Australian Government
Department of Health
Therapeutic Goods Administration

Consultation: Proposed amendments to the Poisons Standard in relation to substances when used in oral contraceptives – ACMS #34, June 2021

27 April 2021

TGA Health Safety Regulation

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Contents

Oral contraceptive proposals and substances referred to ACMS #34

Subdivision 3D.2 of the *Therapeutic Goods Regulations 1990* (the Regulations) sets out the procedure to be followed where the Secretary receives an application under section 52EAA of the *Therapeutic Goods Act 1989* (the Act) to amend the current Poisons Standard or decides to amend the Poisons Standard on his or her own initiative and decides to refer the proposed amendment to an expert advisory committee. These include, under regulation 42ZCZK, that the Secretary publish (in a manner the Secretary considers appropriate) the proposed amendment to be referred to an expert advisory committee, the committee to which the proposed amendment will be referred, and the date of the committee meeting. The Secretary must also invite public submissions to be made to the expert advisory committee by a date mentioned in the notice as the closing date, allowing at least 20 business days after publication of the notice.

In accordance with regulation 42ZCZK of the Regulations, the Secretary invites public submissions on scheduling proposals referred to the June 2021 meetings of the Advisory Committee on Medicines Scheduling (ACMS #34). Submissions must be received by close of business **27 May 2021**.

1. Applications

The TGA has received two applications to down-schedule substances when used in oral contraceptive pills from Schedule 4 to Schedule 3, subject to proposed Appendix M controls.

This public notice is organised in parts:

- **Part 1 -** a summary of each application, including a list of substances targeted by the proposal and a summary of the applicant's reasons.
- **Part 2 -** information on each individual substance, including information on how they are regulated and the specific scheduling amendments that were proposed.
- **Part 3 -** outlines the proposed Appendix M entries for each application and substance.

1.1 Application A: ethinylestradiol, levonorgestrel and norethisterone

Summary

The applicant proposes to add a new Schedule 3 entry to the Poisons Standard for two substances when used in oral contraceptive pills, and amend the current Schedule 3 entry for levonorgestrel, subject to new Appendix M requirements.

Please note the proposed Appendix M conditions are described in Part 3 of this document.

Applicant

Private applicant

Substances targeted by proposal

- Ethinylestradiol (at 35 micrograms or less per maximum daily dose in combination with levonorgestrel or norethisterone)
- levonorgestrel
- norethisterone

Key uses / expected use

Oral contraceptives

Summary of the applicant's reasons for proposal

- Oral contraceptives containing levonorgestrel or norethisterone in combination with ethinylestradiol at 35 micrograms or less have been in use since the 1960s and are considered the 'gold standard' for oral contraceptives, in relation to safety.
- This application proposes making the substances when used in low-dose oral contraceptives available through suitably trained pharmacists working within a framework of professional practice standards and guidance issued by the Pharmaceutical Society of Australia.
- In the proposal, the guidelines for pharmacists would specify all patients must have had the same substance prescribed by an authorised health professional within the previous two

years. The pharmacist can determine if it is appropriate and safe to maintain ongoing supply of the medicine or refer the patient to an authorised prescriber for further assessment.

- All scheduling factors for Schedule 3 and Appendix H are addressed by the inherent safety profile of each of the 'selected oral contraceptive substances' and the inclusion of Appendix M controls.
- Benefits of the proposed scheduling include:
  - increased ease of access
  - continuity of supply and engagement with the health care system
  - increased public awareness of contraception
  - a strengthening of primary health care
  - decreasing the burden on emergency departments
  - contributing to a global strategy to improve public health

1.2 Application B: ethinylestradiol, levonorgestrel, norethisterone, cyproterone, desogestrel, dienogest, drospirenone, estradiol, gestodene, mestranol and nomegestrol

Summary

The applicant proposes to add a new Schedule 3 entry to the Poisons Standard for ten substances when used in oral contraceptive pills, and amend the current Schedule 3 entry for levonorgestrel, where they meet proposed Appendix M requirements.

Please note the proposed Appendix M conditions are described in Part 3 of this document.

Applicant

Private applicant

Substances targeted by proposal

- ethinylestradiol (when combined with an progestogen)
- levonorgestrel (when combined with an estrogen)
- norethisterone
- cyproterone (when combined with an estrogen)
- desogestrel (when combined with an estrogen)
- dienogest (when combined with an estrogen)
- drospirenone (when combined with an estrogen)
- estradiol (when combined with an progestogen)
- gestodene (when combined with an estrogen

- mestranol (when combined with an progestogen)
- nomegestrol (when combined with an estrogen

Key uses / expected use

Oral contraceptives

Summary of the applicant's reasons for proposal

- The requirement for healthy patients to physically visit their general practitioner for the sole purpose of obtaining a prescription, for an oral contraceptive they have taken safely for at least 12 months, creates unnecessary barriers to care and access to medicines.
- Enabling these substances when used in oral contraceptive pills to be supplied as Schedule 3 medicines would increase patient access, to reduce avoidable treatment interruptions and unplanned pregnancies – which are a significant public health issue.
- The benefits of use outweigh the risks, especially in relation to venous thromboembolism, where the risk is greater in unplanned pregnancy than it is for oral contraceptive use.
- Risks are mitigated through detailed Appendix M conditions, including limiting Schedule 3 supply to after 12 months of initiation of therapy.
- Pharmacists are highly educated and trained health professionals, committed to continuing professional development, with the competency to safely supply oral contraceptives to patients for continuation of therapy.
- Rescheduling of these substances used in oral contraceptive pills would harmonise Australia's scheduling with New Zealand, and provide patients with increased access to effective contraception for continuing treatment.

2. Substances

2.1 Ethinylestradiol

Proposal

Both applicants (see sections 1.1 and 1.2) propose to add a new Schedule 3 entry to the Poisons Standard for ethinylestradiol for use as an oral contraceptive at low dosages, when combined with a progestin (levonorgestrel or norethisterone in application A) or progestogen (in application B), where it meets proposed Appendix M requirements.

Please note the proposed Appendix M conditions are described in Part 3 of this document and each applicant has proposed different conditions for Appendix M.

CAS number:

57-63-6

Alternative names[1]

Ethinyl estradiol; (17α)-19-Norpregna-1,3,5(10)-trien-20-yne-3,17-diol; 17α-ethynyl-1,3,5(10)-estratriene-3,17β-diol; 17-ethinylestradiol; ethynylestradiol

Current scheduling

Ethinylestradiol is currently listed in Schedule 4 of the Poisons Standard as follows:

Schedule 4

ETHINYLESTRADIOL.

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ETHINYLESTRADIOL

Schedule 4

Proposed scheduling (Application A)

A private applicant proposed to amend the scheduling for ethinylestradiol as follows:

Schedule 4 – Amend Entry

ETHINYLESTRADIOL **except** when included in Schedule 3.

Schedule 3 – New Entry

ETHINYLESTRADIOL in divided preparations for use as an oral contraceptive containing not more than 35 micrograms of ethinylestradiol per dosage unit when combined with levonorgestrel or norethisterone in a primary pack containing not more than 4 months' supply in accordance with the requirements of Appendix M.

[1] According to Merck Index Online: https://www.rsc.org/merck-index

Appendix H – New Entry

ETHINYLESTRADIOL

Appendix M – New Entry[2]

ETHINYLESTRADIOL

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Proposed scheduling (Application B)

A private applicant proposed to amend the scheduling for ethinylestradiol as follows:

Schedule 4 – Amend Entry

ETHINYLESTRADIOL except when included in Schedule 3.

Schedule 3 – New Entry

ETHINYLESTRADIOL in oral preparations for human therapeutic use when combined with a progestogen, for contraception when supplied in accordance with Appendix M requirements, **except** in preparations containing 50 micrograms or more of ethinylestradiol.

Appendix M – New Entry[3]

ETHINYLESTRADIOL when combined with a progestogen in oral preparations for use as contraception.

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ETHINYLESTRADIOL

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Key uses / expected use

Oral contraceptive

Australian regulations

- According to the TGA Ingredient Database,[4] ethinylestradiol is:

[2] See proposed Appendix M criteria in section 3.1.
[3] See proposed Appendix M criteria in section 3.2.
[4] TGA Ingredient Database https://www.ebs.tga.gov.au/

- Available for use as an active ingredient in biologicals, export only and prescription medicines
- Available for use as an excipient ingredient in biologicals, devices and prescription medicines
- Not available as an equivalent ingredient in any application

- As of March 2021, there were 73 medicines currently active on the Australian Register of Therapeutic Goods (ARTG)[5] that contain ethinylestradiol as an active ingredient. These are all prescription medicines.
- Ethinylestradiol is not permitted to be included in listed medicines as it is not included in the Therapeutic Goods (Permissible Ingredients) Determination[6] No.1 of 2021.
- The TGA prescribing medicines in pregnancy database[7] classifies ethinylestradiol as:

Drug name	Category	Classification Level 1	Classification Level 2	Classification Level 3
desogestrel with ethinylestradiol	B3	Contraceptive Agents	Oral contraceptives	
dienogest with ethinylestradiol	B3	Contraceptive Agents	Oral contraceptives	
drospirenone with ethinylestradiol	B3	Contraceptive Agents	Oral contraceptives	
ethinylestradiol	B3	Endocrine System	Oestrogens (see also oral contraceptives)	
norelgestromin with ethinylestradiol	B3	Contraceptive Agents		
Category B3 – Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.				

- There are no warning statements pertaining to ethinylestradiol in the Therapeutic Goods (Medicines Advisory Statements) Specification 2019[8]

[5] ARTG database https://www.tga.gov.au/artg
[6] Therapeutic Goods (Permissible Ingredients) Determination https://www.legislation.gov.au/Search/Therapeutic%20Goods%20LBPermissible%20IngredientsRB%20Determination
[7] TGA prescribing medicines in pregnancy database https://www.tga.gov.au/prescribing-medicines-pregnancy-database
[8] Therapeutic Goods (Medicines Advisory Statements) Specification 2019 https://www.legislation.gov.au/Details/F2019L00213

- Since January 2010, there were 827 reports of adverse events for products containing ethinylestradiol as an active ingredient on the Database of Adverse Event Notifications (DAEN),[9] with 758 reports where ethinylestradiol was the single suspected medicine.
- As of March 2021, there were no products containing ethinylestradiol listed on the Public Chemical Registration Information System Search (PubCRIS).[10]

International regulations

- Ethinylestradiol is included in the WHO Model List of Essential Medicines 2019, in combination with levonorgestrel or norethisterone.
- The Health Products Regulatory Authority of Ireland[11] regulates ethinylestradiol as a prescription-only medicine.
- The United States Food and Drug Administration[12] approve use of ethinylestradiol (ethinyl estradiol) as a prescription-only medicine in the United States.
- Ethinylestradiol (ethinyl estradiol) is approved for use as a prescription-only medicine in Canada, according to the Canadian (Health Canada) Drug Product Database.[13]
- According to the New Zealand Medicines and Medical Devices Safety Authority (Medsafe)[14] ethinylestradiol (oestrogens) is available as a prescription-only medicine in New Zealand.

2.2 Levonorgestrel

Proposal

Both applicants (see sections 1.1 and 1.2) propose to amend the current Schedule 3 entry for levonorgestrel to include its use in an oral contraceptive, where it meets proposed Appendix M requirements.

Please note the proposed Appendix M conditions are described in Part 3 of this document and each applicant has proposed different conditions for Appendix M.

CAS number

6533-00-2 (Norgestrel)

Alternative names[15]

Norgestrel; (17α)-(±)-13-Ethyl-17-hydroxy-18,19-dinorpregn-4-en-20-yn-3-one

[9] Database of Adverse Event Notifications (DAEN) https://apps.tga.gov.au/Prod/daen/daen-entry.aspx
[10] Public Chemical Registration Information System Search (PubCRIS) https://portal.apvma.gov.au/pubcris
[11] Health Products Regulatory Authority https://www.hpra.ie/homepage/medicines/medicines-information/find-a-medicine/results?query=Metoclopramide+hydrochloride&field=ACTIVESUBSTANCES
[12] Food and Drugs Administration Approved Drugs Database: https://www.accessdata.fda.gov/scripts/cder/daf/
[13] Health Canada Drug Product Database: https://health-products.canada.ca/dpd-bdpp/index-eng.jsp
[14] Medsafe Medicine Classification Database: https://www.medsafe.govt.nz/profs/class/classintro.asp
[15] According to Merck Index Online: https://www.rsc.org/merck-index

Current scheduling

Levonorgestrel is currently listed in the Poisons Standard as follows:

Schedule 4

LEVONORGESTREL **except** when included in Schedule 3.

Schedule 3

LEVONORGESTREL for emergency post-coital contraception.

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LEVONORGESTREL.

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LEVONORGESTREL

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Proposed scheduling (Application A)

A private applicant proposed to amend the scheduling for levonorgestrel as follows:

Schedule 3 – Amend Entry

LEVONORGESTREL in divided preparations:

a) for emergency post-coital contraception; or
b) for use as an oral contraceptive in a primary pack containing not more than 4 months' supply in accordance with the requirements of Appendix M.

Appendix M – New Entry[16]

LEVONORGESTREL

Proposed scheduling (Application B)

A private applicant proposed to amend the scheduling for levonorgestrel as follows:

Schedule 4 – Amend Entry

LEVONORGESTREL except when included in Schedule 3.

Schedule 3 – Amend Entry

LEVONORGESTREL in oral preparations for human therapeutic use:

a) for emergency post-coital contraception; or

b) for continuing contraception when supplied in accordance with Appendix M requirements.

[16] See proposed Appendix M criteria in section 3.1.

Appendix M – New Entry[17]

LEVONORGESTREL when combined with an estrogen in oral preparations for use as contraception, **except**:

a) for emergency post-coital contraception.

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LEVONORGESTREL

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Key uses / expected use

Oral contraceptive

Australian regulations

- According to the TGA Ingredient Database,[18] levonorgestrel is:
  - Available for use as an Active Ingredient in: Biologicals, Export Only, Over the Counter, Prescription Medicines
  - Available for use as an Excipient Ingredient in: Biologicals, Devices, Prescription Medicines
  - Not available as an Equivalent Ingredient in any application
- As of March 2021, there were 44 medicines currently active on the Australian Register of Therapeutic Goods (ARTG)[19] that contain levonorgestrel as an active ingredient. These are all prescription medicines.
- Levonorgestrel is not permitted to be included in listed medicines as it is not included in the Therapeutic Goods (Permissible Ingredients) Determination[20] No.1 of 2021.

Drug name	Category	Classification Level 1	Classification Level 2	Classification Level 3
levonorgestrel	B3	Contraceptive Agents	Oral contraceptives	
levonorgestrel / ethinyloestradiol	B3	Contraceptive Agents	Oral contraceptives	

[17] See proposed Appendix M criteria in section 3.2.
[18] TGA Ingredient Database https://www.ebs.tga.gov.au/
[19] ARTG database https://www.tga.gov.au/artg
[20] Therapeutic Goods (Permissible Ingredients) Determination https://www.legislation.gov.au/Search/Therapeutic%20Goods%20LBPermissible%20IngredientsRB%20Determination

Category B3 – Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed.

Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.

- The TGA prescribing medicines in pregnancy database[21] classifies levonorgestrel as:
- There are no warning statements pertaining to levonorgestrel in the Therapeutic Goods (Medicines Advisory Statements) Specification 2019[22]
- Since January 2010, there were 1422 reports of adverse events for products containing levonorgestrel as an active ingredient on the Database of Adverse Event Notifications (DAEN),[23] with 1359 reports where levonorgestrel was the single suspected medicine.
- As of March 2021, there were no products containing levonorgestrel listed on the Public Chemical Registration Information System Search (PubCRIS).[24]

International regulations

- Levonorgestrel is included in the WHO Model List of Essential Medicines 2019.
- The Health Products Regulatory Authority of Ireland[25] regulates levonorgestrel as an over-the-counter and prescription-only medicine.
- The United States Food and Drug Administration[26] approve use of levonorgestrel as an over-the-counter and prescription-only medicine in the United States.
- Levonorgestrel is approved for use as an over-the-counter and prescription-only medicine in Canada, according to the Canadian (Health Canada) Drug Product Database.[27]
- According to the New Zealand Medicines and Medical Devices Safety Authority (Medsafe)[28] levonorgestrel is available in New Zealand as follows:

[21] TGA prescribing medicines in pregnancy database https://www.tga.gov.au/prescribing-medicines-pregnancy-database
[22] Therapeutic Goods (Medicines Advisory Statements) Specification 2019 https://www.legislation.gov.au/Details/F2019L00213
[23] Database of Adverse Event Notifications (DAEN) https://apps.tga.gov.au/Prod/daen/daen-entry.aspx
[24] Public Chemical Registration Information System Search (PubCRIS) https://portal.apvma.gov.au/pubcris
[25] Health Products Regulatory Authority https://www.hpra.ie/homepage/medicines/medicines-information/find-a-medicine/results?query=Metoclopramide+hydrochloride&field=ACTIVESUBSTANCES
[26] Food and Drugs Administration Approved Drugs Database: https://www.accessdata.fda.gov/scripts/cder/daf/
[27] Health Canada Drug Product Database: https://health-products.canada.ca/dpd-bdpp/index-eng.jsp
[28] Medsafe Medicine Classification Database: https://www.medsafe.govt.nz/profs/class/classintro.asp

Ingredient	Conditions	Classification
Levonorgestrel	**except** when specified elsewhere in this schedule; **except** in medicines for use as emergency post-coital contraception when sold by nurses recognised by their professional body as having competency in the field of sexual and reproductive health; **except** when supplied for oral contraception to women who meet the clinical and eligibility criteria of the Pharmacy Council and the Pharmaceutical Society of New Zealand approved training programme on oral contraception, when sold in the manufacturer's original pack that has received the consent of the Minister or Director-General to their distribution as medicines, containing not more than 6 months' supply by a registered pharmacist who has successfully completed the approved training programme	Prescription
Levonorgestrel	in medicines for use as emergency post-coital contraception when in packs containing not more than 1.5 milligrams **except** when sold by nurses recognised by their professional body as having competency in the field of sexual and reproductive health	Restricted[29]

2.3 Norethisterone

Proposal

Both applicants (see sections 1.1 and 1.2) propose to add a new Schedule 3 entry to the Poisons Standard for norethisterone, for use an oral contraceptive, where it meets proposed Appendix M requirements.

Please note the proposed Appendix M conditions are described in Part 3 of this document and each applicant has proposed different conditions for Appendix M.

CAS number

68-22-4

Alternative names[30]

Norethindrone; (17α)-17-Hydroxy-19-norpregn-4-en-20-yn-3-one; 19-nor-17α-ethynyltestosterone; 17α-ethynyl-19-nortestosterone; 19-nor-17α-ethynyl-17β-hydroxy-4-androsten-3-one; 19-nor-17α-ethynylandrosten-17β-ol-3-one; anhydrohydroxynorprogesterone; 19-norethisterone; norpregneninolone; “mini-pill”

[29] Restricted medicines in NZ are also referred to as Pharmacist Only medicines. See https://www.medsafe.govt.nz/Consumers/PharmOnly.asp for details
[30] According to Merck Index *Online:* *https://www.rsc.org/merck-index*

Current scheduling

Norethisterone is currently listed in Schedule 4 of the Poisons Standard as follows:

Schedule 4

NORETHISTERONE.

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NORETHISTERONE

Schedule 4

Proposed scheduling (Application A)

A private applicant proposed to amend the scheduling for norethisterone as follows:

Schedule 4 – Amend Entry

NORETHISTERONE **except** when included in Schedule 3.

Schedule 3 – New Entry

NORETHISTERONE in divided preparations for use as an oral contraceptive in a primary pack containing not more than 4 months' supply in accordance with the requirements of Appendix M.

Appendix H – New Entry

NORETHISTERONE

Appendix M – New Entry[31]

NORETHISTERONE

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NORETHISTERONE

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Proposed scheduling (Application B)

A private applicant proposed to amend the scheduling for norethisterone as follows:

Schedule 4 – Amend Entry

NORETHISTERONE except when included in Schedule 3.

Schedule 3 – New Entry

NORETHISTERONE in oral preparations for human therapeutic use, for contraception when supplied in accordance with Appendix M requirements.

[31] See proposed Appendix M criteria in section 3.1.

Appendix M – New Entry[32]

NORETHISTERONE when in oral preparations for use as contraception.

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LEVONORGESTREL

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Key uses / expected use

Oral contraceptive

Australian regulations

- According to the TGA Ingredient Database,[33] norethisterone is:
  - Available for use as an active ingredient in biologicals, export only and prescription medicines
  - Available for use as an excipient ingredient in biologicals, devices and prescription medicines
  - Not available as an equivalent ingredient in any application
- As of March 2021, there were 17 medicines currently active on the Australian Register of Therapeutic Goods (ARTG)[34] that contain norethisterone as an active ingredient. These are all prescription medicines.
- Norethisterone is not permitted to be included in listed medicines as it is not included in the Therapeutic Goods (Permissible Ingredients) Determination[35] No.1 of 2021.

[32] See proposed Appendix M criteria in section 3.2.
[33] TGA Ingredient Database https://www.ebs.tga.gov.au/
[34] ARTG database https://www.tga.gov.au/artg
[35] Therapeutic Goods (Permissible Ingredients) Determination https://www.legislation.gov.au/Search/Therapeutic%20Goods%20LBPermissible%20IngredientsRB%20Determination

- The TGA prescribing medicines in pregnancy database[36] classifies norethisterone as:

Drug name	Category	Classification Level 1	Classification Level 2	Classification Level 3
norethisterone	D	Endocrine System	Progestogens (see also oral contraceptives)	
Category D – Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.				

- There are no warning statements pertaining to norethisterone in the Therapeutic Goods (Medicines Advisory Statements) Specification 2019[37]
- Since January 2010, there were 102 reports of adverse events for products containing norethisterone as an active ingredient on the Database of Adverse Event Notifications (DAEN),[38] with 76 reports where norethisterone was the single suspected medicine.
- As of March 2021, there were no products containing norethisterone listed on the Public Chemical Registration Information System Search (PubCRIS).[39]

International regulations

- Norethisterone is included in the WHO Model List of Essential Medicines 2019.
- The Health Products Regulatory Authority of Ireland[40] regulates norethisterone as a prescription-only medicine.
- The United States Food and Drug Administration[41] approve use of norethisterone (norethindrone) as a prescription-only medicine in the United States.
- Norethisterone (norethindrone) is approved for use as a prescription-only medicine in Canada, according to the Canadian (Health Canada) Drug Product Database.[42]
- According to the New Zealand Medicines and Medical Devices Safety Authority (Medsafe)[43] norethisterone is available in New Zealand as follows:

[36] TGA prescribing medicines in pregnancy database https://www.tga.gov.au/prescribing-medicines-pregnancy-database
[37] Therapeutic Goods (Medicines Advisory Statements) Specification 2019 https://www.legislation.gov.au/Details/F2019L00213
[38] Database of Adverse Event Notifications (DAEN) https://apps.tga.gov.au/Prod/daen/daen-entry.aspx
[39] Public Chemical Registration Information System Search (PubCRIS) https://portal.apvma.gov.au/pubcris
[40] Health Products Regulatory Authority https://www.hpra.ie/homepage/medicines/medicines-information/find-a-medicine/results?query=Metoclopramide+hydrochloride&field=ACTIVESUBSTANCES
[41] Food and Drugs Administration Approved Drugs Database: https://www.accessdata.fda.gov/scripts/cder/daf/
[42] Health Canada Drug Product Database: https://health-products.canada.ca/dpd-bdpp/index-eng.jsp
[43] Medsafe Medicine Classification Database: https://www.medsafe.govt.nz/profs/class/classintro.asp

Ingredient	Conditions	Classification
Norethisterone	**except** when supplied for oral contraception to women who meet the clinical and eligibility criteria of the Pharmacy Council and the Pharmaceutical Society of New Zealand approved training programme on oral contraception, when sold in the manufacturer's original pack that has received the consent of the Minister or Director-General to their distribution as medicines, containing not more than 6 months' supply by a registered pharmacist who has successfully completed the approved training programme	Prescription

2.4 Cyproterone

Proposal

The applicant (see section 1.2) proposes to add a new Schedule 3 entry to the Poisons Standard for cyproterone, for use in oral contraceptives when combined with an estrogen, where it meets proposed Appendix M requirements.

Please note the proposed Appendix M conditions are described in Part 3 of this document.

CAS number

2098-66-0 (Cyproterone)

427-51-0 (Cyproterone acetate)

Alternative names[44]

(1β,2β)-6-Chloro-1,2-dihydro-17-hydroxy-3′H-cyclopropa[1,2]pregna-1,4,6-triene-3,20-dione; 6-chloro-17-hydroxy-1α,2α-methylenepregna-4,6-diene-3,20-dione; 6-chloro-6-dehydro-17α-hydroxy-1,2α-methyleneprogesterone; 6-chloro-1,2α-methylene-4,6-pregnadien-17α-ol-3,20-dione

Current scheduling

Cyproterone is currently listed in Schedule 4 of the Poisons Standard as follows:

Schedule 4

CYPROTERONE.

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CYPROTERONE

Schedule 4

[44] According to Merck Index *Online:* https://www.rsc.org/merck-index

Proposed scheduling (Application B)

A private applicant proposed to amend the scheduling for cyproterone as follows:

Schedule 4 – Amend Entry

CYPROTERONE except when included in Schedule 3.

Schedule 3 – New Entry

CYPROTERONE in oral preparations for human therapeutic use when combined with an estrogen, for contraception when supplied in accordance with Appendix M requirements.

Appendix M – New Entry[45]

CYPROTERONE when combined with an estrogen in oral preparations for use as contraception.

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CYPROTERONE

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Key uses / expected use

Oral contraceptive

Australian regulations

- According to the TGA Ingredient Database,[46] cyproterone is:
  - Available for use as an active ingredient in biologicals, export only and prescription medicines
  - Available for use as an excipient ingredient in biologicals, devices and prescription medicines
  - Not available as an equivalent ingredient in any application
- As of March 2021, there were 55 medicines currently active on the Australian Register of Therapeutic Goods (ARTG)[47] that contain cyproterone as an active ingredient. These are all prescription medicines.
- Cyproterone is not permitted to be included in listed medicines as it is not included in the Therapeutic Goods (Permissible Ingredients) Determination[48] No.1 of 2021.

[45] See proposed Appendix M criteria in section 3.2.
[46] TGA Ingredient Database https://www.ebs.tga.gov.au/
[47] ARTG database https://www.tga.gov.au/artg
[48] Therapeutic Goods (Permissible Ingredients) Determination https://www.legislation.gov.au/Search/Therapeutic%20Goods%20LBPermissible%20IngredientsRB%20Determination

- The TGA prescribing medicines in pregnancy database[49] classifies cyproterone as:

Drug name	Category	Classification Level 1	Classification Level 2	Classification Level 3
cyproterone acetate (10 mg daily or higher PO)	D	Endocrine System	Antiandrogens	
cyproterone acetate (2 mg daily PO)	B3	Endocrine System	Antiandrogens	

Category B3 – Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed.

Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.

Category D – Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human foetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

- There are no warning statements pertaining to cyproterone in the Therapeutic Goods (Medicines Advisory Statements) Specification 2019[50]
- Since January 2010, there were 189 reports of adverse events for products containing cyproterone as an active ingredient on the Database of Adverse Event Notifications (DAEN),[51] with 155 reports where cyproterone was the single suspected medicine.
- As of March 2021, there were no products containing cyproterone listed on the Public Chemical Registration Information System Search (PubCRIS).[52]

International regulations

- Cyproterone is not included in the WHO Model List of Essential Medicines 2019.
- The Health Products Regulatory Authority of Ireland[53] regulates cyproterone as a prescription-only medicine.
- The United States Food and Drug Administration[54] have not approved use of cyproterone in the United States.

[49] TGA prescribing medicines in pregnancy database https://www.tga.gov.au/prescribing-medicines-pregnancy-database
[50] Therapeutic Goods (Medicines Advisory Statements) Specification 2019 https://www.legislation.gov.au/Details/F2019L00213
[51] Database of Adverse Event Notifications (DAEN) https://apps.tga.gov.au/Prod/daen/daen-entry.aspx
[52] Public Chemical Registration Information System Search (PubCRIS) https://portal.apvma.gov.au/pubcris
[53] Health Products Regulatory Authority https://www.hpra.ie/homepage/medicines/medicines-information/find-a-medicine/results?query=Metoclopramide+hydrochloride&field=ACTIVESUBSTANCES
[54] Food and Drugs Administration Approved Drugs Database: https://www.accessdata.fda.gov/scripts/cder/daf/

- Cyproterone is approved for use as a prescription-only medicine in Canada, according to the Canadian (Health Canada) Drug Product Database.[55]
- According to the New Zealand Medicines and Medical Devices Safety Authority (Medsafe),[56] cyproterone is available as a prescription-only medicine in New Zealand.

2.5 Desogestrel

Proposal

The applicant (see section 1.2) proposes to add a new Schedule 3 entry to the Poisons Standard for desogestrel, for use in oral contraceptives when combined with an estrogen, where it meets proposed Appendix M requirements.

Please note the proposed Appendix M conditions are described in Part 3 of this document.

CAS number

54024-22-5

Alternative names[57]

(17α)-13-Ethyl-11-methylene-18,19-dinorpregn-4-en-20-yn-17-ol; 17α-ethynyl-18-methyl-11-methylene-Δ4-estren-17β-ol

Current scheduling

Desogestrel is currently listed in Schedule 4 of the Poisons Standard as follows:

Schedule 4

DESOGESTREL.

Index

DESOGESTREL

Schedule 4

Proposed scheduling (Application B)

A private applicant proposed to amend the scheduling for desogestrel as follows:

Schedule 4 – Amend Entry

DESOGESTREL except when included in Schedule 3.

Schedule 3 – New Entry

[55] Health Canada Drug Product Database: https://health-products.canada.ca/dpd-bdpp/index-eng.jsp
[56] Medsafe Medicine Classification Database: https://www.medsafe.govt.nz/profs/class/classintro.asp
[57] According to Merck Index Online: https://www.rsc.org/merck-index

DESOGESTREL in oral preparations for human therapeutic use when combined with an estrogen, for contraception when supplied in accordance with Appendix M requirements.

Appendix M – New Entry[58]

DESOGESTREL when combined with an estrogen in oral preparations for use as contraception.

Index – Amend Entry

DESOGESTREL

Schedule 4
Schedule 3
Appendix M

Key uses / expected use

Oral contraceptive

Australian regulations

- According to the TGA Ingredient Database,[59] desogestrel is:
  - Available for use as an active ingredient in biologicals, export only and prescription medicines
  - Available for use as an excipient ingredient in biologicals, devices and prescription medicines
  - Not available as an equivalent ingredient in any application
- As of March 2021, there were 2 medicines currently active on the Australian Register of Therapeutic Goods (ARTG)[60] that contain desogestrel as an active ingredient. These are all prescription medicines.
- Desogestrel is not permitted to be included in listed medicines as it is not included in the Therapeutic Goods (Permissible Ingredients) Determination[61] No.1 of 2021.
- The TGA prescribing medicines in pregnancy database[62] classifies desogestrel as:

[58] See proposed Appendix M criteria in section 3.2.
[59] TGA Ingredient Database https://www.ebs.tga.gov.au/
[60] ARTG database https://www.tga.gov.au/artg
[61] Therapeutic Goods (Permissible Ingredients) Determination https://www.legislation.gov.au/Search/Therapeutic%20Goods%20LBPermissible%20IngredientsRB%20Determination
[62] TGA prescribing medicines in pregnancy database https://www.tga.gov.au/prescribing-medicines-pregnancy-database

Drug name	Category	Classification Level 1	Classification Level 2	Classification Level 3
desogestrel with ethinylestradiol	B3	Contraceptive Agents	Oral contraceptives	
Category B3 – Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.				

- There are no warning statements pertaining to desogestrel in the Therapeutic Goods (Medicines Advisory Statements) Specification 2019[63]
- Since January 2010, there were 5 reports of adverse events for products containing desogestrel as an active ingredient on the Database of Adverse Event Notifications (DAEN),[64] with 5 reports where desogestrel was the single suspected medicine.
- As of March 2021, there were no products containing desogestrel listed on the Public Chemical Registration Information System Search (PubCRIS).[65]

International regulations

- Desogestrel is not included in the WHO Model List of Essential Medicines 2019.
- The Health Products Regulatory Authority of Ireland[66] regulates desogestrel as a prescription-only medicine.
- The United States Food and Drug Administration[67] approve use of desogestrel as a prescription-only medicine in the United States.
- Desogestrel is approved for use as a prescription-only medicine in Canada, according to the Canadian (Health Canada) Drug Product Database.[68]
- According to the New Zealand Medicines and Medical Devices Safety Authority (Medsafe)[69] desogestrel is available in New Zealand as follows:

[63] Therapeutic Goods (Medicines Advisory Statements) Specification 2019 https://www.legislation.gov.au/Details/F2019L00213
[64] Database of Adverse Event Notifications (DAEN) https://apps.tga.gov.au/Prod/daen/daen-entry.aspx
[65] Public Chemical Registration Information System Search (PubCRIS) https://portal.apvma.gov.au/pubcris
[66] Health Products Regulatory Authority https://www.hpra.ie/homepage/medicines/medicines-information/find-a-medicine/results?query=Metoclopramide+hydrochloride&field=ACTIVESUBSTANCES
[67] Food and Drugs Administration Approved Drugs Database: https://www.accessdata.fda.gov/scripts/cder/daf/
[68] Health Canada Drug Product Database: https://health-products.canada.ca/dpd-bdpp/index-eng.jsp
[69] Medsafe Medicine Classification Database: https://www.medsafe.govt.nz/profs/class/classintro.asp

Ingredient	Conditions	Classification
Desogestrel	**except** when supplied for oral contraception to women who meet the clinical and eligibility criteria of the Pharmacy Council and the Pharmaceutical Society of New Zealand approved training programme on oral contraception, when sold in the manufacturer's original pack that has received the consent of the Minister or Director-General to their distribution as medicines, containing not more than 6 months' supply by a registered pharmacist who has successfully completed the approved training programme	Prescription

2.6 Dienogest

Proposal

The applicant (see section 1.2) proposes to add a new Schedule 3 entry to the Poisons Standard for dienogest, for use in oral contraceptives when combined with an estrogen, where it meets proposed Appendix M requirements.

Please note the proposed Appendix M conditions are described in Part 3 of this document.

CAS number

65928-58-7

Alternative names[70]

(17α)-17-Hydroxy-3-oxo-19-norpregna-4,9-diene-21-nitrile; 17α-cyanomethyl-17β-hydroxy-13β-methylgona-4,9-dien-3-one; 17α-cyanomethyl-17β-hydroxy-4,9-estradien-3-one; dienogestril

Current scheduling

Dienogest is currently listed in Schedule 4 of the Poisons Standard as follows:

Schedule 4

DIENOGEST.

Index

DIENOGEST

Schedule 4

[70] According to Merck Index *Online:* https://www.rsc.org/merck-index

Proposed scheduling (Application B)

A private applicant proposed to amend the scheduling for dienogest as follows:

Schedule 4 – Amend Entry

DIENOGEST except when included in Schedule 3.

Schedule 3 – New Entry

DIENOGEST in oral preparations for human therapeutic use when combined with an estrogen, for contraception when supplied in accordance with Appendix M requirements.

Appendix M – New Entry[71]

DIENOGEST when combined with an estrogen in oral preparations for use as contraception.

Index – Amend Entry

DIENOGEST

Schedule 4
Schedule 3
Appendix M

Key uses / expected use

Oral contraceptive

Australian regulations

- According to the TGA Ingredient Database,[72] dienogest is:
  - Available for use as an active ingredient in biologicals, export only and prescription medicines
  - Available for use as an excipient ingredient in biologicals, devices and prescription medicines
  - Not available as an equivalent ingredient in any application
- As of March 2021, there were 6 medicines currently active on the Australian Register of Therapeutic Goods (ARTG)[73] that contain dienogest as an active ingredient. These are all prescription medicines.
- Dienogest is not permitted to be included in listed medicines as it is not included in the Therapeutic Goods (Permissible Ingredients) Determination[74] No.1 of 2021.

[71] See proposed Appendix M criteria in section 3.2.
[72] TGA Ingredient Database https://www.ebs.tga.gov.au/
[73] ARTG database https://www.tga.gov.au/artg
[74] Therapeutic Goods (Permissible Ingredients) Determination https://www.legislation.gov.au/Search/Therapeutic%20Goods%20LBPermissible%20IngredientsRB%20Determination

- The TGA prescribing medicines in pregnancy database[75] classifies dienogest as:

Drug name	Category	Classification Level 1	Classification Level 2	Classification Level 3
dienogest with ethinylestradiol	B3	Contraceptive Agents	Oral contraceptives	
Category B3 – Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.				

- There are no warning statements pertaining to dienogest in the Therapeutic Goods (Medicines Advisory Statements) Specification 2019[76]
- Since January 2010, there were 15 reports of adverse events for products containing ethinylestradiol as an active ingredient on the Database of Adverse Event Notifications (DAEN),[77] with 13 reports where dienogest was the single suspected medicine.
- As of March 2021, there were no products containing dienogest listed on the Public Chemical Registration Information System Search (PubCRIS).[78]

International regulations

- Dienogest is not included in the WHO Model List of Essential Medicines 2019.
- The Health Products Regulatory Authority of Ireland[79] regulates dienogest as a prescription-only medicine.
- The United States Food and Drug Administration[80] approve use of dienogest as a prescription-only medicine in the United States.
- Dienogest is approved for use as a prescription-only medicine in Canada, according to the Canadian (Health Canada) Drug Product Database.[81]
- According to the New Zealand Medicines and Medical Devices Safety Authority (Medsafe),[82] dienogest is available as a prescription-only medicine in New Zealand.

[75] TGA prescribing medicines in pregnancy database https://www.tga.gov.au/prescribing-medicines-pregnancy-database
[76] Therapeutic Goods (Medicines Advisory Statements) Specification 2019 https://www.legislation.gov.au/Details/F2019L00213
[77] Database of Adverse Event Notifications (DAEN) https://apps.tga.gov.au/Prod/daen/daen-entry.aspx
[78] Public Chemical Registration Information System Search (PubCRIS) https://portal.apvma.gov.au/pubcris
[79] Health Products Regulatory Authority https://www.hpra.ie/homepage/medicines/medicines-information/find-a-medicine/results?query=Metoclopramide+hydrochloride&field=ACTIVESUBSTANCES
[80] Food and Drugs Administration Approved Drugs Database: https://www.accessdata.fda.gov/scripts/cder/daf/
[81] Health Canada Drug Product Database: https://health-products.canada.ca/dpd-bdpp/index-eng.jsp
[82] Medsafe Medicine Classification Database: https://www.medsafe.govt.nz/profs/class/classintro.asp

2.7 Drospirenone

Proposal

The applicant (see section 1.2) proposes to add a new Schedule 3 entry to the Poisons Standard for drospirenone, for use in oral contraceptives when combined with an estrogen, where it meets proposed Appendix M requirements.

Please note the proposed Appendix M conditions are described in Part 3 of this document.

CAS number

67392-87-4

Alternative names[83]

(2′S,6R,7R,8R,9S,10R,13S,14S,15S,16S)-1,3′,4′,6,7,8,9,10,11,12,13,14,15,16,20,21-Hexadecahydro-10,13-dimethylspiro[17H-dicyclopropa[6,7:15,16]-cyclopenta[a]phenanthrene-17,2′(5′H)-furan]-3,5′(2H)-dione; 6β,7β,15β,16β-dimethylene-3-oxo-4-androstene-[17(β-1′)-spiro-5′]-perhydrofuran-2′-one; 6β,7β,15β,16β-dimethylen-3-oxo-17α-pregn-4-ene-21,17-carbolactone; dihydrospirorenone

Current scheduling

Drospirenone is currently listed in Schedule 4 of the Poisons Standard as follows:

Schedule 4

DROSPIRENONE.

Index

DROSPIRENONE

Schedule 4

Proposed scheduling (Application B)

A private applicant proposed to amend the scheduling for drospirenone as follows:

Schedule 4 – Amend Entry

DROSPIRENONE except when included in Schedule 3.

Schedule 3 – New Entry

DROSPIRENONE in oral preparations for human therapeutic use when combined with an estrogen, for contraception when supplied in accordance with Appendix M requirements.

Appendix M – New Entry[84]

[83] According to Merck Index Online: https://www.rsc.org/merck-index
[84] See proposed Appendix M criteria in section 3.2.

DROSPIRENONE when combined with an estrogen in oral preparations for use as contraception.

Index – Amend Entry

DROSPIRENONE

Schedule 4
Schedule 3
Appendix M

Key uses / expected use

Oral contraceptive

Australian regulations

- According to the TGA Ingredient Database,[85] drospirenone is:
  - Available for use as an active ingredient in biologicals, export only and prescription medicines
  - Available for use as an excipient ingredient in biologicals, devices and prescription medicines
  - Not available as an equivalent ingredient in any application
- As of March 2021, there were 25 medicines currently active on the Australian Register of Therapeutic Goods (ARTG)[86] that contain drospirenone as an active ingredient. These are all prescription medicines.
- Drospirenone is not permitted to be included in listed medicines as it is not included in the Therapeutic Goods (Permissible Ingredients) Determination[87] No.1 of 2021.
- The TGA prescribing medicines in pregnancy database[88] classifies drospirenone as:

[85] TGA Ingredient Database https://www.ebs.tga.gov.au/
[86] ARTG database https://www.tga.gov.au/artg
[87] Therapeutic Goods (Permissible Ingredients) Determination https://www.legislation.gov.au/Search/Therapeutic%20Goods%20LBPermissible%20IngredientsRB%20Determination
[88] TGA prescribing medicines in pregnancy database https://www.tga.gov.au/prescribing-medicines-pregnancy-database

Drug name	Category	Classification Level 1	Classification Level 2	Classification Level 3
drospirenone with ethinylestradiol	B3	Contraceptive Agents	Oral contraceptives	
Category B3 – Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.				

- There are no warning statements pertaining to drospirenone in the Therapeutic Goods (Medicines Advisory Statements) Specification 2019[89]
- Since January 2010, there were 439 reports of adverse events for products containing drospirenone as an active ingredient on the Database of Adverse Event Notifications (DAEN),[90] with 404 reports where drospirenone was the single suspected medicine.
- As of March 2021, there were no products containing drospirenone listed on the Public Chemical Registration Information System Search (PubCRIS).[91]

International regulations

- Drospirenone is not included in the WHO Model List of Essential Medicines 2019.
- The Health Products Regulatory Authority of Ireland[92] regulates drospirenone as a prescription-only medicine.
- The United States Food and Drug Administration[93] approve use of drospirenone as a prescription-only medicine in the United States.
- Drospirenone is approved for use as a prescription-only medicine in Canada, according to the Canadian (Health Canada) Drug Product Database.[94]
- According to the New Zealand Medicines and Medical Devices Safety Authority (Medsafe),[95] drospirenone is available as a prescription-only medicine in New Zealand.

[89] Therapeutic Goods (Medicines Advisory Statements) Specification 2019 https://www.legislation.gov.au/Details/F2019L00213
[90] Database of Adverse Event Notifications (DAEN) https://apps.tga.gov.au/Prod/daen/daen-entry.aspx
[91] Public Chemical Registration Information System Search (PubCRIS) https://portal.apvma.gov.au/pubcris
[92] Health Products Regulatory Authority https://www.hpra.ie/homepage/medicines/medicines-information/find-a-medicine/results?query=Metoclopramide+hydrochloride&field=ACTIVESUBSTANCES
[93] Food and Drugs Administration Approved Drugs Database: https://www.accessdata.fda.gov/scripts/cder/daf/
[94] Health Canada Drug Product Database: https://health-products.canada.ca/dpd-bdpp/index-eng.jsp
[95] Medsafe Medicine Classification Database: https://www.medsafe.govt.nz/profs/class/classintro.asp

2.8 Estradiol

Proposal

The applicant (see section 1.2) proposes to add a new Schedule 3 entry to the Poisons Standard for estradiol, for use in oral contraceptives when combined with a progestogen, where it meets proposed Appendix M requirements.

Please note the proposed Appendix M conditions are described in Part 3 of this document.

CAS number

50-28-2 (Estradiol)

979-32-8 (Estradiol valerate)

Alternative names[96]

(17β)-Estra-1,3,5(10)-triene-3,17-diol; β-estradiol; cis-estradiol; 3,17-epidihydroxyestratriene; dihydrofollicular hormone; dihydrofolliculin; dihydroxyestrin; dihydrotheelin

Current scheduling

Estradiol is currently listed in the Poisons Standard as follows:

Schedule 5

ESTRADIOL in implant preparations for growth promotion in animals.

Schedule 4

ESTRADIOL **except** when included in Schedule 5.

Appendix G

Poison	**Concentration (quantity per litre or kilogram)**
ESTRADIOL	10 micrograms

Index

ESTRADIOL

Schedule 5
Schedule 4
Appendix G

Proposed scheduling (Application B)

A private applicant proposed to amend the scheduling for estradiol as follows:

[96] According to Merck Index *Online:* https://www.rsc.org/merck-index

Schedule 4 – Amend Entry

ESTRADIOL except when included in Schedule 3.

Schedule 3 – New Entry

ESTRADIOL in oral preparations for human therapeutic use when combined with a progestogen, for contraception when supplied in accordance with Appendix M requirements.

Appendix M – New Entry[97]

ESTRADIOL when combined with a progestogen in oral preparations for use as contraception.

Index – Amend Entry

ESTRADIOL

Schedule 4
Schedule 3
Appendix G
Appendix M

Key uses / expected use

Oral contraceptive

Australian regulations

- According to the TGA Ingredient Database,[98] estradiol is:
  - Estradiol, estradiol hemihydrate and estradiol valerate are available for use as an active ingredient in biologicals, export only and prescription medicines
  - Estradiol phenylpropionate and estradiol benzoate are available for use as an active ingredient in biologicals and prescription medicines
  - Estradiol and its derivatives are all available for use as an excipient ingredient in biologicals, devices and prescription medicines
  - Estradiol and estradiol hemihydrate are available for use as an equivalent ingredient in prescription medicines
  - Estradiol valerate, estradiol phenylpropionate and estradiol benzoate are not available as an equivalent ingredient in any application.
- As of March 2021, there were 44 medicines currently active on the Australian Register of Therapeutic Goods (ARTG)[99] that contain estradiol as an active ingredient. These are all prescription medicines.

[97] See proposed Appendix M criteria in section 3.2.
[98] TGA Ingredient Database https://www.ebs.tga.gov.au/
[99] ARTG database https://www.tga.gov.au/artg

- Estradiol is not permitted to be included in listed medicines as it is not included in the Therapeutic Goods (Permissible Ingredients) Determination[100] No.1 of 2021.
- The TGA prescribing medicines in pregnancy database[101] classifies estradiol as:

Drug name	Category	Classification Level 1	Classification Level 2	Classification Level 3
dydrogesterone with estradiol	B3	Endocrine System	Progestogens (see also oral contraceptives)	
estradiol	B3	Endocrine System	Oestrogens (see also oral contraceptives)	
nomegestrol with estradiol	B3	Contraceptive Agents		

Category B3 – Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed.

Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.

- There are no warning statements pertaining to estradiol in the Therapeutic Goods (Medicines Advisory Statements) Specification 2019[102]
- Since January 2010, there were 192 reports of adverse events for products containing estradiol as an active ingredient on the Database of Adverse Event Notifications (DAEN),[103] with 149 reports where estradiol was the single suspected medicine.
- As of March 2021, there were three products containing estradiol listed on the Public Chemical Registration Information System Search (PubCRIS).[104]
- Since January 2010, the following adverse experiences were recorded for estradiol in the APVMA Adverse Experience Reporting Program database (AERP):[105]
  - 12 reports of serious incidents classified as related to animal health
  - 1 report of a serious incident classified as related to human health

[100] Therapeutic Goods (Permissible Ingredients) Determination https://www.legislation.gov.au/Search/Therapeutic%20Goods%20LBPermissible%20IngredientsRB%20Determination
[101] TGA prescribing medicines in pregnancy database https://www.tga.gov.au/prescribing-medicines-pregnancy-database
[102] Therapeutic Goods (Medicines Advisory Statements) Specification 2019 https://www.legislation.gov.au/Details/F2019L00213
[103] Database of Adverse Event Notifications (DAEN) https://apps.tga.gov.au/Prod/daen/daen-entry.aspx
[104] Public Chemical Registration Information System Search (PubCRIS) https://portal.apvma.gov.au/pubcris
[105] APVMA Adverse Experience Reporting Program database (AERP) https://apvma.gov.au/node/10946

International regulations

- A derivative of estradiol, estradiol cypionate, is included in the WHO Model List of Essential Medicines 2019, in combination with medroxyprogesterone acetate.
- The Health Products Regulatory Authority of Ireland[106] regulates estradiol as a prescription-only medicine.
- The United States Food and Drug Administration[107] approve use of estradiol as a prescription-only medicine in the United States.
- Estradiol is approved for use as a prescription-only medicine in Canada, according to the Canadian (Health Canada) Drug Product Database.[108]
- According to the New Zealand Medicines and Medical Devices Safety Authority (Medsafe)[109] estradiol (oestradiol) is available in New Zealand as follows:

Ingredient	Conditions	Classification
Oestradiol	**except** in medicines containing 10 micrograms or less per litre or per kilogram	Prescription
Oestradiol	in medicines containing 10 micrograms or less per litre or per kilogram	General Sale

2.9 Gestodene

Proposal

The applicant (see section 1.2) proposes to add a new Schedule 3 entry to the Poisons Standard for gestodene, for use in oral contraceptives when combined with an estrogen, where it meets proposed Appendix M requirements.

Please note the proposed Appendix M conditions are described in Part 3 of this document.

CAS number

60282-87-3

Alternative names[110]

(17α)-13-Ethyl-17-hydroxy-18,19-dinorpregna-4,15-dien-20-yn-3-one; 17α-ethynyl-17β-hydroxy-18-methyl-4,15-estradien-3-one; 17α-ethynyl-13-ethyl-17β-hydroxy-4,15-gonadien-3-one

[106] Health Products Regulatory Authority https://www.hpra.ie/homepage/medicines/medicines-information/find-a-medicine/results?query=Metoclopramide+hydrochloride&field=ACTIVESUBSTANCES
[107] Food and Drugs Administration Approved Drugs Database: https://www.accessdata.fda.gov/scripts/cder/daf/
[108] Health Canada Drug Product Database: https://health-products.canada.ca/dpd-bdpp/index-eng.jsp
[109] Medsafe Medicine Classification Database: https://www.medsafe.govt.nz/profs/class/classintro.asp
[110] According to Merck Index Online: https://www.rsc.org/merck-index

Current scheduling

Gestodene is currently listed in Schedule 4 of the Poisons Standard as follows:

Schedule 4

GESTODENE.

Index

GESTODENE

Schedule 4

Proposed scheduling (Application B)

A private applicant proposed to amend the scheduling for gestodene as follows:

Schedule 4 – Amend Entry

GESTODENE except when included in Schedule 3.

Schedule 3 – New Entry

GESTODENE in oral preparations for human therapeutic use when combined with an estrogen, for contraception when supplied in accordance with Appendix M requirements.

Appendix M – New Entry[111]

GESTODENE when combined with an estrogen in oral preparations for use as contraception.

Index – Amend Entry

GESTODENE

Schedule 4
Schedule 3
Appendix M

Key uses / expected use

Oral contraceptive

Australian regulations

- According to the TGA Ingredient Database,[112] gestodene is:
  - Available for use as an active ingredient in biologicals, export only and prescription medicines
  - Available for use as an excipient ingredient in biologicals, devices and prescription medicines

[111] See proposed Appendix M criteria in section 3.2.
[112] TGA Ingredient Database https://www.ebs.tga.gov.au/

- Not available as an equivalent ingredient in any application

- As of March 2021, there were two medicines currently active on the Australian Register of Therapeutic Goods (ARTG)[113] that contain gestodene as an active ingredient. These are both prescription medicines.
- Gestodene is not permitted to be included in listed medicines as it is not included in the Therapeutic Goods (Permissible Ingredients) Determination[114] No.1 of 2021.
- Gestodene is not listed in the TGA prescribing medicines in pregnancy database[115].
- There are no warning statements pertaining to gestodene in the Therapeutic Goods (Medicines Advisory Statements) Specification 2019[116]
- Since January 2010, there were two reports of adverse events for products containing gestodene as an active ingredient on the Database of Adverse Event Notifications (DAEN),[117] with no reports where gestodene was the single suspected medicine.
- As of March 2021, there were no products containing gestodene listed on the Public Chemical Registration Information System Search (PubCRIS).[118]

International regulations

- Gestodene is not included in the WHO Model List of Essential Medicines 2019.
- The Health Products Regulatory Authority of Ireland[119] regulates gestodene as a prescription-only medicine.
- The United States Food and Drug Administration[120] have not approved use of gestodene in the United States.
- Use of gestodene is not approved in Canada, according to the Canadian (Health Canada) Drug Product Database.[121]
- According to the New Zealand Medicines and Medical Devices Safety Authority (Medsafe),[122] gestodene is available as a prescription-only medicine in New Zealand.

[113] ARTG database https://www.tga.gov.au/artg
[114] Therapeutic Goods (Permissible Ingredients) Determination https://www.legislation.gov.au/Search/Therapeutic%20Goods%20LBPermissible%20IngredientsRB%20Determination
[115] TGA prescribing medicines in pregnancy database https://www.tga.gov.au/prescribing-medicines-pregnancy-database
[116] Therapeutic Goods (Medicines Advisory Statements) Specification 2019 https://www.legislation.gov.au/Details/F2019L00213
[117] Database of Adverse Event Notifications (DAEN) https://apps.tga.gov.au/Prod/daen/daen-entry.aspx
[118] Public Chemical Registration Information System Search (PubCRIS) https://portal.apvma.gov.au/pubcris
[119] Health Products Regulatory Authority https://www.hpra.ie/homepage/medicines/medicines-information/find-a-medicine/results?query=Metoclopramide+hydrochloride&field=ACTIVESUBSTANCES
[120] Food and Drugs Administration Approved Drugs Database: https://www.accessdata.fda.gov/scripts/cder/daf/
[121] Health Canada Drug Product Database: https://health-products.canada.ca/dpd-bdpp/index-eng.jsp
[122] Medsafe Medicine Classification Database: https://www.medsafe.govt.nz/profs/class/classintro.asp

2.10 Mestranol

Proposal

The applicant (see section 1.2) proposes to add a new Schedule 3 entry to the Poisons Standard for mestranol, for use in oral contraceptives when combined with a progestogen, where it meets proposed Appendix M requirements.

Please note the proposed Appendix M conditions are described in Part 3 of this document.

CAS number

72-33-3

Alternative names[123]

(17α)-3-Methoxy-19-norpregna-1,3,5(10)-trien-20-yn-17-ol; 17α-ethynyl-3-methoxy-1,3,5(10)-estratrien-17β-ol; 17α-ethynylestradiol 3-methyl ether

Current scheduling

Mestranol is currently listed in Schedule 4 of the Poisons Standard as follows:

Schedule 4

MESTRANOL.

Index

MESTRANOL

Schedule 4

Proposed scheduling (Application B)

A private applicant proposed to amend the scheduling for mestranol as follows:

Schedule 4 – Amend Entry

MESTRANOL except when included in Schedule 3.

Schedule 3 – New Entry

MESTRANOL in oral preparations for human therapeutic use when combined with a progestogen, for contraception when supplied in accordance with Appendix M requirements.

Appendix M – New Entry[124]

MESTRANOL when combined with a progestogen in oral preparations for use as contraception.

Index – Amend Entry

[123] According to Merck Index Online: https://www.rsc.org/merck-index
[124] See proposed Appendix M criteria in section 3.2.

MESTRANOL

Schedule 4
Schedule 3
Appendix M

Key uses / expected use

Oral contraceptive

Australian regulations

- According to the TGA Ingredient Database,[125] mestranol is:
  - Available for use as an active ingredient in biologicals, export only and prescription medicines
  - Available for use as an excipient ingredient in biologicals, devices and prescription medicines
  - Not available as an equivalent ingredient in any application
- As of March 2021, there was one medicine currently active on the Australian Register of Therapeutic Goods (ARTG)[126] that contains mestranol as an active ingredient. This is a prescription medicine.
- Mestranol is not permitted to be included in listed medicines as it is not included in the Therapeutic Goods (Permissible Ingredients) Determination[127] No.1 of 2021.
- The TGA prescribing medicines in pregnancy database[128] classifies mestranol as:

[125] TGA Ingredient Database https://www.ebs.tga.gov.au/
[126] ARTG database https://www.tga.gov.au/artg
[127] Therapeutic Goods (Permissible Ingredients) Determination https://www.legislation.gov.au/Search/Therapeutic%20Goods%20LBPermissible%20IngredientsRB%20Determination
[128] TGA prescribing medicines in pregnancy database https://www.tga.gov.au/prescribing-medicines-pregnancy-database

Drug name	Category	Classification Level 1	Classification Level 2	Classification Level 3
mestranol	B3	Endocrine System	Oestrogens (see also oral contraceptives)	
Category B3 – Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.				

- There are no warning statements pertaining to mestranol in the Therapeutic Goods (Medicines Advisory Statements) Specification 2019[129]
- Since January 2010, there were two reports of adverse events for products containing mestranol as an active ingredient on the Database of Adverse Event Notifications (DAEN),[130] where mestranol was the single suspected medicine in both cases.
- As of March 2021, there were no products containing mestranol listed on the Public Chemical Registration Information System Search (PubCRIS).[131]

International regulations

- Mestranol is not included in the WHO Model List of Essential Medicines 2019.
- The Health Products Regulatory Authority of Ireland[132] have not approved use of mestranol.
- The United States Food and Drug Administration[133] previously approved use of mestranol as a prescription-only medicine in the United States, but all products containing mestranol have since been discontinued.
- Mestranol was previously approved for use as a prescription-only medicine in Canada, according to the Canadian (Health Canada) Drug Product Database[134], but all products containing mestranol have since been cancelled.
- According to the New Zealand Medicines and Medical Devices Safety Authority (Medsafe),[135] mestranol is available as a prescription-only medicine in New Zealand.

[129] Therapeutic Goods (Medicines Advisory Statements) Specification 2019 https://www.legislation.gov.au/Details/F2019L00213
[130] Database of Adverse Event Notifications (DAEN) https://apps.tga.gov.au/Prod/daen/daen-entry.aspx
[131] Public Chemical Registration Information System Search (PubCRIS) https://portal.apvma.gov.au/pubcris
[132] Health Products Regulatory Authority https://www.hpra.ie/homepage/medicines/medicines-information/find-a-medicine/results?query=Metoclopramide+hydrochloride&field=ACTIVESUBSTANCES
[133] Food and Drugs Administration Approved Drugs Database: https://www.accessdata.fda.gov/scripts/cder/daf/
[134] Health Canada Drug Product Database: https://health-products.canada.ca/dpd-bdpp/index-eng.jsp
[135] Medsafe Medicine Classification Database: https://www.medsafe.govt.nz/profs/class/classintro.asp

2.11 Nomegestrol

Proposal

The applicant (see section 1.2) proposes to add a new Schedule 3 entry to the Poisons Standard for nomegestrol, for use in oral contraceptives when combined with an estrogen, where it meets proposed Appendix M requirements.

Please note the proposed Appendix M conditions are described in Part 3 of this document.

CAS number

58652-20-3 (Nomegestrol acetate)

Alternative names[136]

19-Norpregna-4,6-diene-3,20-dione, 17-(acetyloxy)-6-methyl-; 17-(Acetyloxy)-6-methyl-19-norpregna-4,6-diene-3,20-dione; 6-Methyl-17α-acetoxy-Δ6-19-norprogesterone; TX 066

Current scheduling

Nomegestrol is currently listed in Schedule 4 of the Poisons Standard as follows:

Schedule 4

NOMEGESTROL.

Index

NOMEGESTROL

Schedule 4

Proposed scheduling (Application B)

A private applicant proposed to amend the scheduling for nomegestrol as follows:

Schedule 4 – Amend Entry

NOMEGESTROL except when included in Schedule 3.

Schedule 3 – New Entry

NOMEGESTROL in oral preparations for human therapeutic use when combined with an estrogen, for contraception when supplied in accordance with Appendix M requirements.

Appendix M – New Entry[137]

NOMEGESTROL when combined with an estrogen in oral preparations for use as contraception.

[136] No results in Merck Index. Given alternative names are taken from CAS Common Chemistry: https://commonchemistry.cas.org/

[137] See proposed Appendix M criteria in section 3.2.

Index – Amend Entry

NOMEGESTROL

Schedule 4
Schedule 3
Appendix M

Key uses / expected use

Oral contraceptive

Australian regulations

- According to the TGA Ingredient Database,[138] nomegestrol is:
  - Nomegestrol and nomegestrol acetate are available for use as an active ingredient in biologicals, export only and prescription medicines
  - Nomegestrol and nomegestrol acetate are not available as an excipient ingredient in any application
  - Nomegestrol is available for use as an equivalent ingredient in export only and prescription medicines
  - Nomegestrol acetate is not available as an equivalent ingredient in any application
- As of March 2021, there was one medicine currently active on the Australian Register of Therapeutic Goods (ARTG)[139] that contains nomegestrol as an active ingredient. This is a prescription medicine.
- Nomegestrol is not permitted to be included in listed medicines as it is not included in the Therapeutic Goods (Permissible Ingredients) Determination[140] No.1 of 2021.
- The TGA prescribing medicines in pregnancy database[141] classifies nomegestrol as:

[138] TGA Ingredient Database https://www.ebs.tga.gov.au/
[139] ARTG database https://www.tga.gov.au/artg
[140] Therapeutic Goods (Permissible Ingredients) Determination https://www.legislation.gov.au/Search/Therapeutic%20Goods%20LBPermissible%20IngredientsRB%20Determination
[141] TGA prescribing medicines in pregnancy database https://www.tga.gov.au/prescribing-medicines-pregnancy-database

Drug name	Category	Classification Level 1	Classification Level 2	Classification Level 3
nomegestrol with estradiol	B3	Contraceptive Agents		
Category B3 – Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.				

- There are no warning statements pertaining to nomegestrol in the Therapeutic Goods (Medicines Advisory Statements) Specification 2019[142]
- Since January 2010, there were 11 reports of adverse events for products containing nomegestrol as an active ingredient on the Database of Adverse Event Notifications (DAEN),[143] with nine reports where nomegestrol was the single suspected medicine.
- As of March 2021, there were no products containing nomegestrol listed on the Public Chemical Registration Information System Search (PubCRIS).[144]

International regulations

- Nomegestrol is not included in the WHO Model List of Essential Medicines 2019.
- The Health Products Regulatory Authority of Ireland[145] regulates nomegestrol (nomegestrol acetate) as a prescription-only medicine.
- The United States Food and Drug Administration[146] have not approved use of nomegestrol in the United States.
- Use of nomegestrol is not approved in Canada, according to the Canadian (Health Canada) Drug Product Database.[147]
- According to the New Zealand Medicines and Medical Devices Safety Authority (Medsafe),[148] nomegestrol is available as a prescription-only medicine in New Zealand.

[142] Therapeutic Goods (Medicines Advisory Statements) Specification 2019 https://www.legislation.gov.au/Details/F2019L00213
[143] Database of Adverse Event Notifications (DAEN) https://apps.tga.gov.au/Prod/daen/daen-entry.aspx
[144] Public Chemical Registration Information System Search (PubCRIS) https://portal.apvma.gov.au/pubcris
[145] Health Products Regulatory Authority https://www.hpra.ie/homepage/medicines/medicines-information/find-a-medicine/results?query=Metoclopramide+hydrochloride&field=ACTIVESUBSTANCES
[146] Food and Drugs Administration Approved Drugs Database: https://www.accessdata.fda.gov/scripts/cder/daf/
[147] Health Canada Drug Product Database: https://health-products.canada.ca/dpd-bdpp/index-eng.jsp
[148] Medsafe Medicine Classification Database: https://www.medsafe.govt.nz/profs/class/classintro.asp

3. Additional requirements for pharmacy supply

3.1 Appendix M entry proposed in Application A

Summary

The applicant (see section 1.1) proposed a separate Appendix M entry for each of the three substances covered by application A. The proposed entries would restrict pharmacy dispensing of each oral contraceptive to cases where:

- the pharmacist has completed an accredited training course; the prescription complies with professional practice standards
- a previous prescription from a health professional is confirmed
- supply is documented in a clinical information system

Proposed Appendix M wording

The applicant proposed to create new entries for ethinylestradiol, levonorgestrel and norethisterone in Appendix M of the Poisons Standard as follows:

Appendix M – New Entry (1)

ETHINYLESTRADIOL in combination with levonorgestrel or norethisterone for use as an oral contraceptive where the pharmacist providing professional advice:

- Has demonstrated achievement of competency through completion of an accredited training course that meets the requirements set out in the Pharmaceutical Society of Australia competency-based education framework for supply of ethinylestradiol as a Pharmacist Only medicine; and
- Complies in all respects with the relevant professional practice standards, and the Pharmaceutical Society of Australia professional practice guidance for supply of ethinylestradiol as a Pharmacist Only medicine; and
- Confirms that ethinylestradiol in combination with levonorgestrel or norethisterone has previously been prescribed for the patient by a health professional authorised under state or territory legislation to prescribe ethinylestradiol in combination with levonorgestrel or norethisterone for use as an oral contraceptive; and
- Documents the supply of ethinylestradiol in combination with levonorgestrel or norethisterone in a clinical information system in accordance with professional practice guidance.

Appendix M – New Entry (2)

LEVONORGESTREL for use as an oral contraceptive, excluding use for emergency post-coital contraception, where the pharmacist providing professional advice:

- Has demonstrated achievement of competency through completion of an accredited training course that meets the requirements set out in the Pharmaceutical Society of Australia competency-based education framework for

supply of levonorgestrel as a Pharmacist Only medicine for regular contraception; and
- Complies in all respects with the relevant professional practice standards, and the Pharmaceutical Society of Australia professional practice guidance for supply of levonorgestrel as a Pharmacist Only medicine for regular contraception; and
- Confirms levonorgestrel has previously been prescribed for the patient by a health professional authorised under state or territory legislation to prescribe levonorgestrel for use as an oral contraceptive, excluding use for emergency post-coital contraception; and
- Documents the supply of levonorgestrel in a clinical information system in accordance with professional practice guidance.

Appendix M – New Entry (3)

NORETHISTERONE for use as an oral contraceptive where the pharmacist providing professional advice:

- Has demonstrated achievement of competency through completion of an accredited training course that meets the requirements set out in the Pharmaceutical Society of Australia competency-based education framework for supply of norethisterone as a Pharmacist Only medicine; and
- Complies in all respects with the relevant professional practice standards, and the Pharmaceutical Society of Australia professional practice guidance for supply of norethisterone as a Pharmacist Only medicine; and
- Confirms norethisterone has previously been prescribed for the patient by a health professional authorised under state or territory legislation to prescribe norethisterone for use as an oral contraceptive; and
- Documents the supply of norethisterone in a clinical information system in accordance with professional practice guidance.

3.2 Appendix M entry proposed in Application B

Summary

The applicant (see section 1.2) proposed a single Appendix M entry that would cover all 11 substances listed in Application B. The proposed entry would restrict pharmacy dispensing of each oral contraceptive to cases where:

- a previous prescription from a health professional is confirmed
- the pharmacist is satisfied that the person's therapy is stable
- the person undergoes clinical review by a prescriber or pharmacist at least annually
- a maximum of quantity of 4 months' is prescribed
- the supply is appropriately recorded

Substances proposed to be included in the Appendix M conditions:

- ethinylestradiol

- levonorgestrel
- norethisterone
- cyproterone
- desogestrel
- dienogest
- drospirenone
- estradiol
- gestodene
- mestranol
- nomegestrol

Proposed wording

The applicant proposed to create a new entry in Appendix M of the Poisons Standard as follows:

Appendix M – New Entry

An approved pharmacist may supply for continuing therapy an oral contraceptive pill under the following conditions:

a) Previous supply of an oral contraceptive pill

The approved pharmacist is satisfied that the person has previously been supplied the substance on the basis of a prescription from a prescriber, including but not exclusive to: as evidenced by the My Health Record, the pharmacy's patient management system (for existing patients of the pharmacy), being presented with a recent dispensed and labelled product.

b) Stability of therapy

The approved pharmacist is satisfied that the person's therapy is stable, and that:

i. the person has been taking the substance regularly for an uninterrupted period; and

ii. supply is not within 12 months of the person initiating therapy.

c) Clinical review by prescriber or pharmacist

The approved pharmacist is satisfied that:

i. a prescriber has initially assessed the person's suitability for treatment, and in consultation with the person determined that treatment with the substance is appropriate, as evidenced by initial supply on the basis of a prescription; and

ii. the person undergoes clinical review by a prescriber or pharmacist at least annually, or earlier if the person is unknown to the prescriber or pharmacist. (e.g. the pharmacist would be required to complete a clinical review for a person new to the pharmacy).

d) Maximum quantity of supply

At each supply the pharmacist can supply a maximum quantity of 4 months' or the maximum quantity in a standard proprietary pack, whichever is less.

e) Recording

At each supply the approved pharmacist must:

i. record the supply in the pharmacy's dispensing software; and

ii. record the information that the pharmacist used to support his or her decision to supply the substance; and

iii. provide the patient with printed documentation of supply for their records.

4 How to respond

Submissions must be provided by the closing date of **27 May 2021** through our consultation hub. Any submission about any of the proposals to amend the Poisons Standard will be considered at the next meeting of the Advisory Committee on Medicines Scheduling (ACMS).

5 What will happen

All public submissions will be published on the TGA website at Public submissions on scheduling matters, unless marked confidential or indicated otherwise.

Following consideration of public submissions received before the closing date and advice from the expert advisory committee, decisions on the proposed amendments will be published as interim decisions on the TGA website: Scheduling delegate's interim decisions & invitations for further comment in **September 2021**.