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Consultation: Proposed amendments to the Poisons Standard - Advisory Committee on Medicines Scheduling meeting, June 2019

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Purpose

The Pharmaceutical Society of Australia (PSA) makes this submission on proposed amendments to the Poisons Standard being referred for scheduling advice to the June 2019 meeting of the Advisory Committee on Medicines Scheduling (ACMS).

PSA's comments relate to proposed amendments to finasteride and arbutin.

About PSA

PSA is the only Australian Government-recognised peak national professional pharmacy organisation representing all of Australia's 31,000 pharmacists working in all sectors and across all locations.

PSA is committed to supporting pharmacists in helping Australians to access quality, safe, equitable, efficient and effective health care. PSA believes the expertise of pharmacists can be better utilised to address the health care needs of all Australians.

PSA works to identify, unlock and advance opportunities for pharmacists to realise their full potential, to be appropriately recognised and fairly remunerated.

PSA has a strong and engaged membership base that provides high-quality health care and are the custodians for safe and effective medicine use for the Australian community.

PSA leads and supports innovative and evidence-based healthcare service delivery by pharmacists. PSA provides high-quality practitioner development and practice support to pharmacists and is the custodian of the professional practice standards and guidelines to ensure quality and integrity in the practice of pharmacy.

Summary of PSA's position

Finasteride *–*

PSA supports the proposed amendments to the Poisons Standard to include finasteride in Schedule 3 in preparations containing not more than 1 mg per dose unit in packs not greater than 30 dosage units for use in males with androgenetic alopecia.

PSA suggests that specific consideration is warranted on whether an upper limit on age should be stipulated for Schedule 3 use given the range of published information regarding age-related efficacy.

The inclusion of finasteride in Appendix H is also supported.

Arbutin *–*

PSA supports the inclusion of arbutin in the Poisons Standard as specific entries in Schedules 2 and 4, and removal of the cross reference to hydroquinone.

However, PSA believes specific consideration is warranted on whether different or additional controls should be applied for: different arbutin derivatives for external use; the use of oral arbutin preparations for urinary tract infections in males; and the recommended duration of use of oral arbutin preparations.

PSA does not object to the proposal to exempt arbutin-containing hair preparations and cosmetic nail preparations from scheduling in the concentration limits specified.

Comments on finasteride

Current proposal

Finasteride is currently listed in Schedule 4 (S4) of the Poisons Standard. PSA understands the scheduling proposal seeks to:

- amend the S4 entry to include the words "for human therapeutic use except when included in Schedule 3 (S3)"
- create a new entry for finasteride in S3 for use in males (noted in the proposal as men over 18 years of age) with androgenetic alopecia (male pattern hair loss) in preparations containing not more than 1 mg per dose unit in packs not greater than 30 dosage units
- include finasteride in Appendix H.

The proposal cites the following reasons in support of the application.

- Finasteride fulfils the criteria for a S3 substance and will provide an alternative to topical minoxidil for consumers.

- Consumers can easily identify the symptoms of male pattern hair loss and it can quite easily be verified by the pharmacist to ensure that there is no other reason for the hair loss.

- The product has been on the market for a number of years and pharmacists are well equipped to provide advice to consumers on the adverse effects, interactions and contraindications (in particular, the potential risk to the male foetus if finasteride is handled by pregnant women).

- The risk profile of the medicine is well defined and there are no identified drug interactions of clinical significance.

- There is little risk of misuse, abuse or illicit use as it does not have any effect outside of its use in hair loss or in larger doses for benign prostatic hyperplasia (BPH).

Suitability for Schedule 3 and Appendix H

Androgenetic alopecia is a common form of hair loss. PSA understands the rationale underpinning this proposal and agrees that finasteride 1 mg meets the scheduling factors for S3 (Pharmacist Only) medicines, including the following:

- the condition can be readily identified by the person

- the medicine is substantially safe and the risk factors are known and minimal

- use of the medicine is not expected to produce dependency

- pharmacist intervention is warranted to support safety and optimal treatment outcomes.

Given finasteride for androgenetic alopecia would be expected to be used long term, PSA believes the pack size for S3 supply should allow at least one months' supply to adequately support and improve access for patients.

In view of the safety profile of finasteride 1 mg oral preparations, and to support optimal treatment options for androgenetic alopecia in men, PSA believes it is appropriate to include finasteride in Appendix H of the Poisons Standard.

Implementation guidance for pharmacists

As the peak professional body for pharmacists, PSA has a key role in the design, development and implementation of education and training relevant to the rescheduling of finasteride to S3. Resources to support professional practice is created by PSA, in consultation with relevant experts. PSA independently determines the range, scope and content of required materials (e.g. guidance document for the provision of a substance (i.e. finasteride) as a S3 medicine, case studies, practice support tools) although it is envisaged that the sponsor or applicant would facilitate the means to produce the necessary resources.

In order to ensure appropriate and safe use of S3 finasteride, issues including the following will need to be considered and information, guidance and practice support provided to pharmacists.

- Current therapy – the person may be using minoxidil, already taking finasteride (under medical supervision), or not had any treatment.

- Age – intended for men over 18. PSA notes that there is a range of published studies with variable advice on the efficacy of finasteride for androgenetic alopecia in older men, including that: it is a safe and effective treatment for controlling male pattern baldness with long-term daily use even in men over the age of 40 years[1]; efficacy has not been demonstrated in men over the age of 41 years[2]; and, it is not likely to be effective for those over 60.[3] Therefore, PSA suggests that the ACMS should give consideration to whether or not an upper limit on age should be stipulated for S3 use.

- Informed choice – range of therapy options available, including no treatment; preference for type of therapy i.e. dermal (foam, lotion) or oral (tablet); possible side effects (and expected frequency); recommended or likely duration of therapy; cost of therapy.

- Understanding how finasteride may help – intended for men with mild to moderate hair loss, not complete hair loss; prevent further hair loss; increase hair growth; does not affect hair on other parts of the body.

- Establish reasonable treatment expectations – hair loss is part of the aging process with a family history component; unlikely that all the hair will regrow; may take several months to see results if commencing treatment for the first time; long term maintenance of treatment to sustain/improve outcome; hair loss is likely to resume if treatment is ceased.

- Storage and handling of finasteride tablets – important to keep in blister pack until time for a dose; women who are or may be pregnant must not handle the tablets; safety risk if ingested by children.

- Monitoring ongoing treatment – given the need for long term use, regular follow-up counselling and advice should be implemented.

- May require clarification regarding the existence of 5 mg finasteride products which will continue to be a Prescription Only medicine with a different approved indication.

- Practice advice around recording or labelling requirements, and uploading of information in the patient's My Health Record.

In summary, PSA supports the rescheduling of finasteride as proposed including a new entry in Appendix H of the Poisons Standard.

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[1] Rossi A, Cantisani C, Scarnò M, et al. Finasteride, 1 mg daily administration on male androgenetic alopecia in different age groups: 10-year follow-up. Dermatol Ther 2011;24:455–61.

[2] Finasteride GH 1 product information, v. 2.0. 2017;Jun. At: **https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent&id=CP-2013-PI-02480-1&d=201905081016933**

[3] Sansom LN, ed. Australian pharmaceutical formulary and handbook. 24th edn. Canberra: Pharmaceutical Society of Australia; 2018.

Comments on arbutin

Current proposal

Arbutin currently does not have a specific entry in the Poisons Standard but is cross referenced to its parent compound, hydroquinone. PSA understands this scheduling proposal seeks to include arbutin in the Poisons Standard as specific entries in Schedules 2 and 4, and to remove the cross reference to hydroquinone.

Thus, preparations for human therapeutic or cosmetic use would be S4 except:

- proposed to be Schedule 2 (S2) – preparations for human external therapeutic or cosmetic use containing 5 per cent or less of arbutin
- proposed to be exempt from scheduling –
    - oral herbal preparations containing 500 mg or less of arbutin per recommended daily dose
    - hair preparations containing 0.75 per cent of arbutin
    - cosmetic nail preparations containing 0.05 per cent of arbutin.

The proposal provides the following reasons for this scheduling application.

- Commonplace and frequent population exposure to arbutin and hydroquinone via common dietary components at levels equal to likely levels arising from herbal exposure, combined with a lack of reports of adverse or toxic effects linked to naturally occurring arbutin, provides an established history of safety.
- Available evidence shows that almost all hydroquinone released upon ingestion of arbutin is rapidly conjugated and eliminated with the urine.
- Available evidence shows that the quantity of free, unconjugated hydroquinone released from arbutin in vivo is two orders of magnitude lower than the European Medicines Agency permitted daily exposure level for hydroquinone.
- Naturally occurring arbutin in herbal medicines therefore does not present an unacceptable risk to human health.

Creating a specific entry for arbutin

Arbutin is a naturally occurring compound found in the dried leaves of plant species including bearberry, blueberry and cranberry. Reported traditional therapeutic uses have included as an anti-infective for the urinary system and a diuretic.[4,5] More recently it was also suggested to be

[4] National Toxicology Program, U.S. Food & Drug Administration. Chemical information review document for arbutin [CAS No. 497-76-7] and extracts from *Arctostaphylos uva-ursi*. 2006;Jan.

[5] Herbal medicines. 4th edn. London: Pharmaceutical Press; 2013.

one of the most widely prescribed skin-lightening and de-pigmenting agent worldwide.[6] With the broadening use of arbutin, it is reported that plant extracts are replaced by chemically and biotechnologically synthesised arbutin and its derivatives.[7]

Some pharmacists have reported to PSA of the increasing availability and popularity of cosmetic products containing arbutin in a range of preparations (e.g. serum, powder) which are promoted, for example, to "fade hyperpigmentation, dark spots and acne scars".

Given these changes and observed trend in utilisation, PSA believes it is appropriate to create a specific entry for arbutin rather than rely on a cross reference to hydroquinone.

PSA notes that the concentration limits cited in the proposal for arbutin are equivalent to the limits currently in the Poisons Standard for hydroquinone (taking into account their different molecular weights).

Criteria for inclusion in Schedule 2

It is proposed that preparations for human external therapeutic or cosmetic use containing 5 per cent or less of arbutin would be included in S2. The proposed 5 per cent limit for arbutin is equivalent to the current 2 per cent limit for hydroquinone in the Poisons Standard.

PSA understands there have been concerns around potential side effects of arbutin based on the similarity in properties with hydroquinone. However, on balance it has been reported that there is a lack of significant side effects in effective doses of arbutin.[8]

Pharmacists have noted that some arbutin-containing products carry claims that α-arbutin is "much stronger in effect than arbutin or β-arbutin".

Further, PSA notes that the Scientific Committee on Consumer Safety (SCCS) of the European Commission has published the following opinions on the two arbutin derivatives:

> *The use of α-arbutin is considered to be safe for consumers in cosmetic products in a concentration up to 2 per cent in face creams and up to 0.5 per cent in body lotions.*[9]

and

> *The use of β-arbutin is considered to be safe for consumers in cosmetic products in a concentration up to 7 per cent in face creams provided that the contamination of hydroquinone in the cosmetic formulations remain below 1 part per million.*[10]

Therefore, PSA suggests the ACMS should consider whether different concentration limits need to be applied to the two arbutin derivatives if they are to be included in the Poisons Standard.

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6 Sarkar R, Arora P, Garg KV. Cosmeceuticals for hyperpigmentation: what is available? J Cutan Aesthet Surg 2013; 6(1):4–11.

7 Migas P, Krauze-Baranowska M. The significance of arbutin and its derivatives in therapy and cosmetics. Phytochem Lett 2015; 13:35–40.

8 ibid.

9 Scientific Committee on Consumer Safety, European Commission. Opinion on α-arbutin. SCCS/1552/15. 27 May 2015.

10 Scientific Committee on Consumer Safety, European Commission. Opinion on β-arbutin. SCCS/1550/15. 25 Mar 2015.

Proposed exemption from scheduling

Oral herbal preparations

It is proposed that oral herbal preparations containing 500 mg or less of arbutin per recommended daily dose would be exempt from scheduling.

As listed in the reasons for this proposal, upon ingestion, arbutin is rapidly absorbed in the small intestine and forms hydroquinone conjugates. Although concerns were initially raised about this process yielding free hydroquinone and glucose, and thereby inducing hepatotoxicity, nephrotoxicity and other toxicities, no direct evidence regarding human data was found.[11]

An assessment report by the European Medicines Agency indicates that oral preparations of arbutin include herbal teas, and liquid or solid dosage forms.[12] Based on published data and information,[13,14] the oral use of arbutin is accepted as traditional use and is primarily for its antibacterial activity in the urinary tract. Guidelines suggest 400–800 mg daily in 2–3 doses is effective in urinary tract infection treatment. From this, the proposed limit for oral herbal preparations of 500 mg or less of arbutin per recommended daily dose appears to be within acceptable range.

However, it is also reported that traditional use of arbutin can only be recommended for females. The use of arbutin by men is only recommended when advised by a medical practitioner due to the risk of more severe infections (and not on the basis of traditional use).[15] There is also reference to the recommended time of use being limited to two weeks.[16]

Based on these guidance, PSA suggests the proposed exemption from scheduling of oral herbal preparations containing 500 mg or less of arbutin per recommended daily dose will require careful consideration by the ACMS and the possible inclusion of additional restrictions.

Hair preparations and cosmetic nail preparations

Hair preparations containing 0.75 per cent of arbutin and cosmetic nail preparations containing 0.05 per cent of arbutin are proposed to be exempt from scheduling.

The proposed limits for arbutin are equivalent to the current limits in the Poisons Standard for hydroquinone (0.3 per cent for hair preparations and 0.02 per cent for cosmetic nail preparations).

PSA has no objections to this part of the scheduling proposal for arbutin.

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[11] Garcia de Arriba S, Naser B, Nolte K-U. Risk assessment of free hydroquinone derived from *Arctostaphylos Uva-ursi folium* herbal preparations. Int J Toxicol 2013; 32(6):442–53.

[12] European Medicines Agency. Assessment report on *Arctostaphylos uva-ursi* (L.) Spreng., folium. 30 Jan 2018.

[13] Migas, op. cit.

[14] European Medicines Agency, op. cit.

[15] ibid.

[16] Migas, op. cit.

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