system in that state has rolled out. This system is designed to enable real time secure reporting of the S8 medicines dispensed from Tasmanian pharmacies and is being further developed for roll-out in other jurisdictions under the 'Electronic Recording and Reporting of Controlled Medicines'[17] as part of the Fifth Community Pharmacy Agreement. The access to accurate dispensing information in real time has increased the capacity for Tasmanian Pharmaceutical Services Branch (PSB) pharmacists to identify potential problems, and to make clinically significant interventions to promote best practice/improve public health outcomes. This is in contrast to having to wait 6-8 weeks after supply to receive dispensing information, as was previously the case.[18] The critical role of effective information and monitoring systems, and limitations of current systems, has been raised in coronial inquiries into medicine-related deaths.[19]

What is interesting however is that Tasmania has identified an issue specifically with alprazolam abuse/misuse and is addressing this by applying additional reporting requirements as with an S8 medicine while retaining it as a S4 medicine.[20] As the issue is not necessarily a drug-class issue, the Guild would prefer identifying the most problematic benzodiazepines and have jurisdictions manage this as Tasmania is doing with alprazolam – retaining them as a S4 medicine with S8 reporting requirements. Such an approach can also be used if other problematic S4 medicines are identified in the future as warranting monitoring and reporting. Implementing systems that facilitates real-time reporting and monitoring without impacting other aspects of medicine management and supply such as storage, transport or patient administration would resolve such issues without unintended consequences on pharmacies, wholesalers or other health provider or care facilities.

Smaller PBS quantities

Reducing the PBS maximum quantity for benzodiazepines would encourage short term use of benzodiazepines and reduce the risk of misuse or abuse by at-risk individuals. It would also make it more difficult for people most at-risk of misusing or abusing benzodiazepines to accumulate a stockpile of medicines through doctor or pharmacy shopping. Legitimate patients requiring long-term supply would continue to have access to larger quantities under the current PBS 'Authority Required' arrangements.

Promotion of benzodiazepine contracts/staged supply

Staged supply[21] is the process by which pharmacists supply medicines to consumers in periodic instalments of set small quantities at agreed intervals. A staged supply service is aimed at improving the safety and efficacy of medicine use in vulnerable consumers and is of particular value to those with a mental illness, medicine dependency or who are otherwise unable to manage their medicines safely. Instalments are supplied at agreed intervals, which may be daily, weekly or as otherwise determined in consultation with the prescriber and consumer. The provision of staged supply services are being supported under the Pharmacy Practices Incentive (PPI) Program, funded by the Australian Government under the Fifth Community Pharmacy Agreement.[22] In jurisdictions such as the ACT[23] and NT[24], many people at-risk of benzodiazepine abuse/misuse agree to a 'Benzodiazepine Contract', initiated by their doctor, in which they are managed by one doctor (or through one practice) and attend one pharmacy. Such a service involves a commitment from the consumer, prescriber and pharmacist to work together to manage the abuse/misuse problem.

Alternative options to manage sleep/anxiety disorders

Research indicates non-medicine therapies directed at the physiological, psychological, behavioural and environmental factors that affect sleep have comparable efficacy to benzodiazepines and other related medicines.[25] Primary care practitioners can start non-medicine therapies or refer patients to a specialist sleep clinic, sleep physician, psychiatrist or psychologist. [26]

Many anxiety disorders can be successfully managed through psychological treatments such as cognitive behaviour therapy or exposure therapy and can be ultimately more effective than pharmacological treatment.[27] Cognitive Behavioural Therapy has also been shown to be an effective treatment option for chronic pain. [28]

It is the responsibility of primary healthcare providers to determine the best treatment option for individuals. This may involve managing demands from patients for medicines such as benzodiazepines as a 'quick-fix' to their symptoms and facilitating patient access to other relevant health care professionals or support providers and facilities. Research suggests that benzodiazepines should only be prescribed for short-term use in patients who have failed to respond to at least two therapies (e.g. psychological therapy, antidepressant).[29]

Community pharmacy is able to play a role in assisting patients and referring them to appropriate healthcare professional support where required.

Recommendation

The Guild notes the concerns over the misuse and abuse of benzodiazepines, particularly in the context of poor health outcomes for individuals and social impact from associated accidents and crime. However, re-scheduling as a mechanism for addressing misuse/abuse of medicines is problematic, as it imposes greater administrative burdens and limits access for legitimate patients, without necessarily targeting the cohort of people involved in the misuse. Therefore the Guild does not support the proposal to reschedule benzodiazepines from S4 to S8.

The Guild instead proposes a range of other options to address the issues and recommends the Committee supports retaining benzodiazepines in S4 of the SUSMP and to refer the matter of misuse and abuse of benzodiazepines to other appropriate bodies to consult on and consider strategies and options that will not have as significant unintended consequences.

2. Diclofenac – Proposal to exempt diclofenac when presented in a transdermal delivery system (containing 140 mg or less).

In our submission to the October 2012 ACMS meeting, the Guild indicated its view that transdermal diclofenac would be more appropriate as a S3 medicine, however we note the recent interim decision by the delegate to amend the S2 entry for diclofenac to include transdermal preparations.[30]

The SUSMP defines 'transdermal use' as 'application to the skin primarily for systemic use, as opposed to 'topical use' meaning application for the purpose of a localised effect on the surface of the organ or within the tissue to which it is applied. Regarding this scheduling exemption proposal for transdermal diclofenac, a clear distinction must be made between incidental absorption from topically applied drugs and that of transdermally absorbed drugs, whose action depends on systemic absorption. Although both types of formulation are applied directly to the skin, transdermal formulations are specifically designed to facilitate drug diffusion through the skin into the systemic circulation with the goal of achieving systemic levels comparable with those obtained from oral medications.[31]

We have assumed that the 'transdermal' diclofenac under consideration is for a 'patch' dosage unit. Although aware of diclofenac patches being used overseas for the treatment of acute pain caused by minor strains, sprains and contusions, these products are marketed as a 'topical treatment'[32] requiring a prescription in the United States.[33,34] The Guild remains unaware of any diclofenac transdermal delivery system proposed for supply in Australia and has not been approached by any sponsor to discuss the introduction of this new delivery system.

Diclofenac continues to be associated with increased risk of cardiovascular events as well as adverse effects with kidney and liver function, gastrointestinal bleeding asthma and skin reactions and these risks are greater from systemically absorbed diclofenac. As a category C medicine, it is not recommended in pregnancy nor is it recommended in lactation.[35] A 2011 article in Heartwire[36] advised that while the risk of cardiovascular events may be low in people at very low risk of a heart attack, those with more risk factors (overweight and obesity, tobacco use, hypertension, hyperlipidaemia, diabetes)[37] have a more significant absolute risk. With such risk factors, a significant portion of the Australian population is at a higher risk of adverse events from systemic use diclofenac.

We also assume that in seeking either exemption or S2 entry for transdermal diclofenac, the approved indication will be for short-term relief of minor inflammatory conditions. We are concerned that some people familiar with using diclofenac for more serious chronic conditions may use the transdermal products without any healthcare professional support and it may reduce medical oversight for such serious conditions. In the Guild's view, this would be detrimental to the overall health outcomes of these people. As a S3 product, there is greater scope for pharmacists to monitor use and refer people requiring medical review to their doctor. Even as an S2 product, pharmacy assistants have general training to triage and refer to the pharmacist for advice where appropriate. If transdermal diclofenac remains as a S2 medicine, the Guild would expect the sponsor supports the pharmacy sector

with training materials for pharmacy assistants. As a non-scheduled medicine, people can access these medicines from supermarkets or service stations without any recourse to healthcare professional advice or intervention. Consumer safety relies entirely on labelling advisories and consumers reading and understanding these advisories.

If a scheduling exemption is given to a diclofenac product with a systemic effect, we feel this may set precedence for exemption applications for oral diclofenac products. Given the associated risks, the Guild believes it is essential for any diclofenac product having a systemic effect to be scheduled to facilitate access to advice from a health care professional.

We hope the Committee continues to believe this product should remain as a scheduled medicine, though, given the lack of consultation to date with the pharmacy sector regarding transdermal diclofenac and any commitment to supporting the sector with professional resources, the Guild still believes that S3 is the more appropriate schedule.

Recommendation

The Guild does not support the proposal to exempt from scheduling diclofenac when presented as a 140mg or less transdermal medicine delivery system and recommends it remain as a scheduled medicine.

3. Oseltamivir – Proposal to reschedule oseltamivir for the treatment and prevention of influenza type A and type B from Schedule 4 (S4) to Schedule 3 (S3).

The Guild has supported this proposal in the past and the position remains unchanged.

The current Prescription Only status of oseltamivir requires people with the symptoms of influenza to seek an appointment with a doctor to obtain a prescription. Doctor shortages in many parts of Australia mean that urgent appointments are often difficult to obtain. In the 2012 Menzies-Nous Health survey[38], it was reported Australians living outside capital cities were significantly less likely to secure an appointment with a general practioner on the same day with just over one-third (36%) of people being able to secure an appointment compared to more than half (54%) of people living in capital cities. The survey also indicated that 16% of respondents waited three to five days for an appointment and 14% waited more than five days.

Treatment with oseltamivir should begin within the first 24 to 48 hours after onset of the symptoms of influenza.[39] Down-scheduling oseltmivir to S3 (Pharmacist Only) would enable people with the symptoms of influenza to seek more timely advice from their local pharmacist, who would be able to assess their symptoms, dispense oseltamivir if appropriate and refer at-risk patients for further medical advice. The convenient access to a pharmacist will facilitate treatment with oseltamivir.

The Guild notes previous considerations to reschedule oseltamivir were rejected on the basis of the perceived potential for increased resistance, misdiagnosis, reduced vaccine uptake, pandemic stockpiling and a reduction of available supplies during a pandemic.[40] However data for nearly 5 years of pharmacist supply of oseltamivir in New Zealand (oseltamivir has been available off prescription in New Zealand since 2007) indicated the aforementioned concerns were not realised and pharmacist supply did not result in a large increase in overall usage.[41] The report also concludes funding oseltamivir provision from pharmacists during a pandemic may improve access and could be considered (along with influenza immunisations from pharmacy) for future pandemics. [42]

The rescheduling of oseltamivir to S3 would represent a public health initiative that would significantly reduce the impact of influenza on the community. Pharmacists are well positioned to play a major role in the prevention and treatment from a biological threat, including an influenza pandemic.[43] Community pharmacists are already very familiar with triaging people with cold and flu symptoms and managing the condition with non-prescription medicines or referral for medical review as appropriate.

The consumer is well able to identify the symptoms of cold and flu and routinely seek community pharmacy advice on the most appropriate product for their set of symptoms.

In a meeting with the Guild, the sponsor of oseltamivir has indicated a willingness to work with the pharmacy sector in providing professional support resources if the proposal is successful. A factsheet already available to pharmacists in New Zealand

provides a clear and simple guide for pharmacists to follow to accurately diagnose influenza and when to dispense oseltamivir. [44] Such a resource could be adapted for similar use in Australia.

Oseltamivir has been shown to be well tolerated with a low incidence of adverse events. Most adverse events are mild or moderate. The most common and the only clinically important side effect is mild gastrointestinal upset; mainly nausea and vomiting. However it has been shown that the incidence of nausea had been further reduced when the first dose was taken with food.[45]

Information derived from pharmacology and pharmacokinetic studies suggest that clinically significant medicine interactions are unlikely. In studies over 5 years involving more than 11,000 patients Hoffman-La Roche have published data to demonstrate that oseltamvir has simple uncomplicated pharmacology and lacks potential for medicine interactions.[46]

Recommendation

The Guild supports the proposal to re-schedule oseltamivir from S4 to S3. Based on the available evidence, the risks cited previously with this proposal have been shown to be unfounded. In contrast the public benefits of allowing pharmacists to supply oseltamvir without a prescription have been well documented and would enable more timely supply of the medicine, which is crucial for effective treatment.

4. Nabiximols – Proposal to reschedule nabiximols from Paragraph 3 of the Appendix D to Paragraph 1 of the Appendix D.

The Guild offers its in-principle support of this proposed change. Sativex (nabiximols) is listed on the Australian Register of Therapeutic Goods (ARTG) which means it has been tested for safety, quality and efficacy. It is indicated specifically as treatment for improvement in patients with moderate to severe spasticity due to multiple sclerosis that has not responded adequately to other anti-spasticity medication and demonstrates clinically significant improvement in spasticity related symptoms during an initial trial of therapy.[47] The Guild therefore agrees with the proposal that Appendix D paragraph 3 is not appropriate and paragraph 1 is more suitable.

The Guilds notes the ARTG indicates that Sativex must be stored between 2 and 8 degrees Celsius (i.e. refrigerated). As a S8 medicine, this poses a problem regarding in-pharmacy storage and the need to meet jurisdictional requirements. There should not be any requirement to move or purchase additional refrigerators to store one S8 product. Storage exemptions or specific guidance on order/supply arrangements may address this issue. Pharmacists will need clear direction on this matter. The Guild will be happy to work with the sponsor and jurisdictional Health Departments to assist with this.

Pharmacists would also benefit from having professional resources available to support them. In a meeting with the Guild, the sponsor has indicated a willingness to work with the sector in providing professional support resources if the proposal is successful.

Recommendation

The Guild offers its in-principle support to reschedule nabiximols from Paragraph 3 of the Appendix D to Paragraph 1 of the Appendix D. Owing to the medicine's need for refrigeration, storage requirements need to be managed. The Guild believes pharmacists would also benefit from professional resources being made available to them.

5. Hydrocortisone – Proposal to reschedule preparations containing 1 per cent or less hydrocortisone and hydrocortisone acetate when combined with antifungal substances for dermal use from Schedule 3 to Schedule 2.

The Guild does not support this proposal as it believes if a patient requires a combination medicine, their condition is at a level of severity that is not met by either product alone and would benefit from pharmacist oversight.

The Guild is particularly concerned about risks of misuse or adverse effects in more vulnerable patient groups such as the elderly and infants. While the most frequent adverse effects include atrophy, striae, rosacea, perioral dermatitis, acne, and purpure[48], the Guild is concerned that people may inadvertently use the combination product with other cortisone products, increasing the risk of systemic absorption and adverse effects.

We also have not been approached by any sponsor regarding the proposed schedule change and how pharmacy could be supported to mitigate any patient risks associated with the change. We would expect there to be some commitment from the sponsor/s to assist in training pharmacy assistants about these products.

Recommendation

The Guild does not support the proposal to reschedule preparations containing 1 per cent or less hydrocortisone and hydrocortisone acetate when combined with antifungal substances for dermal use from S3 to S2. The Guild believes the severity of the condition the medicine is intended to treat combined with the potential adverse effects of this medicine warrants the continuation of pharmacist oversight.

Attachment A PBS & RPBS Items processed from July 2011 to June 2012

PBS Code	PBS			RPBS			Total
	General - Ordinary	General - Safety Net	Concessional - Ordinary	Concessional - Free Safety Net	RPBS - Ordinary	RPBS - Safety Net	
	Services	Services	Services	Services	Services	Services	Services
Benzodiazepines							
Alprazolam							
2132F	377	2,841	103.099	25,648	3.238	1,461	136,664
8118G	1,003	1,406	103,836	14,659	1,044	485	122,433
2130D	56	736	30,241	10,331	2,432	1,153	44,949
2131E	126	2,029	71,224	20,936	3,467	1,751	99,533
Total							403,579
Bromazepam							
4150K					227	126	353
4151L					435	232	667
Total							1,020
Clonazepam							
1805B	7	369	14,899	3,207	888	464	19,834
1806C	22	165	11,542	1,928	376	183	14,216
1807D	50	72	1,512	443	176	47	2,300
1808E	17	24	2,508	403	25	18	2,995
3478C (Doctors Bag Order Form)			2,085				
5337X	1	18	463	132	55	32	701
5338Y		4	109	31	6	6	156

PBS & RPBS Items processed from July 2011 to June 2012

PBS Code	PBS			RPBS			Total
	General - Ordinary	General - Safety Net	Concessional - Ordinary	Concessional - Safety Net	RPBS - Ordinary	RPBS - Safety Net	
	Services	Services	Services	Services	Services	Services	Services
Clonazepam continued							
5339B	1	69	1,970	712	230	82	3,064
5340C	2	11	339	139	14	15	520
5341D		7	119	50	3	1	180
5342E	3	17	361	187	56	19	643
Total							46,694
Diazepam							
2558P	12	111	1,511	1,050	120	48	2,852
3161J	334	2,488	139.702	33,615	6,487	2,897	185,523
3162K	1,778	23,137	1,134,066	270,553	25,647	11,820	1,467,001
3458B (Doctor's Bag Order Form)			10,242				10,242
5071X	8	195	18		3		224
5072Y	1	46	1,487	112	20		1,666
5355W		5	55	19	6	5	90
5356X		6	247	88	11	5	357
5357Y		3	26	25	2	4	60
5358B		2	155	93	3	1	254
Total							1,668,269

PBS & RPBS Items processed from July 2011 to June 2012

PBS Code	PBS			RPBS			Total
	General - Ordinary	General - Safety Net	Concessional - Ordinary	Concessional - Free Safety Net	RPBS - Ordinary	RPBS - Safety Net	
	Services	Services	Services	Services	Services	Services	Services
Flunitrazepam							
4216X					2,233	1,281	3,514
Total							3514
Nitrazepam							
2723H	235	4,322	245,884	114,066	18,001	9,449	391,957
2732T	1	42	4,565	1,812	1,130	719	8,269
5189D			23	2	3		28
5359C		8	134	81	25	15	263
5360D		3	191	65	4	1	264
Total							400,781
Oxezepam							
3132W	137	2,139	145,042	53,316	16,639	7,761	225,034
3133X	460	6,436	491,019	184,386	35,524	16,171	733,996
3134Y	90		5,889	2,690	1,084	607	10,360
3135B	57		4,117	2,169	1,615	977	8,935
5192G			35	6			41
5193H			73	8	3		84
5371Q	2		126	52	13	4	197
5372R		5	192	96	26	19	338

PBS & RPBS Items processed from July 2011 to June 2012

PBS Code	PBS			RPBS			Total
	General - Ordinary	General - Safety Net	Concessional - Ordinary	Concessional - Safety Net	RPBS - Ordinary	RPBS - Safety Net	
	Services	Services	Services	Services	Services	Services	Services
Oxezepam continued							
5373T		4	92	48		3	147
5374W		11	169	93	7	13	293
Total							979,425
Temazepam							
2088X	4	487	24,332	12,581	8,526	5,320	51,250
2089Y	2000	26,070	1,169,406	426,498	115,050	52,857	1,791,881
5221T	1	9	265	30	33	2	340
5375X	1	30	934	403	116	77	1,561
5376Y	1	28	551	279	19	8	886
Total							1,845,918
Total Benzodiazepines items processed							5,349,200
Additional annual PBS costs if DD fee ($2.71) applied	18,973	198,792	10,094,357	3,206,044	664,010	314,737	14,496,332

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Medicare Australia recommends that users exercise their own care, skill and diligence with respect to the use and interpretation of the information and data.

ACMS – March 2013
The Pharmacy Guild of Australia

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Pharmaceutical Society of Australia

Purpose

The Pharmaceutical Society of Australia (PSA) makes this submission in relation to items referred by the Delegate for scheduling advice to the March 2013 meeting of the Advisory Committee on Medicines Scheduling (ACMS).

Recommendations

PSA provides the following recommendations to the ACMS:

***Benzodiazepines**: The proposal to reschedule from Schedule 4 to Schedule 8 is firmly opposed.*

***Diclofenac**: The proposal to exempt from scheduling when presented as a 140 mg (or less) transdermal drug delivery system is not supported.*

***Hydrocortisone and hydrocortisone acetate**: The proposal to reschedule 1% dermal preparations when combined with antifungal substances from Schedule 3 to Schedule 2 is not supported.*

***Oseltamivir**: The proposal to reschedule from Schedule 4 to Schedule 3, for the treatment and prevention of type A and type B influenza, is supported.*

Specific comments

Benzodiazepines

Proposal to reschedule benzodiazepines from Schedule 4 to Schedule 8.

At the outset, PSA feels compelled to once again express its ongoing concern regarding the lack of detail provided in association with proposals for rescheduling. In the interests of public safety and quality use of medicines, PSA firmly believes that presentation of the rationale or evidence base which underpins any proposal is necessary and warranted. It is inappropriate that individuals and organisations who are invited to make a submission are asked to do so without

information that adequately explains the purpose of, and justification for a proposal. We do not regard this as an open and transparent public consultation process.

PSA's concern is particularly relevant to the proposal to reschedule benzodiazepines from Schedule 4 to Schedule 8. Such a proposal is substantially more restrictive than current and longstanding arrangements and further, has the potential to apply to many substances within the class rather than a single substance.

Use of benzodiazepines

Benzodiazepines are used widely for many therapeutic purposes including as a sedative or hypnotic, anxiolytic, anaesthetic and for epilepsy. Intended therapeutic effects are exerted through the central nervous system and therefore side effects (e.g. drowsiness, lethargy) can also arise from this pathway. Higher doses or long-term use without careful supervision or medical attention are generally not recommended.

A recent publication[1] reports that data[2] on the utilisation of psychotropic medications[3] in Australia from 2000 to 2011 show the following.

- In 2000, sedatives and anxiolytics together represented 29% of all of the psychotropics studied but this declined to 17% in 2011.
- There was little change in the dispensing of anxiolytics over the study period (an increase from 14.0 to 14.9 DDDs/1000/day[4]). The most popular anxiolytic dispensed in 2011 was diazepam (41.5%) but its use remained stable between 2000 and 2011. The most striking feature was the 87.2% increase (over the study period) in alprazolam dispensing such that it reached 41.0% in 2011.
- Dispensing of sedatives decreased by 26.4% over the study period (from 9.8 to 7.2 DDDs/1000/day) with the trend particularly evident over the last four years (2008–11).

Therefore, dispensing of benzodiazepines, with the exception of alprazolam, remained static or decreased over the period of 2000 to 2011.

Hospitalisations due to injury

In 2009–10, close to 7,000 people were hospitalised due to accidental poisoning by pharmaceuticals. This represented 1.5% of all community injury hospitalisations.

[1] Stephenson CP, Karanges E, McGregor IS. Trends in the utilisation of psychotropic medications in Australia from 2000 to 2011. Aust N Z J Psychiatry 2012;47(1):74–87.

[2] Data consisted of prescriptions subsidised under the Pharmaceutical Benefits Scheme and Repatriation Pharmaceutical Benefits Scheme, and estimates of non-subsidised prescriptions from a survey of selected community pharmacies.

[3] For the purpose of the study, benzodiazepines considered were classified as: anxiolytics (alprazolam, bromazepam, clobazam, diazepam, lorazepam and oxazepam) or sedatives (flunitrazepam, midazolam, nitrazepam, temazepam and triazolam). 'Anxiolytics' also included buspirone while 'sedatives' also included zolpidem, zopiclone, chloral hydrate and phenobarbitone.

[4] Defined daily dose per 1000 of population per day.

Benzodiazepines were regarded as the principal cause in just over 1,000 cases (or 16% of all pharmaceutical poisoning cases). The rate of hospitalisation due to intentional self-harm was about four times that due to accidental poisoning.[5]

Possible misuse/abuse

Benzodiazepines have been associated with a level of misuse or abuse often by (but not limited to) individuals who use other illicit substances. Benzodiazepines themselves are generally regarded as safe however they can contribute to the negative effects of illicit substances and alcohol. Temazepam was the subject of significant physical harm experienced by misusers over a decade ago, however this was due to their use in an unintended and unapproved manner (e.g. injection of contents of oral liquid capsule formulations).

PSA notes that consideration of rescheduling benzodiazepines to Schedule 8 was suggested as a result of a Victorian Inquiry in 2007.[6] However, a response from the Victorian Government did not support this citing several reasons including that[7]:

- the additional controls associated with a Schedule 8 classification would impose significant additional costs. PSA agrees there would be significant and unjustifiable impact on health professionals (e.g. prescribers, pharmacists, nurses), the supply chain, industry, regulators and consumers with a genuine therapeutic need; and
- rationale or evidence that benefits associated with a Schedule 8 classification would outweigh the costs of additional controls was not presented.

PSA is not aware of what, if any, actions have followed on from this Victorian review.

Impact on health professionals and the supply chain

PSA would envisage substantial impact on pharmacists and other health professionals (e.g. general practitioners and specialists, nurses) ranging from professional practice issues as well as other administrative requirements associated with Controlled Drugs. Pharmacists for example would not be able to accommodate storage space in existing drug safes and other dispensing and recording requirements would be extremely onerous.

Other stakeholders will also be significantly affected including: government and regulators (e.g. additional cost of dangerous drug fees, issuing permits to prescribers or authorities for prescriptions); industry (e.g. secure storage and transport costs); science and medical researchers (e.g. increased cost for those who use benzodiazepines in their research).

[5] Tovell A, McKenna K, Bradley C, Pointer S. Hospital separations due to injury and poisoning, Australia 2009–10. Injury research and statistics series no. 69. Cat. no. INJCAT 145. Canberra: Australian Institute of Health and Welfare; 2012.

[6] Drugs and Crime Prevention Committee, Parliament of Victoria. Inquiry into the misuse/abuse of benzodiazepines and other forms of pharmaceutical drugs in Victoria. Final report. 2007, Dec.

[7] Victorian Government response to the DCPC Inquiry into misuse/abuse of benzodiazepines and other pharmaceutical drugs. 2008, May.

The additional costs would be associated with the additional controls on the storage, administration and handling of 10–12 benzodiazepines and the estimated 5 million prescriptions per annum of these substances.

Another major concern identified has been the potential impact on staff and residents of residential aged care facilities. Pharmacists have highlighted rescheduling benzodiazepines to Schedule 8 would be particularly burdensome in these facilities and add significantly, for example, to nursing staff time for the administration of these medicines to residents as well as other issues such as storage and handling.

Alternative strategies

Overall we have not found any evidence to suggest overuse of benzodiazepines, with the possible exception of alprazolam. Therefore we do not believe that rescheduling benzodiazepines as a class to Schedule 8 provides any meaningful solution from a public health perspective. Even where misuse/abuse of a substance is possible or likely, it is necessary to balance the negative behaviour with therapeutic benefits provided to consumers and carers. In addition, implementing a single initiative (rescheduling) often does not provide a complete solution to the 'problem' and therefore, other strategies must be considered.

Depending on the reason for this rescheduling proposal, PSA suggests consideration of, for example:

- other forms of 'restrictions' to supply e.g. authority prescription requirements, delisting from the Pharmaceutical Benefits Scheme, voluntary undertakings, staged supply arrangements;
- professional decision support resources covering clinical and non-clinical aspects, e.g.:
    - professional guidelines on the prescribing of specific substances e.g. *Alprazolam prescribing guidelines* by the Royal Australian College of General Practitioners;
    - guidelines on withdrawal treatment e.g. withdrawal of benzodiazepines in the primary care setting;
    - education for prescribers on how to manage suspected prescription shoppers;
    - education and support of prescribers and pharmacists to develop strategies to prevent the misuse of prescription medicines and harms associated with it;
    - dissemination of best practice policies to health professionals and health care facilities (e.g. residential aged care facilities);
- real time reporting by prescribers and dispensers. In this regard, PSA would like to see a coordinated and consistent system of real time reporting by pharmacists that provides the capacity to flag and track any substance of interest and which enables timely health interventions for at-risk consumers while also informing law enforcement activities where appropriate. This could be included in the current negotiation with all states and territories regarding installation of real time reporting software for Controlled Drugs;
- a public awareness or community education campaign.

PSA member pharmacists at the coalface have also reported an apparent growing trend to use Schedule 8 medicines for non-medicinal purposes. This highlights the importance to include strategies to prevent and detect this form of substance misuse. It also indicates that rescheduling to Schedule 8 does not necessarily provide the most appropriate outcome.

Summary

There is no substantial evidence of overuse or increasing trend in use of benzodiazepines as a class. Importantly we envisage that rescheduling to Schedule 8 would have profound negative impact on logistics for health care facilities and the ability of health care practitioners to provide timely professional care. It will also create unnecessary barriers to consumers and carers receiving quality therapeutic care and the potential to significantly impact on their health outcomes. Overall we see substantial negative outcomes and very little, if any, benefit arising from this proposal. Therefore PSA firmly opposes the proposal to reschedule benzodiazepines from Schedule 4 to Schedule 8. We strongly suggest consideration of other strategies to promote appropriate use of benzodiazepines, and to minimise misuse and harm arising from inappropriate use of any of these medicines.

Diclofenac

Proposal to exempt from scheduling for diclofenac when presented as a 140 mg or less diclofenac transdermal drug delivery system.

PSA notes that a decision to amend the Schedule 2 diclofenac entry to include "transdermal preparations for topical use containing 140 mg or less of diclofenac" is currently pending (Delegate's interim decision was released on 7 January 2013).

Dermal preparations of diclofenac are unscheduled, however, this new product formulation has not previously been available in Australia. Data and experience on use in this country should be available for several years before any exemption to scheduling is contemplated. In addition, although any systemic absorption is likely to be small, several cautionary statements will be required (e.g. prolonged use, history of gastric ulcers, renal disease). We believe pharmacist advice on correct and safe use should be available to the consumer at the time of purchase.

Therefore, in summary, PSA does not support the proposal to exempt diclofenac from scheduling when presented as a 140 mg (or less) transdermal drug delivery system.

Hydrocortisone and hydrocortisone acetate

Proposal to reschedule preparations containing 1% or less hydrocortisone and hydrocortisone acetate when combined with antifungal substances for dermal use from Schedule 3 to Schedule 2.

Combined topical treatment with a mild corticosteroid such as 1% hydrocortisone and an antifungal agent is warranted for some common dermatological conditions. Topical therapy is readily available over-the-counter to facilitate appropriate management of such conditions as single ingredient products as well as combination products (e.g. hydrocortisone 1% combined with clotrimazole 1% or miconazole 2%).

The use of a fixed combination product is not regarded as first line treatment for most mild dermatological complaints. The need for such a product would reflect a more serious condition. PSA believes pharmacist advice is warranted to ensure optimal use of a combination product and therefore Schedule 3 remains appropriate.

A further consideration is that a fixed dose combination product can pose a disadvantage in instances when the use of the two substances needs to be tailored according to the symptoms or response to treatment. For example, it may be appropriate to cease use of hydrocortisone when inflammation has subsided but necessary to continue treatment with an antifungal until several days after the rash has healed (e.g. for nappy rash[8]). In such cases, simply continuing to use the combination product does not provide optimal therapy as it can increase the risk of adverse effects or rebound from the cortisone component. PSA's member pharmacists report that they often encounter situations where consumers are unaware of the need to tailor therapy. This type of advice and other individualised information should be provided by the pharmacist and therefore Schedule 3 is most appropriate.

In summary, PSA does not support the proposal to reschedule dermal preparations of 1% hydrocortisone / hydrocortisone acetate when combined with antifungal substances from Schedule 3 to Schedule 2.

Oseltamivir

Proposal to reschedule oseltamivir for the treatment and prevention of influenza type A and type B from Schedule 4 to Schedule 3.

Oseltamivir is substantially safe and well tolerated. The more common gastrointestinal side effects include nausea and abdominal pain, however, these are generally transient and may also be minimised by taking doses with or after food.[9]

Timely commencement of treatment is vital with oseltamivir. General advice is to commence treatment as soon as possible but no later than 48 hours after the flu symptoms started or within two days of exposure to an infected person.[10] Appropriate use of oseltamivir can reduce the duration and severity of symptoms, and the incidence of secondary bacterial infections. Not only can timely and appropriate treatment with oseltamivir benefit the affected individual and their close contacts, it is also likely to benefit the overall health and productivity of the wider community.

As a Schedule 4 medicine currently, there are some barriers for consumers to access oseltamivir in a timely manner. When rescheduling of oseltamivir was considered previously in Australia, PSA supported Schedule 3 on the basis of the safety profile of the substance and the essential link between timely access and maximal therapeutic benefit. PSA suggested that the treatment and prevention of influenza is a significant public health area where community pharmacists can

[8] Sansom LN, ed. Australian pharmaceutical formulary and handbook. 22nd edn. Canberra: Pharmaceutical Society of Australia; 2012.

[9] Ibid.

[10] Ibid.

assist consumers through appropriate provision of treatment and advice, or referral to a medical practitioner where warranted.

Previously, in the context of a possible Schedule 3 entry in Australia, several concerns were raised[11] including potential for misdiagnosis, increase in resistance and decline in vaccination rates. In New Zealand, oseltamivir has been available without a prescription since 2007. PSA understands that a five-year study in New Zealand following this regulatory change has shown that pharmacist supply (equivalent to Schedule 3 in Australia) of oseltamivir was not associated with increased resistance or change in rates of immunisation.[12]

Various models of pharmacist supply of oseltamivir have been implemented overseas. For example in the United Kingdom, tailored Patient Group Directions enable trained pharmacists (and other health professionals) to supply oseltamivir without a prescription in accordance with an approved protocol.

The mechanism implemented in New Zealand initially was for oseltamivir to remain as a prescription only medicine but pharmacists were able to supply it for several months during the influenza season. The restricted supply period has however been extended several times over the years to accommodate the postulated months of actual seasonal influenza. We believe currently pharmacist supply can occur between the months of April to November (inclusive). However, we also understand that recently another reclassification application for oseltamivir was considered and approved for the equivalent of Australia's Schedule 3.[13]

Although direct comparisons cannot be made because of the differences in the overseas models, we believe all of the models and experience have delivered benefits for consumers and the wider community through provision of oseltamivir in a safe and timely manner. We believe similar benefits can be delivered to Australian consumers through implementation of Schedule 3 oseltamivir in Australia.

PSA supports the proposal to reschedule oseltamivir to Schedule 3 for the treatment and prevention of type A and type B influenza. If Schedule 3 status is granted, PSA will be in a position to develop professional resources to support pharmacists to provide appropriate therapeutic oversight. PSA will also seek the opportunity to work with relevant government and industry bodies, and health professionals and consumers.

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[11] For example, at the meetings of the National Drugs and Poisons Schedule Committee in October 2004 and June 2008.

[12] Gauld NJ, Jennings LC, Frampton C, Huang QS. Five years of non-prescription oseltamivir: effects on resistance, immunization and stockpiling. J Antimicrob Chemother 2012;67(12):2949–56.

[13] Reported in the minutes of the October 2012 Medicines Classification Committee (New Zealand) meeting.

Contacts:

[redacted]

[redacted]

17 January 2013

Proposed amendments to the Poisons standard January 2013

Submission from the Australian Veterinary Association Ltd

17 January 2013

[redacted]

The Australian Veterinary Association (AVA) is the national organisation representing veterinarians in Australia. Its 7000 members come from all fields within the veterinary profession. Clinical practitioners work with companion animals, horses, farm animals, such as cattle and sheep, and wildlife. Government veterinarians work with our animal health, public health and quarantine systems while other members work in industry for pharmaceutical and other commercial enterprises. We have members who work in research and teaching in a range of scientific disciplines. Veterinary students are also members of the Association.

Recommendations

- That benzodiazepines are not rescheduled to S8
- That the combination of adrenaline, bupivacaine and lignocaine are not rescheduled to S6
- That tylosin is rescheduled to S4

Benzodiazepines

Benzodiazepines are very widely used in veterinary practice in Australia, particularly in the treatment of dogs and cats. The primary uses are for pre-anaesthetic medication to reduce anxiety in animals about to undergo surgery, behavioural modification therapy, and to treat anxiety and related disorders. They are also used for the treatment of epilepsy and emergency seizures.

This class of drugs is so widely used in veterinary practice for similar reasons as for their widespread use in human medicine – safety and efficacy. They work equally well in many animal species as in humans.

Australia's 2500 veterinary practices are extremely aware of the risk of theft and misuse of drugs from veterinary premises and vehicles. Many practices already store supplies of benzodiazepines in their drug safes because of their appeal to thieves and their potential misuse by those who have access to them.

However, the additional regulation involved in rescheduling benzodiazepines to S8 would impose significant difficulties on veterinarians. Benzodiazepines are very valuable drugs, including in emergency situations, and ease of access for treating veterinarians is important.

Veterinarians are also concerned about the possible 'normalisation' of S8-category drugs which could increase the risk of other more dangerous or addictive S8 drugs being misused.

The Australian Veterinary Association recommends that benzodiazepines are not rescheduled to S8.

Adrenaline, bupivacaine and lignocaine

The combination of adrenaline, bupivacaine and lignocaine (marketed as Trisolfen®) is used as a topical anaesthetic to reduce pain after surgical mulesing of merino sheep. This procedure is effective in preventing life-threatening blowfly strike in wool producing sheep. The use of topical anaesthesia is important to improve welfare outcomes for sheep undergoing the mulesing procedure. Great advances are currently being made through genetic selection of animals with minimal skin folds which may reduce the need to mules sheep in the future, however the use of this drug combination currently remains an essential welfare management tool.

Under the initial 'minor use permit', the preparation was only available through veterinarians and now approximately 70% of sheep mulesed in Australia are successfully post-treated with this topical anaesthetic. Rescheduling will have little effect to increase current usage.

More importantly, veterinarians are concerned about the potential for misuse if the proposed rescheduling goes ahead. In particular, it may be used for non-intended purposes such as on castration wounds or those caused by injury. These are not the uses that the product has been developed for, and it may not be safe or appropriate to use it for other purposes.

The product contains a higher concentration of lignocaine than other preparations currently scheduled as S6, and this is another reason why it should remain a prescription-only medication.

Finally, removing the oversight of a veterinarian on the products use could adversely impact the sheepmeat trade. It has a long withholding period compared to most animal medications (90 days). While most mulesed lambs are used for growing wool rather than for meat, should a withholding period not be complied with, a residue detection may impact negatively on our international trade.

The Australian Veterinary Association recommends that the combination of adrenaline, bupivacaine and lignocaine are not rescheduled to S6.

Tylosin

In 1999 the Joint Expert Technical Advisory Committee on Antibiotic Resistance (JETACAR) recommended that "that all antibiotics for use in humans and animals (including fish) be classified as S4 (prescription only)".

The JETACAR also recommended that a review of the macrolides be undertaken as a priority to ensure that continued use is "not likely to impair the efficacy of any other prescribed therapeutic antibiotic or antibiotics for animal or human infections through the development of resistant strains of organisms." Both recommendations were supported by the Australian Government.

The Australian Pesticides and Veterinary Medicines Authority (APVMA) advised the Government that it would complete a review of the macrolides by June 2003. The tylosin review by APVMA has **not** been completed and tylosin remains in Schedule 5 for animal feed premixes containing 5 per cent or less of antibiotic substances for growth promotion, for the prevention of liver abscesses in cattle or for the prevention of ileitis in pigs.

The scientific literature reveals widespread and increasing resistance to tylosin and the macrolides in a large number of pathogens of cattle, poultry and pigs. Furthermore, co-selection of resistance by tylosin has been repeatedly described and has been well known for more than 10 years.

The Australian Veterinary Association recommends that tylosin is rescheduled to S4 as recommended by JETACAR.

NOVARTIS

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The Secretary
Scheduling Secretariat
GPO Box 9848
CANBERRA ACT 2601

16 January 2013

Dear Sir/Madam,

Nabiximols - Proposal to move from Paragraph 3 of Appendix D to Paragraph 1 of the Appendix D in Schedule 8

The TGA Delegate has referred the above matter to the Advisory Committee on Medicines Scheduling (ACMS) for advice.

Novartis Pharmaceuticals is the sponsor of an oromucosal spray containing nabiximols (Sativex®, AUST R 181978). We would like to take this opportunity to comment on the proposed amendment to the scheduling of nabiximols. In addition, we wish to provide salient information we consider should be taken into account in accord with matters referred to in Section 52(E) subsection 1 of the *Therapeutic Goods Act, 1989* [the Act].

Proposed amendment to the schedule

Novartis has no objection to the proposal to move nabiximols from Paragraph 3 of Appendix D to Paragraph 1 of Appendix D in Schedule 8. Paragraph 3 does not apply to medicines on the ARTG. Paragraph 1 of Appendix D applies to poisons available only from, or on the prescription or order of an authorised medical practitioner.

Sativex was entered onto the ARTG on 26 November 2012. To give effect to the registration, an amendment to Appendix D of the Poisons Standard is required to move nabiximols from paragraph 3. An amendment is necessary because section 19 approvals are not available for a drug once it is registered, and therefore nabiximols can no longer be listed in paragraph 3 of Appendix D. The removal of nabiximols from that section therefore automatically flows from the decision by the Minister's delegate to register Sativex.

The proposed amendment to move nabiximols from Paragraph 3 of Appendix D to Paragraph 1 of the Appendix D in Schedule 8 would be the relevant decision in order to give effect to the registration of Sativex under the Act. A decision to move nabiximols to paragraph 1 would be consistent with the conditions of the registration of Sativex that limit the prescriber population to neurologist and rehabilitation physicians. An alternative the Committee may also wish to consider would be to simply specify a class of medical practitioners by creating another paragraph under Appendix D similar to paragraph 7.

Matters that should be taken into account

Sativex was approved by the TGA on the basis that there was sufficient evidence of quality, efficacy and safety. The product was subsequently entered onto the ARTG under Section 25 of the Act on 26 November 2012. Matters relating to the safety and toxicity have been addressed as part of the registration application. In this submission, we wish to focus on other matters under Section 52E(1), in particular the need for access and the potential for abuse.

The need for patient access

All the patients who would be considered for treatment with Sativex have a major neurological illness with spasticity that is not adequately controlled with current therapies. It is this group of patients for whom there is a need for access to Sativex. The efficacy of Sativex was established in a number of randomised double-blind placebo controlled trials that formed part of our application for registration. In every Sativex study, patients remained on the best currently available oral spasticity treatments and received Sativex or placebo on top of this standard care. Hence, any improvements seen on Sativex were by definition improvements not otherwise obtainable on current treatments. The approved wording of the indication is as follows:

> *Sativex is indicated as treatment for symptom improvement in patients with moderate to severe spasticity due to multiple sclerosis (MS) who have not responded adequately to other anti-spasticity medication and who demonstrate clinically significant improvement in spasticity related symptoms during an initial trial of therapy.*

The TGA also imposed a number of conditions on the registration of Sativex before the product can be marketed including the development of a RMP. The RMP includes the implementation of a mechanism that limits supply to patients of a registered prescriber population; specifically, neurologists and rehabilitation physicians. Under the conditions of registration, Sativex can only be prescribed by these specialists for use in patients who do not respond to other available treatments. In addition, prescribers must successfully complete a suitable education program accredited with specialty bodies for Continuing Professional Development (CPD) points and that assesses their understanding of the safe use of Sativex.

The potential for abuse

There is no evidence to suggest the abuse of Sativex in clinical development or in Periodic Safety Update Reports for Sativex issued since the international birthdate of the product in 2005. The TGA Delegate noted that the potential for abuse can be reduced through application of the dose titration and maximum doses recommended in the Product Information (see attachment) in addition to the appropriate scheduling of nabiximols as a Schedule 8 drug and the range of conditions of registration that were imposed by the TGA.

The restrictions under the Schedule 8 classification in addition to the limitation of the prescription of Sativex to neurologists and rehabilitation physicians, the warning statements in the PI and measures undertaken as part of Novartis' RMP are appropriate to mitigate any potential risks and abuse potential.

Other matters that should be considered

Although the invitation for public comment is limited to the proposed changes to Appendix D of the SUSMP, we wish to take this opportunity to comment on the current labelling requirements for nabiximols and Appendix K (human medicines required to be labelled with a sedation warning).

Under Appendix K, products containing nabiximols must be labelled with either of following warnings: *"This medication may cause drowsiness. If affected do not drive a vehicle or operate machinery. Avoid alcohol."* or *"This medication may cause drowsiness and may increase the effects of alcohol. If affected do not drive a vehicle or operate machinery"*.

The TGA, on the other hand, imposed the following condition: "The product label must include the statement *'Patients taking Sativex should not drive or operate machinery'*". This warning is also included in the approved PI and CMI.

Novartis has no objection to including an appropriate warning statement on the label. For the sake of consistency, Novartis would recommend an amendment to the requirements of Appendix K to allow inclusion of a warning on the label that is consistent with the conditions of registration imposed by the TGA.

Concluding remarks

Spasticity is a disabling symptom of MS which causes great distress to patients and has a significant impact on their lives and the lives of their caregivers. All the patients who would be considered for treatment with Sativex have a major neurological illness with spasticity that is not adequately controlled with current therapies, and it is this group of patients for whom there is an unmet clinical need. It will only be prescribed by specialist neurologists and rehabilitation physicians who have completed the perquisite educational program for patients who do not respond to other available treatments.

Following the registration of Sativex, the entry in Appendix D needs to be changed to enable patients to access to the product and Novartis. We have no objection to the proposal to move nabiximols from Paragraph 3 of Appendix D to Paragraph 1 of Appendix D in Schedule 8. Novartis would welcome the opportunity to work with individual State/Territory Health Authorities and other stakeholders on appropriate controls to enable patients who do not respond to other available treatments to access this medicine.

[redacted]

SATIVEX®

nabiximols

WARNING

The maximum recommended dose of Sativex should not be exceeded. High doses of Sativex increase the risk of serious psychiatric adverse events including psychosis, hallucinations, delusions, and homicidal and suicidal ideation.

NAME OF THE MEDICINE

Active ingredient: nabiximols (AAN)

Each mL Sativex oromucosal spray contains:

80 mg of extracts (nabiximols) from *Cannabis sativa* L., folium cum flore (Cannabis leaf and flower), corresponding to 27 mg delta-9-tetrahydrocannabinol (THC) and 25 mg cannabidiol (CBD) and lesser amounts of other cannabinoids (56 mg total cannabinoids).

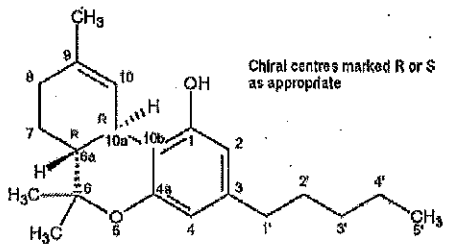
The name 'dronabinol' is used for pure, synthetically-derived delta-9-tetrahydrocannabinol rather than the extracted delta-9-tetrahydrocannabinol present in Sativex.

Extraction solvent: Liquid carbon dioxide.

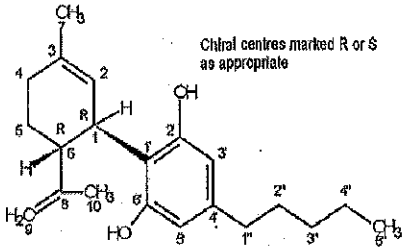
Each 100 microlitre spray contains 2.7 mg THC and 2.5 mg CBD.

Each 100 microlitre spray also contains up to 0.04 g alcohol.

THC is trans-delta[9]-tetrahydrocannabinol. The molecular formula of THC is $C_{21}H_{30}O_2$, its molecular weight is 314.47, and it is assigned CAS Number 1972-08-3. CBD is cannabidiol. The molecular formula of CBD is $C_{21}H_{30}O_2$, its molecular weight is 314.47 and it is assigned CAS Number 13956-29-1. The chemical structures of THC and CBD are shown below:



delta-9-Tetrahydrocannabinol



Cannabidiol

DESCRIPTION

Sativex is supplied as a solution in a spray container and is for use as an oromucosal spray only.

The drug substances are produced from cultivated *Cannabis sativa* L. plants. The drug substances are partially purified extracts, therefore botanical drug substances (BDS). The plants have been specifically bred to produce two separate chemotypes, expressing their cannabinoid content as high delta-9-tetrahydrocannabinol (THC) or high cannabidiol (CBD) chemotypes. The physical descriptions of both THC BDS and CBD BDS are brown, viscous, semi-solid (soft) extracts with a characteristic odour of cannabis and are almost insoluble in water, but exhibit good solubility in most organic solvents.

Sativex contains ethanol absolute, propylene glycol and peppermint oil as inactive ingredients.

PHARMACOLOGY

Pharmacodynamic Properties

Pharmacotherapeutic group: Other Analgesics and Antipyretics

ATC Code: N02BG10

Mechanism of Action and Pharmacodynamic Effects

There are at least two types of cannabinoid (CB) receptors as part of the human endocannabinoid system. CB_1 is found mainly in nerve terminals in the CNS where it modulates neurotransmitter release and CB_2 is found primarily in cells of the immune system. THC, the main psychotropic constituent of cannabis, acts as a partial agonist at both CB_1 and CB_2 receptors.

In animal models of MS and spasticity CB receptor agonists have been shown to ameliorate limb stiffness and improve motor function. These effects are prevented by CB antagonists, and CB_1 knockout mice show more severe spasticity. In the CREAE (chronic relapsing experimental autoimmune encephalomyelitis) mouse model, Sativex produced a dose-related reduction in the hind limb stiffness.

CBD has little activity at cannabinoid receptors, but does have neuroprotective properties, most likely mediated by its ability to modulate intra-cellular calcium. It is also able to modulate the course of the disease in animal models of MS. The key pharmacology of CBD in MS probably relates to its ability to inhibit microglial activity and T-cell proliferation. It is unknown whether CBD in Sativex has a facilitating or antagonising effect on the anti-spasticity action of THC.

Pharmacokinetics

Absorption:

Following administration of Sativex (four sprays), both THC and CBD are absorbed fairly rapidly and appear in the plasma within 15 minutes after single oromucosal administration. With Sativex, a mean C_{max} of about 4 ng/mL was reached some 45-120 minutes after a

single dose administration of a 10.8 mg THC dose, and was generally well tolerated with little evidence of significant psychoactivity.

There is a high degree of variability in pharmacokinetic parameters between patients. Following a single dose administration of Sativex (four sprays) under fasted conditions, the mean plasma level of THC showed a 57.3% CV for C_{max} (range 0.97-9.34 ng/mL) and a 58.5% CV for AUC (range 4.2-30.84 h*ng/mL). Similarly the %CV for CBD was 64.1% (range 0.24-2.57ng/mL) and 72.5% (range 2.18-14.85 ng/mL) for the same parameters respectively. After nine consecutive days of dosing the % CV values for the same parameters were 54.2% (C_{max} range = 0.92-6.37) and 37.4% (AUC_0-τ = 5.34-15.01 h*ng/mL) for THC and 75.7% (C_{max} range 0.34-3.39 ng/mL) and 46.6% (AUC_0-τ = 2.40-13.19 h*ng/mL) for CBD respectively.

There is a high degree of variability in pharmacokinetic parameters within patients following single and repeat dosing. Of 12 subjects who received four sprays of Sativex as a single dose, eight had reductions in C_{max} after nine days of multiple dosing, whilst three had increases (1 drop-out). For CBD, seven had reductions in C_{max} after multiple dosing, whilst four had increases.

When Sativex is administered oromucosally, plasma levels of THC and other cannabinoids are lower compared with the levels achieved following inhalation of cannabinoids at a similar dose. A dose of 8 mg of vaporised THC extract, administered by inhalation resulted in mean plasma C_{max} of more than 100 ng/mL within minutes of administration, with significant psychoactivity.

Table 1 PK parameters for Sativex, for vaporised THC extract and smoked cannabis

	C_{max} THC ng/mL	T_{max} THC minutes	AUC $_{(0\text{-}t)}$ THC ng/mL/min
Sativex (providing 21.6 mg THC)	5.40	60	1362
Inhaled vaporised THC extract (providing 8 mg THC)	118.6	17.0	5987.9
Smoked cannabis* (providing 33.8 mg THC)	162.2	9.0	No data

**Huestis et al, Journal of Analytical Toxicology 1992; 16:276-82.*

Distribution:

As cannabinoids are highly lipophilic, they are quickly absorbed and distributed into body fat. The resultant concentrations in the blood following oromucosal administration of Sativex are lower than those obtained by inhaling the same dose of THC because absorption is slower and redistribution into fatty tissues is rapid. Additionally some of the THC undergoes hepatic first pass metabolism to 11-OH-THC, the primary metabolite of THC, and CBD similarly to 7-OH-CBD. Protein binding of THC is high (~97%). THC and CBD may be stored for as long as four weeks in the fatty tissues from which they are slowly released at sub-therapeutic levels back into the blood stream, then metabolised and excreted via the urine and faeces.

Metabolism:

THC and CBD are metabolised in the liver, and approximately one third of the parent drugs and their metabolites are excreted in the urine (the remainder via the faeces). Several THC metabolites may be psychoactive. Additionally some of the THC undergoes hepatic first pass metabolism to 11-OH-THC, the primary metabolite of THC, and CBD similarly to 7-OH-CBD. Human hepatic P_{450} 2C9 isozyme catalyses the formation of 11-OH-THC, the primary metabolite, which is further metabolised by the liver to other compounds including 11-nor-carboxy-Δ^9-THC (THC-COOH), the most abundant metabolite in human plasma and urine. The P_{450}-3A subfamily catalyses the formation of other hydroxylated minor metabolites. CBD is extensively metabolised and more than 33 metabolites have been identified in urine. The major metabolic route is hydroxylation and oxidation at C-7 followed by further hydroxylation in the pentyl and propenyl groups. The major oxidised metabolite identified is CBD-7-oic acid containing a hydroxyethyl side chain.

See INTERACTIONS WITH OTHER MEDICINES for information on drug interaction and metabolism by the cytochrome P_{450} enzyme system.

Excretion:

From clinical studies with Sativex, a non-compartmental PK analysis shows that the first order terminal elimination half life from plasma is 1.94, 3.72 and 5.25 hours for THC and 5.28, 6.39 and 9.36 for CBD following the administration of 2, 4 and 8 sprays respectively.

From the literature, elimination of oral cannabinoids from plasma is bi-phasic with an initial half-life of approximately four hours and the terminal elimination half-lives are of the order of 24 to 36 hours or longer. Cannabinoids are distributed throughout the body; they are highly lipid soluble and accumulate in fatty tissue. The release of cannabinoids from fatty tissue is responsible for the prolonged terminal elimination half-life.

CLINICAL TRIALS

Sativex has been studied at doses of up to 48 sprays/day in controlled clinical trials of up to 19 weeks duration in more than 1500 patients with MS. In the pivotal trials to assess the efficacy and safety of Sativex for symptom improvement in patients with moderate to severe spasticity due to MS the primary efficacy measure was a 0 to 10 point Numeric

Rating Scale (NRS) on which patients indicated the average level of their spasticity related symptoms over the last 24 hours where 0 is no spasticity and 10 is the worst possible spasticity.

In a first Phase 3 placebo controlled trial over a 6-week treatment period, the difference from placebo reached statistical significance but the difference between treatments of 0.5 to 0.6 points on the 0-10 point NRS was not great. In a responder analysis 40% Sativex and 22% placebo responded to treatment using the criterion of greater than a 30% reduction in NRS score.

A second 14-week Phase 3 study failed to show a significant treatment effect. The difference from placebo on the NRS score was 0.2 points.

It was postulated that a clinically useful treatment effect in some patients might be partly masked by data from non-responders in the analyses of mean changes. In analyses comparing NRS scores with patient global impression of change (PGI), a 19% NRS response was estimated to represent a clinically relevant improvement on the PGI and a response of 28% "much improved" on the PGI. In post hoc exploratory combined analyses of the above two studies, a 4-week trial period using a 20% NRS response threshold was predictive of eventual response defined as a 30% reduction.

A third Phase 3 trial incorporated a formalised 4-week therapeutic trial period prior to randomisation. The aim of the trial was to assess the benefit of continued treatment for patients who achieve an initial response to treatment. 572 patients with MS and refractory spasticity all received single blind Sativex for four weeks. Of these, 272 subjects (48%) responded with a reduction of at least 20% on the spasticity symptom NRS, with a mean change from the start of treatment of -3.0 points on the 10 point NRS. Of these, 241 patients were eligible to be randomised to either continue to receive active or switch to placebo for the 12-week double-blind phase, for a total of 16 weeks treatment overall.

During the double-blind phase the mean NRS scores for patients receiving Sativex generally remained stable (mean change from randomisation in NRS score -0.19), while the mean NRS score for patients switched to placebo increased towards pre-treatment levels (mean change in NRS score +0.64). The difference* between treatment groups was 0.84 (95% CI -1.29, -0.40).

(Difference adjusted for centre, baseline NRS and ambulatory status).* Thus, the primary outcome measure was highly statistically significantly in favour of Sativex (p=0.0002).

Of those patients who had at least a 20% reduction from screening in NRS spasticity score at week 4 and who continued in the trial to receive randomised treatment, 74% (Sativex) and 51% (placebo) achieved a 30% reduction at week 16. Thus, the attributable response rate was 23% in the randomised cohort (which equates to around 10% of the original cohort).

The results over the 12-week randomised phase are shown below for the secondary endpoints. The majority of secondary endpoints showed a similar pattern to the NRS score, with patients who continued to receive Sativex maintaining the improvement seen

from the initial 4-week treatment period, while patients switching to placebo begin to decline back to pre-treatment levels.

Modified Ashworth Score:	Sativex -0.1 ; Placebo +1.8 ;
	Adjusted Difference -1.75 (95% CI -3.80, 0.30)
Spasm frequency (per day):	Sativex -0.05 ; Placebo +2.41
	Adjusted Difference -2.53 (95% CI -4.27, -0.79)
Sleep disruption by spasticity:	Sativex -0.25 ; Placebo +0.59 ;
(0 to 10 NRS)	Adjusted Difference -0.88 (95% CI -1.25, -0.51)
Timed 10 metre walk (seconds):	Sativex -2.3; Placebo +2.0;
	Adjusted Difference -3.34 (95% CI -6.96, 0.26)
Motricity index (arm and leg):	No differences between treatment groups were seen.
Barthel Activities of Daily Living:	Odds ratio for improvement: 2.04

Subject global impression of change (OR = 1.71), carer global impression of change (OR = 2.40) and physician global impression of change (OR = 1.96) all showed highly statistically significant superiority of Sativex over placebo.

The benefit of continued treatment in the long-term was studied in a placebo controlled, parallel group, randomised withdrawal trial, in subjects taking long-term Sativex. Thirty-six patients with a mean duration of Sativex use prior to the trial of 3.6 years were randomised to either continue with Sativex treatment or switch to placebo for 28 days. The primary endpoint was time to treatment failure, defined as the time from the first day of randomised treatment to a 20% increase in NRS or premature withdrawal from randomised treatment. Treatment failure was experienced by 44% of Sativex patients and 94% of placebo patients, hazard ratio 0.335 (95% CI 0.16, 0.69). The primary efficacy endpoint was significantly in favour of Sativex (p=0.013). It is possible that some treatment failures on placebo could have reflected temporary factors associated with drug withdrawal. It is not known whether such patients would have improved again if they had remained off Sativex.

INDICATIONS

Sativex is indicated as treatment, for symptom improvement in patients with moderate to severe spasticity due to multiple sclerosis (MS) who have not responded adequately to other anti-spasticity medication and who demonstrate clinically significant improvement in spasticity related symptoms during an initial trial of therapy.

CONTRAINDICATIONS

Sativex is contraindicated in patients:

- With hypersensitivity to cannabinoids or to any of the excipients.

- With any known or suspected history or family history of schizophrenia, or other psychotic illness; history of severe personality disorder or other significant psychiatric disorder other than depression associated with their underlying condition.
- Who are breast feeding (in view of the considerable levels of cannabinoids likely in maternal breast milk and the potential adverse developmental effects in infants. See PRECAUTIONS – Use in Lactation).

PRECAUTIONS

Individual response to Sativex varies widely and patients being considered for treatment with Sativex should therefore be assessed by a neurologist or rehabilitation physician. Patients who then commence a trial of Sativex should be reassessed by a neurologist or rehabilitation physician after 4 weeks of treatment. Patients who do not show a clinically significant improvement in spasticity on reassessment should not continue Sativex.

Mild or moderate dizziness is commonly reported. This most frequently occurs in the first few weeks of treatment.

Sativex is not recommended for use in children or adolescents below 18 years of age due to lack of safety and efficacy data.

Alterations in pulse rate and blood pressure have been observed following initial dose introduction so caution during initial dose titration is essential. Fainting episodes have been observed with use of Sativex.

Use of Sativex is not recommended in patients with serious cardiovascular disease. However, following dosing in healthy volunteers with Sativex up to 18 sprays twice daily, there were no clinically relevant changes in QTc, PR or QRS interval duration, heart rate, or blood pressure.

Until further information is available, caution should be taken when treating patients with a history of epilepsy, or recurrent seizures.

Psychiatric adverse events

Psychiatric adverse events including disorientation (4.1% vs 0.8%), depression (2.9% vs 2.0%), euphoric mood (2.2% vs 0.9%), and dissociation (1.7% vs 0.1%) occurred more frequently in patients given Sativex than in those given placebo in clinical trials. Approximately 10% more patients given Sativex experienced a psychiatric adverse event than those given placebo (17.6% vs 7.8%). Patients with a personal or family history of psychotic illness should not receive Sativex. Patients with a history of depression should be closely monitored and Sativex discontinued if clinically significant worsening of symptoms occurs on therapy.

In a few cases a causal association between Sativex administration and suicidal ideation could not be ruled out. In this circumstance, Sativex should be stopped immediately and the patient monitored until the symptom has completely resolved.

The maximum recommended dose should not be exceeded. Serious psychiatric adverse events including transient psychosis occurred in 4/41 healthy volunteers given 18 actuations of Sativex twice daily.

No specific studies have been carried out in patients with significant hepatic or renal impairment. THC and CBD are metabolised in the liver, and approximately one third of the parent drugs and their metabolites are excreted in the urine (the remainder via the faeces). Several THC metabolites may be psychoactive. Thus, the systemic exposure and the effects of Sativex are dependent on both renal and hepatic function and in patients with significant impaired hepatic or renal function the effects of Sativex may be exaggerated or prolonged (see PHARMACOKINETICS - Metabolism). Frequent clinical evaluation by a clinician is recommended in these patient populations.

Sativex contains approximately 50% v/v of ethanol. Each actuation contains up to 0.04g of ethanol. A small glass of wine (125 mL) of nominal ethanol content 12% v/v would contain approximately 12g ethanol. Most patients respond at doses up to and including 12 sprays a day which would contain less than 0.5 g of ethanol.

There is a risk of an increase in incidence of falls in patients whose spasticity has been reduced and whose muscle strength is insufficient to maintain posture or gait. In addition to an increased risk of falls, the CNS adverse reactions of Sativex could potentially have an impact on various aspects of personal safety, such as with food and hot drink preparation.

Although there is a theoretical risk that there may be an additive effect with muscle-relaxing agents such as baclofen and benzodiazepines, thereby increasing the risk of falls, this has not been seen in clinical trials with Sativex. However, patients should be warned of this possibility.

Patients who have a history of substance abuse may be more prone to abuse Sativex as well (see CLINICAL TRIALS).

The abrupt withdrawal of long-term Sativex treatment has not resulted in a consistent pattern or time-profile of withdrawal-type symptoms and the likely consequence will be limited to transient disturbances of sleep, emotion or appetite in some patients. No increase in daily dosage has been observed in long-term use and patient self-reported levels of 'intoxication' are low. For these reasons, dependence on Sativex is unlikely.

Adverse reactions have been reported which could be associated with the route of administration of the medicine. Application site type reactions consisted of mainly mild to moderate stinging at the time of application. Common application site reactions include application site pain, oral pain and discomfort, dysgeusia, mouth ulceration and glossodynia. Two cases of possible leukoplakia were observed but neither was confirmed histologically; a third case was unrelated. In view of this, patients who observe discomfort or ulceration at the site of application of the medicine are advised to vary the site of application within the mouth and should not continue spraying onto sore or inflamed mucous membrane. Regular inspection of the oral mucosa is also advised in long-term

administration. If lesions or persistent soreness are observed, medication should be interrupted until complete resolution occurs.

Genotoxicity

Sativex or a mixture of its component extracts was not genotoxic in *in vitro* tests for bacterial reverse mutation and *in vivo* micronucleus tests for clastogenicity in mice and rats, or in an *ex vivo* assay for unscheduled DNA synthesis in rat hepatocytes. No consistent genotoxicity was seen in an *in vitro* test for forward mutation in mouse L5178Y cells.

Carcinogenicity

A long-term carcinogenicity study has been conducted in rats with CBD BDS using dietary doses of 5-50 mg/kg/day, with no oncogenic response being observed. The highest dose resulted in estimated CBD and THC exposures (based on AUC) that were respectively 350 and 40 times that expected in humans with the maximum recommended dose. No studies were conducted with Sativex or its other component, THC BDS, but results were available from a published source for mouse and rat studies with oral administration of THC. Doses of THC used in the mouse were 125, 250 and 500 mg/kg/day (17, 35 and 70 times the maximum recommended human dose in terms of body surface area). There was an increase in thyroid follicular cell adenomas in males and females, but only with the lowest dose and the significance of this finding is uncertain. No oncogenic responses were seen in rats with THC doses of 12.5-50 mg/kg/day (3-14 times the maximum recommended human dose based on body surface area), associated with estimated exposures (AUC) of 90-550 times that expected in humans with the maximum recommended dose.

Effects on Fertility

Fertility in rats was unaffected by oral treatment with a 1:1 mixture of THC BDS and CBD BDS, at doses up to 12.5 mg/kg/day or each active component. This dose resulted in estimated exposures that were well in excess of that expected in humans with the maximum recommended dose (>300 fold based on AUC). Effects on various male reproductive parameters have been reported with cannabinoids in some animal studies, but findings were inconsistent or observed at high/toxic doses and their clinical significance is uncertain.

Use in Pregnancy (Category B2)

There is insufficient experience in humans regarding the effects of Sativex on reproduction. Sativex should not be used during pregnancy unless the potential risks to the foetus and/or embryo are considered to be outweighed by the benefit of treatment.

There was no evidence for teratogenicity in rats and rabbits treated with oral doses of a 1:1 THC BDS and CBD BDS mixture of up to 12.5 mg/kg/day of each active component. This dose resulted in respective THC and BDS exposures (based on AUC) that were approximately 490 and 320 fold (rats) or 12.5 and 3 fold (rabbits) those expected in humans with the maximum recommended dose. The highest dose was maternotoxic in

rabbits and resulted in a slightly lower foetal weight and impaired skeletal ossification. Reduced foetal weights and increased incidences of skeletal variants were seen in rabbits, associated with maternal toxicity which was apparent with all doses tested.

Oral treatment of rats with 4 mg/kg/day of a 1:1 THC BDS and CBD BDS mixture from the time of implantation to weaning of the offspring resulted in a lower pup body weight gain and slightly impaired righting reflex on day 5 of lactation. The NOEL for these findings (2 mg/kg/day) was below the maximum recommended human dose in terms of body surface area.

Use in Lactation

High concentrations of THC and CBD were measured in the milk of lactating rats after oral treatment with a 1:1 mixture of THC BDS and CBD BDS, as may be expected due to the lipophilic nature of cannabinoids. Oral treatment of rats with a 1:1 THC BDS and CBD BDS mixture from the time of implantation to weaning was associated with impaired nursing behaviour and pup survival at doses of 5 mg/kg/day or greater (less than the maximum recommended human dose in terms of body surface area).

Following repeat dosing, high levels of cannabinoids are concentrated in breast milk. Doses in excess of normal clinical doses may affect growth rates of breast-fed infants.

In view of the considerable levels of cannabinoids likely in maternal breast milk and the potential adverse developmental effects in infants, Sativex is contraindicated in breast feeding mothers (see CONTRAINDICATIONS).

Paediatric Use (<18 years)

Sativex is not recommended for use in children or adolescents below 18 years of age due to lack of safety and efficacy data.

Use in the Elderly (> 65 years)

No specific studies have been carried out in elderly patients, although patients up to 90 years of age have been included in clinical trials. However, as elderly patients may be more prone to develop some CNS adverse reactions, care should be taken in terms of personal safety such as preparation of hot food and drinks. In clinical trials patients aged over 65 years were three times more likely to have a CNS adverse event on Sativex than on placebo, and more than a third of all elderly subjects on active treatment had a CNS adverse event.

Effect on Laboratory Tests

During clinical trials with Sativex, no clinically relevant effects on laboratory tests were observed.

Effects on Ability to Drive and Use Machines

Sativex may produce undesirable effects such as dizziness and somnolence which may impair judgement and performance of skilled tasks. Therefore, given the combination of

existing disability from MS plus the common effects of Sativex, patients taking Sativex should not drive, operate dangerous machinery or engage in hazardous activities.

INTERACTION WITH OTHER MEDICINES

The two main components of Sativex, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) are metabolised by the cytochrome P_{450} enzyme system.

The inhibitory effects of Sativex on the cytochrome P_{450} system seen *in vitro* were only seen at concentrations significantly higher than the maximum observed in clinical trials.

In an *in vitro* study with 1:1% (v/v) THC botanical drug substance (BDS) and CBD BDS, no relevant induction of cytochrome P_{450} enzymes was seen for human CYP1A2, CYP2C9, CYP2C19 and CYP3A4 enzymes in human hepatocytes, at doses of up to 1µM (314 ng/mL).

When Sativex is co-administered with food the mean C_{max} and AUC for THC were 1.6- and 2.8-fold higher compared with fasting conditions. Corresponding figures for CBD were 3.3- and 5.1-fold.

Concomitant treatment with the CYP3A4 inhibitor ketoconazole produced an increase in C_{max} and AUC of THC (1.2- and 1.8-fold, respectively), its primary metabolite (3- and 3.6-fold, respectively) and of CBD (2- and 2-fold, respectively). Therefore, if concomitant drug treatment with CYP3A4 inhibitors (e.g. ketoconazole, ritonavir, clarithromycin) is started or stopped during treatment with Sativex, a new dose titration may be required.

Following treatment with the CYP3A4 inducer rifampicin reductions in C_{max} and AUC of THC (40% and 20% reduction, respectively), its primary metabolite (85% and 87% reduction, respectively),and CBD (50% and 60% reduction, respectively),were observed. Therefore, if concomitant drug treatment with strong enzyme inducers (e.g.rifampicin, carbamazepine, St John's Wort) is started or stopped during treatment with Sativex, a new dose titration may be required.

Concomitant treatment with the CYP2C19 inhibitor omeprazole resulted in no notable change in any of the pharmacokinetic parameters.

Based on *in vitro* data an inhibition of p-glycoprotein at the intestinal level by CBD cannot be excluded. Therefore, caution is recommended upon concomitant treatment with digoxin and other drugs being substrates for p-glycoprotein.

Care should be taken with hypnotics, sedatives and drugs with potential sedating effects as there may be an additive effect on sedation and muscle relaxing effects.

Although there has been no greater rate of adverse events in patients already taking anti-spasticity agents with Sativex, care should be taken when co-administering Sativex with such agents since a reduction in muscle tone and power may occur, leading to a greater risk of falls.

Sativex may interact with alcohol, affecting co-ordination, concentration and ability to respond quickly. In general, alcoholic beverages should be avoided whilst using Sativex

especially at the beginning of treatment or when changing dose. Patients should be advised that if they do drink alcohol while using Sativex additive CNS effects could increase the risk of falls and other accidents.

ADVERSE EFFECTS

The Sativex clinical program has so far involved over 1500 patients with MS in placebo controlled trials and long-term open label studies in which some patients used up to 48 sprays per day.

The most commonly reported adverse reactions in the first four weeks of exposure were dizziness, which occurs mainly during the initial titration period, and fatigue. These reactions are usually mild to moderate and resolve within a few days even if treatment is continued (see DOSAGE AND ADMINISTRATION). When the recommended dose titration schedule was used, the incidence of dizziness and fatigue in the first four weeks was much reduced.

Treatment emergent all-causality adverse events with an incidence of at least 1% for Sativex in placebo controlled trials in patients with MSare given below (some of these adverse events may be part of the underlying condition).

	All Causality			Treatment-related		
	Comparative Subjects		Non-comparative Subjects	Comparative Subjects		Non-comparative Subjects
System Organ Class Preferred Term	Sativex Total (n=805)	Placebo Total (n=741)	Sativex Total (n=1016)	Sativex Total (n=805)	Placebo Total (n=741)	Sativex Total (n=1016)
Overall Subjects with an Event	628 (78.0%)	492 (66.4%)	686 (67.5%)	532 (66.1%)	330 (44.5%)	599 (59.0%)
Cardiac Disorders						
Tachycardia	8 (1.0%)	3 (0.4%)	4 (0.4%)	5 (0.6%)	1 (0.1%)	4 (0.4%)
Ear and Labyrinth Disorders						
Vertigo	52 (6.5%)	15 (2.0%)	34 (3.3%)	48 (6.0%)	14 (1.9%)	32 (3.1%)
Eye Disorders						
Vision blurred	15 (1.9%)	3 (0.4%)	16 (1.6%)	13 (1.6%)	2 (0.3%)	8 (0.8%)
Gastrointestinal Disorders						
Nausea	77 (9.6%)	42 (5.7%)	98 (9.6%)	62 (7.7%)	27 (3.6%)	70 (6.9%)
Dry Mouth	49 (6.1%)	23 (3.1%)	60 (5.9%)	49 (6.1%)	22 (3.0%)	56 (5.5%)
Diarrhoea	44 (5.5%)	29 (3.9%)	84 (8.3%)	25 (3.1%)	14 (1.9%)	64 (6.3%)
Vomiting	28 (3.5%)	16 (2.2%)	57 (5.6%)	17 (2.1%)	11 (1.5%)	28 (2.8%)
Constipation	19 (2.4%)	4 (0.5%)	47 (4.6%)	8 (1.0%)	3 (0.4%)	27 (2.7%)
Oral Pain	17 (2.1%)	16 (2.2%)	48 (4.7%)	17 (2.1%)	16 (2.2%)	45 (4.4%)
Oral Discomfort	15 (1.9%)	14 (1.9%)	20 (2.0%)	14 (1.7%)	14 (1.9%)	20 (2.0%)
Mouth Ulceration	12 (1.5%)	6 (0.8%)	28 (2.8%)	11 (1.4%)	5 (0.7%)	26 (2.6%)
Dyspepsia	11 (1.4%)	12 (1.6%)	26 (2.6%)	8 (1.0%)	9 (1.2%)	17 (1.7%)
Abdominal pain upper	11 (1.4%)	2 (0.3%)	11 (1.1%)	3 (0.4%)	1 (0.1%)	8 (0.8%)
Glossodynia	9 (1.1%)	10 (1.3%)	32 (3.1%)	9 (1.1%)	10 (1.3%)	31 (3.1%)
General Disorders and Administration Site Conditions						
Fatigue	101 (12.5%)	62 (8.4%)	99 (9.7%)	89 (11.1%)	49 (6.6%)	77 (7.6%)
Asthenia	45 (5.6%)	23 (3.1%)	63 (6.2%)	37 (4.6%)	16 (2.2%)	40 (3.9%)

	All-Causality			Treatment-related		
	Comparative Subjects		Non-comparative Subjects	Comparative Subjects		Non-comparative Subjects
System Organ Class Preferred Term	Sativex Total (n=805)	Placebo Total (n=741)	Sativex Total (n=1016)	Sativex Total (n=805)	Placebo Total (n=741)	Sativex Total (n=1016)
Feeling drunk	24 (3.0%)	3 (0.4%)	19 (1.9%)	23 (2.9%)	3 (0.4%)	19 (1.9%)
Feeling abnormal	19 (2.4%)	4 (0.5%)	25 (2.5%)	19 (2.4%)	4 (0.5%)	25 (2.5%)
Application site pain	16 (2.0%)	17 (2.3%)	27 (2.7%)	16 (2.0%)	17 (2.3%)	27 (2.7%)
Pain	10 (1.2%)	17 (2.3%)	29 (2.9%)	3 (0.4%)	7 (0.9%)	9 (0.9%)
Malaise	8 (1.0%)	3 (0.4%)	15 (1.5%)	8 (1.0%)	1 (0.1%)	8 (0.8%)
Infections and Infestations						
Urinary Tract Infection	71 (8.8%)	66 (8.9%)	164 (16.1%)	1 (0.1%)	5 (0.7%)	8 (0.8%)
Nasopharyngitis	22 (2.7%)	25 (3.4%)	74 (7.3%)	2 (0.2%)	0	2 (0.2%)
Pharyngitis	10 (1.2%)	8 (1.1%)	26 (2.6%)	6 (0.7%)	3 (0.4%)	15 (1.5%)
Viral infection	10 (1.2%)	2 (0.3%)	12 (1.2%)	0	0	2 (0.2%)
Lower respiratory tract infection	8 (1.0%)	10 (1.3%)	33 (3.2%)	1 (0.1%)	0	3 (0.3%)
Injury, Poisoning and Procedural Complications						
Fall	12 (1.5%)	4 (0.5%)	43 (4.2%)	8 (1.0%)	1 (0.1%)	14 (1.4%)
Metabolism and Nutrition Disorders						
Anorexia	17 (2.1%)	5 (0.7%)	30 (3.0%)	11 (1.4%)	4 (0.5%)	23 (2.3%)
Increased appetite	11 (1.4%)	3 (0.4%)	8 (0.8%)	11 (1.4%)	3 (0.4%)	8 (0.8%)
Musculoskeletal and Connective Tissue Disorders						
Muscle Spasms	24 (3.0%)	20 (2.7%)	48 (4.7%)	7 (0.9%)	3 (0.4%)	12 (1.2%)
Back Pain	19 (2.4%)	14 (1.9%)	37 (3.6%)	1 (0.1%)	1 (0.1%)	3 (0.3%)
Pain In Extremity	16 (2.0%)	19 (2.6%)	35 (3.4%)	2 (0.2%)	1 (0.1%)	6 (0.6%)
Muscular Weakness	11 (1.4%)	10 (1.3%)	30 (3.0%)	8 (1.0%)	4 (0.5%)	21 (2.1%)
Arthralgia	9 (1.1%)	3 (0.4%)	32 (3.1%)	3 (0.4%)	0	2 (0.2%)
Nervous System Disorders						
Dizziness	201 (25%)	61 (8.2%)	211 (20.8%)	200 (24.8%)	52 (7.0%)	200 (19.7%)
Somnolence	66 (8.2%)	17 (2.3%)	65 (6.4%)	65 (8.1%)	14 (1.9%)	64 (6.3%)
Headache	49 (6.1%)	56 (7.6%)	82 (8.1%)	41 (5.1%)	41 (5.5%)	48 (4.7%)
Disturbance in Attention	31 (3.9%)	1 (0.1%)	37 (3.6%)	30 (3.7%)	1 (0.1%)	36 (3.5%)
Dysgeusia	25 (3.1%)	6 (0.8%)	36 (3.5%)	25 (3.1%)	6 (0.8%)	34 (3.3%)
Muscle spasticity	26 (3.2%)	25 (3.4%)	21 (2.1%)	18 (2.2%)	15 (2.0%)	8 (0.8%)
Balance disorder	23 (2.9%)	13 (1.8%)	46 (4.5%)	20 (2.5%)	6 (0.8%)	26 (2.6%)
Multiple Sclerosis Relapse	20 (2.5%)	24 (3.2%)	46 (4.5%)	1 (0.1%)	3 (0.4%)	4 (0.4%)
Dysarthria	16 (2.0%)	3 (0.4%)	13 (1.3%)	13 (1.6%)	3 (0.4%)	11 (1.1%)
Lethargy	12 (1.5%)	5 (0.7%)	26 (2.6%)	10 (1.2%)	4 (0.5%)	21 (2.1%)
Paraesthesia	12 (1.5%)	12 (1.6%)	12 (1.2%)	8 (1.0%)	6 (0.8%)	9 (0.9%)
Memory Impairment	11 (1.4%)	1 (0.1%)	20 (2.0%)	11 (1.4%)	1 (0.1%)	19 (1.9%)
Amnesia	9 (1.1%)	2 (0.3%)	13 (1.3%)	8 (1.0%)	1 (0.1%)	10 (1.0%)
Tremor	9 (1.1%)	6 (0.8%)	10 (1.0%)	6 (0.7%)	3 (0.4%)	7 (0.7%)
Psychiatric Disorders						
Disorientation	33 (4.1%)	6 (0.8%)	21 (2.1%)	32 (4.0%)	4 (0.5%)	18 (1.8%)
Depression	23 (2.9%)	15 (2.0%)	47 (4.6%)	15 (1.9%)	6 (0.8%)	27 (2.7%)
Euphoric Mood	18 (2.2%)	7 (0.9%)	24 (2.4%)	18 (2.2%)	7 (0.9%)	24 (2.4%)
Dissociation	14 (1.7%)	1 (0.1%)	12 (1.2%)	14 (1.7%)	1 (0.1%)	11 (1.1%)
Insomnia	11 (1.4%)	16 (2.2%)	23 (2.3%)	5 (0.6%)	7 (0.9%)	13 (1.3%)

	All Causality			Treatment-related		
	Comparative Subjects		Non-comparative Subjects	Comparative Subjects		Non-comparative Subjects
System Organ Class Preferred Term	Sativex Total (n=805)	Placebo Total (n=741)	Sativex Total (n=1016)	Sativex Total (n=805)	Placebo Total (n=741)	Sativex Total (n=1016)
Respiratory, Thoracic and Mediastinal Disorders						
Cough	11 (1.4%)	7 (0.9%)	20 (2.0%)	3 (0.4%)	3 (0.4%)	3 (0.3%)
Pharyngolaryngeal pain	8 (1.0%)	11 (1.5%)	1 (0.1%)	3 (0.4%)	4 (0.5%)	1 (0.1%
Vascular Disorders						
Hypertension	9 (1.1%)	4 (0.5%)	15 (1.5%)	5 (0.6%)	1 (0.1%)	3 (0.3%)

A single case of ventricular bigeminy has been reported though this was in the context of acute nut allergy.

Abuse potential

In a study designed to identify its abuse potential, Sativex at a dose of 4 sprays taken at one time, did not differ significantly from placebo. At 8 sprays there was a moderate effect, significantly different from placebo, and the results were more marked at 16 sprays. Sativex taken at the maximum recommended doses of up to twelve sprays per day sprays has moderate potential for abuse. Patients with a history of substance abuse may abuse Sativex and if Sativex is being considered for these patients close monitoring is recommended.

Psychiatric and cognitive adverse effects

In a QTc study a dose of Sativex 4 sprays over 20 minutes twice daily was well-tolerated, but a substantially supratherapeutic dose of 18 sprays over 20 minutes twice daily resulted in significant psychoactivity and cognitive impairment. 4/41 (9.7%) patients taking substantial multiples of the therapeutic dose experienced psychiatric adverse effects including hallucinations, delusions, and homicidal and suicidal ideation.

Please also refer to the PRECAUTIONS section.

DOSAGE AND ADMINISTRATION

Patients being considered for treatment with Sativex should be assessed by a neurologist or rehabilitation physician. Patients who then commence a trial of Sativex should be reassessed by a neurologist or rehabilitation physician after 4 weeks of treatment. Patients who do not show a clinically significant improvement in spasticity on reassessment should not continue Sativex.

Treatment must be initiated and supervised by a specialist neurologist or rehabilitation physician with expertise in treating patients with spasticity due to multiple sclerosis.

Sativex is for oromucosal use only.

Sativex is intended to be used in addition to the patient's current anti-spasticity medication.

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Adults

Patients should be advised that it might take up to two weeks to find the optimal dose and that undesirable effects can occur during this time, most commonly dizziness. These undesirable effects are usually mild and resolve in a few days. However, physicians should consider maintaining the current dose, reducing the dose or interrupting, at least temporarily, the treatment depending on seriousness and intensity.

To minimise variability of bioavailability in the individual patient, administration of Sativex should be standardised as far as possible in relation to food intake (see INTERACTIONS WITH OTHER MEDICINES).

Titration period:

A titration period is required to reach optimal dose. The number and timing of sprays will vary between patients.

The number of sprays should be increased each day following the pattern given in the table below. The afternoon/evening dose should be taken at any time between 4 pm and bedtime. When the morning dose is introduced, it should be taken at any time between waking and midday. The patient may continue to gradually increase the dose by one spray per day, up to a maximum of 12 sprays per day, until they achieve optimum symptom relief. There should be at least a 15 minute gap between sprays. The maximum number of consecutive sprays must not exceed 7 within a 3 hour period.

Day	Number of sprays in the morning	Number of sprays in the evening	(Total number of sprays per day)
1	0	1	1
2	0	1	1
3	0	2	2
4	0	2	2
5	1	2	3
6	1	3	4
7	1	4	5
8	2	4	6
9	2	5	7
10	3	5	8
11	3	6	9
12	4	6	10
13	4	7	11
14	5	7	12

Maintenance period:

Following the titration period, patients are advised to maintain the optimum dose achieved. The median dose in clinical trials for patients with multiple sclerosis was eight sprays per day. Once the optimum dose has been achieved, patients may spread the doses throughout the day according to individual response and tolerability. Re-titration upwards or downwards may be appropriate if there are any changes in the severity of the patient's condition, changes in their concomitant medication or if troublesome adverse reactions develop. Doses must not exceed 12 sprays in any 24-hour period.

Review by the physician:

A thorough evaluation of the severity of spasticity related symptoms and of the response to standard anti-spasticity medication should be performed prior to initiation of treatment. Sativex is only indicated in patients with moderate to severe spasticity that have responded inadequately to other anti-spasticity medication. The patient's response to Sativex should be reviewed after four weeks of treatment. If a clinically significant improvement in spasticity related symptoms is not seen during this initial trial of therapy, then treatment should be stopped. In the clinical trials this was defined as at least a 20% improvement in spasticity related symptoms on a 0-10 patient reported numeric rating scale (see CLINICAL TRIALS). The value of long term treatment should be re-evaluated periodically.

Children

Sativex is not recommended for use in children or adolescents below 18 years of age due to lack of safety and efficacy data.

Elderly

No specific studies have been carried out in elderly patients, although patients up to 90 years of age have been included in clinical trials. However, as elderly patients may be more prone to develop some CNS adverse reactions, care should be taken in terms of personal safety such as preparation of hot food and drinks.

Patients with significant hepatic or renal impairment

There are no studies in patients with impaired hepatic or renal function. However, in these sub-populations the effects of Sativex may be exaggerated or prolonged. Frequent clinical evaluation by a clinician is recommended in these patient populations (see PRECAUTIONS).

Method of administration

Priming:

The spray container needs to be primed before first use and if not used for more than 21 days. To this end, the spray container should be shaken gently and the protective cap removed. The vial then needs to be held in an upright position while the actuator is pressed firmly and quickly for two or three times, directing into a tissue until a fine spray appears.

Normal use: The spray container should be shaken before use and the spray should be directed at different sites on the oromucosal surface changing the application site each time the product is used.

OVERDOSAGE

There is no experience of deliberate overdose with Sativex in patients. However, in a thorough QT study of Sativex in 257 subjects, with 18 sprays taken over a 20-minute period twice daily, signs and symptoms of overdose/poisoning were observed. These consisted of acute intoxication type reactions including dizziness, hallucinations, delusions, paranoia, tachycardia or bradycardia with hypotension. In three of 41 subjects dosed at 18 sprays twice a day, this presented as a transient toxic psychosis which resolved upon cessation of treatment. Twenty-two subjects who received this substantial multiple of the recommended dose successfully completed the 5-day study period.

In the case of overdose, treatment should be symptomatic and supportive.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

Presentation

Sativex is a yellow-brown oromucosal spray solution containing 27 mg/mL of THC and 25 mg/mL of CBD. The Type I amber glass spray container with brown plastic coating is fitted with a metering pump possessing a polypropylene dip tube and elastomer neck covered with a polyethylene cap. The metering pump delivers 100 microlitres per spray.

Pack Size: 10 mL.

10 mL pack size allows delivery after priming of up to 90 actuations (sprays) of 100 microlitres.

1 or 3 glass spray containers per carton.

Not all pack sizes may be marketed.

Storage Conditions

Store below 8°C (Refrigerate). Store upright. Keep away from heat and direct sunlight.

Once the spray container is opened and in use, refrigerated storage is not necessary but do not store above 25°C.

Use within 42 days from date of opening.

Special precautions for disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

NAME AND ADDRESS OF SPONSOR

Novartis Pharmaceuticals Australia Pty Limited

ABN 18 004 244 160

54 Waterloo Road

North Ryde NSW 2113

Sativex® is a registered trade mark of GW Pharma Limited, United Kingdom.

POISON SCHEDULE OF THE MEDICINE

Poison schedule: Controlled Drug - Schedule 8

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

26 November 2012

FROM:

[redacted]

6 January 2013

TO:
The Secretary
Scheduling Secretariat
GPO Box 9848
Canberra ACT 2601

Dear Sir

SATIVEX

I am writing in regard to the above medication that is currently not available in Australia.

I was diagnosed with multiple sclerosis in 1983. The painful stiffness of my leg muscles is relentless - I therefore have great trouble walking. Unfortunately, medication that should help my situation, does not. I have read about Sativex, plus have seen programmes on the National Geographic channel regarding Sativex - I believe this medication may help me.

I am aware that it is available in a number of countries now.

This medication should not be banned here in Australia. I truly hope it becomes available to those who suffer with Multiple Sclerosis very, very soon.

My email address and phone numbers follow - [redacted]

Yours faithfully

[redacted]

[redacted]

January 15, 2013

The Secretary
Scheduling Secretariat
GPO Box 9848
CANBERRA ACT 2601

Dear Sir/Madam

Re: SATIVEX

I am writing in regard to the above medication which is currently not available in Australia.

I was diagnosed with relapsing remitting multiple sclerosis in October 2001. MS is often referred to as the 'Invisible' disease and in my case there are no visible symptoms or impairments. Sadly for me, MS drains my energy, impairs my balance and often befuddles my thinking.

I have read about Sativex, as well as seeing programmes on the National Geographic channel regarding **Sativex**. Unfortunately my symptoms would not respond to Sativex but I do know scores of PwMS (People with MS) who would benefit enormously from its efficacy.

I believe this medication should be available to people with MS who could use it. While this may not be me, people who have MS and who are unable to get relief from other medications should have as much quality of life as possible. **Sativex** will provide an additional treatment option to supplement current physical and other existing symptomatic therapies. Several people in our support group are unable to get relief from any medication for their spasticity, stiffness and muscle pain. This medication will be of use to them once they have access to it.

I understand the complications that **Sativex** provides to the TGS since this medicine contains chemicals derived from cannabis. Therefore a more lengthy process is required for the scheduling of **Sativex**. I also understand that any changes to the National Poisons Schedule will need to be followed by state-based regulatory changes.

I would like to offer my unqualified support the introduction of this medication for people have MS and will benefit from Sativex.

This medication should be available in Australia to those of us with Multiple Sclerosis who are unable to have other medications that provide relief from our symptoms.

I am aware that it is now available in a number of countries.

My email address is [redacted]
and
My phone number is [redacted]

Yours faithfully

[redacted]

[redacted]

January 15, 2013

The Secretary
Scheduling Secretariat
GPO Box 9848
CANBERRA ACT 2601

Dear Sir/Madam

Re: SATIVEX

I am writing in regard to the above medication that is currently not available in Australia.

I was diagnosed with Remitting/Intermittent Multiple Sclerosis in 1993. Over the past 20 years my Neurologist prescribed Betaferon, but I developed Sarcoidosis, which was a side-effect, then she changed me to Copaxone without any side-effect. My new Neurologist has since changed me to Tysabri, which I have been on for the past 9 months, without any adverse reaction.

People who have MS and who are unable to get relief from other medications should have as much quality of life as possible. I believe this medication should be available to people with MS.

Sativex may provide an additional treatment option to supplement current physical and other existing symptomatic therapies. Several people in our support group are unable to get relief from any medication for their spasticity, stiffness and muscle pain. This medication could be of use to them.

I understand the complications that **Sativex** provides to the TGS since this medicine contains chemicals derived from cannabis so a more lengthy process is required for the scheduling of **Sativex**. I also understand that any changes to the National Poisons Schedule will need to be followed by state-based regulatory changes.

I would support the introduction of this medication for people who, through no apparent fault of their own, have MS.

This medication should be available in Australia to those of us with Multiple Sclerosis who are unable to have other medications that provide relief from our symptoms.

I am aware that it is now available in a number of Countries.

My email address is: [redacted]

My Telephone Nos are:

Yours faithfully

[redacted]

[redacted]

January 13, 2013

The Secretary
Scheduling Secretariat
GPO Box 9848
CANBERRA ACT 2601

Dear Sir/Madam

Re: SATIVEX

I am writing in regard to the above medication that is currently not available in Australia.

I was diagnosed with multiple sclerosis in 1995. The chronic pain, sensitivity and stiffness in my legs means I have to sleep with a cradle as I cannot bear anything touching my legs. I have to permanently wear shorts (knee length is the longest I can bear), which is not good for a 70 year old woman.

I believe this medication would help alleviate my symptoms and should be available to those with MS whose life would be enhanced. I am unable to get relief from other medications, and have been under Professor Cousins of the chronic pain clinic at the Royal North Shore hospital for many years, but there is no other drug which works for me. **Sativex** could provide an effective treatment for the above symptoms, which have been making my life a misery for a long time. Several people in our support group are unable to get relief from any medication for their spasticity, stiffness and muscle pain. This medication could be of use to them.

I understand the complications that **Sativex** provides to the TGS since this medicine contains chemicals derived from cannabis so a more lengthy process is required for the scheduling of **Sativex**. I also understand that any changes to the National Poisons Schedule will need to be followed by state-based regulatory changes.

I support the introduction of this medication for people who, through no fault of their own, have this type of MS. This medication should be available in Australia to those of us with Multiple Sclerosis whose symptoms are not alleviated by any other medication.

I am aware that it is now available in a number of countries.

My email address is:
[redacted]

My phone number is:
[redacted]

Yours faithfully

[redacted]

[redacted]

January 15, 2013

The Secretary
Scheduling Secretariat
GPO Box 9848
CANBERRA ACT 2601

Dear Sir/Madam

Re: SATIVEX

I am writing in regard to the above medication that is currently not available in Australia.

I believe this medication should be available to people with MS who could use it. *While this may not be me,* people who have MS and who are unable to get relief from other medications should have as much quality of life as possible. **Sativex** may provide an additional treatment option to supplement current physical and other existing symptomatic therapies.

I understand the complications that **Sativex** provides to the TGS since this medicine contains chemicals derived from cannabis so a more lengthy process is required for the scheduling of **Sativex**. I also understand that any changes to the National Poisons Schedule will need to be followed by state-based regulatory changes.

I would support the introduction of this medication for people who, through no apparent fault of their own, have MS.

This medication should be available in Australia to those with Multiple Sclerosis who are unable to have other medications that provide relief.

I am aware that it is now available in a number of countries.

My email address is [redacted] and My phone number is [redacted]

Yours faithfully,

[redacted]

ego the science of healthy skin

January 07, 2012

The Secretary
Scheduling Secretariat
GPO Box 9848
CANBERRA ACT 2601

To the Secretary,

Ego Pharmaceuticals would like to submit comment in regards to the following proposed rescheduling.

Substance/s	Scheduling proposal
Hydrocortisone and hydrocortisone acetate	Proposal to reschedule preparations containing 1 per cent or less hydrocortisone and hydrocortisone acetate when combined with antifungal substances for dermal use from Schedule 3 to Schedule 2.

Ego Pharmaceuticals fully supports the rescheduling of preparations containing 1 per cent or less hydrocortisone and hydrocortisone acetate when combined with antifungal substances for dermal use from Schedule 3 to Schedule 2.

Ego Pharmaceuticals is the Sponsor of two products that contain a combination of hydrocortisone and the antifungal miconazole nitrate as listed below:

- Resolve Plus 0.5 AUST R 75602. This product is S2 as it contains a combination of 0.5% hydrocortisone and 2% miconazole nitrate.
- Resolve Plus 1.0 AUST R 75601. This product is S3 as it contains a combination of 1.0% hydrocortisone and 2% miconazole nitrate.

Both products were approved for sale in Australia in August 2000 and have been marketed continuously since approved (originally approved as 'Fungocort'[1]).

[1] Brand name changed to Resolve Plus in 2002.

Ego Pharmaceuticals Pty Ltd
21-31 Malcolm Road, Braeside, 3195, Australia
Tel: +61 3 9587 1088 Fax: +61 3 9580 7647 ask@egopharm.com
ABN 86 005 142 361

Safety

A search conducted of the Database of Adverse Event Notifications available from the Therapeutic Goods Administration (TGA), on December 10, 2012 identified that since it was approved for sale, only 1 adverse event has been reported to the TGA for Resolve Plus (see Attachment 1) in June 2001.

In 2009, two additional reports were made to the TGA for "Resolve Plus" however no indication of the concentration of hydrocortisone was made in these reports, so they could be for either of Resolve Plus 0.5 and 1.0 (see Attachment 2).

In the last financial year 2011/2012, 106,675 units of Resolve Plus 1.0 were sold in Australia, with 48,695 units of Resolve Plus 0.5% sold in the same period.

Given the sales volume, and the very low level of adverse events, the proposed rescheduling would not be a safety issue if approved.

Labelling

Despite the difference in scheduling status, there is no labelling difference between Resolve Plus 1.0 and Resolve Plus 0.5. Both carry the same cautions, directions and indications (see Attachment 3). This supports the adverse event evidence that shows that using a 1% hydrocortisone, as compared to the 0.5% hydrocortisone combination product does not increase the risk associated with the product.

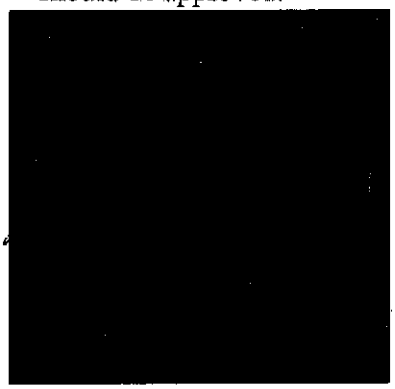
Potency

The potency of a corticosteroid depends on the concentration used, the intrinsic activity of the compound and its ability to penetrate the barrier of the epidermis. Hydrocortisone and hydrocortisone acetate are both classed as mild potency corticosteroids at concentrations of 0.5% and 1.0% (see Attachment 4), indicating that there is no change in drug potency with the increase in concentration.

Ego Pharmaceuticals fully supports the rescheduling of preparations containing 1 per cent or less hydrocortisone and hydrocortisone acetate when combined with antifungal substances for dermal use from Schedule 3 to Schedule 2 for the following reasons:

- There is no potency difference between 0.5% and 1.0% hydrocortisone and hydrocortisone acetate,
- The is no labelling difference between existing combination products (i.e. Resolve Plus 1.0 and 0.5),
- The absence of adverse events reported in the more than 12 years Resolve Plus 1.0 has been marketed.

Taken as a whole, we believe this data supports the safety of the proposed rescheduling and it should be approved.



Attachment 1

Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Database of Adverse Event Notifications

List of reports

You searched for the following **1 medicine** between **01/01/1971 – 10/09/2012**:

- Fungocort 1% (Hydrocortisone; Miconazole nitrate)

Important information

The TGA uses adverse event reports to identify when a safety issue may be present. An adverse event report does not mean that the medicine is the cause of the adverse event. If you are experiencing an adverse event, or think you may be experiencing one, please seek advice from a health professional as soon as possible. The TGA strongly advises people taking prescription medicines not to change their medication regime without prior consultation with a health professional.

About the Database of Adverse Event Notifications (DAEN)

- The DAEN contains information from reports of adverse events that the TGA has received in relation to medicines including vaccines used in Australia.
- The DAEN does not contain all known safety information about a particular medicine. Please do not make an assessment about the safety of a medicine based on the information in the DAEN.

The TGA medicine safety monitoring program

More information about the DAEN and the TGA medicines safety monitoring program is available at:

- About the Database of Adverse Event Notifications <http://www.tga.gov.au/safety/daen-about.htm>
- Medicines safety <http://www.tga.gov.au/safety/information-medicines.htm>

You are encouraged to report an adverse event suspected of being related to a medicine used in Australia. Reports of adverse events in relation to medicines and vaccines can be reported using the 'blue card' reporting form, by phone and online <http://www.tga.gov.au/safety/problem.htm>.

Other useful sources of information on Australian medicines

More information about a medicine is available from the Product Information (PI) <http://www.tga.gov.au/hp/information-medicines-pi.htm> and Consumer Medicine Information (CMI) <http://www.tga.gov.au/consumers/information-medicines-cmi.htm> leaflet. Australian Public Assessment Report for Prescription Medicines (AusPARs) <http://www.tga.gov.au/industry/pm-auspar.htm> for some prescription medicines, are also available from this website.
Information on medicines used in Australia is available from NPS MedicineWise <http://www.nps.org.au/>.

About the release of this information

While reasonable care is taken to ensure that the information is an accurate record of the adverse events reported to the TGA, the TGA does not guarantee or warrant the accuracy, reliability, completeness or currency of the information or its usefulness in achieving any purpose.
To the fullest extent permitted by law, including but not limited to section 61A of the Therapeutic Goods Act 1989, the TGA will not be liable for any loss, damage, cost or expense incurred in or arising by reason of any person relying on this information.
Copyright restrictions apply to the DAEN <http://www.tga.gov.au/about/website-copyright.htm>.

Results

Number of reports (cases): 1
(Multiple adverse events have been reported for some patients)
Number of cases with a single suspected medicine: 1
(The TGA thinks there is a possibility that the medicine caused the adverse event)
Number of cases where death was a reported outcome: 0
(These reports of death may or may not have been a result of taking a medicine)

Case number[i]	Report entry date[ii]	Age (yrs)[iii]	Gender[iv]	Medicines reported as being taken[v]	MedDRA reaction terms[vi]
AU00165363	04/06/2001	41	F	• Fungocort 1% (Hydrocortisone; Miconazole nitrate) - Suspected	• Application site reaction • Bronchospasm

Footnotes

[i] A unique number that permits reference to a particular case

[ii] The date that information from the original report was entered into the database

[iii] Age of patient at time of adverse event, '-' if unknown

[iv] Gender of patient, '-' if unknown

[v] Medicines reported to have been taken by the patient

[vi] A description of the adverse event as defined by the Medical Dictionary for Regulatory Activities (MedDRA). You can use the MedlinePlus medical dictionary <http://www.nlm.nih.gov/medlineplus/mplusdictionary.html> to look up terms.

Attachment 2

Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Database of Adverse Event Notifications

List of reports

You searched for the following 1 **medicine** between **01/01/1971 – 10/09/2012**:

- Resolve Plus (Miconazole-Hydrocortisone)

Important information

The TGA uses adverse event reports to identify when a safety issue may be present. An adverse event report does not mean that the medicine is the cause of the adverse event. If you are experiencing an adverse event, or think you may be experiencing one, please seek advice from a health professional as soon as possible. The TGA strongly advises people taking prescription medicines not to change their medication regime without prior consultation with a health professional.

About the Database of Adverse Event Notifications (DAEN)

- The DAEN contains information from reports of adverse events that the TGA has received in relation to medicines including vaccines used in Australia.
- The DAEN does not contain all known safety information about a particular medicine. Please do not make an assessment about the safety of a medicine based on the information in the DAEN.

The TGA medicine safety monitoring program

More information about the DAEN and the TGA medicines safety monitoring program is available at:

- About the Database of Adverse Event Notifications <http://www.tga.gov.au/safety/daen-about.htm>
- Medicines safety <http://www.tga.gov.au/safety/information-medicines.htm>

You are encouraged to report an adverse event suspected of being related to a medicine used in Australia. Reports of adverse events in relation to medicines and vaccines can be reported using the 'blue card' reporting form, by phone and online <http://www.tga.gov.au/safety/problem.htm>.

Other useful sources of information on Australian medicines

More information about a medicine is available from the Product Information (PI) <http://www.tga.gov.au/hp/information-medicines-pi.htm> and Consumer Medicine Information (CMI) <http://www.tga.gov.au/consumers/information-medicines-cmi.htm> leaflet. Australian Public Assessment Report for Prescription Medicines (AusPARs) <http://www.tga.gov.au/industry/pm-auspar.htm> for some prescription medicines, are also available from this website.
Information on medicines used in Australia is available from NPS MedicineWise <http://www.nps.org.au/>.

About the release of this information

While reasonable care is taken to ensure that the information is an accurate record of the adverse events reported to the TGA, the TGA does not guarantee or warrant the accuracy, reliability, completeness or currency of the information or its usefulness in achieving any purpose.
To the fullest extent permitted by law, including but not limited to section 61A of the Therapeutic Goods Act 1989, the TGA will not be liable for any loss, damage, cost or expense incurred in or arising by reason of any person relying on this information.
Copyright restrictions apply to the DAEN <http://www.tga.gov.au/about/website-copyright.htm>.

Results

Number of reports (cases): 2

(Multiple adverse events have been reported for some patients)

Number of cases with a single suspected medicine: 2

(The TGA thinks there is a possibility that the medicine caused the adverse event)

Number of cases where death was a reported outcome: 0

(These reports of death may or may not have been a result of taking a medicine)

Case number[i]	Report entry date[ii]	Age (yrs)[iii]	Gender[iv]	Medicines reported as being taken[v]	MedDRA reaction terms[vi]
AU00248524	11/02/2009	-	F	• Resolve Plus (Miconazole-Hydrocortisone) - Suspected	• Application site reaction • Blister • Erythema
AU00250291	20/04/2009	-	F	• Resolve Plus (Miconazole-Hydrocortisone) - Suspected	• Application site reaction • Blister • Erythema

Footnotes

[i] A unique number that permits reference to a particular case

[ii] The date that information from the original report was entered into the database

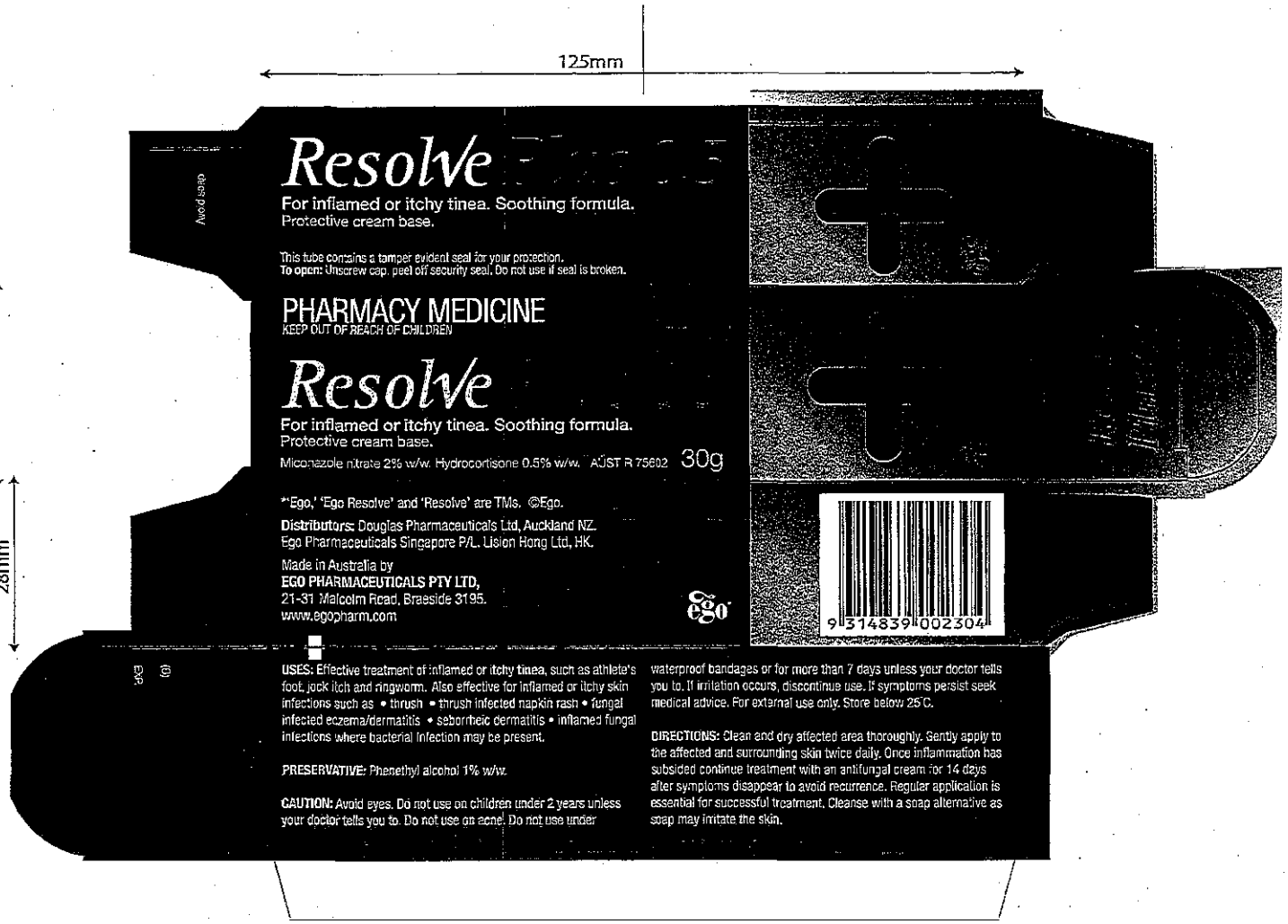
[iii] Age of patient at time of adverse event, '-' if unknown

[iv] Gender of patient, '-' if unknown

[v] Medicines reported to have been taken by the patient

[vi] A description of the adverse event as defined by the Medical Dictionary for Regulatory Activities (MedDRA). You can use the MedlinePlus medical dictionary <http://www.nlm.nih.gov/medlineplus/mplusdictionary.html> to look up terms.

Attachment 3

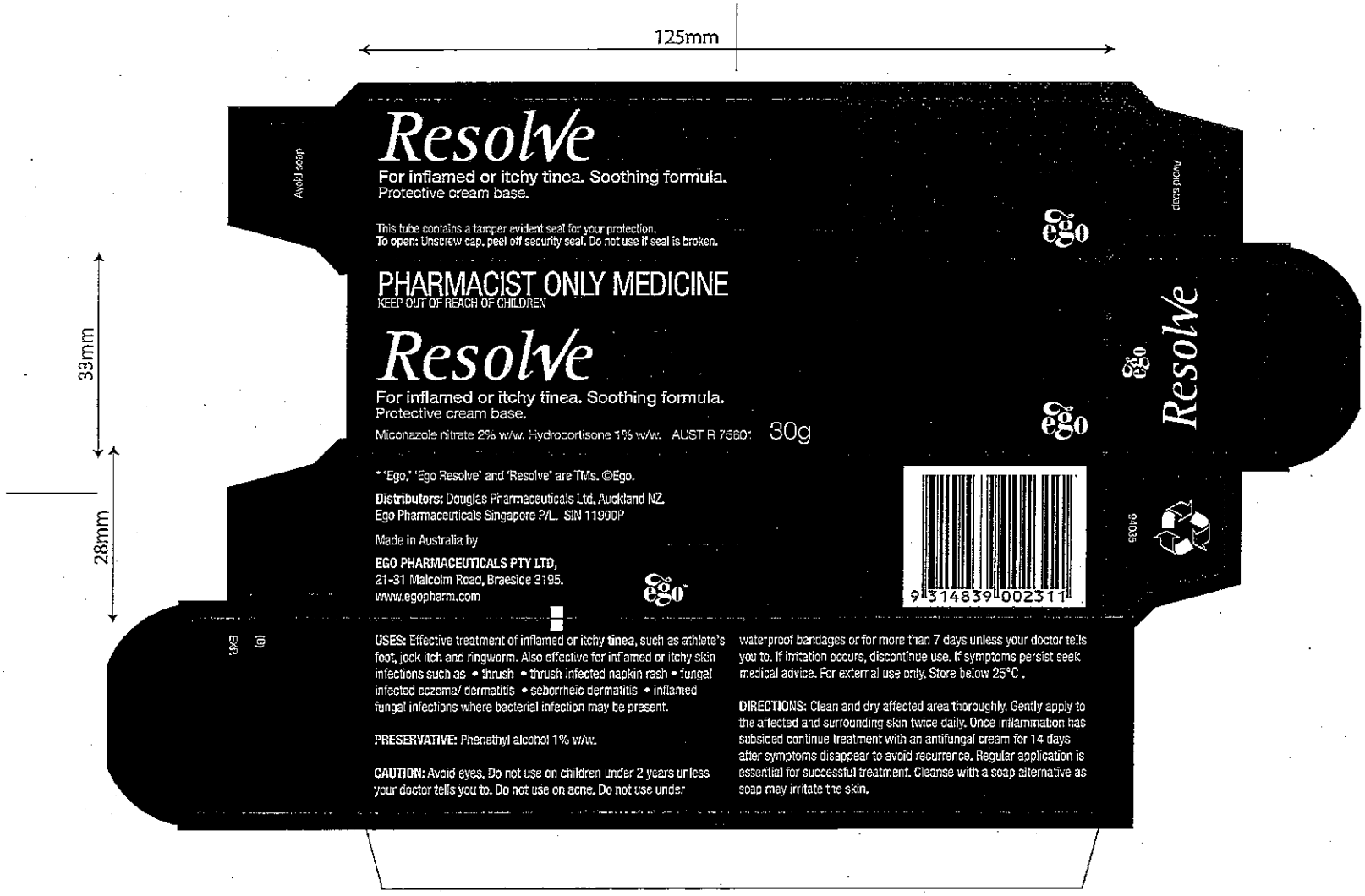


Hydrocortisone and Hydrocortisone acetate

Cool Grey 10 | silver ink | 3015 | Spot UV | forme

ego	F/N: CAR-ResolvePlus.5-30g	JobBag#: 1953/013	Carton Z	Special Instructions:
	Supplier: CHH	Ver#: 3	Size: 28x33x125mm	
	BrandMngr: Kat H	Date: 28-05-10	Name: Eugene C	

100 90 80 70 60 50 40 30 20 10 0



Hydrocortisone and Hydrocortisone acetate

3015 | 8643 Metallic Yellow | 8862 Metallic Orange | spot varnish | fonne

ego	P/N: CAR_ResolvePlus1 30g	JobBag#: 1956/013	CARTON Z	Special Instructions:
	Supplier:CarterHoltHarvey	Ver#: 5	Size: H 33, W 28, L 125	
	BrandMngr: Kat H	Date: 29-11-10	Name: Eugene C	

100 90 80 70 60 50 40 30 20 10 0

Attachment 4

Therapeutic Guidelines

Dermatology

2009
VERSION 3

Suggested citation:

Dermatology Expert Group. Therapeutic guidelines: dermatology. Version 3. Melbourne: Therapeutic Guidelines Limited; 2009.

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Email: sales@tg.org.au
Website: http://www.tg.org.au

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Opportunistic infections, such as listeriosis, are also more common in patients using TNF inhibitors. There may be an increased risk of lymphoma and perhaps other malignancies with the use of TNF inhibitors.

An increased incidence of multiple sclerosis has been detected in patients treated with TNF inhibitors. The presence of antinuclear antibodies is more common after treatment with TNF inhibitors, but this appears to be associated with systemic lupus erythematosus (SLE) only rarely and, when it does occur, it is a milder form.

TNF inhibitors can aggravate pre-existing congestive heart failure.

Monitoring

Before starting a TNF inhibitor the patient should have appropriate TB screening (as described above), hepatitis B and C serology, full blood examination, and liver function tests. If used alone, a full blood count and liver function tests should be performed every 3 to 6 months. A baseline antinuclear antibodies (ANA) titre may also be useful.

Efalizumab

Efalizumab is a recombinant humanised monoclonal antibody that binds to the CD11a chain of lymphocyte function associated antigen-1, thereby inhibiting T cell activation and migration into the skin. It is used to treat psoriasis but is not effective in psoriatic arthritis. As with the tumour necrosis factor inhibitors, the risk of infection is increased in patients receiving efalizumab.

BOTULINUM TOXIN TYPE A

Botulinum toxin type A (produced by *Clostridium botulinum*) blocks the release of acetylcholine from cholinergic neurones and induces chemical denervation. This results in loss of muscle tone and contractility, and subsequent atrophy. Since the terminal axon of the neurone sprouts new motor endplates, the effects of the toxin wane with time and reinnervation generally results within 3 to 4 months.

Dermatological uses include temporary improvement in the appearance of upper facial rhytides (crow's feet, forehead, glabellar lines) in adults and primary hyperhidrosis of the axillae. If muscles in the vicinity of the injection site are inadvertently affected, unintentional paralysis of affected muscles may occur.

Commercially available preparations of botulinum toxin are not interchangeable as the units by which potency is measured are not therapeutically equivalent.

CORTICOSTEROIDS

Topical and systemic corticosteroids have anti-inflammatory and immunosuppressant effects that are useful in a number of skin disorders. Modification of the naturally occurring hydrocortisone molecule has produced a large number of drugs with varying anti-inflammatory potency.

Topical corticosteroids

Potency classification

Topical corticosteroids can be classified into groups according to their potency (see Table 3, below). The potency depends on the concentration used, the intrinsic activity of the compound, and its ability to penetrate the barrier of the epidermis, which may be influenced by the vehicle in which it is applied and the use of occlusion.

Table 3. Classification of potencies of topical corticosteroids

Mild	
desonide	0.05%
hydrocortisone	0.5%, 1%
hydrocortisone acetate	0.5%, 1%
Moderate	
betamethasone valerate	0.02%, 0.05%
clobetasone butyrate	0.05%
methylprednisolone aceponate	0.1%
triamcinolone acetonide	0.02%
Potent	
betamethasone dipropionate	0.05%
betamethasone valerate	0.1%
mometasone furoate	0.1%
triamcinolone acetonide	0.1%
Very potent	
betamethasone dipropionate	0.05% in optimised vehicle
clobetasol propionate*	0.05%

* Clobetasol propionate is not registered for use in Australia; available through compounding pharmacies, or via the Special Access Scheme. It should only be used under the supervision of a dermatologist.

UnitingCare Australia

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25 January 2013

The Secretary
Scheduling Secretariat
Therapeutic Goods Administration
GPO Box 9848
CANBERRA ACT 2601

Dear Sir/Madam

Public Submission
Proposed Amendment: Proposal to Reschedule Benzodiazepines from Schedule 4 to Schedule 8
(Regulation 42ZCZK, Therapeutic Goods Regulations 1990)

About UnitingCare Australia
UnitingCare Australia is the Uniting Church's national body supporting community services and advocacy for children, young people, families, people with disabilities and older people.

UnitingCare Australia takes up community service issues within the theological framework of the Uniting Church, particularly the Church's social justice perspectives. We develop and reflect on the policies and practices of the Uniting Church in community services. We pursue appropriate issues within the Uniting Church, with Government and the community sector, with the Australian community and with other parts of the Church.

UnitingCare Australia represents the network of UnitingCare community services operating nationally across more than 1300 sites. The UnitingCare network is one of the largest providers of community services in Australia, providing services to over 2 million people each year, with an annual turnover in excess of $2 billion and employing 35,000 staff and 24,000 volunteers nationally.

UnitingCare agencies provide services across Australia to people living in urban, rural and remote communities. Services delivered by our agencies employ a holistic approach to supporting individuals and communities to access the resources, support and opportunities needed to live a decent life. The building blocks of which are being able to access appropriate food, clothing and healthcare; safe and secure housing; meaningful work, education, rest and enjoyment, and; the opportunity to participate in and contribute to communities. UnitingCare agencies, through their community linkages are also able to provide people of goodwill – either as individuals or as organisations – a vehicle to make their own contribution to improving the wellbeing of people and communities that are disadvantaged and vulnerable. We partner with Governments, other organisations, communities and people of goodwill to ensure all people have access to the means and opportunity for a decent life.

The UnitingCare network includes services that provide residential and community care services to older people and their families in every state and territory in Australia, including 12 per cent of residential care places. These services have an enduring commitment to working in partnership with the aged care sector, communities and governments to improve service quality, transparency and consumer outcomes.

Introduction

Whilst the proposed amendment may seek to provide a control measure for illicit use/misuse/abuse of benzodiazepine medications, and we acknowledge the need for such use to be monitored, we see the focus of control and regular review primarily linked to those who prescribe medication, that is, the General Practitioner (and medical specialists or others authorized to prescribe). The proposed amendments have key impacts on those involved in the administration of such drugs, we appreciate the legitimate and appropriate existing use of such medication and the proposed amendments will create many significant unintended consequences for residential aged care facilities as well as community service providers .

Background

Benzodiazepines, also known as "minor tranquillisers", are most commonly prescribed by medical practitioners to relieve stress and anxiety and to help people sleep. Common benzodiazepines include Diazepam, Oxazepam, Alprazolam, Nitrazepam and Temazepam. Benzodiazepines are produced by different drug companies using different trade names for the same medication.

Using benzodiazepines without a prescription from a medical practitioner, or selling or giving the medications to another person, is illegal. Legislation is in place against forging or altering a prescription or making false representation to obtain benzodiazepines or a prescription for these medications. Regular use of benzodiazepines can develop dependence and tolerance. Dependence on benzodiazepines can be psychological, physical, or both. The effects of benzodiazepines (as with any medication) depend on the amount taken and period of time over which use occurs. Use of any medication carries some risk as medications can produce unwanted side effects.

The benzodiazepine group of medications is commonly prescribed for older people who require residential aged care and community care service, in an appropriate manner, by the treating general practitioner, a treating medical specialist or an authorised nurse practitioner. The decision to prescribe these types of medications is assumed to be done with full consideration and review by the appropriate officer prescribing.

It is of note that these medications are also reviewed regularly through the Medicare Australia Residential Medication Management Review and Quality Use of Medicine reviews undertaken by an appropriately qualified Clinical Pharmacist in both residential and community care.

As benzodiazepines are more commonly prescribed than any current Schedule 8 medication, the inclusion of this group of medications to the Schedule 8 group poses a potential reduction in quality of care for the older person.

Impact on Residential Care Services

- Changes such as those announced risk the limited resources available to support residents. In their current format, broader service supports will need to be transferred to support this change. Such changes and the impact on the residents' quality of life overall, have to be given serious consideration before they are introduced. We believe the impact of this change on work practices which we will discuss in the following points needs to be understood in terms of the corresponding impact on the quality of life of residents in a negative manner overall.

- If the proposed change is implemented it will result in **significant** resourcing issues for registered nurses and care staff working in residential aged care facilities across all shifts. The change in practice will require two staff having to check every episode of administration of a benzodiazepine medication – regular and PRN (as required) orders. The biggest resourcing impact will be experienced during evening and night duty shifts when access to the registered nurse is significantly reduced.

- Reclassification of benzodiazepines will increase time taken to manage the delivery of medication from the pharmacy to the aged care facility, requiring counting at the time of delivery and 'checking in' of the delivered medications into the site's medication safe.

- The proposed change will have significant impact on the time taken for medication count of Schedule 8 medications that occurs at staff shift change. The number of medications requiring counting will significantly increase.

- The change in practice will have significant impact on medication storage. Regular benzodiazepine medication would have to be packed separately to other regular prescribed medications and stored accordingly. Medication storage facilities are currently at capacity with those medications already listed as Schedule 8.

For those residents of residential aged care facilities who currently self-medicate, the change for benzodiazepines to the schedule 8 classification would significantly impact the administration and management of these medications, removing this level of independence for these older people.

Impact on Community Services

- We are concerned with the related resourcing impact on community services involved in supporting individuals in their homes and the transfer of resources currently used for other worthy support outcomes will be directed towards the management of this outcome.

- Protocols exist for home support workers to, in the absence of family, collect and deliver Schedule 8 packed medications to a client's home. If benzodiazepines were reclassified to Schedule 8 medications this would place an enormous burden on the volume of related processes, staff time and service cost.

- Within a number of community service organisations, the respite centres currently need to access a registered nurse to administer Schedule 8 medications. With this proposed change and the potential to have a marked increase in Schedule 8 medications, aged care services would require additional registered nurses across a 24 hour period. The current funding via the National Respite for Carers Program would not meet cost increases. Such an outcome would risk the viability of such services at all times and more particularly overnight and weekend services.

- The proposed change will impact credentialing and supervision of home support workers. Current Schedule 8 medications are managed using slow release medication delivery presentations. Inclusion of benzodiazepine medications as Schedule 8, with related regulations, will require increased home visits by registered nurses.

In addition to the resourcing issues as a key challenge related to the proposed changes, are also the risks associated with the quality and timeliness of services provided. This unintended consequence of the changes to the Schedule for benzodiazepines, if not appropriately managed, will place older people at significant risk.

UnitingCare Australia strongly requests reconsideration of the proposed rescheduling of benzodiazepine medications to Schedule 8 classification.

[redacted]

SUBMISSION IN RELATION TO THE PROPOSAL TO RESCHEDULE BENZODIAZAPINES FROM SCHEDULE 4 TO SCHEDULE 8

Basis of the Submission

This submission is made by Regis Aged Care (Regis) in response to an Invitation for Public Comment under Regulation 42ZCZK of the Therapeutic Goods Regulations 1990 dated 29 November 2012.

The invitation sought comments regarding the scheduling proposal in relation to Benzodiazepines (the Proposal) to be considered by the Advisory Committee on Medicines Scheduling.

This submission addresses one of the matters specifically mentioned in section 52E of the Therapeutic Goods Act 1989 (the Act); namely, 'other matters that the Secretary considers necessary to protect public heath' (paragraph 52E(1)(f)).

It is also noted that subsection 52E(1) of the Act mandates that the Secretary must take into account the matters set out in that subsection. However, the list of matters is not exhaustive and the Secretary may consider other information.

It is our submission that the matters set out below fall within paragraph 52E(1)(f) as any effect on the financial capacity of aged care providers to provide care to residents of aged care facilities and the ability of registered nurses to deliver care is relevant to the protection of public health.

Submission

Regis fully supports the prudent management of medication in the aged care setting and notes the Therapeutic Goods Administration's expertise in public health administration.

However, it is important that the Committee be aware of the potential consequences to aged care providers of the Proposal in terms of increased administration and direct costs and the impact on registered nurses delivering care in the aged care sector.

It is hoped that with this information the Committee may consider other ways in which the desired policy outcomes may be achieved without imposing a significant administrative and financial burden on aged care providers.

If implemented, the Proposal will impact in a number of areas as set our below:

Impact on Human Resource Management and cost impacts

If the proposed changes are implemented there will be a significant impact on the workload of registered nurses at aged care facilities (ACFs). Impacts are related to:

1. Registered nurses are responsible for the administration of S8 medications to residents and the inclusion of Benzodiazepines on the S8 schedule would increase the number of events when an S8 medication is administered on average by 131%. With an average of 26% of current residents being prescribed drugs from the Benzodiazepine group of drugs.

    - The cost impact on a 100 bed facility within our group is expected to increase costs by $4.60 per resident per day. This equates to an annual spend of an additional $137k per annum. The total impact on Regis wages and salaries is conservatively $7M. Unless commonwealth increases the level of funding to mitigate this impact Regis suspects many providers will be unable to meet the legal and human resource requirements of the proposed changes.

2. It should be noted that in some States EENs cannot administer S8 medications. The Proposal will, therefore, impact significantly on areas of ACFs where the most senior nurse in that area is an EEN. In some States EENs can administer however this must be under the direct supervision of a registered nurse.

3. Non regulated workers, i.e. personal care attendants or assistants in nursing, who have a medication competency, are not able to assist residents with S8 medications increasing the workload of registered nursing staff.

4. The increase in the number of S8 drugs will result in an increase in the amount of time needed to administer medications. The process for administration of an S8 medication involves:

    a) the counting of number of the medication in the S8 safe by 2 staff,

    b) recording of the administration in the drug register by 2 staff,

    c) delivery of the drug to the resident and monitoring of ingestion of the medication by 2 staff and

    d) signing of the administration on the medication chart.

    It is estimated that this process will take a minimum of 5 minutes for each drug, for each ACF resident.

    Our estimate is that there will need to be an average increase of 37% for registered nurse hours to administer the increased drugs that are scheduled as S8 medications.

    This does not include the increased time for checks of S8 drugs. In this regard, it is noted that there is also a need for a second person to check these S8 drugs that is not reflected in this increase. Estimated time to complete S8 drug checks for registered staff for a 130 bed ACF would be 4 hours in every 24 hour period.

5. Due to the nature of Benzodiazepines and their effects the time of administration of these drugs is often in the evening when there is typically less registered staff rostered on duty. As these drugs will need to be administered by registered staff there will be an impact on the number of registered nurses that need to be rostered in the evening.

6. There is a risk for escalation of behaviours in residents who require PRN medication that would be reclassified as S8, to minimise challenging behaviours due to availability of qualified staff and time taken to access and follow process for the delivery of S8 medications.

7. S8 medication register has to be checked on a shift basis in some States and at least daily in other States by registered nurses and the increase in the number of S8 medications that will result from any change to the schedule will result in an increase in the amount of time that will be necessary to complete these checks.

   The increase in the number of drugs to be counted will result in an increase in the time these counts take to on average 131% longer to complete.

8. The increased time that will need to be spent by registered staff on the administration of S8 drugs will impact on the other duties that are part of the registered nurse role. This could lead to a reduction in the supervision of delivery of care, the completion of clinical assessments and the evaluation of effectiveness of current clinical care.

9. The increase in the time spent by registered staff on medication management makes the position less diverse and interesting and this may have an impact on the level of retention for registered nurse positions.

Impact on Administration

The Proposal would require consideration to be given to storing S8 medications in resident rooms to minimise the time used in delivering from a centralised storage area.

However the storage containers would need to meet State legislation i.e. would need to be a drug safe that is attached to the wall in accordance with legislative requirements. There would also still be a requirement for two staff to administer the medication in each room.

The cost factor will be significant as this facility will need to be provided in each room as it is not possible to predict which resident will be on S8 medications when admitted or during the course of their stay at the ACF.

Centralised or wing storage requirements: e.g

The capacity requirements due to the increase in the number of S8 drugs held in each facility in Queensland e.g. will mean an upgrade to existing drug safes – a

cost that will increase from approximately $500 to $3000 per safe not including installation. This does not take into account whether our facilities actually have the space to install a larger safe for drugs.

On each occasion that an S8 medication is delivered to the ACF a registered nurse has to accept the delivery of the drug and two people have to count the number of drugs and enter the drug into the drug register

The increase in the number of S8 drugs being delivered by the pharmacy will increase the amount of time registered nurses have to spend accepting S8 drugs from the pharmacy and entering into the drug register.

Delivery of drugs can be on a daily basis and does not always occur within office hours. This is another impact on the level of registered nurse staffing after hours.

The bulk of regular S8 drugs are delivered once per week and with the expected increase this could require 2 staff checking the drugs for approximately one and a half hours for 130 bed facility.

Impact on Staffing Structure and Role Responsibilities.

The Proposal would impact the staffing structure of care staff assisting with medications will be impacted as

a. the number of residents who require administration of S8 medications by registered nurses will increase significantly and

b. it is impractical for the registered nurse to only administer S8 medications when a resident is on multiple drugs as two staff can not access the medication chart at the same time without difficulty and delays

c. there may be confusion for some residents who may become resistant if requested to take medications by another staff member at the same time.

The packaging of medications for residents will be impacted as S8 drugs can not be packed in multi dose packs. This will raise a number of issues around packaging including:

- The number of rolls of medication per resident will increase as S8 drugs will have to be packaged separately. The cost per resident per day for packaging will also be affected.

- If S8 medications are in rolls then the amount of storage space required in the safes will increase. This will necessitate the installation of additional safes at ACFs.

- If original packages are used then the storage space required will still increase and may lead to the need for additional drug safes.

- If a resident is on both regular and PRN (as required) doses of the same drug packaging will present challenges as all drugs, whether for regular or PRN, will need to be recorded in the drug register and this may necessitate that drug being provided in original packaging rather than being packaged in sachets or blister packs.

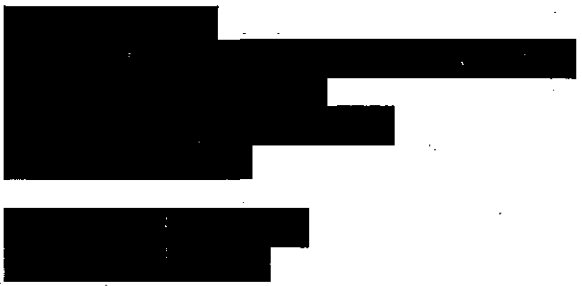
Impact on Community Care Services

Currently S8 medications for community care clients are managed by the client or their carer or if not appropriate, by the District Nurse or Palliative Care Team.

The consequences of the Proposal to scheduling of Benzodiazepines would include:

- If the client is not able to manage medication or does not have a carer the drugs would need to be administered by the District Nurse.

- The cost of using the District Nurse would increase for clients who are on a high care package only.



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17 January 2013

Mr Peter Balmer
Policy Officer
Aged and Community Services Australia
Level 1, 10 Thesiger Court
Deakin ACT 2600

Submission related to the Impact of Benzodiazepine reclassification to Schedule 8 Medication

RSL Care wishes to respond to the proposed changes to the classification of Benzodiazepines to Schedule 8 medications and outline the ramifications to the organisation should this occur.

RSL Care has investigated the impact of reclassification of Benzodiazepines to Schedule 8 medication and questions the benefits to consumers of this change.

The medication management systems and processes implemented across RSL Care ensure that each dose of Benzodiazepines in our facilities is fully accounted for and management of all medication fully complies with the Australian Government, Department of Health and Ageing "Guiding principles for medication management in residential aged care facilities" (October 2012). There is no documented or anecdotal evidence to suggest that RSL Care has any issues related to the safe administration and storage of Benzodiazepines.

RSL Care utilises a sachet system for medication administration and, to date, the impact of administration of Benzodiazepines within RSL Care is minimal as this class of medication is able to be packed with all other appropriate medications. This ensures a seamless, safe and effective service to our residents with minimal impact on the time taken for administration. Schedule 1 is attached which highlights the usage of Benzodiazepines in the 25 facilities across RSL Care. The data covers a period from 1 July 2012 to 31 December 2012 providing total usage of Benzodiazepines across the 25 facilities. The data also provides the number of doses administered daily (922) across the organisation.

The additional cost to RSL Care of daily management and administration of Benzodiazepines should they be reclassified is prohibitive. Schedule 2 reflects the cost to the organisation of two staff members checking, recording and administering each dose administration required, an estimated time of five (5) minutes per staff member at an estimated cost of $2.2 million annually to RSL Care. As required by legislation, it would also be necessary for these drugs to be receipted by a registered nurse, checked at least daily by two staff members (one registered) and checked weekly by a Senior Clinician and one other registered nurse. In order to meet our statutory obligations, RSL Care would be required to recruit additional

registered staff at each of the 25 sites, a process which is widely known to be extremely difficult not only in the aged care industry but in all facets of nursing. These additional costs have not been calculated in Schedule 2.

Consideration also needs to be given to the fact that staff time taken managing and administering additional Schedule 8 medication will, based on RSL Care data, reduce face to face contact and care of our residents by at least 154 hours per day across the organisation. This is an average of six hours per day per facility less personal care.

It is also to be noted that the majority of this class of medication is administered in the evening, the period of the day when historically all Residential Aged Care Facilities (RACS) have the least number of registered staff rostered.

Currently medications, other than Schedule 8 medications, are stored in locked medication trolleys configured to ensure that each resident's medication is maintained separately. Minimal storage is required in each site in order to comply with legislation for storage of Schedule 8 medication. Should rescheduling of Benzodiazepines occur, RSL Care would be required to determine whether medication is to be supplied in original packs or in separate sachet rolls. In either case, this would impact on the storage capacity of all sites requiring, at the very least, the purchase of 25 additional drug safes and could in fact, necessitate refurbishment of locked medication storage areas in many of our sites in order to comply with legislation. Schedule 3 provides the cost for purchase and installation of appropriate drug safes.

Based upon the information we have supplied, RSL Care strongly argues that the proposal to reclassify Benzodiazepines as Schedule 8 medications would be a prohibitive cost to the organisation without identifiable benefit. In the current climate of changes to the industry's funding and the uncertainty surrounding this, yet another impost would render some aged care providers unable to maintain their services.

We trust this information assists the Guild in responding to the Therapeutic Goods and Administration authority.

Kind regards

[redacted]

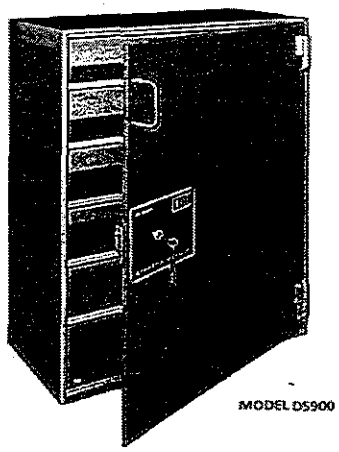
Cc Mr Stan Macionis – Chief Executive Officer, RSL Care
Mr Richard Olley – Executive Manager Care Services, RSL Care

Schedule 1

lumber of Sites	Number of Residents	Regular Prescribed Benzodiazepines 01/07/12 - 31/12/12									Total Administered
25 RACFs	*2,359*	*Alprazolam tabs*	*Bromazepam tabs*	*Clonazepam tabs*	*Diazepam tabs*	*Flunitrazelapam tabs*	*Lorazepam tabs*	*Oxazepam tabs*	*Nitrazepam tabs*	*Temazepam tabs*	Benzodiazepines
es administered for 6 month period /07/12 - 31/12/12		4,666	350	7,000	13,166	50	2,750	76,500	7,333	5,433	**166,148**
es Administered day											**923**

Schedule 3

CSI Drug Safe - Model DS900	Constructed from 10mm steel plate door and body to Health Department specifications
Cost	$2,288
Freight	$240
Installation	$500
Total	$3,028
Cost for 25 safes	**$75,700**



MODEL DS900

Benzodiazepines

The Secretary
Scheduling Secretariat
GPO Box 9848
Canberra, ACT 2601
SMP@health.gov.au

17 January 2013

Dear Sir/Madam,

Regulation 42ZCZK of the Therapeutic Goods Regulations 1990 – Proposal to amend benzodiazepines from Schedule 4 to 8

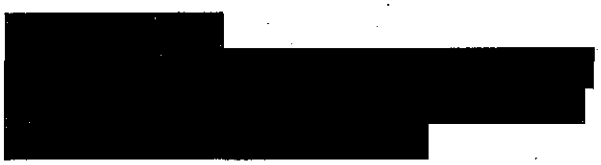
I'm submitting my personal recommendation that all benzodiazepines be rescheduled to Schedule 8, and in the event that this is not done, that alprazolam be rescheduled to Schedule 8.

My reasoning is described in the attached document with 5 appendices.

The main document contains confidential information about a large number of forged prescriptions on counterfeit prescription stationery in Victoria that is a particular concern that would be addressed to a large extent by rescheduling to Schedule 8, because this Schedule provides for additional safeguards to prevent dispensing of forged and altered prescriptions.

I ask that this information not be made public.

Yours sincerely



Alprazolam: argument for rescheduling alprazolam to Schedule 8

Dr Malcolm Dobbin, PhD MBBS DRANZCOG MPH FAFPHM
Senior Medical Advisor (Alcohol and Drugs)
Mental Health, Drugs and Regions Division
Victorian Department of Health

[redacted]

Rescheduling of all benzodiazepines to Schedule 8.
I support the rescheduling of all benzodiazepines to Schedule 8, because of the problems associated with their misuse, and their contribution to opioid poisoning deaths as a result of combined drug toxicity involving CNS depressant drugs. Benzodiazepines may contribute to combined drug toxicity in many of these deaths involving illicit (heroin) and prescription opioids[1], often in combination with other CNS depressant substances such as alcohol or other prescription drugs.

Benzodiazepines are recommended for the short-term treatment of anxiety or insomnia, so ideally appropriate prescribing would be limited in duration in most cases. This would obviate the need for practitioners to obtain a permit to prescribe a Schedule 8 drug from State and Territory jurisdictions for chronic prescribing so would not impede appropriate prescribing.

The Australian Statistics on Medicines describes as a Practice Point:

> "reserve (benzodiazepines) for short-term use only (eg 2–4 weeks); they should be part of a broader treatment plan, not a first or sole treatment"

Rescheduling of alprazolam to Schedule 8.
In the event that rescheduling of all benzodiazepines is not accepted, I believe there is a special case for selective rescheduling of alprazolam to Schedule 8.

Evidence of increasing problems with alprazolam include:

- Increasing contribution of alprazolam to illicit opioid (heroin) and prescription opioid combined drug toxicity deaths.
- A disproportionate contribution to non-fatal drug toxicity emergencies presenting to a Victorian emergency department.
- A disproportionate increase in involvement of alprazolam compared to all benzodiazepines in ambulance attendances in Victoria.
- A disproportionate Increase in misuse and injection by people who inject drugs
- Identification of a disproportionate level of harm in patients admitted to drug treatment in four States of Australia, including dependence, withdrawal, effects on memory and range of injecting-related harms. While diazepam was the main benzodiazepine used by this sample, a large proportion of individuals reporting seizures (55%), traffic accidents (50%), and crime (30%) while under the influence of benzodiazepines, identified that alprazolam was the main benzodiazepine involved.
- The Victorian Parliamentary Drugs and Crime Prevention Committee examining misuse and abuse of benzodiazepines and other pharmaceutical drugs identified from witness submissions and presentations that alprazolam was uniquely problematic.
- A number of sources describe trafficking of alprazolam, with street prices reported to be from $2 to $20 in different jurisdictions across Australia while there is no reporting of a street price for other benzodiazepines.

[1] White JM, Irvine RJ. Mechanisms of fatal opioid overdose. Addiction 1999;94:961-72.

- There is a disproportionate over-representation of alprazolam in data relating to forged prescriptions.
- There are also reports of other crime associated with alprazolam, and concerns from the courts about the contribution of Xanax to crime.
- Evidence from investigation of the role of benzodiazepines in injured drivers in Victoria describes that alprazolam had the most concerning contribution to collisions.

ALPRAZOLAM

Approved indications. Alprazolam is registered in Australia for the short-term symptomatic treatment of anxiety including treatment of anxious patients with some symptoms of depression. It is also registered for panic disorder.

Pharmaceutical Benefits Scheme listing. Alprazolam is listed as: **Authority required:** Panic disorder where other treatments have failed or are inappropriate. It is not approved as a benefit for the treatment of generalised anxiety disorder.

Other commonly prescribed anxiolytics diazepam and oxazepam can be prescribed without requiring an Authority to prescribe as a PBS benefit, and with no restrictions for an approved indication.

Despite these constraints, and recommendations of guidelines for the management of panic disorder describing alprazolam as a second line treatment, supply of alprazolam has steadily increased since it became a PBS benefit in 1992.

Recommendations for treatment of panic disorder.
Guidelines from three countries recommend that when pharmacotherapy is required for the management of panic disorder, treatment with a selective serotonin reuptake inhibitor (SSRI) or tricyclic antidepressants are the agents of choice[2] [3] [4]. Benzodiazepines are either no longer recommended or recommended only as a secondary treatment strategy.

Alprazolam pharmacology. Alprazolam is a potent short-acting benzodiazepine with a rapid onset and offset of effect, pharmacokinetic properties that are associated with a greater risk of dependency and withdrawal[5]. There is evidence that benzodiazepines with a short elimination half-life cause a more severe withdrawal syndrome than those with a long elimination half-life, and there is an increasing body of literature suggesting that quickly eliminated, high potency benzodiazepines including alprazolam may be more likely to cause severe withdrawal reactions than slowly eliminated benzodiazepines such as diazepam[6]. The intensity and prevalence of rebound anxiety with alprazolam seems greater than with other benzodiazepines, and interviews with clinicians with experience of detoxifying patients dependent on benzodiazepines overwhelmingly describe that alprazolam is especially problematic with respect to the intensity and/or duration of the withdrawal syndrome[7]. Alprazolam may also be more toxic than other benzodiazepines in overdose[8]

[2] RANZCP Guideline Team for Panic Disorder and Agoraphobia. Australian and New Zealand clinical practice guidelines for the treatment of panic disorder and agoraphobia. Aust N Z J Psychiatry. 2003;37:641-656

[3] Work Group On Panic Disorder. Practice guideline for the treatment of patients with panic disorder (second edition). American Psychiatric Association 2009. Available at: http://www.guidelines.gov/content.aspx?id=14230. Accessed January 2013

[4] National Institute for Health and Clinical Excellence. Anxiety: NICE Guideline (Amended). London, UK: National Institute for Health and Clinical Excellence; 2007

[5] Moylan S et al. The efficacy and safety of alprazolam versus other benzodiazepines in the treatment of panic disorder. J Clin Psychopharmacol 2011;31:647-52.

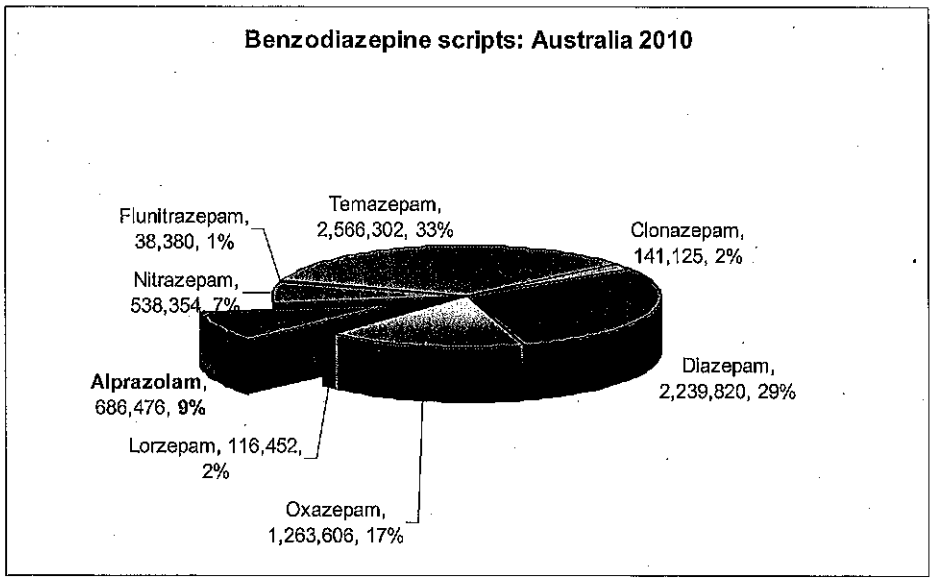
[6] Tesar GE. High potency benzodiazepines for short-term management of panic disorder: The US experience. J Clin Psychiatry 1990;51 (suppl):4-10

[7] Wolf B, Griffiths R. Physical dependence on benzodiazepines: differences within the class. Drug Alcohol Depend 1991;29:153-6.

[8] Isbister GK et al. Alprazolam is relatively more toxic than other benzodiazepines in overdose. Brit J Clin Pharmacol 2004;58:88-95.

There is also evidence to suggest that alprazolam produces more subjective euphoria[9] and is subject to greater abuse liability[10].

Benzodiazepine prescriptions: Australia 2008.
Data from the Australian Statistics on Medicines (ASOM) describes the supply of benzodiazepines to Australia. In 2008 ASOM reported that there were 7,948,000 prescriptions for benzodiazepines dispensed in Australia, and alprazolam prescriptions comprised 9% of all benzodiazepine prescriptions.



Data from the Australian Statistics on Medicines suggests that a higher proportion of alprazolam prescriptions (37.2%) are privately prescribed than for other commonly prescribed benzodiazepine anxiolytics or hypnotics (see table), possibly as a result of the requirement to obtain an authority to prescribe alprazolam as a PBS benefit.

The cost of standard packs of benzodiazepines is low, and many are available as products from generic pharmaceutical companies, thus making these products available at low cost without the need for PBS subsidy.

Flunitrazepam is available only as an RPBS benefit.

COMMUNITY PRESCRIPTION DRUG USE in DDD/1000/DAY for high prescription volume benzodiazepines 2009

	alprazolam	diazepam	oxazepam	flunitrazepam	nitrazepam	temazepam
PBS/RPBS	3.886	4.815	1.878	0.036	1.549	3.263
SURVEY	2.306	1.516	0.409	0.289	0.286	1.042
total DDD	6.192	6.331	2.287	0.325	1.835	4.305
PBS/RPBS (%)	62.8	76.1	82.1	11.1	84.4	75.8

Source: Australian Statistics on Medicines, 2009. Australian Government, Department of Health and Ageing.

[9] Iguchi MY, Griffiths RR, Bickel WK et al. Relative abuse liability of benzodiazepines in methadone maintained populations in three cities. NIDA Research Monographs 1989;95:364-5.

[10] Mumford G, Evans S, Fleishaker J, et al. (1995) Alprazolam absorption kinetics affects abuse liability. *Clinical Pharmacology and Therapeutics* 57: 356–365

Trends in supply of alprazolam.
The following figure describes trends in the rate of supply per 100,000 population of alprazolam to Victoria. The total rate of supply increased shortly after this benzodiazepine was listed as a PBS benefit in 1992. The most remarkable feature of the trends in supply is the markedly disproportionate increase of prescriptions for the high dose 2 mg tablet.