[redacted]

Proposed Amendments to Poisons Standard –ACMS meeting, July 2016

Comments by [redacted] to the proposed amendments referred by the delegate for scheduling advice for consideration by the Advisory Committee on Medicines Scheduling

Fexofendaine – Amend Schedule exemption

Ulipristal – New Schedule 3 entry

May 2016

[redacted]

FEXOFENADINE

Proposal to increase the pack size of unscheduled fexofenadine from not more than 5 days' supply to not more than 10 days' supply in a primary pack containing 20 dosage units or less.

Overview

[redacted] does not support this proposal and is not supportive of fexofenadine being exempt from scheduling. Irrespective of fexofenadine's reasonable safety profile, there are still public risks associated with its use.

[redacted] does not believe it is in the public interest to further increase the scheduling exemption to allow longer doses of fexofenadine to be available in general retail where there is no access to health professional advice.

The risk and benefits of the use of the substance[1]

Use in pregnancy

Fexofenadine has a pregnancy category rating of B2[2] and fexofenadine in medicines for oral use must be accompanied by the following advisory statement: "*If you are pregnant or breastfeeding, check with your doctor or pharmacist before using this medicine."*[3] Other studies recommend the use of second generation antihistamines should be avoided during pregnancy and they should never be administered to nursing mothers.[4]

[redacted] argues adherence to these advisory guidelines is less likely to occur if fexofenadine is purchased in general retail where there is no ready access to professional advice.

While labelling may provide useful guidance for woman who are pregnant or breastfeeding, studies suggest not all consumers read information provided with the medicine. A survey of 1000 people conducted in Northern Ireland identified only 80% of participants always or often read the instructions on non-prescription medicine packages and that 3.4% rarely or never read the information. Combined with participants that only sometimes read the manufacturer's information, 10% of people could be at risk of misusing these medicines.[5]

Given this proposal would double the maximum quantity of tablets that could be sold in general retail, this exacerbates the current risk on non-adherence to important advisory statements.

Pro-arrhythmic potential

A study conducted in Europe investigated the pro-arrhythmic potential of antihistamines by combining safety reports of the FDA Adverse Event Reporting System (FAERS) with drug utilisation data from 13 European Countries. The study found five agents, which included fexofenadine had strong signals for torsadogenicity and recommends regulators and clinicians should consider risk-minimisation activities.[6]

[redacted] believes that a further relaxing of the scheduling exemption for fexofenadine would increase the risk of medicine misadventure for consumers that have a pre-existing heart condition.

[1] Section 52E(1a)- *Therapeutic Goods Act 1989*
[2] Prescribing medicines in pregnancy database – Accessed 28/04/2016 https://www.tga.gov.au/prescribing-medicines-pregnancy-database
[3] Medicines Advisory Statements Specification 2014 https://www.comlaw.gov.au/Details/F2015C00557
[4] Horak, F., & Stübner, U. P. (1999). Comparative tolerability of second generation antihistamines. *Drug safety*, *20*(5), 385-401.
[5] M Wazaify, E Shields, CM Hughes et al; Societal perspectives on OTC medicines; Family Practice 2005 22:170-176
[6] Poluzzi, E., Raschi, E., Godman, B., Koci, A., Moretti, U., Kalaba, M., ... & De Ponti, F. (2015). Pro-arrhythmic potential of oral antihistamines (H1): combining adverse event reports with drug utilization data across Europe. *PloS one*, *10*(3), e0119551.

The purposes for which a substance is to be used and the extent of use of a substance[7]

Doubling the maximum number of dosage units available in general retail may lead to consumers using fexofenadine products for conditions other than allergic rhinitis such as dermatitis, soap allergies or severe reactions to substances or insect bites. When medicines are sold outside pharmacy, there is no access to health professional advice regarding diagnosis nor the appropriateness of particular treatments.

This could result in a greater number of consumers self-medicating for undiagnosed conditions other than the product indications (allergic rhinitis) over a longer period without contact with a health professional. This risk is exacerbated by the lack of restrictions on the number of packs that can be purchased in a single transaction in general retail.

Co-morbidity with other conditions

Allergic rhinitis often coexists with asthma and atopic dermatitis.[8] Up to 80 per cent of patients with allergic asthma have comorbid rhinitis.[9] Guidelines indicate it is important to recognise and treat allergic rhinitis as part of ongoing management of asthma as the condition contributes to frequent symptoms and is associated with worse asthma control in children and adults.[10] This is less likely to occur if consumers are purchasing these products from general retail where there is no access to health professional advice.

Consumer Health literacy

Previous research conducted by the Australian Bureau of Statistics, identified that almost 60 per cent of adult Australians have low health literacy. This means that they may not be able to effectively exercise their choice when making healthcare decisions. [11] It has been estimated that people with low individual health literacy are between one-and-a-half and three times more likely to experience an adverse medicine outcome. More specifically, low individual health literacy has found to be associated with a lesser ability to demonstrate taking medicines appropriately and interpret labels and health messages.

Consequently, it is the view [redacted] that consumers should receive advice on the correct and proper use of medicines and this is best achieved by consumers having access to professional advice form pharmacy staff. This is particularly important for the most vulnerable consumer groups, particularly children, the elderly, those from low socio-economic and/or culturally and linguistically diverse backgrounds as well as those with chronic or multiple disease conditions. Providing consumer access to information via hand-outs or labelling is not sufficient for such an important area such as health, especially given the low level of health literacy in Australia as outlined above. 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 toxicity of a substance[12]

The key feature of toxicity in overdose of less-sedating antihistamines is prolongation of the QT interval with associated risk of torsades de pointes.[13] As mentioned previously given there are usually no restrictions on the number of packs that can be purchased by customers from general retail, this increases this risk of toxicity occurring.

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[7] Section 52E(1a)- *Therapeutic Goods Act 1989*
[8] Allergic rhinitis and conjunctivitis - Therapeutic Guidelines online
[9] Australian asthma handbook. Melbourne: National Asthma Council Australia, 2014. [Online] (accessed 4 March 2014. Accessed from NPSMediceinewise – Asthma and allergic rhinitis – accessed 2/05/2016
[10] National Asthma Council Australia. Allergic rhinitis and the patient with asthma. 2006. [Fulltext] (accessed 18 February 2014). Accessed from NPSMediceinewise – Asthma and allergic rhinitis – accessed 2/05/2016
[11] Australian Bureau of Statistics. *Health Literacy, Australia*. Canberra: Australian Bureau of Statistics, 2008
[12] Section 52E(1c)- *Therapeutic Goods Act 1989*
[13] Management of poisoning caused by less-sedating antihistamines – Therapeutic Guidelines online

Summary

[redacted] does not support the scheduling exemption for fexofenadine and consequently does not support any further scheduling exemptions.

Given the potential risk relating to use while pregnant or breastfeeding, pro-arrhythmic potential, the co-morbidity of allergic rhinitis with other conditions and concerns regarding consumer using fexofenadine for conditions other than allergic rhinitis, [redacted] believes fexofenadine should be a scheduled substance so it is only available in pharmacy with ready access to pharmacy staff who can provide appropriate advice on quality use of medicines.

ULIPRISTAL

To amend the existing Schedule 4 entry and create a new Schedule 3 entry to allow for emergency post-coital contraceptive use.

Overview

[redacted] supports the creation of a Schedule 3 entry for ulipristal for emergency post-coital contraceptive use. Pharmacists have the knowledge and experience to handle and supply medicines for emergency contraception as levonorgestrel has been available as a Schedule 3 medicine since 2004.

If ulipristal is listed as a Schedule 3 medicine, [redacted] will collaborate with sponsors and other professional organisations to provide guidance on training materials for pharmacists.

The risk and benefits of the use of the substance[14]

Studies examining the efficacy and safety profile of ulipristal compared to levonorgestrel for emergency contraception have shown that ulipristal could be more effective in reducing the rate of pregnancy and that the safety profile is similar to levonorgestrel, with the most common adverse event being headaches.[15] Other studies that have specifically examined the safety of ulipristal in emergency contraception have concluded no safety concerns emerge from a sizable database of reported adverse reactions following ulipristal acetate exposure among varying ethnicities and regions.[16]

In November 2014, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) recommended that ulipristal be made available as an OTC medicine. Based on the assessment of available information, the CHMP found that ulipristal can be used safely and effectively without prescription and its safety profile is comparable to levonorgestrel.[17]

Summary

[redacted] has no objection to the creation of a new Schedule 3 entry for ulipristal for emergency contraceptive use. The efficacy and safety profile is similar to that of levonorgestrel which has been available as a Schedule 3 medicine in Australia for more ten years.

[14] Section 52E(1a)- *Therapeutic Goods Act 1989*
[15] Glasier, A. F., Cameron, S. T., Fine, P. M., Logan, S. J., Casale, W., Van Horn, J.& Jaspart, A. (2010). Ulipristal acetate versus levonorgestrel for emergency contraception: a randomised non-inferiority trial and meta-analysis. *The Lancet*, *375*(9714), 555-562.
[16] Levy, D. P., Jager, M., Kapp, N., & Abitbol, J. L. (2014). Ulipristal acetate for emergency contraception: postmarketing experience after use by more than 1 million women. *Contraception*, *89*(5), 431-433.
[17] EMA recommends availability of ellaOne emergency contraceptive without prescription – accessed 29/04/2016

[redacted]

Consultation on proposed amendments to the Poisons Standard, July 2016 – for consideration by the Advisory Committee on Medicines Scheduling

MAY
2016

Purpose

[redacted] makes this submission on proposed amendments to the Poisons Standard referred by the delegate for scheduling advice for consideration by the Advisory Committee on Medicines Scheduling in July 2016.

[redacted] comments relate to proposed amendments to:

- fexofenadine
- ulipristal.

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

[redacted]

[1] [redacted]

[redacted]

Summary of [redacted] position

Fexofenadine

[redacted] *does not support the proposal to amend the scheduling of fexofenadine to increase the pack size of unscheduled fexofenadine from not more than 5 days' supply to not more than 10 days' supply in a primary pack containing 20 dosage units or less.*

[redacted] *believes the current availability of small packs sufficiently accommodates the needs of consumers who may require rapid and short term relief and an increase is not warranted from a perspective of good clinical practice and optimal therapeutic outcomes.*

Ulipristal

[redacted] *supports the proposal to amend the existing Schedule 4 entry for ulipristal and create a new Schedule 3 entry to allow for emergency post-coital contraceptive use.*

[redacted] *believes the safety profile of ulipristal is similar to that of levonorgestrel which is currently Schedule 3 for emergency contraception.*

[redacted] *believes the efficacy profile of ulipristal has advantages over levonogestrel in some situations and will offer women a choice of emergency contraception.*

Comments on specific substances

Fexofenadine

Proposal to increase the pack size of unscheduled fexofenadine from not more than 5 days' supply to not more than 10 days' supply in a primary pack containing 20 dosage units or less.

Seasonal allergic rhinitis is one of the two most common respiratory conditions affecting an estimated 3.7 million Australians.[2] [redacted] notes that allergic rhinitis is classified according to pattern of symptoms (intermittent or persistent) and severity (mild or moderate-to-severe) rather than the previously used terms of seasonal and perennial.[3]

The goals of treatment are to reduce symptoms and to improve daily functioning and quality of life.[4] Optimal management of allergic rhinitis can also have other benefits such as reducing the risk of developing asthma or obstructive sleep apnoea.[5]

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[2] Australian Institute of Health and Welfare. Australia's health 2014. Australia's health series no. 14. Cat. No. AUS 178. Canberra: AIHW; 2014.

[3] Bousquet J, Khaltaev N, Cruz AA, et al. Allergic rhinitis and its impact on asthma (ARIA) 2008. Allergy 2008;63(Suppl. 86):8–160.

[4] Sansom LN, ed. Australian pharmaceutical formulary and handbook. 23rd edn. Canberra: Pharmaceutical Society of Australia; 2015. pp. 577–80.

A range of OTC medicines is available for the management of symptoms and include intranasal corticosteroids, oral and intranasal antihistamines, and topical and oral decongestants. Oral antihistamines can provide rapid relief of symptoms such as sneezing, itching and rhinorrhoea and often (but not always) a preference is shown for less sedating antihistamines. Treatment guidelines[6,7,8] however generally recommend intranasal corticosteroids as first line therapy for adults and children although maximal effect requires regular use. It would therefore seem unnecessary to increase pack size of unscheduled fexofenadine from five to 10 days' supply.

Current arrangements with the availability of small packs of fexofenadine already cater for five days of therapy with the advice that if the condition does not improve or is not well controlled after a few days the consumer should seek advice from a doctor or pharmacist. [redacted] would contend that an increase in pack size of unscheduled fexofenadine to 10 days' supply is therefore not warranted from a therapeutic perspective.

It is reported that when a health professional such as a pharmacist guides allergic rhinitis management the consumer experiences better outcomes than those who set their own goals for treating the disease.[9] Consistent with this, [redacted] strongly favours arrangements which promote the opportunity for consumers and carers to discuss their allergic rhinitis management with a pharmacist.

The support of pharmacists is important for those who self-manage effectively with OTC medicines or non-pharmacological measures and is also beneficial in assisting those who have an allergic rhinitis treatment plan[10] developed through a medical or nurse practitioner. Providing information, advice and education, and assisting and monitoring tailored treatments are important areas that pharmacists have a core role in supporting individuals.

In summary, [redacted] believes changes to the current arrangements of availability of fexofenadine are not warranted and therefore we do not support the proposal to increase the pack size of unscheduled fexofenadine.

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5 Australasian Society of Clinical Immunology and Allergy, Allergy and Anaphylaxis Australia. National Allergy Strategy. 2015; Aug. At: www.nationalallergystrategy.org.au/images/doc/NAS_Document_Final_WEB.pdf

6 Bousquet J. op. cit. pp. 55–7.

7 Walls RS, Heddle RJ, Tang MLK, Basger BJ, Solley GO, Yeo GT. Optimising the management of allergic rhinitis: an Australian perspective. Med J Aust 2005; 182:28–33. At: https://www.mja.com.au/system/files/issues/182_01_030105/wal10248_fm.pdf

8 Seidman MD, Gurgel RK, Lin SY, et al. Clinical practice guideline: allergic rhinitis. Otolaryngology – Head and Neck Surgery 2015;152(1 Suppl.):S1–S43.

9 Australian Institute of Health and Welfare. Allergic rhinitis ('hay fever') in Australia. Cat. No. ACM 23. Canberra: AIHW; 2011. At: www.aihw.gov.au/WorkArea/DownloadAsset.aspx?id=10737420519

10 Australasian Society of Clinical Immunology and Allergy. Treatment plan for allergic rhinitis (hay fever). 2015. At: www.allergy.org.au/images/pcc/ASCIA_Treatment_Plan_for_Allergic_Rhinitis_2015.pdf

Ulipristal

Proposal to amend the existing Schedule 4 entry and create a new Schedule 3 entry to allow for emergency post-coital contraceptive use.

Resources for pharmacists

Pharmacists have appropriate skills and knowledge to assist women gain timely access to emergency contraception.

[redacted] provides practice support tools and resources to guide pharmacists in the provision of levonorgestrel for emergency contraception. [redacted] currently produces a flow-chart for guidance on the provision of levonorgestrel as a Schedule 3 (S3) medicine for emergency contraception, a checklist to use when counselling the consumer, a consumer factsheet, and a contact list of numbers for Family Planning and Sexual Assault Centres.

At the time when levonorgestrel was rescheduled to S3, [redacted] education materials and other resources to support pharmacists and consumers in the implementation of a new classification for levonorgestrel. Other tools and information to support timely provision of emergency contraception were also needed.

As advocated previously, [redacted] would be keen to work with relevant stakeholders to produce practice support tools for a new S3 product for ulipristal. At the present time we believe there may be scope to integrate information on ulipristal into the existing practice support tools for emergency contraception. However there are certain differences between ulipristal and other products that pharmacists would need guidance on, such as use in breastfeeding.

Efficacy

[redacted] believes the efficacy profile of ulipristal is non-inferior to levonorgestrel for emergency contraception. There is evidence that ulipristal is more effective than levonorgestrel in the first 24 hours after unprotected intercourse.[11]

Ullipristal was compared with levonorgestrel in a study of 1696 women who received emergency contraception within 72 hours of unprotected intercourse (ulipristal n=844, levonorgestrel n=852). There were15 pregnancies in the ulipristal group (1.8%) and 22 in the levonorgestrel group (2.6%). Further, in 203 women who received emergency contraception between 72 hours and 120 hours after unprotected intercourse there were three pregnancies, all in the levonorgestrel group.[12]

[redacted] notes that levonorgestrel is only approved for use up to 72 hours following unprotected intercourse. However it can be supplied ‘off-label’ for up to 120 hours after unprotected

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[11] Fine PM. Ulipristal acetate: a new emergency contraceptive that is safe and more effective than levonorgestrel. Womens Health (Lond Engl) 2011; 7(1):9–17. At: **www.ncbi.nlm.nih.gov/pubmed/21175385**

[12] Glasier AF, Cameron ST, Fine PM, et al. Ulipristal acetate versus levonorgestrel for emergency contraception: a randomised non-inferiority trial and meta-analysis. *Lancet* 2010; 375:555–62. At: **www.ncbi.nlm.nih.gov/pubmed/20116841**

intercourse if the woman is informed of the potential risks (e.g. reduced effectiveness).[13]

Alternatively, a copper intra-uterine device (IUD) is effective as a form of emergency contraception if inserted up to five days following unprotected intercourse[14]. However [redacted] is aware, anecdotally, that access to timely insertion in Australia can be a problem.

In contrast ulipristal is approved and effective when used up to 120 hours following unprotected intercourse. This will be an advantage for some women and offer them a new choice for emergency contraception.

Safety

Ulipristal has a similar safety profile to levonorgestrel. The most commonly (>10%) reported adverse effects included headache, nausea and abdominal pain.[15]

The Therapeutic Goods Administration's Australian Public Assessment Report for ulipristal acetate cites that Study HRA-2914-555 investigated the safety profile in subjects aged under 18 years. In 44 subjects the most frequent adverse events were nausea in four (9.09%) and headache in three (6.82%).[16]

Ulipristal is not recommended for breastfeeding women as it may be excreted into breastmilk.[17] This appears to be a key difference when compared to levonorgestrel which is regarded as safe to use while breastfeeding.[18]

Both ulipristal and levonorgestrel are classified as Category D in pregnancy.[19]

Ulipristal has been available as a prescription medicine in the United Kingdom since 2009.[20] It was reclassified as a non-prescription medicine in the European Union in January 2015 and in the United Kingdom in April 2015, following a recommendation by the European Medicines Agency in November 2014.[21]

[redacted]

[14] International Consortium of Emergency Contraception. The Intrauterine Device (IUD) for Emergency Contraception. 2012. At: **www.cecinfo.org/custom-content/uploads/2014/01/ICEC_IUD-FactSheet_Sep-2012.pdf**

[15] Richardson AR, Maltz FN. Ulipristal acetate: review of the efficacy and safety of a newly approved agent for emergency contraception. Clin Ther 2012; 34(1):24-36. At: **www.ncbi.nlm.nih.gov/pubmed/22154199**

[16] Therapeutic Goods Administration. Australian Public Assessment Report for ulipristal acetate. 2015; Sep. At: **https://www.tga.gov.au/sites/default/files/auspar-ulipristal-acetate-150904.pdf**

[17] Richardson AR, op. cit.

[18] Rossi S, ed. Australian medicines handbook. Adelaide: Australian Medicines Handbook; 2016.

[19] Therapeutic Goods Administration, op. cit.

[20] The Pharmaceutical Journal. New emergency hormonal contraceptive effective for up to five days after sex. 2009; Vol. 283, p. 375.

[21] The Pharmaceutical Journal. ellaOne emergency contraception available for sale through UK pharmacies. 2015; Vol 294, No 7860, online. DOI: 10.1211/PJ.2015.20068393

Timely access

A fundamental therapeutic consideration for emergency contraception is timely access. It is vital that this is complemented by provision of information and advice to support the immediate and ongoing needs of the consumer around contraception. Relevant information includes:

- dosage
- possible side effects and action to take if experienced
- ongoing contraceptive advice
- recommendation for a sexual health check
- referral for further medical advice if menstrual period is delayed.

These and other types of information are included in the [redacted] document for S3 levonorgestrel.

[redacted] notes that the Royal Australian and New Zealand College of Obstetricians and Gynaecologists states prompt and easy access to emergency contraception is crucial. The College notes “emergency contraception can be promptly and safely supplied by suitably trained health professionals including pharmacists” provided relevant information accompanies the medicine.[22]

Summary

Overall, given the evidence around the safety profile of ulipristal and the non-inferior efficacy profile when compared to levonorgestrel, [redacted] supports the proposal to reschedule ulipristal from Schedule 4 to Schedule 3 for emergency post-coital contraceptive use.

Submitted by:

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Contacts:

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[22] The Royal Australian and New Zealand College of Obstetricians and Gynaecologists. Emergency contraception. 2015; Jul. At: **www.ranzcog.edu.au/document-library/emergency-contraception.html**