Australian Government

Department of Health

Therapeutic Goods Administration

Notice of interim decisions to amend (or not amend) the current Poisons Standard (oral contraceptive substances)

TGA Health Safety Regulation

Confidentiality
All submissions received will be placed on the TGA's Internet site, unless marked confidential. Any confidential material contained within your submission should be provided under a separate cover and clearly marked "IN CONFIDENCE". Reasons for a claim to confidentiality must be included in the space provided on the TGA submission form. For submission made by individuals, all personal details, other than your name, will be removed from your submission before it is published on the TGA's Internet site. In addition, a list of parties making submissions will be published. If you do not wish to be identified with your submission you must specifically request this in the space provided on the submission form.

Contents

1. Notice of interim decisions made under Regulation 42ZCZN of the *Therapeutic Goods Regulations 1990*

This web publication constitutes a notice for the purposes of regulation 42ZCZP of the *Therapeutic Goods Regulations 1990* (the **Regulations**). In accordance with regulation 42ZCZP, this notice sets out:

- the interim decisions made by a delegate of the Secretary under regulation 42ZCZN in relation to proposed amendments to the current Poisons Standard which were referred to an expert advisory committee under subdivision 3D.2 of the Regulations in June 2021;
- the proposed date of effect of the proposed amendments (in circumstances where the interim decision proposes an amendment to the current Poisons Standard).

In accordance with regulation 42ZCZP, interested persons (including the applicant requesting the amendment) are invited to make submissions to the Secretary in relation to these interim decisions on or before **1 November 2021**.

We have changed the way to make submissions.

Submissions should now be provided through our consultation hub. Submissions will be considered by the Delegate in making the final decision.

Please note that in accordance with subregulation 42ZCZQ(4) of the Regulations, the Secretary must publish all relevant submissions received, unless the Secretary considers the information to be confidential information.

2. Interim decisions on proposed amendments referred to the Advisory Committee on Medicines Scheduling (ACMS #34, June 2021)

2.1 Interim decision in relation to oral contraceptive substances

Proposal

Two applicants proposed to move substances used in oral contraceptive pills from Schedule 4 to Schedule 3. A brief summary of each application is given below:

- Application A: Proposal to create a new Schedule 3 entry for ethinylestradiol and norethisterone, and expand the current Schedule 3 entry for levonorgestrel. Under the proposal, the three substances would also be subject to requirements set out in Appendix M. Advertising would also be permitted via inclusion in Appendix H.
- Application B: Proposal to create a new Schedule 3 entry for ethinylestradiol, norethisterone, cyproterone, desogestrel, dienogest, drospirenone, estradiol, gestodene, mestranol and nomegestrol, and expand the current Schedule 3 entry for levonorgestrel. Under the proposal, the eleven substances would also be subject to requirements set out in Appendix M.

Interim decision

Pursuant to regulation 42ZCZN of the Regulations, a Delegate of the Secretary has, in relation to the proposed amendment, made an interim decision not to amend the scheduling for oral contraceptive substances in the current Poisons Standard.

Materials considered

In making this interim decision, the Delegate considered the following material:

- The two applications to amend the current Poisons Standard with respect to oral contraceptive substances;
- The 27 public submissions, 23 including a written component, received in response to the pre-meeting consultation under regulation 42ZCZK of the Regulations;
- The advice received from the Meeting of the Advisory Committee on Medicines Scheduling (ACMS #34);
- Subsection 52E(1) of the *Therapeutic Goods Act 1989,* in particular (a) risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (f) any other matters that the Secretary considers necessary to protect public health;
- The Australian Health Ministers' Advisory Council's Scheduling Policy Framework (SPF 2018);
- The Scheduling handbook: Guidance for amending the Poisons Standard; and

- A medicines safety update on the risk of venous thromboembolism associated with oral contraceptive use.

Summary of ACMS advice to the delegate

The Committee advised that the current scheduling for oral contraceptive substances remains appropriate.

Members agreed that the relevant matters under Section 52E(1) of the *Therapeutic Goods Act 1989* included: (a) the risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (f) any other matters that the Secretary considers necessary to protect public health. The committee considered the proposals for each substance separately, noting that many of the risks and benefit were common across the oral contraceptive substances under consideration.

The reasons for the advice included:

a) the risks and benefits of the use of a substance

Benefits:

- Prevents or reduces the risk of unintended pregnancy, with up to 93% effectiveness with typical use and 99.5% effectiveness with perfect use.
- Offers some non-contraceptive benefits that depend on the specific product.
- Increased ease of oral contraceptive access under the proposed amendments.

Risks:

- Relatively low risk for second generation oral contraceptives (ethinylestradiol in combination with norethisterone or levonorgestrel), but eligibility criteria is complex.
- Increased risk of thromboembolism.
- Increased cardiovascular risks (including stroke), particularly women who are over 35, smokers, obese, or have migraines with aura.
- Small increased risk of cervical cancer.
- Some risk of contraceptive failure.
- Increased risk of weight gain.
- Patient risks change over time.

b) the purposes for which a substance is to be used and the extent of use of a substance

- Primary purpose is for oral contraception, with the exception of cyproterone.
- Cyproterone is indicated for the treatment of signs of androgenisation in women, including:
  - severe acne (involving inflammation or nordularity or risk of scarring) where prolonged oral antibiotics or local treatment alone has not been successful; or
  - idiopathic hirsutism of mild to moderate degree.
- Also used for non-contraceptive effects

- Commonly used.
- Dieongest is also indicated for treatment of heavy and/or prolonged menstruation and treatment of mild to moderate acne in women seeking contraception.
- Drosperinone is also indicated for acne vulgaris and pre-menstrual dysphoric disorder in women seeking contraception.

c) the toxicity of a substance

- Well established toxicity profile.
- Most are in category B3 for use in pregnancy, and are generally not recommended in breastfeeding.

d) the dosage, formulation, labelling, packaging and presentation of a substance

- Once daily oral tablet with varying amounts of substances depending on product and place in cycle.
- Labelled as Prescription Only.
- Either 3 or 4 months' worth of medication per supply depending on the product.
- Venous thromboembolism risk increases with estrogen dosage. If ethinylestradiol is considered for inclusion in Schedule 3, it should be limited to a maximum of 35 µg.

e) the potential for abuse of a substance

- Nil

f) any other matters that the Secretary considers necessary to protect public health

- Internationally, most are only available as prescription only medicines, if approved for use at all. Exceptions are ethinylestradiol, levonorgestrel, norethisterone and desogestrel, which are available as over the counter medicines in New Zealand in certain limited contexts.
- Appendix H listing may bias decisions for consumers and cause them to overlook more suitable contraceptive options.
- While increasing access to contraception is important, promoting oral contraceptives over other more effective (and often safer) options may have unintended consequences.
- Despite being common medicines, good medical management of contraception is complex and needs medical oversight.
- Health risks for women using oral contraceptives are addressed by maintaining initiation of supply by an authorised prescriber.
- A woman can determine whether she needs oral contraception.
- Down-scheduling will mean that if a woman runs out of her prescription, she can access oral contraceptives without the delay of booking a GP appointment; such access may reduce the risk of unwanted pregnancies.
- Women can already access emergency contraception from pharmacies, and this potentially provides a supply model for the proposals.

- PBS Continued Dispensing rules already allow the continued supply (4 months) of the oral contraceptive pill by pharmacists (maximum PBS quantity once in a 12 month period). For oral contraceptive preparations that are not listed on the PBS, 4-month continued dispensing arrangements are available in many Australian states and territories.
- There may be a better mechanism to achieve the same outcome, such as extending the maximum number of repeats under the PBS, or the period of validity of prescriptions.
- Several details of the proposals are unclear, including:
  - how long patients can continue to access over the counter oral contraceptives under each proposal;
  - how to handle high-risk patients, including how information would be shared between doctors and pharmacists;
  - details of proposed pharmacist reviews; and
  - how pharmacists would record the dispensing of oral contraceptives.

Reasons for the interim decision (including findings on material questions of fact)

I have made an interim decision not to amend the scheduling for oral contraceptive substances in the current Poisons Standard. The detailed reasons for my decision follow.

I agree with the Committee's findings that the relevant provisions of section 52E of the *Therapeutic Goods Act 1989* are: (a) risks and benefits of the use of a substance; (b) the purposes for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

I note that the eleven substances under consideration cover the full scope of active ingredients available in oral contraceptive pills in Australia. These pills generally consist of an estrogen and progestogen component in various ratios, often with these ratios changing throughout a monthly cycle. Despite the variation in the active substances and dosing regimens for each product, there are broad similarities regarding the mechanism of action, risk factors and considerations for prescribing. As such, I consider that it is appropriate to document the reasons for my decision on both applications to down-schedule oral contraceptives as a group (though differences between substances are specifically discussed).

The use of oral contraceptive pills can cause significant adverse effects that are not consistent with over the counter medicines. These effects include weight gain, emotional anxiety, heavy bleeding and thromboembolism, particularly with increasing age. Even oral contraceptive products with the most favourable safety profiles lead to a rate of 5-7 cases of thromboembolism per 10,000 women per year, compared to a baseline of 2 in 10,000[1]. I also note the Committee's advice that these preparations can exacerbate the risks of cardiovascular disease (including stroke) – especially in women who are over 35, obese, smoke, have diabetes, have uncontrolled hypertension or get migraines with aura. I am of the view that the adverse effects of oral contraceptive substances, and the potential for evolving risks over time, are significant and require management by a medical practitioner.

[1] https://www.tga.gov.au/publication-issue/update-dienogest-and-risk-venous-thromboembolism

In considering access through a pharmacist, I note the Committee's analysis of oral contraceptive preparations against the Schedule 3 scheduling factors outlined in the Scheduling Policy Framework (SPF 2018):

- Consumers can identify when they require (oral) contraception, but consultation with a pharmacist is not sufficient to ensure safety, particularly over extended periods of time.
- The medicine is not expected to produce dependency and there is no risk of abuse or illicit use.
- The risk factors for adverse effects, interactions and contraindications are known, but are numerous and complex. These are more appropriately managed by a medical practitioner.
- Patient risk factors generally increase over time, necessitating close medical management by a medical practitioner – even after the initial establishment of safe treatment.
- The use of oral contraceptives may mask symptoms, or delay the diagnosis, of serious conditions such as endometriosis.

On balance, I find that the general properties of oral contraceptive substances do not align with the Schedule 3 factors, and do not warrant any scheduling action – even if additional controls were implemented as proposed through Appendix M. The complexity of the risk factors, adverse effects and interactions necessitates regular medical reviews with a GP, even after the initial establishment of treatment.

I note that internationally, oral contraceptive substances are generally only available as prescription medicines. As noted by the Committee, in New Zealand ethinylestradiol, levonorgestrel, norethisterone and desogestrel can be supplied without a doctor's prescription by a registered pharmacist who has successfully completed the approved training program. I note that while pharmacist supply without a prescription can occur in very limited circumstances, these substances are not formally classified as over the counter medicines in New Zealand.

While recognising that there are many similarities in the risks associated with oral contraceptive substances, I have also considered individual substances, and groups of substances, to ensure due consideration of each against the scheduling factors. As such, I note that the public submissions and the Committee's advice highlighted several substances that have distinct safety profiles or indications:

- Second generation oral contraceptive pills, containing ethinylestradiol in combination with norethisterone or levonorgestrel, have the lowest thrombosis risk[2] and are generally considered to be the 'gold standard' in relation to their safety profile. However, the seriousness, severity and frequency of adverse effects/interactions are such that monitoring by a medical practitioner is required.
- Cyproterone-containing pills have efficacy as oral contraceptives, but their primary indication is for treating acne and hirsutism. These conditions require consultation with a medical practitioner.
- Mestranol-containing pills are rarely prescribed in Australia. These products have been discontinued in the United States and Canada. The risk profiles of these medicines are not well defined.

[2] https://www.tga.gov.au/publication-issue/update-dienogest-and-risk-venous-thromboembolism

I am satisfied that the common and substance specific risks and indications are consistent with my finding that use of these oral contraceptive substance requires management by a medical practitioner.

In considering whether any other public health considerations warrant over the counter supply of these substances, I note that timely access to contraceptives may prevent unintended pregnancies and improve the health, well-being and choices available to women. Improving access to contraceptive options may particularly assist those that live in rural or remote areas with limited access to GPs. However, while there may be prescriber access challenges in some communities, I note the Committee's findings that the proposed changes would not address these issues. I also note that there are already mechanisms in place to allow for access to oral contraceptives without the need to physically visit a GP, including telehealth and emergency pharmacy supply arrangements of up to four months' supply.

On balance, I consider that the proposed changes would introduce new risks which outweigh the potential benefits.

I note that under current scheduling, patients visit their doctor on a yearly basis to get prescriptions for their medication. These annual GP visits allow women to review the most appropriate form of contraception for them from a full range of options including long acting reversible contraceptives (LARCs), which are increasingly recommended as the first-line form of contraception. By moving conversations about contraception to pharmacies, I am concerned that the proposals would impede women from accessing the most appropriate form of contraception for their circumstances and individual risk factors.

The applicants have also proposed Appendix M entries. I note the Committee's advice that it is not clear how these Appendix M entries could be implemented and enforced. As such, I have concerns that the proposed amendments, including the potentially unenforceable Appendix M entries, could lead to confusion among consumers, doctors and pharmacists, rather than achieve certainty and improved access.

I have also considered the 27 public submissions received during the pre-meeting public consultation, noting that support for rescheduling varied depending on the proposal and substance. Submissions outlined potential risks and benefits of the proposals from a wide range of perspectives. For example:

- The Australian Medical Association (AMA)[3] noted that taking oral contraceptives is not without risks, and that other contraceptives such as LARCs should be promoted. Moreover, their use may mask particular medical conditions such as endometriosis, and supply under Schedule 3 may fragment patient care by GPs. As such, the AMA expressed that they "vehemently" oppose both applications.
- The Pharmaceutical Society of Australia (PSA)[4] noted that, after holding discussions with Applicant A, they had considered a preliminary outline of a wide range of materials that would supplement the implementation of this proposal. The PSA did not support Application B – in part because they considered that the risk profile of several substances was unfavourable for Schedule 3 supply.
- Family Planning NSW[5] were broadly supportive of the proposed amendments listed in both applications, but identified a wide range of specific concerns and areas for clarification.

[3] https://consultations.health.gov.au/tga/june_2021_acms_oral_contraceptives/user_uploads/ama-submission-to-the-tga---proposed-amendments-to-the-poisons-standard---june-2021-proposals---oral-contraceptives---final_redacted.pdf
[4] https://consultations.health.gov.au/tga/june_2021_acms_oral_contraceptives/user_uploads/2021may27_acms_oc_psa_sub_final_redacted.pdf
[5] https://consultations.health.gov.au/tga/june_2021_acms_oral_contraceptives/user_uploads submitted_fpnsw-public-consultation-on-proposed-amendments-to-the-poisons-standard--oral-contraceptives--26may2021.pdf

Alongside their position, they noted that pharmacist provision should not replace ongoing care by medical practitioners – and that several resources would need to be developed, and mechanisms put in place, to ensure safe implementation.

On balance, I consider that neither applicant's proposal can be implemented at this time and that the risks in doing so outweigh the benefits. All eleven substances are associated with risks of significant adverse effects, interactions and contraindications that require regular review by a doctor – and their inclusion in Schedule 3 would put many Australian women at unnecessary risk. While there are recognised benefits to widening the availability of oral contraceptives, I do not consider that the proposals would significantly reduce current barriers to access. In making my decision, I acknowledge that timely access to contraceptives is vital to many women's health and autonomy; however, upon careful consideration of the risks and benefits, I have decided to retain the current scheduling of all eleven oral contraceptive substances.