The Pharmacy Guild of Australia

PROPOSED AMENDMENTS TO POISONS STANDARD

ACMS Meeting March 2019[1]

Comments by The Pharmacy Guild of Australia to the proposed amendments referred by the delegate for scheduling advice for consideration by the Advisory Committee on Medicines Scheduling

1. **Glyceryl trinitrate**
2. **Isosorbide dinitrate**
3. **Cetirizine hydrochloride**
4. **Mometasone furoate**

Date 21 January 2019
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[1] https://www.tga.gov.au/consultation-invitation/consultation-proposed-amendments-poisons-standard-accs-acms-and-joint-accsacms-meetings-march-2019

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1. GLYCERYL TRINITRATE

Proposal
To include Glyceryl trinitrate on Appendix H to allow for advertising.

We note that in the TGA Consultation Paper on *Proposed Schedule 3 substances to be added to Appendix H of the Poisons Standard* the following criteria[2] were used to justify exclusion from Appendix H:

Reference	Description
1a	Negative impact on public health due to potential misuse, abuse or diversion
1b	Negative impact on public health due to potential interactions (drug-drug, drug-food)
1c	Negative impact on public health due to additional risks associated with dosage form
1d	Negative impact on public health due to other specified factors
2	No longer a relevant ARTG entry / out dated substance

Negative impact on public health due to potential misuse, abuse or diversion
We do not believe that there is a potential for misuse, abuse or diversion. We note that the use of glyceryl trinitrate is associated with vascular headaches which would limit its potential for abuse.

Negative impact on public health due to potential interactions (drug-drug, drug-food)
As detailed in the product information for glyceryl trinitrate[3] there is a risk of orthostatic hypotension and syncope with the use of:

antihypertensives, tricyclic antidepressants, phenothiazines, levodopa, opioid analgesics, hydralazine, calcium channel blocking agents, minoxidil and prazosin.

As most patients would be under the ongoing care of a medical practitioner if prescribed these medicines this would not appear to be a problem. Access to glyeryl trinitrate as a Schedule 3 medicine, as with substances like salbutamol, adrenalin or naloxone, enables access for patients without the need of a prescription in urgent situations.

Negative impact on public health due to additional risks associated with dosage form
Glyceryl trinitrate is available as a sublingual tablet 600 mcg, a sublingual spray and also an ointment for relief and treatment of anal fissure. We do not believe that there is a negative impact on public health due to additional risks associated with these dosage forms.

Negative impact on public health due to other specified factors
We are not aware of other factors that would have a negative impact on public health.

No longer a relevant ARTG entry / out dated substance

[2] https://www.tga.gov.au/consultation/consultation-proposed-schedule-3-substances-be-added-appendix-h-poisons-standard
[3] MIMS Online accessed 17 Jan 2019 for [redacted] tablets

Not applicable in this instance. There are a number of products containing glyceryl trinitrate listed on the ARTG.

We do not see any reason why glyceryl trinitrate should not be included in Appendix H.

2. ISOSORBIDE DINITRATE

Proposal
To include isosorbide dinitrate on Appendix H to allow for advertising.

As with glyceryl trinitrate we do not see any reason why isosorbide dinitate should not be included in Appendix H.

3. CETIRIZINE HYDROCHLORIDE

Proposal:
Amend the Schedule 2 entry such that the substance would be unscheduled in divided preparations for the treatment of seasonal allergic rhinitis in adults and children 12 years of age and over when in a primary pack containing not more than 20 days' supply and labelled with a recommended daily does not exceeding 10 mg of cetirizine.

Overview

We did not support scheduling exemptions for cetirizine when considered at the November 2016 meeting and does not support increasing the maximum pack size exemption from Schedule 2. Cetirizine is listed on Appendix K (drugs required to be labelled with a sedation warning). The Guild argues that if a medicine is deemed to be of sufficient risk that it must carry a warning label such as this, then it is not appropriate for sale in general retail with no access to professional advice. If the current quantity is increased to 20 days' supply then consumers could purchase long term treatment without the opportunity for advice on their condition.

The risk and benefits of the use of the substance

There is no public need for a further relaxation of the scheduling exemption and we believe the risk of sedation and its potential impact on driving ability is best mitigated by facilitating access to professional advice via a Schedule 2 listing.

Although the second generation antihistamines are known to have similar efficacy, there is a significant difference in the extent of their sedative effects, with cetirizine more likely to result in sedation and impairment than other non-sedating antihistamines.[4] Cetirizine is a medicine that can affect psychomotor and cognitive functions, potentially having an adverse influence on the ability to drive. Psychomotor skills include reaction times and hand-eye coordination while the ability to make appropriate decisions relates to cognitive skills. Combining cetirizine with other impairing drugs, including alcohol, is noted as increasing the opportunity for impairment and the risk of serious road accidents.

[4] Ramaekers, J. G., Uiterwijk, M. M. C., & O'hanlon, J. F. (1992). Effects of loratadine and cetirizine on actual driving and psychometric test performance, and EEG during driving. *European journal of clinical pharmacology*, *42*(4), 363-369.

The Guild argues that simply including warnings on the medicine packs is insufficient. A survey of 2500 Australians showed that 21% have driven after taking prescription or OTC medicines, despite pack warning labels, with the biggest offenders (27%) aged over 55 years of age, and the next group (25%) being drivers aged 18 to 34 years.[5] Consequently, experts in an Australian study on drugs and driving suggest warning labels should be supported by verbal information from doctors and pharmacists.[6]

Summary

The Guild did not support the scheduling exemption for cetirizine and hence does not support a further relaxation of the scheduling exemption for this medicine to a maximum of 20 days' supply. The additional sedation risk specific to cetirizine as evidenced by its listing on Appendix K makes it inappropriate for largers pack sizes to be exempt from scheduling.

[5] Quoted in presentation; Dr Jenny Gowan, Northern & North East valley Divisions of general Practice April 2010; http://www.druginfo.adf.org.au/attachments/064_JennyGowan_DrugsDrivingSeminar_14Apr10.pdf

[6] J Mallick, J Johnston, N Goren et al; Drugs and driving in Australia: A survey of community attitudes, experience and understanding; Australian Drug Foundation; http://www.druginfo.adf.org.au/attachments/400_Drugs_and_Driving_in_Australia_fullreport.pdf

4. MOMETASONE FUROATE

Proposal:
Amend Schedule 2 entry to include "and when packed in a primary pack containing 200 actuations or less, for the short term…"

And

Add a Schedule 3 entry:

> MOMETASONE as the only therapeutically active substance in preparations for dermal use containing 0.1 percent or less of MOMETASONE in packs containing 15g or less

Overview

We do not object changing the Schedule 2 entry relating to the primary pack size of 200 actuations for aqueous nasal sprays.

With respect to the new Schedule 3 entry for dermal use we do not disagree but would be interested to know further details of the Appendix M restriction.

We note that the ACMS last considered mometasone at its meeting in October 2012[7]. The Delegate decided not to reschedule mometasone from Schedule 4 to Schedule 3 for the following reasons:

- adverse dermatological effects.
- inappropriate diagnosis of potentially severe skin conditions.
- use of mometasone should be limited to the treatment of severe skin conditions requiring diagnosis and monitoring by a medical practitioner.
- increased risk of toxicity due to potency.
- potential for misuse by consumers where lower potency corticosteroid would be more appropriate.

Each of these reasons will be addressed in turn:

Adverse dermatological effects
As outlined in the TGA-approved PI for mometasone:

> ***Contraindications***
> *Hypersensitivity to mometasone furoate or to other corticosteroids.*
> *As with other corticosteroids, mometasone is contraindicated in most viral infections of the skin, tuberculosis, acne rosacea, perioral dermatitis, fungal skin infections and ulcerative conditions.*
>
> ***Special warnings and Precautions for Use***
> *For external use only. Avoid contact with eyes.*
> *If irritation or sensitisation develops, treatment should be discontinued and appropriate therapy instituted.*
> *In the presence of an infection, an antibacterial or antifungal agent, as appropriate should be added to the treatment regimen. If the infection does not resolve promptly, corticosteroid therapy should be discontinued until the infection is controlled.*
> *As with all topical corticosteroids in general, systemic absorption will be increased if the product/s is/are applied to large areas of the body, under occlusion, where the epidermal barrier is compromised and where the treatment is long-term. These considerations are especially important in infants and children due to the larger skin surface to bodyweight ratio and the possibility of occlusive napkins and plastic pants being used. Use of corticosteroids in children should be limited to the least amount required for therapeutic effect.*

[7] https://www.tga.gov.au/book/part-final-decisions-matters-referred-expert-advisory-committee

Use in the elderly.
Clinical studies in adults have typically included elderly patients. No overall differences in safety or effectiveness were observed between these subjects and younger subjects and other reported clinical experience has not identified differences in responses between the elderly and younger patients. However greater sensitivity of older individuals cannot be ruled out.

Paediatric use.
The use of mometasone furoate 0.1% once daily has been documented in a number of studies in children from 7 months to 12 years of age, with moderate to severe dermatitis involving at least 15% of the body surface area. Duration of treatment was usually only for 3 weeks, with up to 6 weeks in one study. No skin thinning was observed in any of these studies or change in plasma cortisol levels, where this was monitored. In general, mometasone furoate was well tolerated. Local reactions were minor, e.g. stinging, and occurred in few patients.

However, although mometasone appears to be safe in young children and may have less effect on the HPA axis than other corticosteroids of similar strength, caution is advised when prescribing mometasone or any other corticosteroid for prolonged use in children. Care should be taken that application sites in infants and young children are not occluded with tightly fitting napkins or plastic pants.

Effects on laboratory tests. No data available.

Visual disturbance.
Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Adverse Effects (Undesirable Effects) See Table 1.

Adverse drug reactions in patients treated with mometasone furoate 0.1% w/w dosage forms

System organ class	Adverse drug reactions	
	Frequency category	
	Very rare (< 1/10,000)	Not known
Infections and infestations	Folliculitis	Infection, Furuncle
Eye disorders		Vision blurred
Nervous system disorders	Burning sensation	Paraesthesia
Skin and subcutaneous tissue disorders	Pruritis	Dermatitis contact, skin hypopigmentation, hypertrichosis, skin striae, dermatitis acneiform, skin atropy
General disorders and administration site conditions		Application site pain, application site reactions

In general, mometasone furoate 0.1%, applied once daily, without occlusion, appears to be well tolerated.
Local adverse reactions.
Mild to moderate stinging, itching, burning, mild skin atrophy and acneform reactions have been reported in less than 5% of patients.
Other less common reactions reported in less than 1% of patients include erythema, furunculosis, dermatitis, abscess, aggravated allergy, disease exacerbation, paraesthesia, dry skin, pimples, folliculitis and papular and pustular formation. Infrequent local reactions reported with other topical corticosteroids: irritation, hypertrichosis, hypopigmentation, perioral dermatitis, allergic contact dermatitis, maceration of the skin, secondary infection, striae and miliaria.

Systemic adverse reactions.
Similarly to other topical corticosteroids, mometasone furoate has the potential to suppress the HPA axis. However, in clinical studies of up to 6 weeks duration, the application of mometasone 0.1% once daily, without occlusion, did not affect plasma cortisol.

Overdose
Prolonged use over large areas of the body can suppress pituitary adrenal function resulting in secondary adrenal insufficiency. Infants and young children are likely to be particularly susceptible to HPA axis suppression, Cushing's syndrome and growth suppression under these conditions. Appropriate symptomatic treatment is indicated. Acute hypercorticoid symptoms are virtually reversible. Treat electrolyte imbalance, if necessary. In cases of chronic toxicity, slow withdrawal of corticosteroids is advised.

If a large amount of mometasone is accidentally ingested, particularly by a child, contact the Poisons Information Centre. For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

We do not believe that the adverse dermatological effects from mometasone are different from other corticosteroid products which are Schedule 3 (eg hydrocortisone, clobetasone) and this is evidenced by the TGA-approved PI. The side effects and contraindications for all corticosteroids skin preparations are by nature similar and there should be no reason to single out mometasone as being particularly problematic. Pharmacists are well aware of the issues regarding the inappropriate use of corticosteroids and already warn patients when providing the currently available Schedule 3 products.

Inappropriate diagnosis of potentially severe skin conditions

If inappropriate diagnosis is a problem then wording for Appendix M could be developed such that consumers could access continuing treatment for flare ups of their condition if they have previously been diagnosed and prescribed mometasone. We would be happy to work with the sponsor and other professional organisations to develop an appropriate Appendix M to ensure that supply was only to patients already diagnosed by a medical practitioner. Pharmacists could supply mometasone to patients if documented evidence such as a dispense record or a MyHealthRecord showed that the patient had previously been prescribed and dispensed this product.

Use of mometasone should be limited to the treatment of severe skin conditions requiring diagnosis and monitoring by a medical practitioner.

As above – we believe an Appendix M could be developed to address this issue.

Increased risk of toxicity due to potency.

Whilst it is true that mometasone is considered a potent[8] corticosteroid this does not necessarily mean it has more toxicity than other potent steroids such as betamethasone. A review by Prakash and Benfield[9] showed that:

> *"Although mometasone demonstrates greater anti-inflammatory activity and a longer duration of action than betamethasone, it has low potential to cause adverse systemic effects such as suppression of the hypothalamic-pituitary-adrenal (HPA) axis. Moreover, its atrophogenic potential is low and no greater than that of other glucocorticoids in its class, such as betamethasone valerate. Transient, mild to moderate, local adverse effects such as burning, stinging, folliculitis, dryness, acneiform eruptions and signs of skin atrophy have been reported with mometasone. Mometasone has shown a low risk of primary sensitisation and cross-reactions in preliminary patch test studies. Mometasone is a well-tolerated topical glucocorticoid effective in the management of patients with atopic dermatitis, seborrhoeic dermatitis, scalp psoriasis and psoriasis vulgaris. In addition to its low potential for causing primary sensitisation and cross-reactions with other topical glucocorticoids, mometasone offers the convenience of once-daily administration."*

Potential for misuse by consumers where lower potency corticosteroid would be more appropriate.

Again whilst mometasone may be a potent corticosteroid this does not necessarily mean it has greater side effects. If a consumer were to use a more potent product it would work more effectively for their inflammatory dermatoses and they may use less of it for a shorter time than a weaker product that was less effective. We do not believe that this is a reason to not make the product available as a Schedule 3.

[8] https://amhonline.amh.net.au/chapters/dermatological-drugs/tables/topical-corticosteroids-table
[9] https://www.ncbi.nlm.nih.gov/pubmed/9463794