

**Pharmaceutical Benefits Scheme
Post-market Review Section Report**

**Stocktake of Pharmaceutical Benefits Scheme subsidised
medicines available for endometriosis and related
conditions, and comparison of current Australian
pharmacological treatment guidelines**

November 2022

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Executive Summary

This report provides an overview of medicines available in Australia for use in endometriosis and related conditions according to clinical treatment guidelines and identifies potential gaps between the medicines listed on the Pharmaceutical Benefits Scheme (PBS) and those available via the private market.

Endometriosis currently affects more than 830,000 (11%) Australian women, girls and those who are gender diverse, with the disease often starting in the teenage years. Endometriosis has no known cure.

The available treatments for endometriosis in Australia are limited. Primary care management of endometriosis and clinical guidelines recommend that first line treatments include:

- combined oral contraceptives (COCs),
- intravaginal contraception,
- progestogens,
- intrauterine contraceptives,
- subdermal contraceptive implant,
- gonadotrophin-releasing hormone (GnRH) agonists,
- androgenic hormones,
- and analgesia.

Stakeholders have expressed concerns about the limited list of medications currently available on the PBS specifically for the management of endometriosis and endometriosis related pain. Patients and clinicians report that these medicines may be poorly tolerated, minimally effective or are associated with a risk of addiction. Stakeholders have noted that the addition of several medicines to the PBS would facilitate more readily available treatment for endometriosis related pain. These medicines include dienogest, dienogest and estradiol valerate (Qlaira[®]), diazepam suppositories, botulinum toxin, non-steroidal anti-inflammatory drugs (NSAIDs), gonadotropin releasing hormone (GnRH) analogues and other combined oral contraceptive pills.

The medicines currently listed on the PBS specifically for use in endometriosis include two GnRH agonists (goserelin and nafarelin) and a progestogen; medroxyprogesterone acetate (oral tablet). The medicines identified as TGA registered for use in endometriosis and as unrestricted listings on the PBS include progestogens; norethisterone (oral tablet) and medroxyprogesterone acetate (injection). None of the COCs, intravaginal contraception (Nuvaring[®]), or intrauterine contraceptives (Kyleena[®], Mirena[®]) are TGA registered for use in endometriosis. Some COCs are available for PBS-subsidy as an unrestricted listing, however many of the newer generation COCs which may be preferentially prescribed in endometriosis, are not PBS-listed.

Botulinum toxin and diazepam suppositories are not recommended in any current clinical guidelines for the pharmacological management of endometriosis. Neither botulinum toxin nor diazepam are TGA registered for this use. Diazepam suppositories are not currently available as a proprietary product.

There are several identified barriers to improving access to medicines used in the treatment of endometriosis. These include lack of health professional training in insertion of hormonal devices, lack of access to health care professionals, and the willingness and/or lack of incentive for sponsors to pursue a TGA registration and subsequent PBS listing specifically for endometriosis when they already have access to the private market.

Background

What is endometriosis?

Endometriosis is a progressive, chronic condition where cells similar to those that line the uterus (the endometrium) are found in other parts of the body¹. Whilst endometriosis most often affects the reproductive organs it is frequently found in the bowel and bladder and has been found in muscle, joints, the lungs, and the brain².

The causes of endometriosis are unclear, but factors that seem to increase the risk of endometriosis include a family history of endometriosis and menstrual cycle factors such as early age at first period, short menstrual cycles, and heavy or long periods³. Some people with endometriosis experience no symptoms; others may experience pain, heavy menstrual bleeding, bleeding between periods, lethargy, and reduced fertility, among other symptoms.

It can take on average six and a half years for those living with endometriosis to be diagnosed. Definitive diagnosis is only through laparoscopy although symptom management may occur in general practice without progressing to this procedure. Endometriosis has no known cure.

Prevalence of endometriosis in Australia

More than 830,000 (11%) Australian women, girls and those who are gender diverse suffer from endometriosis at some point in their life with the disease often starting in teenagers³. Data from the Australian Institute of Health and Welfare (AIHW) released in 2019 showed that 1 in 9 women born in 1973-78 were diagnosed with endometriosis by the age of 40-44. There were around 34,200 endometriosis related hospitalisations in 2016-17 and nearly 4 in 5 (79%) endometriosis-related hospitalisations in 2016-17 were among females aged 15-44.

Impact in Australia

The economic burden of endometriosis is similar to other chronic diseases (diabetes, Crohn's disease, rheumatoid arthritis), and costs an individual suffering from endometriosis an average of \$30,000 per year through direct healthcare costs and lost work productivity². The condition cost an estimated \$7.4 billion in Australia in 2017-18. This may be an underestimate due to difficulties in diagnosing endometriosis and underdiagnosis³.

Context for the Report

As part of the 2022-23 Budget, an investment of \$58 million was announced to further address endometriosis and pelvic pain under the National Action Plan for Endometriosis. The investment is across several different measures including specific clinics in general practice, research, development of guidelines, and promotion of access to the suite of MBS and PBS items for diagnosis and treatment of endometriosis.

The Endometriosis Action Plan uses the terms endometriosis and chronic pelvic pain with the intention that, where appropriate, this reflects connections between endometriosis and other related conditions. This can include related conditions such as polycystic ovary syndrome, adenomyosis, pelvic inflammatory disease and chronic pelvic and period pain.

Pharmaceutical Benefits Scheme (PBS)

The PBS provides reliable, timely and affordable access to a wide range of medicines for all Australians. Under the PBS, the Australian Government subsidises medicine costs to help people afford prescription medicines for most medical conditions.

The Pharmaceutical Benefits Advisory Committee (PBAC)

The PBAC is an independent expert body appointed by the Australian Government, comprised of doctors, health professionals, health economists and consumer representatives. The PBAC meets three times a year, usually in March, July, and November. Additional intra-cycle meetings may be held as required.

The PBAC is responsible for evaluating the clinical and cost-effectiveness of medicines to make recommendations to the Government to list a medicine on the PBS. Recommendations for new listings are informed by evidence of a medicine's clinical effectiveness, safety, and cost-effectiveness ('value for money') compared with other treatments.

The PBAC has a broad statutory function under the *National Health Act 1953*, to advise the Minister on any matters concerning the operation of the PBS. This includes making further recommendations regarding the safety, effectiveness, and cost-effectiveness of medicines after they have been listed. The PBAC considers the need for, and provides recommendations on, post-market reviews of PBS-listed medicines.

The PBAC has two sub-committees to assist with analysis and advice: the Drug Utilisation Sub-Committee (DUSC) and the Economics Sub-Committee (ESC). Information relating to the PBS, and the PBAC, DUSC and ESC meeting dates, agendas and outcomes are available on the PBS website.

In May 2022, the PBAC agreed with the approach as proposed to address the request by the Chronic Conditions Section (Population Health Division, Department of Health) regarding promotion of access to PBS items for treatment of endometriosis. The PBAC requested that a preliminary report on pharmacological therapies for endometriosis and related conditions be provided for its consideration. The PBAC also requested further information on National Action Plan for Endometriosis timeframes to assist in determining the need to request a full post-market review.

The PBAC recalled previously raised concerns about the range of oral contraceptives and hormone replacement products for menopause remaining on the PBS due to several product de-listings. The PBAC requested a stocktake of current PBS listings for these products to be incorporated into this project.

Post-market monitoring

The Post-Market Review (PMR) programme is a systematic approach to monitoring medicines subsidised by the PBS. PMRs were initiated under the 2011-12 Budget measure '*Improving sustainability of the PBS through enhanced post-market surveillance*'.

PMRs are established under the quality use of medicines objective of the National Medicines Policy framework; promoting the safe and effective use of medicines, with the aim to improve health outcomes for all Australians.

The PMR programme contributes to the following:

- Improved patient safety through better understanding of adverse events and medicine-related harms, including hospitalisations.
- A more sustainable Pharmaceutical Benefits Scheme (PBS) through better targeting of medicines, and avoidance of preventable wastage, or inappropriate prescribing.
- A better knowledge base to understand medicines utilisation, to validate the intended clinical benefit which will inform medicines evaluation processes.
- A strengthened approach to medicine pricing management, including through better management of clinical and economic uncertainty.

Post-market reviews can be initiated when concerns related to the quality use of a medicine, cost-effectiveness, clinical effectiveness, higher than predicted utilisation and/or international differences are raised. A full post-market review will only proceed following PBAC agreement and Ministerial approval.

Endometriosis Expert Advisory Group (EAG)

The Endometriosis Expert Advisory Group (EAG) provides input to the Department on matters related to implementation of the National Action Plan for Endometriosis (NAPE).

Individual members of the EAG have outlined the following concerns related to the PBS subsidy of medicines for endometriosis and related conditions, including:

- there is a limited list of medications currently available on the PBS for pain relief and management of endometriosis. Patients and gynaecologists find the available medications on the PBS to be often poorly tolerated, minimally effective or increasing risk of addiction.
- Several medications need to be added to the PBS to facilitate better readily available treatment for endometriosis pain management, such as dienogest, Qlaira® (dienogest and estradiol valerate), diazepam suppositories, botulinum toxin, non-steroidal anti-inflammatory drugs (NSAIDs), gonadotropin releasing hormone (GnRH) analogues, combined oral contraceptive pills.

The National Action Plan for Endometriosis (NAPE)

The National Action Plan for Endometriosis was launched in 2018 with the goal of ‘a tangible improvement in the quality of life for individuals living with endometriosis, including a reduction in the impact and burden of disease at individual and population levels’⁴. The plan has 3 priority areas:

- awareness and education—this involves developing and delivering community awareness campaigns, promoting early education on women’s health in schools, improving access to information for people living with endometriosis, and improving awareness and understanding of endometriosis among health professionals
- clinical management and care—this involves developing clinical guidelines and clinical care standards; promoting early access to intervention, care and treatment options; improving affordability, accessibility and consistency of management; ensuring endometriosis is recognised as a chronic condition by all health practitioners; and narrowing the gap in quality of life between people with endometriosis and their peers

- research—this involves building a collaborative environment for endometriosis research, mining existing data and improving data linkage between sources, and conducting further research to understand causes and impacts and progress towards a cure.

Methodological approach to the report

This report was prepared with the intention of identifying a list of medicines used in endometriosis and related conditions in Australia. This list of medicines was compiled by contrasting current Australian clinical guidelines for the pharmacological treatment of endometriosis and related conditions, Therapeutic Goods Administration (TGA) registered indications and Pharmaceutical Benefits Scheme (PBS) restrictions for any medications mentioned in the guidelines.

The medicines identified for endometriosis and related conditions and clinical guidelines used to guide the treatment of endometriosis and related conditions were organised into the following areas. The key findings for each area are included in the report:

- A summary of Australian clinical guidelines for the pharmacological management of endometriosis and related conditions, compiled from the electronic Therapeutic Guidelines (eTG)⁵, the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG) Endometriosis Guideline (released May 2021⁶), and the Australian Medicines Handbook (AMH)⁷ rationale for drug use in endometriosis.
- PBS listed⁸ and TGA registered⁹ medicines for endometriosis and related conditions in Australia.
- Hormonal contraceptives available on prescription in Australia.
- Non-steroidal anti-inflammatory drugs (NSAIDs) currently PBS-listed in Australia.
- PBS restriction level and TGA approved indications for the medicines recommended in the eTG for acute neuropathic pain.

Key evidence

1. Australian Clinical Guidelines for pharmacological management of endometriosis

Table 1 presents a summary of Australian clinical guidelines for the pharmacological management of endometriosis.

Table 1: Summary of Australian clinical guidelines for pharmacological management of endometriosis

Treatment/Drug/ Drug Class	eTG – Therapeutic Guidelines <small>Error! Bookmark not defined.</small>	RANZCOG Guidelines <small>Error! Bookmark not defined.</small>	Australian Medicines Handbook <small>Error! Bookmark not defined.</small>
Combined hormonal contraception	<p><u>First-line treatment</u> alone or in combination with analgesia</p> <ul style="list-style-type: none"> - Combined oral contraceptive (COC) with low or standard dose estrogen. <ul style="list-style-type: none"> • COC's can be used cyclically or continuously if menstruation elimination is required to manage symptoms. Review effectiveness after 3 months. - If a non-oral form of combined hormonal contraception is preferred for endometriosis use: <ul style="list-style-type: none"> • Ethinylestradiol + esonogestrel ring intravaginally 	No hormonal treatment between COC, progestogen or GnRH agonists have shown to be superior. Treatment should be based on a shared decision-making approach.	COC's can be taken long term. Extended regimens may be used in women with dysmenorrhoea. There is no evidence that one combination product is more effective than another.
Progestogens	<p>Long-acting progestogens:</p> <ul style="list-style-type: none"> - Alternative first line treatment to combined hormonal contraception, particularly if estrogen is contraindicated. <ul style="list-style-type: none"> • Etonogestrel subdermal implant • Levonorgestrel IUD • Medroxyprogesterone deep intramuscular injection <p>Oral progestogens:</p> <ul style="list-style-type: none"> - Indicated if there is a contraindication to estrogens and long-acting progestogens <p>First line:</p> <ul style="list-style-type: none"> • Norethisterone 	No hormonal treatment between COC, progestogen or GnRH agonists have shown to be superior. Treatment should be based on a shared decision-making approach.	Progestogens can be used long term. Continuous norethisterone, IM medroxyprogesterone and levonorgestrel IUD also provide contraception; an effective non-hormonal method of contraception must be used during treatment with dienogest.

Treatment/Drug/ Drug Class	eTG – Therapeutic Guidelines <small>Error! Bookmark not defined.</small>	RANZCOG Guidelines <small>Error! Bookmark not defined.</small>	Australian Medicines Handbook <small>Error! Bookmark not defined.</small>
	Second line: <ul style="list-style-type: none"> • Dienogest • Medroxyprogesterone 		
Gonadotrophin-releasing hormone (GnRH) agonists	Use of GnRH agonists for endometriosis require specialist advice. They may be used after surgery, especially if endometriotic lesions were not completely excised, or when other treatments have failed. GnRH agonists may cause hypoestrogenic adverse effects (e.g., hot flushes, vaginal dryness, decreased bone mineral density), which limit their duration of use to 6 months. Estrogen and progestogen replacement (with doses typically used for combined menopausal hormone therapy) reduce these adverse effects, allowing GnRH agonist use for up to 2 years. Use GnRH agonists with caution in young people, particularly adolescents, because GnRH agonists may limit peak bone mass.	Further to the above, GnRH are used as an adjunct to surgery for deep endometriosis involving the bowel, bladder, or ureter, consider 3 months of GnRH agonists prior to surgery.	The GnRH agonists, goserelin and nafarelin, are associated with hypo-estrogenic adverse effects such as hot flushes, vaginal dryness and decreased BMD. Duration of treatment is limited to 6 months due to loss of BMD. Adding combined HRT (add-back therapy) reduces these adverse effects and protects against BMD loss while maintaining efficacy, which may allow longer treatment. An effective non-hormonal method of contraception must be used during treatment (to avoid pregnancy in the event of missed doses).
Androgenic hormones (Danazol)	Danazol is reserved for use by specialists when other treatments are not tolerated. It has significant adverse effects (e.g., hirsutism, acne, voice change, liver toxicity, dyslipidaemia, a small increase in the risk of ovarian cancer), and treatment duration is limited to 6 to 9 months. An effective nonhormonal method of contraception must be used concurrently during treatment with danazol.	Referred to in management strategies to enhance fertility in people with endometriosis, stating that danazol led to fewer expectant pregnancies than placebo.	Danazol has androgenic adverse effects (e.g., hirsutism, voice change) that limit its use; other treatments are preferred. Maximum duration of treatment is 9 months. An effective non-hormonal method of contraception must be used during treatment.
Analgesia	Analgesics are first-line treatment of endometriosis-related pain; they may be used alone or together with hormonal therapies. A 3-month trial of a nonsteroidal anti-inflammatory drug (NSAID) or paracetamol (or a combination of both) is recommended. Pain may also have a neuropathic component because endometrial deposits have been shown to be innervated; correlations are seen between the degree of innervation and intensity of pain. Review response after 3 months to determine need for specialist referral.	For people with pain associated with endometriosis – consider a short trial (for example, 3 months) of a non-steroidal anti-inflammatory drug (NSAID) alone or in combination with paracetamol, if not contraindicated. If such a trial does not provide adequate pain relief, consider other forms of pain management and referral for further assessment.	NSAIDs are first line for pain relief and can be used with other treatments. Although evidence is inconclusive regarding their effect on pain due to endometriosis, they are effective in relieving primary dysmenorrhoea. Paracetamol may be used with, or as an alternative to, NSAIDs but evidence for effectiveness is lacking.

Treatment/Drug/ Drug Class	eTG – Therapeutic Guidelines <small>Error! Bookmark not defined.</small>	RANZCOG Guidelines <small>Error! Bookmark not defined.</small>	Australian Medicines Handbook <small>Error! Bookmark not defined.</small>
		<p>There is no evidence for or against the use of anti-neuropathic pain medications for pain associated with endometriosis. Refer to a pain specialist if the pain is severe and unresponsive to simple analgesics, the pain substantially limits daily activities or if any underlying health condition has deteriorated.</p> <p>Opioids should not be used for chronic non-cancer pain as there are other treatments for endometriosis that are available.</p>	

Abbreviations: eTG electronic Therapeutic Guidelines, RANZCOG Royal Australian and New Zealand College of Obstetricians and Gynaecologists, AMH Australian Medicines Handbook

2. PBS listed and TGA registered medicines for endometriosis and related conditions in Australia

Table 2 presents a summary of PBS listed and TGA registered medicines available specifically for endometriosis and related conditions.

Table 2: Summary of PBS listed and TGA registered medicines for endometriosis and related conditions in Australia

Drug	Brands	Class	PBS listings	TGA Status
goserelin	Zoladex®	Gonadotropin releasing hormone analogues	Endometriosis	<ul style="list-style-type: none"> • Endometriosis: In the management of visually proven endometriosis to reduce symptoms including pain and the size and number of endometrial lesions. • uterine fibroids, endometrial thinning, assisted reproduction.
nafarelin	Synarel®	Gonadotropin releasing hormones	Endometriosis	<ul style="list-style-type: none"> • hormonal management of visually proven endometriosis, including pain relief and reduction of endometriotic lesions. • For use in controlled ovarian stimulation programmes prior to in-vitro fertilisation.
medroxyprogesterone acetate	Ralovera® Provera®	Pregnen (4) derivatives Progestogens	Endometriosis	<ul style="list-style-type: none"> • Endometriosis: For use in the treatment of visually proven (laparoscopy) endometriosis where the required endpoint of treatment is pregnancy, or for the control of symptoms when surgery is contraindicated or has been unsuccessful. • Abnormal uterine bleeding
dienogest	Visanne®	Pregnadien derivatives	Not PBS-listed	<ul style="list-style-type: none"> • Treatment of endometriosis
norethisterone	Primolut N®	Estren derivatives Progestogens	Unrestricted	<ul style="list-style-type: none"> • Dysfunctional bleeding • Endometriosis
medroxyprogesterone acetate	Depo-Ralovera® Depo-Provera®	Pregnen (4) derivatives Progestogens (injection)	Unrestricted	<ul style="list-style-type: none"> • Endometriosis: For use in the treatment of visually proven (laparoscopy) endometriosis where the required endpoint of treatment is pregnancy, or for the control of symptoms when surgery is contra-indicated or has been unsuccessful. • Contraception
danazol	AZOL®	Antigonadotropins and similar agents	Not-PBS listed ¹ (Special Access Scheme access only)	<ul style="list-style-type: none"> • Endometriosis: treatment of visually proven (e.g., laparoscopy) endometriosis, where the required endpoint of treatment is fertility, or for the control of symptoms when surgery is contraindicated or has been unsuccessful. • Menorrhagia: Short-term (up to 6 months) management of intractable primary menorrhagia.

¹ PBS delisted 19 March 2021

3. Hormonal contraceptives

Table 3 details the hormonal contraceptives are available on prescription (PBS and non-PBS) in Australia.

Table 3: Hormonal contraceptives available on prescription in Australia

Progestin (mcg)	Estrogen (mcg)	PBS listed brands (®)	Privately available brands (®)	PBS listed indications	TGA registered indications	Notes
<i>G03AA – Progestogens and estrogens, fixed combinations</i>						
levonorgestrel (150)	ethinylestradiol (30)	Eleanor 150/30 ED Evelyn 150/30 ED Femme-Tab ED 30/150 Lenest 30 ED Micronelle 30 ED Monofeme 28 Levlen ED	Microgynon 30 Nordette 21	Unrestricted	Contraception	
levonorgestrel (100)	ethinylestradiol (20)	Femme-Tab ED 20/100	Microgynon 20	Unrestricted	Contraception	
levonorgestrel (125)	ethinylestradiol (50)	Microgynon 50 ED	Nordette 50	Unrestricted	Contraception	
norethisterone (500)	ethinylestradiol (35)	Norimin 28 Day	N/A	Unrestricted	Contraception	
norethisterone (1000)	ethinylestradiol (35)	Norimin-1 28 Day Brevinor-1	N/A	Unrestricted	Contraception	
norethisterone (1000)	mestranol (50)	Norinyl-1/28	N/A	Unrestricted	Contraception	Supply only
nomegestrol acetate (2500)	estradiol (1500)	N/A	Zoely	Not PBS-listed	Contraception	
desogestrel (150)	ethinylestradiol (30)	N/A	Madeline Marvelon	Not PBS-listed	Contraception	
drospirenone (3000)	ethinylestradiol (30)	N/A	Petibelle Yasmin	Not PBS-listed	Contraception	
drospirenone (3000)	ethinylestradiol (20)	N/A	Yaz	Not PBS-listed	<ul style="list-style-type: none"> • Contraception • treatment of moderate acne vulgaris in women seeking oral contraception 	

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Progestin (mcg)	Estrogen (mcg)	PBS listed brands (®)	Privately available brands (®)	PBS listed indications	TGA registered indications	Notes
					<ul style="list-style-type: none"> treatment of symptoms of premenstrual dysphoric disorder 	
gestodene	ethinylestradiol (30)	N/A	Minulet	Not PBS-listed	Contraception	
norgestrel (2500mcg)	estradiol (1500)	N/A	Zoely	Not PBS-listed	Contraception	
dienogest (2000)	ethinylestradiol (30)	N/A	Valette	Not PBS-listed	<ul style="list-style-type: none"> Contraception Treatment of mild to moderate acne in women who seek oral contraception 	
<i>G03HB – Antiandrogens and estrogens</i>						
cyproterone (2000)	ethinylestradiol (35)	N/A	Diane-35 ED Estelle-35 ED Jene-35 ED Juliet-35 Laila-35 Carolyn-35 Brenda-35	Not PBS-listed	<ul style="list-style-type: none"> Contraception Androgenisation in women, severe acne (where prolonged oral antibiotics, local therapy unsuccessful) Mild-moderate idiopathic hirsutism 	
<i>G03AB – Progestogens and estrogens, sequential preparations</i>						
levonorgestrel (50, 75, 125)	ethinylestradiol (30, 40, 30)	Logynon ED Trifeme 28 Triphasil 28 Triquilar ED	N/A	Unrestricted	Contraception	
levonorgestrel (150)	ethinylestradiol (30, 10)	N/A	Seasonique	Not PBS-listed	Contraception	
dienogest (0, 2000, 3000, 0, 0)	estradiol (3000, 2000, 2000, 1000, 0)	N/A	Qlaira	Not PBS-listed	<ul style="list-style-type: none"> Contraception. Treatment of heavy and/or prolonged menstrual bleeding in women without organic pathology who desire oral contraception. 	
<i>G03AC – Progestogens</i>						
levonorgestrel (30)	None	Microlut 28	Microval 28	Unrestricted	Contraception	
norethisterone (350)	None	Noriday 28	Micronor	Unrestricted	Contraception for women who will not, or cannot tolerate other oral	

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Progestin (mcg)	Estrogen (mcg)	PBS listed brands (®)	Privately available brands (®)	PBS listed indications	TGA registered indications	Notes
					contraceptives or intrauterine devices	
drospirenone (4000)	None	N/A	Slinda	Not PBS-listed	Contraception	
dienogest (2000)	None	N/A	Visanne	Not PBS-listed	Treatment of endometriosis	
medroxyprogesterone 150 mg/mL injection	None	Depo-Ralovera Depo-Provera		Unrestricted	<ul style="list-style-type: none"> Endometriosis: For use in the treatment of visually proven (laparoscopy) endometriosis where the required endpoint of treatment is pregnancy, or for the control of symptoms when surgery is contra-indicated or has been unsuccessful. Contraception Carcinoma 	
etonogestrel 68 mg implant	None	Implanon NXT (3 years)	N/A	Unrestricted	<ul style="list-style-type: none"> Contraception 	
<i>G02BB – Intravaginal contraceptives</i>						
etonogestrel (releases 120 mcg/day)	ethinyl estradiol (releases 15 mcg/day)	N/A	Nuvaring	Not PBS-listed	Contraception	
<i>G02BA – Intrauterine contraceptive</i>						
levonorgestrel 52 mg (releases 20 mcg/day)	None	Mirena (5 years)	N/A	Restricted benefit: <ul style="list-style-type: none"> Contraception Idiopathic menorrhagia 	<ul style="list-style-type: none"> Contraception. Treatment of idiopathic menorrhagia. Prevention of endometrial hyperplasia during oestrogen replacement therapy 	
levonorgestrel 19.5 mg (releases 17.5 mcg/day)	None	Kyleena (5 years)	N/A	Restricted benefit: <ul style="list-style-type: none"> Contraception 	Contraception	
copper IUD	None	N/A	Cu375 (5 years) TT 380 standard (10 years)	Not PBS-listed	Contraception	

Key findings

Table 1: Summary of Australian clinical guidelines for pharmacological management of endometriosis

Table 2: Summary of PBS listed and TGA registered medicines for endometriosis and related conditions in Australia

Table 3: Hormonal contraceptives available on prescription in Australia

- Five classes of medicines were identified for use in endometriosis from the Australian clinical guidelines for the pharmacological treatment of endometriosis and related conditions:
 - Combined hormonal contraceptives
 - Progestogens
 - Gonadotrophin-releasing hormone (GnRH) agonists
 - Androgenic hormones (Danazol)
 - Analgesia
- RANZCOG guidelines state that none of the combined oral contraceptives (COCs), progestogens or GnRH agonists are superior in the management of endometriosis. However, there are no COCs available in Australia currently TGA registered, or PBS listed for use specifically in endometriosis.
- The eTG for pharmacological management of endometriosis and related conditions list COCs as an important and alternative first-line treatment option for endometriosis, either alone or in combination with analgesia as first line treatment. The AMH states COCs are well tolerated and can be taken long term.
- The eTG positions long-acting progestogens as alternative first-line treatment options for endometriosis (refer table 1). The etonogestrel implant currently holds an unrestricted PBS-listing, however it is not TGA registered for use in endometriosis (refer table 3). Stakeholders report the etonogestrel subdermal implant is widely regarded as one of the most effective hormonal contraceptives for relieving endometriosis symptoms.
- The only medicines that are available for PBS subsidy listed specifically for use in endometriosis from the identified medicine classes are the following:
 - goserelin (injection) – GnRH agonist
 - nafarelin (nasal spray) – GnRH agonist
 - medroxyprogesterone acetate (oral tablets) – progestogens
- The medicines identified with unrestricted PBS listings allowing subsidy for use in endometriosis include:
 - norethisterone (oral tablet) – Progestogens
 - medroxyprogesterone acetate (injection) – Progestogens
- The medicines identified that are TGA registered for use in endometriosis but are not PBS-listed include:
 - dienogest (oral tablet) – Progestogen

- danazol (oral tablet), SAS only – Androgenic hormones²
- None of the COCs, intravaginal contraception (Nuvaring®), or intrauterine contraceptives (Kyleena®, Mirena®) are TGA registered for use in endometriosis (refer table 3). Intrauterine contraceptives are restricted to use on the PBS for contraception and idiopathic menorrhagia and intravaginal contraception is not PBS-listed (refer table 3).
- The COCs that are currently subsidised on the PBS as an unrestricted PBS-listing include:
 - levonorgestrel+ethinylestradiol in fixed combinations:
 - levonorgestrel (150mcg), ethinylestradiol (30mcg) tablets
 - levonorgestrel (100mcg), ethinylestradiol (20mcg) tablets
 - levonorgestrel (125mcg), ethinylestradiol (20mcg) tablets
 - levonorgestrel+ethinylestradiol in sequential combinations:
 - levonorgestrel (50mcg, 75mcg, 125mcg) + ethinylestradiol (30mcg, 40mcg, 30mcg) tablets
 - norethisterone+ethinylestradiol in fixed combinations:
 - norethisterone (500mcg), ethinylestradiol (35mcg) tablets
 - norethisterone (1000mcg), ethinylestradiol (35mcg) tablets
 - norethisterone+mestranol in fixed combinations:
 - norethisterone (1000mcg), mestranol (50mcg) tablets
- There are ten other COC formulations available to be prescribed in Australia that are neither TGA registered specifically for use in endometriosis nor currently PBS-listed (refer Table 3). These newer COCs may be preferentially prescribed as alternative first line treatments for the management of the symptoms of endometriosis and related conditions. Non-PBS listed COCs vary in price, with many of the newer COCs being higher cost products. This creates a high economic burden for those patients who cannot tolerate or achieve symptom relief from the currently available PBS subsidised options.

² PBS delisted 19 March 2021

4. Non-steroidal anti-inflammatory drugs

Table 4 lists the nine different NSAIDs available in various strengths and forms currently PBS-listed in Australia:

Table 4: NSAIDs available on prescription in Australia including PBS restriction level and TGA indications

Drug	Brands	Class	PBS restriction level	TGA approved indications
mefenamic acid 250mg capsule	Ponstan®	Fenamates	Restricted benefit (dysmenorrhea)	<ul style="list-style-type: none"> • Treatment of primary dysmenorrhoea and primary menorrhoea. • Short-term relief of mild to moderate pain such as dental pain and soft tissue pain
diclofenac sodium 25mg & 50mg tablet	Voltaren® Diclofenac Sandoz® APO-Diclofenac®	Acetic acid derivatives and related substances	Unrestricted	<ul style="list-style-type: none"> • Inflammatory and degenerative forms of rheumatism: rheumatoid arthritis and osteoarthritis. • Relief of acute or chronic pain states in which there is an inflammatory component. • Symptomatic treatment of primary dysmenorrhoea
indomethacin 25mg capsule	Arthrexin® Indocid®	Acetic acid derivatives and related substances	Restricted benefit (chronic arthropathies)	<ul style="list-style-type: none"> • rheumatoid arthritis • osteoarthritis • degenerative joint disease of the hip • ankylosing spondylitis • gout • Acute musculoskeletal disorders • inflammation, pain and oedema following orthopaedic surgical procedures and nonsurgical procedures associated with reduction and immobilisation of fractures or dislocations • pain and associated symptoms of primary dysmenorrhoea
ketoprofen 200mg modified release capsule	Oruvail® Orudis®	Propionic acid derivatives	Restricted benefit (dysmenorrhoea)	<ul style="list-style-type: none"> • rheumatoid arthritis and osteoarthritis • ankylosing spondylitis • acute articular and peri- articular disorders cervical spondylitis • low back pain (strain, lumbago, sciatica, fibrositis) • painful musculo-skeletal conditions • dysmenorrhoea

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Drug	Brands	Class	PBS restriction level	TGA approved indications
naproxen 250mg & 550mg tablet	Naprosyn® Crysanal® Anaprox®	Propionic acid derivatives	Restricted benefit (chronic arthropathies)	<ul style="list-style-type: none"> • acute migraine attacks • treatment of gout • rheumatoid arthritis • osteoarthritis • ankylosing spondylitis • relief of acute and/or chronic pain states in which there is an inflammatory component.
naproxen 750mg & 1g modified release tablet	Proxen SR® Naprosyn SR®	Propionic acid derivatives	Restricted benefit (chronic arthropathies)	<ul style="list-style-type: none"> • Rheumatoid arthritis • osteoarthritis • ankylosing spondylitis • relief of chronic pain states in which there is an inflammatory component.
ibuprofen 400mg tablet	Brufen® APO-Ibuprofen®	Propionic acid derivatives	Unrestricted	<ul style="list-style-type: none"> • Rheumatoid arthritis • osteoarthritis • juvenile rheumatoid arthritis • primary dysmenorrhoea • pyrexia • relief of acute and/or chronic pain states in which there is an inflammatory component.
piroxicam 10mg & 20mg dispersible tablet and capsule	Mobilis D® Mobilis® Feldene®	Oxicams	Restricted benefit (chronic arthropathies)	<ul style="list-style-type: none"> • rheumatoid arthritis • osteoarthritis • ankylosing spondylitis
meloxicam 7.5mg & 15mg tablet & capsule	Mobic® APO-Meloxicam® Movalis® Moxicam®	Oxicams	Restricted benefit (osteoarthritis)	<ul style="list-style-type: none"> • osteoarthritis • rheumatoid arthritis
celecoxib 100mg & 200mg capsule	Celebrex® Celaxib® APO-celecoxib® Celecoxib Sandoz®	Coxibs	Restricted benefit (osteoarthritis)	<ul style="list-style-type: none"> • osteoarthritis • rheumatoid arthritis • ankylosing spondylitis • primary dysmenorrhoea in adults • short term treatment of acute pain in adults following surgery or musculoskeletal and/or soft tissue injury.

Key findings from Table 4: NSAIDs available on prescription in Australia including PBS restriction level and TGA indications

- The eTG recommend NSAIDs for first line treatment of endometriosis-related pain, for use alone or together with hormonal therapies.
- RANZCOG guidelines recommend a short trial of NSAIDs for pain associated with endometriosis.
- AMH recommends NSAIDs first line for pain relief, stating though evidence is inconclusive regarding the effect on pain due to endometriosis, NSAIDs are effective in relieving primary dysmenorrhoea, which is a common symptom of endometriosis.
- Six NSAIDs are TGA registered for the treatment of primary dysmenorrhoea:
 - indomethacin
 - celecoxib
 - mefenamic acid
 - diclofenac
 - ketoprofen
 - ibuprofen
- Two of these NSAIDs with the TGA registered indication of primary dysmenorrhoea are also PBS-listed for this indication:
 - mefenamic acid
 - ketoprofen
- A further two of these NSAIDs have unrestricted PBS listings:
 - diclofenac
 - ibuprofen.
- PBS subsidy of the two remaining NSAIDs with TGA registration for dysmenorrhoea (i.e., celecoxib, indomethacin) is restricted to use in chronic arthropathies or osteoarthritis.
- The various strengths of naproxen are all TGA registered for relief of acute and/or chronic pain states in which there is an inflammatory component.
- Expanding the PBS-listing of these NSAIDs or allowing an unrestricted listing would increase access for patients with pain related to endometriosis and ease the financial burden of accessing these medicines privately.

5. Medicines for neuropathic pain

Table 5 lists the PBS restriction level and TGA approved indications of the medicines recommended in the eTG treatment guidelines for acute neuropathic pain:

Table 5: Medicines commonly used for nerve pain in Australia including PBS restriction level and TGA indications

Drug	Brands	Class	PBS restriction level	TGA approved indications
pregabalin 25mg, 75mg, 150mg, 300mg capsules	Lyrica® Lyzalon® APO-Pregabalin® Pregabalin Sandoz®	Other analgesics and antipyretics	Authority Required (STREAMLINED) – neuropathic pain	<ul style="list-style-type: none"> • treatment of neuropathic pain in adults • adjunctive therapy in adults with partial seizures with or without secondary generalisation.
gabapentin 100mg, 300mg, 400mg, 600mg, 800mg capsules	Neurontin® Gabapentin APOTEX® Gabapentin Sandoz® Nupentin®	Other antiepileptics	Authority Required (STREAMLINED) – partial epileptic seizures	<ul style="list-style-type: none"> • treatment of partial seizures • treatment of neuropathic pain
amitriptyline 10mg, 25mg, 50mg tablet	Endep® Amitriptyline alphapharm® APO-Amitriptyline®	Tricyclic antidepressants	Unrestricted	<ul style="list-style-type: none"> • treatment of major depression. • Nocturnal enuresis where organic pathology has been excluded.
nortriptyline 10mg, 25mg tablet	Allegron®	Tricyclic antidepressants	Restricted benefit (major depression)	<ul style="list-style-type: none"> • treatment of major depression.
duloxetine 30mg, 60mg capsule	Cymbalta® Tixel® APO-Duloxetine® Duloxetine Sandoz®	Serotonin and noradrenaline reuptake inhibitors	Restricted benefit (major depression)	<ul style="list-style-type: none"> • treatment of major depressive disorder • treatment of diabetic peripheral neuropathic pain • treatment of generalised anxiety disorder.
venlafaxine 37.5mg, 75mg, 150mg capsules	Efexor-XR® Enlifax-XR® APO-Venlafaxine XR® Venlafaxine Sandoz XR®	Serotonin and noradrenaline reuptake inhibitors	Restricted benefit (major depressive disorders)	<ul style="list-style-type: none"> • Major depression • Generalised anxiety disorder • Social Anxiety Disorder • Panic Disorder

Key findings from Table 5: Medicines commonly used for nerve pain in Australia including PBS restriction level and TGA indications

- The eTG recommendations suggest endometriosis pain may have a neuropathic component because endometrial deposits have been shown to be innervated and that correlations are seen between the degree of innervation and intensity of pain.
- According to the eTG treatment guidelines for acute neuropathic pain; gabapentin or pregabalin are both first line treatment, amitriptyline, nortriptyline, duloxetine, or venlafaxine are all second line treatment options.
- RANZCOG endometriosis guidelines state there is no evidence for or against the use of anti-neuropathic pain medications for pain associated with endometriosis.
- The AMH does not mention anti-neuropathic pain medications as a treatment option.
- Pregabalin is available as an Authority Required (STREAMLINED) prescription for neuropathic pain, and amitriptyline has an unrestricted listing.
- Gabapentin is Authority Required (STREAMLINED) for the treatment of partial epileptic seizures and is not PBS subsidised for neuropathic pain.
- Nortriptyline, duloxetine, and venlafaxine are restricted for use on the PBS for the treatment of major depression or depressive disorders.
- Tricyclic antidepressants are restricted for use on the PBS to major depression, apart from amitriptyline which is an unrestricted benefit.

Issues for consideration

Issues for consideration are focussed on the availability of stakeholder requested treatments for the management of endometriosis and related conditions on the Pharmaceutical Benefits Scheme (PBS).

Intrauterine devices (IUDs) and subdermal implants

Intrauterine contraceptives are available on the PBS for contraception and idiopathic menorrhagia. Intravaginal contraception is not PBS-listed. Etonogestrel implant is available on the PBS as an unrestricted benefit, however it is not TGA registered for use in endometriosis.

Feedback from stakeholders is that clinicians consider these to be effective early treatments for endometriosis. Stakeholders report a challenge to enabling better access to the use of IUDs and subdermal implants is limited access to clinicians trained in insertion of these devices. Patients may not be able to access these treatments as early in the treatment pathway as required. Stakeholders suggest that increased training opportunities should be provided to primary care practitioners in community settings. Training and supporting general practitioners (GPs) to insert IUDs and subdermal implants should be a central focus of any plan to increase access to management of endometriosis in primary care.

Botulinum toxin

Stakeholders report a common cause of the most severe endometriosis pain is pelvic muscle spasm, either in the pelvic floor muscles, or the pelvic side wall (obturator internus). Treatments such as pelvic physiotherapy, pain psychology, pain education, neuropathic pain medications, and management of bladder and bowel may be beneficial. For well selected patients with severe pelvic muscle spasm, an injection of botulinum toxin in the affected muscles offers up to 6 months of pain relief. Stakeholders suggested that patients with this symptom typically overused opioid medications, with the associated risks of dependence, pain escalation and unintentional death by overdose.

Botulinum toxin is not recommended in any current clinical guidelines for the pharmacological management of endometriosis. The dose of botulinum toxin varies, depending on the site of administration.

Botulinum toxin has several therapeutic indications but is not currently TGA registered for use in endometriosis or related conditions. The closest indications to the requested use from the ten currently TGA registered indications are:

- treatment of overactive bladder with symptoms of urinary incontinence, urgency, and frequency, in adult patients who have an inadequate response to or are intolerant of an anticholinergic medication,
- treatment of urinary incontinence due to neurogenic detrusor overactivity resulting from a defined neurological illness (such as spinal cord injury or multiple sclerosis) in adult patients who have an inadequate response to or are intolerant of an anticholinergic medication.

Diazepam suppositories

Diazepam is not TGA registered for use in endometriosis or related conditions, however it is listed for the relief of reflex muscle spasm due to local trauma (injury, inflammation) to muscles, bones, and joints. Diazepam in any presentation is not recommended in any current clinical guidelines for the pharmacological management of endometriosis. Diazepam in any form has an increased risk of addiction and abuse.

There are several factors that would make PBS listing challenging. Diazepam suppositories are not currently available as a proprietary product. Availability would depend on compounding as an extemporaneous pharmaceutical product. The PBS extemporaneous schedule does not include extemporaneous suppositories or vaginal pessaries. Standard excipients used in the production of suppositories are not listed on the PBS extemporaneous drug tariff.

Hormonal contraceptives

Stakeholders requested access to two hormonal contraceptives in particular:

- Dienogest 2000 mcg (Visanne®) is not PBS listed and has TGA registration for treatment of endometriosis.
- Dienogest + estradiol is not PBS-listed and has TGA registration for contraception and treatment of heavy and/or prolonged menstrual bleeding in women without organic pathology who desire oral contraception.

PBS listing for a specific indication generally requires that the medicine is TGA registered for that therapeutic indication. Dienogest 2000 mcg does have a specific TGA registered indication for endometriosis, however to date, the PBAC has not considered a submission from the sponsor to PBS-list.

There are a range of older COCs PBS listed, however there are approximately ten other COC formulations available to be prescribed in Australia that are neither TGA registered specifically for use in endometriosis nor currently PBS-listed. These newer COCs are often preferentially prescribed as alternative first line treatments for the management of endometriosis. They are generally higher priced medicines, creating a high economic burden for those patients who cannot tolerate or achieve symptom relief from the currently available PBS subsidised options.

The barriers to access these medicines via the PBS may include:

- the lack of incentive for medicine sponsors to apply for PBS listing given that use of their medicine may be well established in the private market,
- the lack of robust evidence to support an application for a specific TGA registered indication for endometriosis and a specific PBS listing for the same indication and
- sponsors may not be willing to pay the costs involved in making a submission to the PBAC.

The PBAC's consideration is generally initiated by the medicine sponsor responsible for a particular medicine making an application for the medicine to be considered for PBS listing. It is usually the pharmaceutical company that holds the scientific data and other information necessary to inform the PBAC's consideration.

Gonadotropin releasing hormone (GnRH) analogues

All three clinical guidelines for treatment of endometriosis recommend use of GnRH agonists in specific circumstances. There are two GnRH analogues currently PBS subsidised as Restricted Benefits for the treatment of endometriosis that is visually proven:

- Goserelin (injection) –short term treatment up to six months, only one course of not more than six months therapy will be authorised
- Nafarelin (nasal spray) –initial treatment up to 6 months, subsequent treatment up to 6 months, treatment must not be within 2 years of the end of the previous course of treatment with this medicine.

NSAIDS

All three clinical guidelines for treatment of endometriosis recommend use of NSAIDs for the management of endometriosis-related pain. The PBS listed NSAIDs with TGA registration specifically for primary dysmenorrhoea, a symptom commonly associated with endometriosis are: mefenamic acid and ketoprofen (Restricted Benefits for dysmenorrhoea) and diclofenac and ibuprofen (unrestricted benefits). Two additional NSAIDs have TGA registration for dysmenorrhoea (celecoxib, indomethacin) but PBS subsidy is limited to use in chronic arthropathies or osteoarthritis. Most NSAIDs are available for purchase over the counter in smaller quantities.

Neuropathic pain treatments

There is limited evidence for neuropathic pain treatments for use in endometriosis. Some clinical guidelines suggest endometriosis pain may have a neuropathic component because endometrial

deposits have been shown to be innervated; however other clinical guidelines state no evidence for or against the use of anti-neuropathic pain medications for pain associated with endometriosis.

Expanding the PBS restrictions to allow specific use for endometriosis related pain would require medicine sponsors to first pursue TGA registration for this indication and then apply for PBS listing for this indication. Currently, of medicines used to treat neuropathic pain, only pregabalin is PBS listed specifically for neuropathic pain, and amitriptyline has an unrestricted benefit listing which would allow use for neuropathic pain.

There would also be quality use of medicines (QUM) concerns in expanding the PBS restrictions due to the potential for dependency/abuse with pregabalin and risk of use in other non-PBS subsidised nerve pain related conditions.

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