Purpose

makes this submission in relation to proposed amendments to the Poisons standard referred by the delegate for scheduling advice for consideration by the Advisory Committee on Medicines Scheduling (ACMS) at the March 2015 meeting.

comments relate to the proposed amendments to:

- aciclovir;
- oestradiol, desogestrel, ethinylestradiol, norethisterone, levonorgestrel, cyproterone, gestodene, drospirenone, mestranol, medroxyprogesterone, oestrogens and progestogens;
- diphenoxylate;
- esomeprazole;
- hydrocortisone compounded with aciclovir; and
- ranitidine.
Recommendations

**Aciclovir**

does not support the proposal to reschedule aciclovir in muco-adhesive tablets containing 50 mg in a pack of two tablets or less from Schedule 4 to Schedule 2.

For aciclovir in this dosage and pack size, recommends a new Schedule 3 entry and inclusion in Appendix H.

**Oestradiol, desogestrel, ethinylestradiol, norethisterone, levonorgestrel, cyproterone, gestodene, drospirenone, mestranol, medroxyprogesterone, oestrogens and progestogens**

believes the safety profile of the substances under this proposal meet the scheduling factors for Schedule 3.

strongly believes that pharmacists have a role in authorising the continuation and supply of prescribed oral contraceptives under certain specified conditions.

does not support initiation of routine oral contraceptive therapy by pharmacists.

Pharmacists must be appropriately trained to be permitted to authorise the continuation and supply of prescribed oral contraceptive therapy (under certain specified conditions) would ensure clinical rigour in the development of professional guidelines, standards and training for pharmacists in consultation with regulators, consumers, prescribers and sexual health and family planning organisations.

**Diphenoxylate**

does not support the proposal to down schedule diphenoxylate 2.5 mg or less in packs of 8 or less dosage units, when combined with a quantity of atropine sulphate equivalent to at least 1 per cent of the dose of diphenoxylate from Schedule 3 to Schedule 2.

Although supports the status quo (Schedule 3) for its scheduling, the removal of diphenoxylate from Appendix H is recommended based on a higher risk profile of the substance.

**Esomeprazole**

supports the inclusion of esomeprazole in Appendix H for oral preparations containing 20 mg or less per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease (GORD), in packs containing not more than 14 days supply.
Hydrocortisone compounded with aciclovir

- supports amending the Schedule 3 entry for hydrocortisone 1 per cent (1% w/w) when compounded with aciclovir 5% (5% w/w) or less in primary packs of not more than 2 g for dermal use in adults and adolescents (12 years of age and older).
- supports the inclusion of aciclovir in Appendix H.

Ranitidine

- does not support the proposal to exempt ranitidine from Schedule 2 when in divided preparations for oral use containing 300 mg or less per dosage unit in the manufacturer’s original pack containing not more than 7 dosage units.

Comments on proposed amendments

Aciclovir

Proposal to reschedule aciclovir in muco-adhesive tablets containing 50 mg in a pack of two tablets or less from Schedule 4 to Schedule 2.

- In the United States, 50 mg aciclovir is available as a muco-adhesive buccal tablet and is indicated for the treatment of recurrent herpes labialis in immunocompetent adults. Literature reports on the development and evaluation of aciclovir in a muco-adhesive formulation show a favourable outcome for clinical endpoints such as time to healing, incidence of blocked episodes, duration of herpes episodes, and incidence and time to next recurrence. Thus it is suggested that the clinical course may be modified through a decrease in the incidence and delay in the onset of the next recurrence.

- Currently in Australia, consumers have unrestricted access to topical preparations of aciclovir for the treatment of herpes labialis. In addition, famciclovir (in divided oral preparations containing a total dose of 1500 mg or less) is available as a Pharmacist Only Medicine (Schedule 3).

- Assuming the current proposal relates to buccal tablets of aciclovir, this presentation of cold sore treatment will be new in Australia. Therefore believes a Schedule 2 classification would not be appropriate at this time, noting also that a similar preparation (single dose famciclovir) is currently in Schedule 3.

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As a Pharmacist Only Medicine, pharmacists will have an important role in providing information and advice on aciclovir buccal tablets, their place in therapy, and how to maximise treatment efficacy. Consumers will benefit from pharmacist advice on the suitability of the medicine based on presenting signs and symptoms, frequency of episodes, prior treatment and other factors. Treatment options can be discussed as well as treatment expectations, monitoring outcomes and follow-up, and how to avoid trigger factors. Depending on the circumstances, the pharmacist may recommend referral to a medical practitioner.

Since timely intervention and early commencement of treatment is beneficial, recommends the inclusion of aciclovir in Appendix H.

**Summary:** does not support the proposal to reschedule aciclovir from Schedule 4 to Schedule 2 but recommends the creation of a new entry in Schedule 3. In addition supports the inclusion of aciclovir in Appendix H.

Oestradiol, desogestrel, ethinyloestradiol, norethisterone, levonorgestrel, cyproterone, gestodene, drospirenone, mestranol, medroxyprogesterone, oestrogens and progestogens

To create new Schedule 3 entries for these substances when indicated for oral contraception. The applicant has proposed potential conditions of: (i) a minor questionnaire by the pharmacist regarding family history of heart problems, hypertension and stroke; (ii) an in-pharmacy blood pressure test/results from another recent blood pressure test to ensure suitability for medication; and (iii) limit of 3–6 months’ supply in one transaction.

The reclassification of oral contraceptives through down-scheduling has been considered in other countries and therefore welcomes the opportunity to make this submission on the current proposal in the Australian context.

notes the additional detail provided by the applicant around possible conditions for the assessment of cardiovascular risk by the pharmacist and the limits on the supply in a single transaction. While the gazettal of this additional information appears useful, the lack of availability of the full proposal and information on the rationale and evidence which underpin this proposal substantially restricts and other stakeholders to provide a comprehensive response on the merits, appropriateness or risks of the proposal. As has commented before, this lack of transparency in the rescheduling process is extremely disappointing. For example in New Zealand, the applicant’s full submission is made publicly available during the consultation stage and enables interested parties to consider the full detail and implications of the proposal, examine the evidence-base and provide a comprehensive response.

Management of contraception is a very broad and comprehensive topic requiring various issues to be discussed and addressed with the consumer. The best approach for an individual can be influenced by many factorsincluding, but not limited to, the consumer’s


age, health status, relationship status, ethnicity and Indigenous status, and the duration of action and cost of the medicine. Importantly, is cognisant that the selection and provision of an oral contraceptive medicine is only one aspect when considering the wide-ranging issues relevant to reproductive health management.

- is aware that the ACMS is required to consider relevant matters under subsection 52E(1) of the *Therapeutic Goods Act 1989*, for example, risks and benefits of the use of the substance, toxicity of the substance, and the potential for abuse. Further, in considering the factors for the risk-benefit analysis of scheduling, believes that the safety profile of oral contraceptive substances is generally consistent with those listed for Pharmacist Only Medicines (Schedule 3), for example, that the medicine is substantially safe with pharmacist intervention and the use of the medicine at established therapeutic dosages is not expected to produce dependency.

- In undertaking a risk-benefit analysis, believes a factor which is pertinent to this proposal is the one which reads, in part:

  …where the medicine is intended for recurrent or subsequent [treatment]…

  …pharmacist intervention is required to monitor safe use of the medicine following recommendation by a medical practitioner…

- The key consideration here which supports is that the use of the oral contraceptive must be initiated by a medical practitioner. This is to ensure the consumer receives appropriate care through the medical practitioner’s consideration of their medical and family history, relevant risk-factors and contraindications, and to discuss contraceptive options as well as other sexual health issues. From a patient safety and health outcomes perspective, does not support initiation of routine oral contraceptive therapy by pharmacists.

- However, contingent on the initial clinical oversight and initiation of oral contraceptive therapy by a medical practitioner, strongly believes that pharmacists have a role in authorising and providing the continuation of the prescribed oral contraceptive under certain specified conditions (e.g. consumer’s health status has been stable; blood pressure test is conducted or recent test result is available). This could be conducted under strict criteria to safely enhance ongoing access to oral contraception and include formal referral pathways to a medical practitioner if it is not suitable for individuals to receive the medicine through pharmacist intervention.

- Note that this ‘model’ of pharmacist-authorised continuation and supply would be intended to cover a broader range of oral contraceptives and supply conditions than what is currently permitted through, for example, the Fifth Community Pharmacy Agreement *Continued dispensing of Pharmaceutical Benefits Scheme medicines in defined circumstances (Continued dispensing) initiative* or other jurisdiction-specific legislative arrangements.

- believes alternative ways to access and support continuation of contraceptive therapy without compromising patient safety will contribute to better public health, for example,

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around unintended pregnancies which can be associated with significant social, health and financial costs.\(^7\)

- For such a model to be acceptable there must be clear articulation of the necessary competencies for pharmacists. Further it would be expectation that pharmacists will be appropriately trained before being granted the privilege to authorise continuation and supply of oral contraceptive therapy. For example, the competencies required to be demonstrated might relate to: legal requirements for the specific supply arrangements; tailoring advice on oral contraception and other health and medicine-related issues; risk factors which indicate continuation of the oral contraceptive should be determined by a medical practitioner; health factors requiring referral for medical attention or to a sexual health and family planning clinic; consumer factors requiring specific intervention in addition to or instead of continuation of oral contraceptive therapy.

- Upon authorisation of continuation and supply of the oral contraceptive, pharmacists would be expected to provide clear guidance to the consumer on any follow-up requirements and recommendations for the future. In consultation with the consumer, consideration must also be given to timely communication with the prescriber in order to best support the consumer's future health and medication management needs.

- believes that promoting a collaborative model with prescribers and consumers, and including a criterion that pharmacists cannot initiate routine oral contraceptive therapy will be key factors in designing an appropriate model. notes that during the consultation\(^8\) on a proposal to reclassify four oral contraceptive pill ingredients in New Zealand, support was expressed by the Royal Australian and New Zealand College of Obstetricians and Gynaecologists to “allow appropriately trained and accredited pharmacists working in suitable premises (i.e. with an appropriate, private space available for discussion and clinical checks) to write repeat prescriptions”.

- would envisage developing an overall training package for pharmacists in partnership with consumer groups, sexual health and family planning organisations, medical practitioners and other relevant prescribers. would also recommend appropriate requirements be put in place in relation to the standards of pharmacy premises.

**Summary:**

believes the safety profile of the oral contraceptive substances under this proposal meet the scheduling factors for Schedule 3.

strongly believes that pharmacists have a role in authorising the continuation and supply of prescribed oral contraceptives under certain specified conditions.

do not support initiation of routine oral contraceptive therapy by pharmacists.


\(^8\) New Zealand Medicines and Medical Devices Safety Authority. Comments on agenda items for the 51st meeting on 8 April 2014. Medicines Classification Committee public consultation. 2014. Apr. Available at: www.medsafe.govt.nz/profs/class/agen51CommentsOnSubmissions.pdf
recommends that legislation be amended to enable appropriately trained pharmacists to authorise the continuation of prescribed oral contraceptive therapy under certain specified conditions. would ensure clinical rigour in the development of professional guidelines, standards and training for pharmacists in consultation with regulators, consumers, prescribers and sexual health and family planning organisations.

Diphenoxylate

Proposal to down schedule diphenoxylate 2.5 mg or less in packs of 8 or less dosage units, when combined with a quantity of atropine sulphate equivalent to at least 1 per cent of the dose of diphenoxylate from Schedule 3 to Schedule 2. To remove diphenoxylate from Appendix H.

- Several over-the-counter preparations are available for the control and symptomatic relief of acute non-specific diarrhoea. However, certain precautions must be exercised, including issues such as: the importance of initiating supportive treatment (e.g. fluid and electrolyte replacement, nutritional therapy); elimination, if possible, of the underlying cause of diarrhoea; and contraindications if diarrhoea is accompanied by fever or if there is blood or mucus in the stool.

- As a Pharmacist Only Medicine, diphenoxylate is subject to several warning statements including: the possibility of sedation; age restriction (not for children under 12 years of age); maximum duration of treatment (no more than 48 hours); and use in pregnancy or lactation (do not use except on doctor’s advice).

- also notes that a pack size greater than eight dosage units of diphenoxylate and atropine sulphate remains in Schedule 4.

- Diarrhoea can be life-threatening if it is not managed appropriately or if supportive treatment is not instituted. Simple factors can also exacerbate the condition (e.g. hot weather), particularly in the elderly; dehydration in this population group commonly leads to hospitalisation. The pharmacist’s role in monitoring medication use and consumer health outcomes, and referring to a medical practitioner if the condition has not improved or resolved as expected, are extremely important.

- Overall, believes that Schedule 3 remains the most appropriate classification for diphenoxylate and atropine sulfate given its safety profile combined with the potential for an adverse outcome if the condition is not treated appropriately in high-risk individuals.

- Although retention in Schedule 3 is recommended, believes diphenoxylate as a substance carries a higher risk profile than some other medicines with similar indications. For this reason, removal from Appendix H listing is recommended.

Summary: does not support the proposal to reschedule diphenoxylate (when combined with atropine sulfate) from Schedule 3 to Schedule 2. In addition, recommends that diphenoxylate be removed from Appendix H.
Esomeprazole

Proposal to create a new entry in Appendix H for esomeprazole in oral preparations containing 20 mg or less per dosage unit for the relief of heartburn and other symptoms of gastro-oesophageal reflux disease (GORD), in packs containing not more than 14 days supply.

- Proton pump inhibitors (PPIs) are widely available as OTC medicines and well established for use in the relief of heartburn and other symptoms of gastro-oesophageal reflux disease (GORD). A range of PPIs, including esomeprazole, with similar safety profiles have been available as Pharmacist Only Medicines for many years with data supporting efficacy and no reports of significant new safety concerns since being rescheduled.

- The ongoing Schedule 3 entry will best support those consumers who are most likely to benefit from esomeprazole. Pharmacists will give consideration to and support the consumer around general dose recommendations for optimal therapy, the need to assess the consumer’s response to treatment, and provide appropriate and timely referral if further investigation is required.

Summary:  supports the proposal to include esomeprazole as specified in Appendix H.

Hydrocortisone compounded with aciclovir

Proposal to amend the Schedule 3 entry for hydrocortisone 1 per cent (1% w/w) when compounded with aciclovir 5% (5% w/w) or less in primary packs of not more than 2 g for dermal use in adults and adolescents (12 years of age and older). To include aciclovir in Appendix H.

-  believes this proposal is consistent with existing scheduling of hydrocortisone 1 per cent for dermal use when compounded with another active ingredient.  also believes the safety profiles of hydrocortisone and aciclovir in the stated strengths are appropriate for a Schedule 3 classification.

- As stated earlier in this submission,  supports the inclusion of aciclovir in Appendix H to help facilitate timely intervention and early commencement of treatment.

Summary:  supports the proposal to amend the Schedule 3 entry for hydrocortisone 1 per cent to include when compounded with aciclovir as specified.  also supports inclusion of aciclovir in Appendix H.

Ranitidine

Proposal to exempt ranitidine from Schedule 2 when in divided preparations for oral use containing 300 mg or less of ranitidine per dosage unit in the manufacturer’s original pack containing not more than 7 dosage units.

- Many over-the-counter products are available to effectively manage symptoms such as heartburn or acid indigestion. These common presentations, however, can also be part of a range or group of symptoms which may be indicative of a more serious condition.
• Consumers are likely to derive greater benefit from therapy if an appropriate medicine has been selected through pharmacist guidance, careful history taking and advice on monitoring and follow-up. Pharmacists will also frequently refer individuals for medical attention without any medicine supply where atypical or alarm symptoms (e.g. unintentional weight loss, difficulty or painful swallowing, coughing, vomiting blood) are reported or there is a suggestion that the symptoms have been severe, frequent or non-resolving.

• It is important that ranitidine 300 mg remains in Schedule 2 so that consumers have the opportunity to seek information and advice from the pharmacist at the time of purchase of the product. An unregulated environment does not provide the opportunity for discussion or intervention and some consumers may inadvertently persevere with inappropriate self-medication and potentially result in a delay in seeking medical advice.

• It may be suggested that appropriate packaging and labelling will adequately address these concerns. However, would re-iterate that pharmacists have the expertise to tailor information and advice according to the needs of the consumer. Thus pharmacists will help to enhance the benefits of a medicine by providing advice on safe and quality use while also being cognisant of the need for appropriate and timely intervention to prevent harm or to assist vulnerable or at-risk consumers. Information available on the label, which may or may not be read by the consumer, cannot provide the tailored advice and intervention that may be required.

• Retaining ranitidine in Schedule 2 will also be beneficial for consumers seeking advice from the pharmacist or trained pharmacy assistant as it can be considered in the context of the broader range of medicines available in the pharmacy and provide better choice for consumers.

Summary: does not support the proposal to exempt ranitidine (in divided oral preparations, 300 mg or less per dosage unit, not more than 7 dosage units per pack) from Schedule 2.

Submitted by: 

11 December 2014
RE: TGA Consultation: Invitation for public comment – ACMS meeting, March 2015

Dear Sir/Madam,

wishes to provide comment on the below mentioned proposal to create a new Schedule 3 entry for the listed oestrogen and progestogen substances when indicated for contraception.

Proposed amendments referred by the delegate for scheduling advice for consideration by the Advisory Committee on Medicines Scheduling (ACMS)

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<tr>
<th>SUBSTANCE</th>
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<td>Desogestrel</td>
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As an organisation that has a strong commitment to Oral Contraceptive Products (OCPs) through engagement in research and development, manufacture and supply, safety monitoring, regulatory compliance, clinical trials, post marketing studies, providing and promoting education to health care professionals and the public through conferences, training and risk management plans, does not support the above proposal as we believe optimal application of the safe and quality use of these products would not be achieved if the changes are implemented.
While we do not disregard the important and critical role of the pharmacist in counselling on the use of contraceptives and support the widening of access attained through the pharmacists continued dispensing arrangement, we would like to highlight some points for consideration based on the Scheduling Policy Framework (http://tga.gov.au/sites/default/files/scheduling-policy-framework.pdf) developed by the National Coordinating Committee on Therapeutic Goods (NCCTG), as well as other considerations that go beyond the scope of the scheduling factors.

The ‘cascading principle’ determines the scheduling of medicines based on a set of ‘Factors’. Detailed below are some of these Factors for S4 and S3 scheduling, as well as the specific medical considerations which demonstrate why OCPs should remain at the S4 prescribing level.

Factors For Prescription Only Medicines (S4)

Factor 1 & 2:

**The ailment or symptoms that the substance is used for require medical intervention**
- diagnosis, management or monitoring of the medical condition is such that it requires medical intervention before the substance is used

and

**The use of the substance requires adjunctive therapy or evaluation** - medicines/non pharmacology measures or specialised medicine delivery devices. Lab tests or additional clinical assessments

Current guidance would suggest that before an OCP is prescribed a history (including a gynaecological history and a comprehensive medical history) is taken to exclude any contraindications to pill prescription. Potential contraindications may include a personal or family history of venous thromboembolism (VTE), identifying arterial risk factors or long standing diabetes or differentiating a history of severe headaches from migraines with or without aura. Weight, BMI calculation and blood pressure measurement are also recommended, as is an assessment of prescribed medications for potential drug interactions. A thrombophilia screen may also be warranted in some circumstances (SHFPA 2012). Consultation opportunities to assess tolerability, monitor or manage side effects may also be important in optimising contraceptive adherence. Current guidance recommends a review 4-6 months after initial prescription and then yearly. More frequent monitoring may be required if a woman has comorbidities (SHFPA 2012).

A woman’s contraceptive needs may also change over her lifetime and regular review allows assessment of the most suitable option at the time. Down scheduling OCPs would create a disproportionate availability for oral contraception compared to other methods. Other contraceptive options, for example long acting reversible methods may be a more appropriate choice for the woman with regards to their risk factors, comorbidities, life stage and compliance patterns.

Therefore, it can be seen that medical management, monitoring and evaluation is imperative for the safe and effective provision of contraception in women.
**Factor 4: The seriousness/severity/frequency of adverse effects are such that monitoring or intervention by a medical practitioner is required to minimise the risk of using the substance**

While most common adverse events experienced on the OCP are mild and short lived, the combined oral contraceptive pill is associated with rare but potentially serious adverse events of venous thromboembolism (VTE) (7-10/10,000 WY) (Dinger 2007, Dinger 2014). In a 2012 Danish cohort study, Lidegaard and colleagues summarised the risk of arterial thromboembolism (ATE) compared to non-use as a relative risk of 0.9 to 1.7 with a dose of oestrogen of 20µg and from 1.3 to 2.3 with those that included ethinyl oestradiol at a dose of 30µg to 40µg (Lidegaard 2012). These side effects can be fatal or cause permanent disability. The risks of VTE are the greatest when a woman starts an OCP for the first time or re-starts after a 4 week break (Dinger 2014). A woman’s risk for ATE/VTE events may change over time with age, immobilisation such as during surgery or long haul travel, weight gain, changes in blood pressure or smoking status (Reid. 2013). It is important that a medical practitioner constantly assesses the benefit/risk profile, acceptability and patient satisfaction with a chosen contraceptive method and can discuss with patients the suitability of the chosen method at regular intervals as well as offer other contraceptive choices if more appropriate, such as Long Acting Reversible Contraceptive (LARC) methods. As these methods are user independent they have proven to be more effective in typical use than the pill (Trussell 2011).

A thorough and comprehensive evaluation of the individual risk profile of a woman is one of the most essential elements in optimising the benefit/risk profile of the OCP. The Product Information states for currently available pills states that not only single risk factors may change the benefit-risk balance in an individual woman, but that there are also factors which may cumulatively enhance a woman’s risk (Yaz PI 2014)

**Factor 6: The seriousness or severity and frequency of the interactions of the substance are such that monitoring or intervention is required by a medical, veterinary or dental practitioner.**

It is important for contraceptive efficacy that the pill is not prescribed concomitantly with drugs that could decrease serum levels of the contraceptive. Women requiring long term liver enzyme inducing drugs are strongly advised to use an alternative method unaffected by drug interactions. In rare circumstances where a patient needing long term liver enzyme inducing medications continues on the combined pill, higher doses and extended cycles may be recommended and the patient should be monitored for clinical signs of reduced effectiveness (SHFPA 2012).

**Factors For Pharmacist Only Medicines (S3)**

The factors that determine the scheduling of a product under S3 focus on the safety profile and the safe use of the medicine. However, many additional considerations are needed for a woman requiring a long term contraceptive. The S3 Factors will be addressed here to provide perspective on why OCPs would not be suitable for over the counter recommendation.
Factor 1: The medicine is substantially safe with pharmacist intervention to ensure the quality use of the medicine. There may be potential for harm if used inappropriately. The consumer can identify the ailments or symptoms that may be treated by the medicine but counselling and verification by a pharmacist is required before use. Pharmacist-consumer dialogue is necessary to reinforce and/or expand on aspects of the safe use of the medicine.

While patients can determine their need for contraception and pharmacists are trained to counsel on the safe use of medication, pharmacists however, are not trained and are therefore not able to provide the service of determining whether an OCP would firstly be appropriate for a particular woman (risk/benefit analysis) and which method of hormonal contraception would be most suitable. A questionnaire and a blood pressure test would not justly serve this assessment as it is not simply a matter to be addressed by product specific training.

There is a wide variety of OCPs with different benefits beyond contraception. Many OCPs are coupled with secondary indications to treat acne and premenstrual mood disorder. A pharmacist will have to consider the different pharmacological effects of each type of OCP together with a woman’s other gynaecological needs or personal preferences besides contraception and determine the most appropriate option before prescribing. Other considerations would be whether a woman is more suited to a monophasic, biphasic or triphasic pill or a flexible extended regimen.

Most women use more than four methods over their lifetime to meet their changing circumstances. Women would continue to need to consult their medical practitioner, and this introduces a disconnect in assessing their medical history.

Factor 3: The risk profile of the medicine is well defined and the risk factors for adverse effects and interactions are known, identifiable and manageable by a pharmacist.

The risk profile of OCPs are well defined, however they are complicated to assess particularly when more than one risk factor is present (See Factor 2 and 4 of S4 medicines above). They also require in depth assessment of the patients personal and familial medical history, taking into consideration up to date scientific body of evidence and published literature on relative risk factors, concomitant medications, etc. The UKMEC (FSRH 2009) and WHO MEC (WHO 2009) provide an extensive list of medical contraindications and relative contraindications for oral contraceptive use, and require in-depth medical knowledge for their interpretation and application.

Factor 4: Where the medicine is intended for recurrent or subsequent treatment of a chronic condition, pharmacist intervention is required to monitor safe use of the medicine following recommendation by a medical practitioner or a pharmacist. The consumer may not be able to self-monitor the safe ongoing use of the medicine. The condition does not require medical diagnosis or only requires initial medical diagnosis, and the consumer does not require close medical management.

OCPs are indicated for continuous long term use without breaks. Regular review by a doctor is vital to ensure maintenance of a positive benefit/risk profile with ongoing medical
assessment of an individual's risk factors over time, re-assessing appropriateness of the choice of contraception depending on the women's life stage, and checking the status of co-morbidities. This is outside the boundaries of pharmacists training to monitor safe use through dosage reinforcement, compliance checking and patient satisfaction with the product.

The Down Scheduling of OCPs

The down scheduling of OCPs to Pharmacist Only Medicine goes beyond the general scope of current S3 provision in pharmacy practice as it permits the initiation and long term continuation of a pharmacotherapeutic agent without the involvement of a medical doctor. Most Schedule 3 medications are indicated for short term use only, with advice to see a doctor if continuous treatment is required.

Separation of Prescribing and Dispensing

The separation between the art of prescribing and dispensing would be lost for OCPs through this proposal. The importance of keeping these two steps separate has long been recognised and upheld amongst developed health care systems. Although there have been changes to this model in recent years in response to critical rural community needs, we do not believe the same sense of urgency exists in the provision of long term hormonal contraception to the general population of women in Australia.

Objectivity may be lost when pharmacists are faced with the challenge of prescribing a product based on clinical judgment against the commercial pressure to sell what the business stocks or what yields a higher profit margin. The time pressure in completing the assessing, dispensing and counselling process, which pharmacists are not reimbursed for, may also compromise the quality of service provided. These conflicts of interest could undermine quality use of medicine and put undue pressure on the pharmacist’s role.

Other Considerations

While the intention of the proposal may be to provide public health benefit by making effective and reliable contraception more accessible, the missed opportunity to see a medical practitioner may diminish the initial benefit. A contraceptive consultation with a doctor may allow opportunistic screening for breast and cervical cancer as well as the opportunity when discussing contraceptive methods to discuss barrier contraception and Sexually Transmitted Infection (STI) risk. It may also allow the medical practitioner the ability to counsel the patient and promote behaviours to decrease infection risk (Petersen 2004).

The claim that there is a barrier to obtaining a doctors prescriptions or that it places a burden on the health care system is unjustified as doctors only need to see the woman once a year for the prescription of an OCP. This hardly seems an obstacle in light of the various ancillary and important health checks a doctor’s consultation can provide. There is no convincing evidence to suggest that down regulating OCPs to S3 would be able to overcome any potential cost and access barriers, and instead it has the possibility to compromise safe use of the product which will not have the desired outcome, and additionally could still exclude adolescents and young women who are at most risk of unintended pregnancies.
Furthermore, there are important elements that determine a successful counselling process. The setting within which patient consultation occurs is critical as many patients view a contraceptive discussion as extremely sensitive. This should include adequate privacy in a face-to-face setting. Most pharmacies are not designed to provide this kind of private consultation and the environment would compromise the counselling process especially for first time users or a woman looking to switch options.

Pharmacists will also be faced with the moral issue of whether to prescribe to minor’s, what age is appropriate to start on an OCP, and whether parental consent should be required.

**Conclusion**

Overall the proposal to down schedule OCPs to S3 would be complex and challenging. The suggested improvement to through pharmacy may be overshadowed by the loss of important medical consultations providing a wide array of services including cancer screening, STI testing as well as an opportunity to provide broad contraceptive counselling and tailoring contraceptive options for individual patients. does not believe any advantages of down scheduling OCPs would outweigh the considerable disadvantages of the deregulation. As such, is not in favour of the proposal.

### References:


3. Faculty of Sexual and Reproductive Healthcare. UK Medical Eligibility Criteria for Contraceptive Use, 2009


5. National Coordinating Committee on Therapeutic Goods. *Scheduling policy framework for medicines and chemicals.* 1 July 2010


7. Reid R and the Clinical Practice Gynaecology Committee 2010 Oral Contraceptives and the risk of Venous Thromboembolism: An Update SOGC 252 December
8. Truseell J. Contraceptive failure in the United States Contraception 83 (2011) 397-404


Re: Invitation for public comment – ACMS meeting March 2015

I would like to provide comments to the members of the Scheduling Committee in relation to the proposal to create a new Schedule 3 entry for the following substances when indicated for oral contraception:

- oestradiol, desogestrel ethinylestradiol, norethisterone, levonorgestrel, cyproterone, gestodene, drospirenone, mestranol, medroxyprogesterone, oestrogens and progestogens.

I note the party who made the submission did not disclose their name or details of the submission but I, in the interests of transparency, have no problems with this submission being published on the TGA website for all to see.

Yours sincerely
Submission to the
Advisory Committee on Medicines
Scheduling

(ACMS)
### Summary

The members of the committee are recommend not to support this proposal as the risks associated with the supply of these medicines as “oral contraceptives” are inconsistent with Schedule 3 classification. The conditions of supply proposed by the application, namely a ‘minor questionnaire’ and a blood pressure test are not sufficient to address the risks inherent in the use of these substances.

The Committee should not accept that it is within the scope of practice of a pharmacist to carry out a full medical examination which is required when commencing or re-assessing a patient undergoing treatment with these substances.

It is noted that under Section 52E of the *Therapeutic Goods Act 1989* the Secretary in exercising a power subsection 52D(2) **must** take the following matters into account (where relevant):

- (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;
- (e) the potential for abuse of a substance;
- (f) any other matters that the Secretary considers necessary to protect public health

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<table>
<thead>
<tr>
<th>Substance</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Oestradiol</td>
<td>To create new Schedule 3 entries for these substances when indicated for oral contraception.</td>
</tr>
<tr>
<td>Desogestrel</td>
<td>The applicant has proposed potential conditions of:</td>
</tr>
<tr>
<td>Ethinylestradiol</td>
<td>A minor questionnaire by the pharmacist regarding family history of heart problems, hypertension and stroke</td>
</tr>
<tr>
<td>Norethisterone</td>
<td>An in-pharmacy blood pressure test/results from another recent blood pressure test to ensure suitability for medication</td>
</tr>
<tr>
<td>Levonorgestrel</td>
<td>Limit of 3-6 months' supply in one transaction</td>
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<tr>
<td>Cyproterone</td>
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<td>Gestodene</td>
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<td>Drospirenone</td>
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<tr>
<td>Mestranol</td>
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<td>Oestrogens</td>
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<td>Progestogens</td>
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</table>
(A) The risks and benefits of the use of the substance

The Therapeutic guidelines: endocrinology (the ‘Guidelines’) states the following with respect to these substances when used as oral contraceptives:

“A thorough medical history should be taken before prescribing a COCP to ensure it is not contraindicated.

Choice of preparation depends on the women's medical history and preference.

Counselling before starting oral contraception is essential to address concerns and encourage the women to take the tablets correctly.

It is important to highlight that bioavailability of the COCP may be reduced in certain situations (e.g. during episodes of vomiting or diarrhoea, when taking antibiotics that induce liver enzymes).

Women should be: shown how to use their particular COCP (since packaging varies between brands) given instructions on what to do if they miss a pill.”

The Guidelines also state that these substances should not be prescribed for women with the following:

- current or previous venous thromboembolism
- a genetic thrombophilia
- coronary artery disease
- cerebrovascular disease
- uncontrolled hypertension
- severely impaired liver function
- malignancy of the breast or genital tract
- migraine with aura

It should also be noted that the Australian Medicines Handbook states the following factors that should be taken into consideration:

- Breast Cancer (current or recent)
- Smoking
- BMI>30
- VTE,
- Cervical Cancer
Any cursory inspection of the TGA-approved Product Information documents for any of the oral contraceptives will also state the Precautions and Contraindications that should be taken into account either when initiating or monitoring long term use.

For example the TGA-approved product information for ethinyloestradiil + drospirenone (Yasmin®) states the following:

“Medical examination/consultation. A complete medical history and physical examination should be taken prior to the initiation or reinstitution of COC use, guided by the contraindications and precautions, and should be repeated at least annually during the use of COCs.”

The product information for levonorgestrel + ethinyloestradiol (Trifeme®) states the following:

“As a general rule, oral contraceptives should not be prescribed for longer than one year without another physical examination being performed. Papanicolaou smears should be performed before prescribing these drugs and periodically during their administration. Baseline and periodic blood glucose determinations should be performed in patients predisposed to diabetes mellitus.”

The product information for levonorgestrel + ethinyloestradiol (Levlen®) states the following:

**Precautions** Use with caution in the following circumstances.
If any of the conditions/risk factors mentioned below are present, the benefits of COC use should be weighed against the possible risks for each individual woman and discussed with the woman before she decides to start taking it. In the event of aggravation, exacerbation or first appearance of any of these conditions or risk factors, the woman should contact her doctor. The doctor should then decide on whether COC use should be discontinued.

**Circulatory disorders.**
Epidemiological studies have suggested an association between the use of COCs and an increased risk of arterial and venous thrombotic and thromboembolic diseases such as myocardial infarction, deep venous thrombosis, pulmonary embolism and of cerebrovascular accidents. These events occur rarely.

**Venous thromboembolism (VTE),** manifesting as deep venous thrombosis and/or pulmonary embolism, may occur during the use of all COCs. The risk of venous thromboembolism is highest during the first year a woman uses a COC. This increased risk is present after initially starting a COC or restarting (following a 4 week or greater pill free interval) the same or a different COC. Data from a large, prospective 3-armed
cohort study (EURAS1 and LASS2) suggest that this increased risk is mainly present during the first 3 months.

A large prospective 3-armed cohort study has shown that the frequency of VTE diagnosis range from 8 to 10 per 10,000 woman years in low oestrogen dose (< 50 microgram ethinyloestradiol) COC users. The most recent data suggests that the frequency of VTE diagnosis is approximately 4.4 per 10,000 woman years in nonpregnant non-COC users and range from 20 to 30 per 10,000 pregnant women or post partum. Overall the risk of VTE in users of low oestrogen dose (< 50 microgram ethinyloestradiol) COCs is two to threefold higher than for nonusers of COCs who are not pregnant and remains lower than the risk associated with pregnancy and delivery. VTE may be life threatening, or in 1-2% of cases may be fatal.

Extremely rarely, thrombosis has been reported to occur in other blood vessels, e.g. hepatic, mesenteric, renal or retinal veins and arteries, in COC users.

**Symptoms of a venous (includes pulmonary embolism (PE) and deep venous thrombosis (DVT)) or arterial thrombotic/ thromboembolic (includes myocardial infarction (MI), vascular occlusion and cerebrovascular accident) events can include unilateral leg pain and/or swelling; pain or tenderness in the leg which may be felt only when standing or walking; increased warmth in the affected leg; red or discoloured skin on the leg; sudden severe pain in the chest which may increase with deep breathing; pain, discomfort, pressure, heaviness, sensation of squeezing or fullness in the chest, arm or below the breastbone; discomfort radiating to the back, jaw, throat, arm, stomach; rapid or irregular heartbeat; sudden onset of unexplained shortness of breath or rapid breathing; sudden onset of coughing which may bring up blood; sudden, severe prolonged headache with no known cause; sudden, partial or complete loss of vision; diplopia; sense of anxiety; dizziness; slurred speech or aphasia; sudden confusion; vertigo; collapse with or without focal seizure; weakness or very marked numbness suddenly affecting one side or one part of the body; motor disturbances; acute abdomen; fullness, indigestion or choking feeling; sweating; nausea; vomiting.**

Some of these symptoms (e.g. shortness of breath, coughing) are nonspecific and might be misinterpreted as more common or less severe events (e.g. respiratory tract infections).

**Arterial thromboembolic events may be life threatening or may have a fatal outcome.**

The potential for an increased synergistic risk of thrombosis should be considered in women who possess a combination of risk factors or exhibit a greater severity of an individual risk factor. This increased risk may be greater than a simple cumulative risk of the factors. **A COC should not be prescribed in case of a negative risk benefit assessment**

The risk of venous or arterial thrombotic/ thromboembolic events or of a cerebrovascular accident increases with:

- age;
• smoking (with heavier smoking and increasing age the risk further increases, especially in women over 35 years of age);
• a positive family history (i.e. venous or arterial thromboembolism ever in a sibling or parent at a relatively early age). If a hereditary predisposition is known or suspected, the woman should be referred to a specialist for advice before deciding about any COC use;
• obesity (body mass index over 30 kg/m2);
• overweight;
• dyslipoproteinaemia;
• hypertension;
• migraine;
• valvular heart disease;
• atrial fibrillation;
• prolonged immobilisation (e.g. long haul flights), major surgery, any surgery to the legs, or major trauma. In these situations it is advisable to discontinue COC use (in the case of elective surgery at least four weeks in advance) and not to resume until two weeks after complete remobilisation.

There is no consensus about the possible role of varicose veins and superficial thrombophlebitis in venous thromboembolism.

The increased risk of thromboembolism during the puerperium must be considered (see Use in pregnancy).

Other medical conditions which have been associated with adverse circulatory events include diabetes mellitus, systemic lupus erythematosus, haemolytic uraemic syndrome, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) and sickle cell disease.

An increase in frequency or severity of migraine during COC use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of the COC.

Biochemical factors that may be indicative of hereditary or acquired predisposition for venous or arterial thrombosis include activated protein C (APC) resistance, hyperhomocysteinaemia, antithrombin III deficiency, protein C deficiency, protein S deficiency, antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant).

When considering risk/benefit, the physician should take into account that adequate treatment of a condition may reduce the associated risk of thrombosis and that the risk associated with pregnancy is higher than that associated with low dose COCs (< 50 microgram ethinyloestradiol).
**Tumours.**
The most important risk factor for cervical cancer is persistent HPV infection. Some epidemiological studies have indicated that long-term use of COCs may further contribute to this increased risk but there continues to be controversy about the extent to which this finding is attributable to confounding effects, e.g. cervical screening and sexual behaviour including use of barrier contraceptives.

A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently taking COCs. The excess risk gradually disappears during the course of the 10 years after cessation of COC use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the overall risk of breast cancer. These studies do not provide evidence for causation. The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in COC users, the biological effects of COCs or a combination of both. The breast cancers diagnosed in ever users tend to be less advanced clinically than the cancers diagnosed in never users.

In rare cases, benign liver tumours, and even more rarely, malignant liver tumours have been reported in users of COCs. In isolated cases, these tumours have led to life threatening intra-abdominal haemorrhages. A liver tumour should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal haemorrhage occur in women taking COCs.

Malignancies may be life threatening or may have a fatal outcome.

**Other conditions.**
Women with hypertriglyceridaemia, or a family history thereof, may be at an increased risk of pancreatitis when taking COCs.

Although small increases in blood pressure have been reported in many women taking COCs, clinically relevant increases are rare. However, if a sustained clinically significant hypertension develops during the use of a COC then it is prudent for the doctor to withdraw the COC and treat the hypertension. Where considered appropriate, COC use may be resumed if normotensive values can be achieved with antihypertensive therapy.

The following conditions have been reported to occur or deteriorate with both pregnancy and COC use, but the evidence of an association with COC use is inconclusive: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; haemolytic uraemic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis related hearing loss.

In women with hereditary angioedema exogenous oestrogens may induce or exacerbate symptoms of angioedema.
Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal. Recurrence of cholestatic jaundice which occurred first during pregnancy or previous use of sex steroids necessitates the discontinuation of COCs.

Although COCs may have an effect on peripheral insulin resistance and glucose tolerance, there is no evidence for a need to alter the therapeutic regimen in diabetics taking low dose COCs (containing < 50 microgram ethinyloestradiol). However, diabetic women should be carefully observed while taking COCs.

Crohn's disease and ulcerative colitis have been associated with COC use.

Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation while taking COCs.

Check the following before use.
Medical examination/consultation. A complete medical history and physical examination should be taken prior to the initiation or reinstitution of COC use, guided by the Contraindications and Precautions, and should be repeated periodically during the use of COCs. In general, an annual examination is recommended.

Periodic medical assessment is also of importance because contraindications (e.g. a transient ischaemic attack, etc.) or risk factors (e.g. a family history of venous or arterial thrombosis) may appear for the first time during the use of a COC. The frequency and nature of these assessments should be adapted to the individual woman but should generally include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology and relevant laboratory tests.

In addition the Committee should take note of The National Cervical Screening Program Guidelines available at http://www.cancerscreening.gov.au/internet/screening/publishing.nsf/Content/papsmear which recommend that “All women over 18 who have ever had sex are advised to have a Pap smear every two years, even if they no longer have sex”. If women do not have to see a medical practitioner for a new prescription they are less likely to have regular Pap smear as recommended.
(B) The purposes for which a substance is to be used and the extent of use of a substance

Whilst the substances listed in the submission are indicated for the prevention of pregnancy these substances are often used for other purposes such as treatment of androgenisation, skin conditions and dysmenorrhoea. It would be difficult to exclude Schedule 3 use to contraception when there are other indications either on or “off label”. As the side effects, contraindications, precautions and the need for regular assessment are the same irrespective of the indication for treatment a health professional experienced in medical examinations would be the most appropriate to initiate and monitor the use of such substances.

According to Department of Human Services – Medicare Australia, there were a total of 606,350 prescriptions for PBS-listed oral contraceptives dispensed from November 2013 to October 2014. However, this underestimates the use of these substances because there are many oral contraceptives that are not listed on the PBS eg brands such as Qlaira, Zoely, Yaz, Marvelon, Valette.

According to the Australian Bureau of Statistics the contraceptive pill is the most popular form of contraception used by women.

| TYPE OF CONTRACEPTION USED BY WOMEN AGED 18-49, 1995 |
|----------------------------------|----------|----------|----------|----------|----------|----------|----------|----------|
| Contraceptive method             | 18-19 % | 20-24 % | 25-29 % | 30-34 % | 35-39 % | 40-44 % | 45-49 % | Total %  |
| Contraceptive pill               | 66.3     | 71.1     | 59.2     | 43.0     | 31.3     | 16.9     | 10.1     | 40.0     |
| Condom(a)                        | 32.2     | 21.6     | 27.0     | 21.2     | 13.9     | 10.5     | 7.2      | 17.6     |
| IUD                              | *        | 2.1      | *        | 2.8      | 3.1      | 6.1      | 2.8      | 3.0      |
| Periodic abstinence              | *        | *        | 3.6      | 4.2      | 3.9      | 3.0      | 2.4      | 3.0      |
| Other temporary methods          | *        | 2.6      | 2.4      | 3.9      | 3.7      | 2.1      | *        | 2.6      |
| Female sterilisation             | 0.0      | *        | 3.6      | 10.7     | 21.6     | 36.1     | 49.9     | 19.2     |
| Male sterilisation(a)            | 0.0      | *        | 2.8      | 14.2     | 22.4     | 25.3     | 25.8     | 14.5     |
| Total women who use contraception| 111.3    | 441.1    | 428.6    | 453.7    | 476.5    | 448.2    | 392.6    | 751.9    |

2 [http://www.abs.gov.au/Ausstats/abs@nsf/2f762f95845417aeeca25706c00834efa/e50a5b60e048fc07ca2570ee01909fb?OpenDocument]
The TGA recently conducted a safety profile review of combination cyproterone + ethinyloestradiol and found an increased risk of VTE and that these products should be used with caution in patients who have risk factors for VTE.³

Whilst the contraceptive pill is used by many women and has been for many years the safety advisory issued by the TGA in May 2013 should act as a reminder to the members of the Committee that just because a substances is widely used does not trivialise its use and there is always the potential for serious adverse events to occur. Making access to these substances without proper medical supervision and assessment on a regular basis is inconsistent with the intent of the scheduling framework.

The Committee should be aware that while risk of these medications may be low the more they are used the higher the chance that there will be increased side effects and these can only be monitored if a medical practitioner with the necessary skills to perform a full medical examination sees the patient on a regular basis.

Neither a minor or major questionnaire carried out by a pharmacist can substitute for the regular assessment by a medical practitioner as recommended in the TGA Product Informations of these substances.

(D) the dosage, formulation, labelling, packaging and presentation of a substance;

As noted in the Guidelines:

“Counselling before starting oral contraception is essential to address concerns and encourage the patient to take the tablets correctly. It is important to highlight that bioavailability of the COCP may be reduced in certain situations (eg during episodes of vomiting or diarrhoea, when taking antibiotics that induce liver enzymes). Women should be:

- shown how to use their particular COCP (since packaging varies between brands)
- given instructions on what to do if they miss a pill.

As noted in the Guidelines there are up to at least 29 different brands of oral contraceptives on the Australian market and all have different packing and directions which can be confusing especially for patients initiating treatment or patients changing to another formulation or brand. Given this and the importance of explaining to the patient what to do in the case of a “missed pill” it is important that a patient has a consultation with a doctor.
(E) Any other matters that the Secretary considers necessary to protect public health

The Committee has no doubt been asked to consider the issue of improved access to contraceptive options for women in Australia. In its deliberations the Committee might like to consider the following:

- Australian women can receive under the Pharmaceutical Benefits Scheme (PBS) a maximum quantity of four months with two repeats which equates to a total of 12 month’s supply which is in accordance with the TGA-approved Product Information which recommend annual assessment by a doctor.

- Where a valid prescription cannot be obtained because a woman cannot access a general practitioner to have a prescription issued they can obtain Emergency Supply of the oral contraceptive under the Medication Continuance in Defined Circumstances. Under this initiative of the Fifth Community Pharmacy Agreement a women can receive a continuation of 4 month’s supply which should provide ample opportunity to see a doctor for a periodic assessment.

Recommendation to the Committee

That the Committee recognise that the risks associated with initiating and continuing the supply of these substances does not meet the requirements of a Schedule 3 classification and that to ensure better health outcomes for Australian women they are best left as Schedule 4 medications.