5.03 DIENOGEST, Tablet 2 mg, Visanne®, Bayer Australia Ltd.

1 Purpose of submission

1.1 The Category 2 submission requested a General Schedule Restricted Benefit Pharmaceutical Benefits Scheme (PBS) listing for dienogest (Visanne®) for the treatment of endometriosis.

1.2 Listing was requested on the basis that the clinical efficacy and safety of dienogest for the treatment of endometriosis is well established and that there is a need for increased treatment options for endometriosis to be made available on the PBS. Dienogest has an established place in therapy for the treatment of endometriosis according to published Australian guidelines such as the Australian Clinical Practice Guidelines for the Diagnosis and Management of Endometriosis (RANZCOG 2021), the Australian Therapeutic Guidelines for Endometriosis (2020) and the Australian Medicines Handbook. This has been previously noted by the Pharmaceutical Benefits Advisory Committee (PBAC)[1].

Table 1: Key components of the clinical issue addressed by the submission

Component	Description
Population	Patients with endometriosis
Intervention	Dienogest 2 mg daily, oral tablets
Comparator	No nominated comparator
Outcomes	Primary outcome: Endometriosis associated pelvic pain (assessed by Visual Analogue Scale), revised American Fertility Society score Secondary outcome: Quality of life (SF-36)
Clinical claim	The submission did not make a clinical claim.

Source: compiled during the evaluation.

2 Background

2.1 The submission cited the Department of Health and Aged Care's National Women's Health Strategy 2020-2030[2], with specific reference to reducing the prevalence and impact of endometriosis through ensuring availability of, and access to, affordable and

[1] Department of Health and Aged Care (2024), A Stocktake of Pharmaceutical Benefit Scheme (PBS)-Funded Medicines Available for Endometriosis and Related conditions. https://www.pbs.gov.au/reviews/endometriosis-and-related-conditions-reports/Consumer-Summary-Stocktake-of-PBS-medicines-available-for-endometriosis-and-related-conditions.pdf , access 5 April 2024.

[2] Department of Health and Aged Care (2018), 'National Women's Health Strategy 2020-2030', https://www.health.gov.au/resources/publications/national-womens-health-strategy-2020-2030?language=en accessed 4 April 2024.

consistent healthcare options, and better treatment options, for endometriosis patients.

2.2 The goals of the National Action Plan for Endometriosis 2018 include affordable and consistent healthcare options, and better treatment options, available nationally to support timely and effective access to endometriosis diagnosis, management and care. One of the actions set out in the National Action Plan was partnering with pharmaceutical companies to pursue PBS listing for endometriosis medications, including the contraceptive pill, menopausal hormone therapy (MHT) – also known as hormone replacement therapy (HRT) – and pain medications. Also, make provisions for Aboriginal and Torres Strait Islander people with endometriosis and associated chronic pelvic pain through the Closing the Gap PBS Co-payment Measure.[3]

2.3 Current PBS-listed treatments specifically for endometriosis include goserelin, nafarelin and medroxyprogesterone 10 mg. Additional hormonal therapies such as norethisterone 5 mg and oral contraceptives are available on the PBS with general/unrestricted benefit (e.g. norethisterone, levonorgestrel and etonogestrel). In March 2024, the PBAC also recommended relugolix with estradiol and norethisterone acetate fixed dose combination (Ryeqo) for the treatment of moderate to severe pain associated with endometriosis.

Registration status

2.4 Dienogest was Therapeutic Goods Administration (TGA) registered on 11 June 2010, for the treatment of endometriosis.

Previous PBAC consideration

2.5 This is the first submission for dienogest to be considered by the PBAC.

For more detail on PBAC's view, see section 7 PBAC Outcome

3 Requested listing

3.1 Suggested deletions are in strikethrough, additions are in italics.

MEDICINAL PRODUCT medicinal product pack	Dispensed Price for Max. Qty	Max. qty packs	Max. qty units	№.of Rpts	Available brands
DIENOGEST					
dienogest 2 mg tablet, 28	$[redacted] published price AEMP $[redacted]	1	28	5	Visanne
Category / Program: {General Schedule}					
Prescriber type: ☒Medical Practitioners ☒*Nurse practitioners*					
Restriction type: ☒Restricted benefit					
Condition: Endometriosis					
Indication: Endometriosis					

[3] Department of Health and Aged Care (2018),'National Action Plan for Endometriosis', https://www.health.gov.au/sites/default/files/national-action-plan-for-endometriosis.pdf, accessed 5 April 2024.

Administrative Advice: *Continuing Therapy Only:* *For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners*
~~**Treatment Phase:** Initial treatment~~
~~**Treatment criteria:**~~
~~The condition must be for endometriosis~~
~~**Category / Program:** {General Schedule}~~
~~**Prescriber type:** ☒Medical Practitioners ☒Nurse practitioners~~
~~**Restriction type:** ☒Restricted benefit~~
~~**Condition:** Endometriosis~~
~~**Indication:** Endometriosis~~
~~**Treatment Phase:** Continuing treatment~~
~~**Treatment criteria:**~~
~~The condition must be for endometriosis~~

3.2 The submission requested a General Schedule Restricted benefit with a maximum quantity of one pack (28 tablets) and five repeats.

3.3 At the recommended dose of one tablet (2 mg) daily, the requested maximum quantity and number of repeats would provide for six months of treatment. The treatment duration provided for in the proposed listing is consistent with the clinical trials provided in the submission (refer to Clinical Trials)). The Therapeutic Guidelines for Endometriosis specify that the usual length of treatment with oral progestogens is 3 to 6 months, but longer or repeat courses are common[4]. The PBS listing for medroxyprogesterone (for the treatment of endometriosis) allows for 3 months' treatment (assuming a 30 mg dose). Note, medroxyprogesterone also has a PBS listing under the maximum dispensed quantity measure that provides for approximately 6 months' treatment. The unrestricted PBS listings for norethisterone 5 mg allows 2 repeats.

3.4 The current PBS listings for nafarelin 200 microgram nasal and goserelin 3.6 mg implant for the treatment of endometriosis allow for 6 months' treatment. However, these listings have additional eligibility criteria, including that the condition must be visually proven.

3.5 It may be appropriate for the PBS listing for dienogest to align with the PBS listings of other oral progestogens for the treatment of endometriosis (allowing up to 3 months' supply under the listing).

3.6 The submission requested prescribing by nurse practitioners within collaborative arrangements as continuing therapy only.

3.7 The submission requested a price for dienogest (AEMP $[redacted] and DMPQ $[redacted]) based on a [redacted]% reduction compared to the current ex-manufacturer price. The submission

[4] Therapeutic Guidelines Limited (December 2020), 'Therapeutic Guidelines: Sexual and Reproductive Health, Endometriosis', Accessed 3 April 2024

provided a comparison of the requested DPMQ to the price of dienogest in the private and other HTA markets. The requested price is lower than the price of dienogest in the private market and in other HTA markets.

3.8 Table 2 presents a summary of the DPMQs (and AEMPs) for dienogest versus other progestogen treatments listed on the PBS. The submission did not discuss the pricing of other hormonal treatments listed on the PBS that may be used to treat endometriosis. The requested price for dienogest ($[redacted]) is higher than the average 28-day cost of medroxyprogesterone ($30.15) and norethisterone ($53.58). As norethisterone is an unrestricted benefit, it is not possible to identify use for endometriosis distinct from other conditions. Note the cost of treatment for medroxyprogesterone was calculated using a dose of 30 mg daily. The cost of treatment with norethisterone was based on a dose of 5-10 mg daily (but can be increased to 10 mg twice daily if needed)

Table 2: Summary of DPMQ and AEMP of oral progestogens on the PBS

Name of Medicine	Benefit type and restriction (item code)	Max Quantity	Treatment duration (per max quantity)	AEMP	DPMQ	Cost per 28 days
Dienogest	-	*28*	*28 days*	*$[redacted]*	*$[redacted]*	*$[redacted]*
Medroxyprogesterone acetate 10 mg tablet; Provera®, Ralovera ®	Restricted Benefit: Endometriosis (2722G)	100	33 days (assuming dose of 10 mg three time daily	$6.39	$35.89*	$30.15*
Norethisterone 5 mg tablet, Primolut N	Unrestricted (2993M)	30	30 days (5 mg dose)	$20.66	$35.20 ($57.41)†	$32.85 ($53.58)†

Source: information published on the PBS website www.pbs.gov.au.

*cost based on generic brand Ralovera

†cost based on a norethisterone dose of 10 mg daily, with an increased quantity of 60 tablets

For more detail on PBAC's view, see section 7 PBAC Outcome

4 Population and disease

4.1 Endometriosis is a chronic hormone dependent gynaecological condition that occurs when tissue similar to the lining of the uterus (endometrium tissue) grows outside the uterine cavity. Endometriosis is characterised by dysmenorrhea, pelvic pain and dyspareunia. Endometriosis is often associated with subfertility or infertility.

4.2 The submission stated that endometriosis affects one in nine Australian women of childbearing age, based on a recently published journal article[5].

4.3 According to clinical guidelines a definite diagnosis of endometriosis requires surgical visualisation which is usually performed via laparoscopy and ideally complemented by

[5] Armour M, Clccla D, Yazdanl A, Rombauts L, Van Nlekerk L, Schubert R, Abbott J. Endometriosis research priorities in Australia. Aust N Z J Obstet Gynaecol. 2023;63:594-598.

histological verification. This requirement for an invasive procedure is often reflected by a significant delay in diagnosis.[6,7]

4.4 The submission stated that endometriosis is associated with a significant economic burden, due to the direct costs associated with hospitalisation, repeat surgical procedures and pharmacological treatment, in addition to the indirect costs resulting from lost productivity.

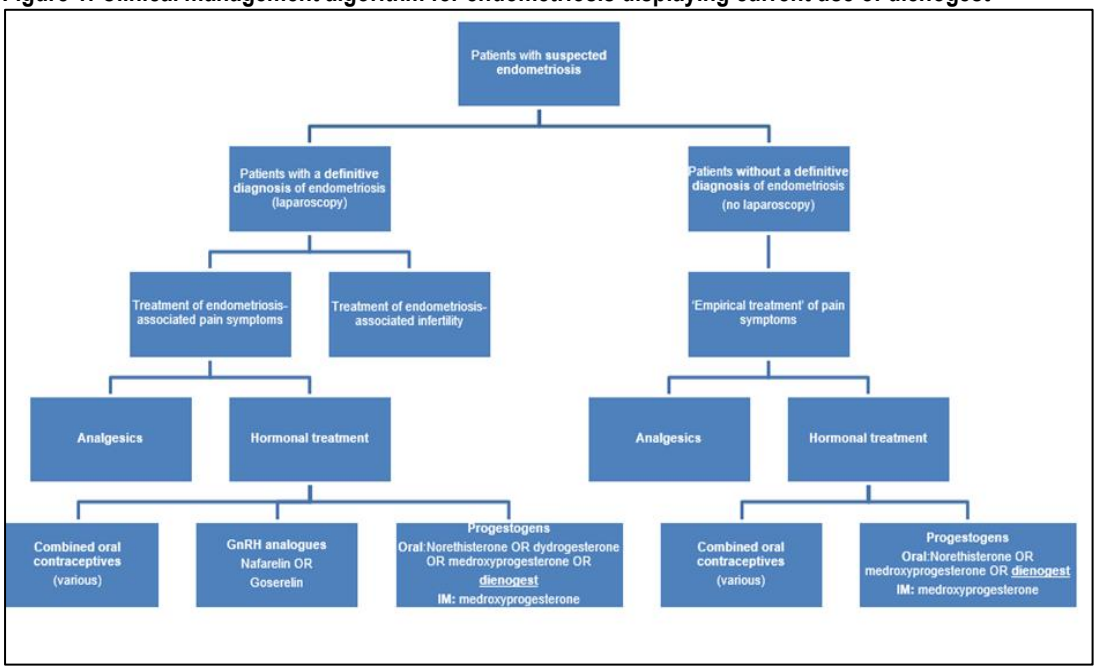
4.5 The clinical management of patients with endometriosis is shown in Figure 1. The treatment pathway for endometriosis is dependent on whether the patient has a definitive diagnosis or not. Treatment for endometriosis can be medical or surgical treatment depending on the severity of the disease and patient circumstances. For patients with a definitive diagnosis, pain may be treated with analgesics and/or hormonal treatments. The ablation of endometriotic lesions is recommended for mild to moderate endometriosis. For severe cases of deep and infiltrating endometriosis, surgery aims to remove entire lesions. For patients without a definitive diagnosis, symptoms are managed with analgesia or hormonal treatments. Both, medical and surgical treatments, are associated with high relapse rates which commonly result in permutations of available treatment options and repeat surgical procedures.

4.6 Hormonal treatments for endometriosis include combined oral contraceptives (off-label use), progestogens (oral, depot injection or intrauterine delivery system (off-label use)) and gonadotrophin-releasing hormone (GnRH) agonists and antagonists (off-label). Selection of hormonal treatment is individualised based on tolerability, adverse effect profile and the patients desire for fertility. Clinical guidelines note that there is no evidence that one hormonal treatment is superior to another. The GnRH antagonists (e.g. elagolix, linzagolix, cetrorelix and ganirelix) have not been TGA registered for the treatment of endometriosis.

[6] National Institute for Health and Care Excellence. Endometriosis: diagnosis and management. 2017. https://www.nice.org.uk/guidance/ng73

[7] RANZCOG. Endometriosis Clinical Practice Guideline Australia. 2021 https://ranzcog.edu.au/wp-content/uploads/2022/02/Technical-Report-Attachment-for-the-Australian-Endometriosis-Guideline.pdf

Figure 1: Clinical management algorithm for endometriosis displaying current use of dienogest



Source: Figure 1, p26 of the submission.

4.7 Dienogest is a progestogen-only hormone preparation for the treatment of endometriosis. It works by suppressing oestradiol production and preventing the growth of the endometrium. In vivo, dienogest has a strong progestogenic effect whilst avoiding significant androgenic, mineralocorticoid or glucocorticoid effects.

4.8 Australian clinical practice guidelines (RANZCOG (2021) endometriosis clinical practice guideline and the Australian Therapeutic Guidelines (2020) (ATG) for Endometriosis) recommend first-line treatment of analgesia with or without hormone therapies. Guidelines recommend a 3-month trial of a nonsteroidal anti-inflammatory drug (NSAID) or paracetamol (or a combination of both). Hormone treatment for endometriosis includes combined hormonal contraception and progestogens, with specialist treatment of GnRH agonists.

4.9 The ATG for Endometriosis advise that oral progestogens are indicated where there are contraindications to estrogens and long-acting progestogens[8]. The ATG lists norethisterone as a first line oral progestogen, with dienogest and medroxyprogesterone listed as second line. All progestogens (or any hormone treatment) are however considered an earlier line of therapy compared to GnRH analogues. GnRH analogues are reserved for later line treatment due to its hypoestrogenic adverse events (e.g. decreased bone mineral density, hot flushes) and are used with add back hormone treatment.

[8] Therapeutic Guidelines Limited (December 2020), 'Therapeutic Guidelines: Sexual and Reproductive Health, Endometriosis', Accessed 3 April 2024

4.10 The broader literature acknowledges that there is a lack of comparative evidence among progestins. A literature search conducted during the evaluation identified limited small studies comparing dienogest to norethisterone, however, the evidence was inconclusive regarding the preferred progestin. The bone protective effect of norethisterone may be an important consideration.[9] In a before and after study, Vercellini 2016 did not find any difference in outcomes between dienogest 2 mg daily and norethisterone 2.5 mg daily, as first-line progestins for symptomatic endometriosis.[10] Side effects were numerically reduced when patients switched to dienogest from norethisterone, but the difference was not statistically significant. In a small, 24-week, pilot study of endometriosis patients with an unsatisfactory response to norethisterone, Morotti 2014[11] reported that dienogest 2 mg per day was associated with significant improvements in patient satisfaction, endometriosis-associated pain symptoms and quality of life and quality of sexual life in symptomatic women with rectovaginal endometriosis. Literature was also identified that supported dienogest for the treatment of extragenital endometriosis.[12,13] Patient out of pocket cost may also be a consideration for the choice of progestin in some contexts.

4.11 The ESC noted that the RANZCOG Endometriosis Clinical Practice Guidelines advise that no hormonal treatment for endometriosis has been demonstrated to be superior. The ESC noted that the ATG strongly recommend long-acting reversible contraceptives for women with endometriosis needing reliable contraception. The ESC noted that dienogest is recommended as a second line oral progestogen in the ATG.

For more detail on PBAC's view, see section 7 PBAC outcome

5 Comparator

5.1 The submission did not nominate a comparator.

5.2 The PBS listed oral progestogens norethisterone (5 mg) and medroxyprogesterone (10 mg) may be appropriate comparators to dienogest. Aspects of the financial impact analysis are supportive of use of these medicines as comparators (cross reference to section 6). The submission provided estimates of number of patients switching from medroxyprogesterone to dienogest in the financial impact analysis. The submission

[9] New Zealand Ministry of Health.(2020). Diagnosis and Management of Endometriosis in New Zealand. Accessed 09 May 2024 https://www.health.govt.nz/system/files/documents/publications/diagnosis-and-management-of-endometriosis-in-new-zealand-mar2020-apr21-update.pdf

[10] Vercellini P, Bracco B, Mosconi P, Roberto A, Alberico D, Dhouha D, Somigliana E. Norethindrone acetate or dienogest for the treatment of symptomatic endometriosis: a before and after study. Fertil Steril 2016;105:734-43.

[11] Morotti M, Sozzi F, Remorgida V, Venturini P, Ferrero S. Dienogest in women with persistent endometriosis-related pelvic pain during norethisterone acetate treatment. European Journal of Obstetrics & Gynecology and Reproductive Biology. 2014; 183:188-192

[12] Angioni S, Nappi L, Pontis A, Sedda F, Luisi S, Mais V, Melis G. Dienogest. A possible conservative approach in bladder endometriosis. Results of a pilot study. Gynecol Endocrinol 2015;31(5):406-408

[13] Dedaiwy M, Allaire C, Alfaraj S. Long-term medical management of endometriosis with dienogest and with gonadotropin-releasing hormone agonist and add-back hormone therapy. Fertil Steril 2017;107:537-4.

noted that norethisterone is used for the treatment of endometriosis but is listed on the PBS as an unrestricted benefit and therefore was not included in the financial impact analysis. Despite this, the submission presented clinical evidence comparing dienogest to placebo and leuprolide acetate (GnRH agonist), given the context of the submission (urgency of timelines), dienogest was TGA registered more than 10 years ago and there are limited controlled studies of different agents in this class. Leuprolide is an GnRH agonist which is usually reserved for patients who have failed prior hormone therapy ±analgesics and are therefore not considered an appropriate comparator for dienogest for the requested restriction.

5.3 The Pre-Sub-Committee Response (PSCR) stated that insights from clinical experts indicate that medroxyprogesterone prescribing is avoided due to significant concerns with adverse effect profile (e.g., vaginal atrophy, breast density, and reduction in bone mineral density (BMD)). The sponsor cited two studies identified during the evaluation comparing dienogest and MPA (Wong & Lee, 2018; Vahid Dastjerdi et al., 2023) as evidence that dienogest is a superior treatment. The PSCR also stated that endometriosis patient groups, QENDO and EndoActive, have provided written support for the PBS listing of dienogest, which indicated benefits of dienogest included safety profile, as dienogest was generally well tolerated, with mild adverse effects and lower risk of severe adverse effects commonly associated with long-term use of hormonal treatments. The PSCR stated that the TGA Product Information for dienogest and norethisterone indicates that these treatments can be used in any patient with endometriosis. MPA, however, is specifically indicated "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" (TGA approved MPA PI). The sponsor therefore concluded that this would imply that dienogest should be used in a broader population than MPA.

5.4 The sponsor (PSCR) also stated that no RCTs comparing dienogest with norethisterone were identified by the sponsor.

5.5 The ESC noted that no comparator was nominated. The ESC advised that the progestogens currently listed on the PBS could be comparators. The ESC noted that while the TGA indication for MPA is for a narrower population, the PBS population is the same. Additionally, the ESC advised that levonorgestrel IUD and etonogestrel implant may also be comparators.

For more detail on PBAC's view, see section 7 PBAC outcome

6 Consideration of the evidence

Sponsor hearing

6.1 The sponsor requested a hearing for this item. The clinicians described the place in clinical practice for dienogest, including for long-term management, and the natural

history of the disease. Clinical input stated that the mechanism of action for dienogest differs from other progestogens currently listed on the PBS, in that it exerts effects on both the ovaries and uterus. It was stated that ovarian activity may have a therapeutic advantage for some patients and assist in preserving fertility. The clinician explained that some patients who commence treatment with dienogest and achieve good results have ceased treatment because of the cost and patients then choose higher risk treatments such as laparoscopy. The clinical input stated that preliminary data from a Medical Research Future Fund funded project suggests that patients receiving treatment with dienogest have comparable quality of life outcomes to patients who have undergone laparoscopy, but at a lower cost to the health system. The clinicians noted that more comparative data is required, but highlighted that the large patient cohort required to conduct comparative studies with older progestogen, due to the many variables influencing menstrual pain, is a barrier to comparative research.

6.2 The clinicians stated that the addition of dienogest to the PBS would provide patients with endometriosis more treatment options. The clinicians stated that dienogest is suitable for most women with endometriosis. Clinical input stated that when considering treatment with dienogest, clinicians evaluate the risks associated with laparoscopy (and also the risks of increased pain due to the stimuli associated with surgery). In some circumstances, laparoscopy would remain the most appropriate treatment. It was the clinician's opinion that any increase in cost to the PBS from dienogest would be offset by benefits in patient care and reduction in surgical costs.

Consumer comments

6.3 The PBAC noted and welcomed comments from individuals with the health condition (15), parent or partner of an individual with the health condition (2), health professional (1) and organisations (2) via the Consumer Comments facility on the PBS website. Comments described the positive impacts of dienogest, particularly its effectiveness in reducing pain, but also in reducing other endometriosis-related symptoms. Comments also stated that alternative treatments have not been as effective at controlling endometriosis growth or symptoms.

6.4 The PBAC noted input stating that the addition of dienogest to the PBS will result in a better selection of progestogens available to consumers, which increases the likelihood of those with endometriosis having access to a suitable medication (given the variability of consumers response to differing progestogens), and that this will result in a reduction of repeated surgeries. Comments described dienogest as being suitable for long-term use and that it allows for a quick return to ovulation cycles should those undergoing treatment wish to conceive. Comments highlighted that the current cost of dienogest is a barrier to patient access.

6.5 Other comments described the impacts of endometriosis on quality of life, including severe pain, an inability to complete daily tasks, reduced social life, and the need for multiple surgeries.

6.6 The PBAC noted the report from EndoActive outlining the economic cost of

endometriosis in Australia and a view of the impact of endometriosis on the Australian community.

6.7 The PBAC noted the input from the National Aboriginal Community Controlled Health Organisation (NACCHO), stating that only a small number of combined oral contraceptives and progestogens that are used as hormonal treatments for endometriosis are listed on the PBS. This creates a significant barrier for patients who are eligible for the Closing-the-Gap (CTG) PBS Co-payment program. Access for those living in remote areas using the Remote Area Aboriginal Health Services (RAAHS) Program, which does not include non-PBS medicines, is further impacted. Input from NACCHO states that listing dienogest on the PBS would increase the range of accessible and affordable treatments for endometriosis. In particular, that it is important to have access to progesterone only treatments for endometriosis for those with higher cardiovascular risk, such as older Aboriginal and Torres Strait Islander women, when exposure to oestrogen can present an unacceptable risk of venous thromboembolism.

6.8 The input from NACCHO highlighted that priority 3.5 of the Australian Government's National Action plan for Endometriosis includes 'Make provisions for Aboriginal and Torres Strait Islander people with endometriosis associated chronic pelvic pain through the Closing the Gap PBS Co-payment Measure'

Clinical trials

6.9 The submission was based on one randomised controlled trial (RCT) comparing dienogest 2 mg versus placebo (A32473), its open-label, single arm, extension study (A39700) and one RCT comparing dienogest 2 mg versus leuprolide acetate (GnRH agonist) (AU19). The submission described A32473, A39700 and AU19 as pivotal trials, given they were included in the TGA registration of dienogest. The submission included as supportive evidence four studies of dienogest (A02266, Caruso 2015, Momoeda 2009, Ebert 2017), which were non-randomised or open-label, non-comparative single arm studies of dienogest treatment in endometriosis. The submission also included a pooled analysis of dienogest (Strowitzki 2015) based on A32473, A39700, AU19 and A02266.

6.10 A literature search conducted during the evaluation identified more recent comparative trials of dienogest for treatment of endometriosis pain. For example, Taha 2021[14] reported the efficacy of dienogest vs drospirenone/ethinylestradiol (Yasmin) treatment over 6 months for endometriosis pain, Kashi 2022[15] investigated

[14] El Taha L, Abu Musa A, Khalifeh D, Khalil A, Abbasi S, Nassif J. Efficacy of dienogest vs combined oral contraceptive on pain associated with endometriosis: Randomized clinical trial. Eur J Obstet Gynecol Reprod Biol. 2021 Dec;267:205-212. doi: 10.1016/j.ejogrb.2021.10.029.

[15] Kashi AM, Niakan G, Ebrahimpour M, Allahqoli L, Hassanlouei B, Gitas G, Alkatout I. A randomized, double-blind, placebo-controlled pilot study of the comparative effects of dienogest and the combined oral contraceptive pill in women with endometriosis. Int J Gynaecol Obstet. 2022 Jan;156(1):124-132. doi: 10.1002/ijgo.13677.

the effects of post-operative dienogest vs levonorgestrel/ethinylestradiol treatment for 6 months on pain and quality of life, Vercelli 2016[16] investigated dienogest vs norethindrone acetate as first-line progestin treatment over 6 months for symptomatic endometriosis and Wong 2018[17] compared dienogest vs medroxyprogesterone acetate for management of endometriosis pain. The evaluation also identified a number of systematic reviews and meta-analyses of dienogest for treatment of endometriosis pain (Brown 2012[18], Andres 2015[19], Lin 2021[20], Morsi 2023[21]), which included the two pivotal trials of the submission (A32473 (Strowitzki 2010a) and AU19 (Strowitzki 2010)) as well as potentially relevant studies excluded from the submission comparing dienogest vs GnRH analogue (Cosson 2002[22], Harada 2009[23], Abdou 2018[24]), placebo (Lang 2018[25]) and/or combined oral contraceptive (COC) (Niakan 2021[26]) on endometriosis pain and safety outcomes including change in bone mineral density (BMD). Overall, the results suggested that dienogest was superior to placebo in reducing endometriosis associated pelvic pain score (EAPP). Compared to other progestin, dienogest was as effective as norethindrone acetate (norethisterone) and medroxyprogesterone in reducing pelvic pain. Dienogest was as effective as COC and GnRH (triptorelin, leuprolide acetate, buserelin) in reducing EAPP and improving QoL. In terms of safety, incidence of AEs was comparable across treatments with the exception of more hypoestrogenic symptoms (e.g. hot flushes,

[16] Vercellini P, Bracco B, Mosconi P, Roberto A, Alberico D, Dhouha D, Somigliana E. Norethindrone acetate or dienogest for the treatment of symptomatic endometriosis: a before and after study. Fertil Steril. 2016 Mar; 105(3):734-743.e3. doi: 10.1016/j.fertnstert.2015.11.016.

[17] WONG Y, LEE M. Dienogest Versus Medroxyprogesterone Acetate for Control of Menstrual Pain in Chinese Women with Endometriosis. Hong Kong J Gynaecol Obstet Midwifery [Internet]. 2018; 18(2):91-97.

[18] Brown J, Kives S, Akhtar M. Progestagens and anti-progestagens for pain associated with endometriosis. Cochrane Database Syst Rev. 2012 Mar 14;2012(3):CD002122. doi: 10.1002/14651858.CD002122.pub2.

[19] Andres Mde P, Lopes LA, Baracat EC, Podgaec S. Dienogest in the treatment of endometriosis: systematic review. Arch Gynecol Obstet. 2015 Sep;292(3):523-9.

[20] Lin SC, Wang XY, Fu XL, Yang WH, Wu H, Bai Y, Shi ZN, Du JP, Wang BJ. Systematic review and Meta-analysis of efficacy and safety of dienogest in treatment of endometriosis. World J Meta-Anal 2021; 9(4): 377-388.

[21] Morsi AA, Ahmed N, Amer WM. Efficacy and Safety of Dienogest in the Management of Women with Endometriosis; Systematic Review and Meta-Analysis. Evidence-based Women's Health Journal 2023; 13(2):119-127.

[22] Cosson M, Querleu D, Donnez J, Madelenat P, Koninckx P, Audebert A, Manhes H. Dienogest is as effective as triptorelin in the treatment of endometriosis after laparoscopic surgery: results of a prospective, multicenter, randomized study. Fertil Steril. 2002 Apr;77(4):684-92. doi: 10.1016/s0015-0282(01)03270-8.

[23] Harada T, Momoeda M, Taketani Y, Aso T, Fukunaga M, Hagino H, Terakawa N. Dienogest is as effective as intranasal buserelin acetate for the relief of pain symptoms associated with endometriosis-a randomized, double-blind, multicenter, controlled trial. Fertil Steril 2009; 91: 675-681.

[24] Abdou AM, Ammar IMM, Alnemr AAA, Abdelrhman AA. Dienogest Versus Leuprolide Acetate for Recurrent Pelvic Pain Following Laparoscopic Treatment of Endometriosis. J Obstet Gynaecol India 2018; 68: 306-313.

[25] Lang J, Yu Q, Zhang S, Li H, Gude K, von Ludwig C, Ren X, Dong L. Dienogest for Treatment of Endometriosis in Chinese Women: A Placebo-Controlled, Randomized, Double-Blind Phase 3 Study. J Womens Health (Larchmt) 2018; 27: 148-155.

[26] Niakan G, Rokhgireh S, Ebrahimpour M, Mehdizadeh Kashi A. Comparing the Effect of Dienogest and OCPS on Pain and Quality of Life in Women with Endometriosis: A Randomized, Double-Blind, Placebo-Controlled Trial. Arch Iran Med. 2021 Sep 1;24(9):670-677.

vaginal dryness) and significant BMD loss in GnRH treated patients compared to dienogest at 16-24 weeks.

6.11 The evaluator requested the sponsor to consider whether there is evidence of a clinical advantage for dienogest in some subgroups. For example a literature search conducted during the evaluation identified a study (Vahid-Dastjerid 2023[27]) reporting that the recurrent rate of endometriosis after laparoscopic surgery was similar in patients randomised to take cyclic dosing of dienogest or cyclic medroxyprogesterone acetate. However, pelvic pain scores and lesion size were significantly lower for the dienogest group.

6.12 Trial and studies presented in the submission are summarised in Table 3. Given leuprorelin is unlikely to be replaced by dienogest in practice, RCT evidence versus leuprorelin is less relevant for the requested restrictions.

[27] Vahid-Dastjerdi M, Hosseini R, Rodi H, Rastad H, Hosseini L, Comparison of the effectiveness of dienogest with medroxyprogesterone acetate in the treatment of pelvic pain and recurrence of endometriosis after laparoscopic surgery. Achieves of Gynecology and Obsetrics. 2023. 30:149-155

Table 3: Trials and studies presented in the submission

Trial ID	Publication title	Publication citation
Dienogest vs Placebo		
A32473	T. Strowitzki, T. Faustmann, C. Gerlinger, C. Seitz. Dienogest in the treatment of endometriosis-associated pelvic pain: a 12-week, randomized, double-blind, placebo-controlled study	European Journal of Obstetrics & Gynecology and Reproductive Biology 2010: 151;193-198
A39700 (extension of A32473)	F. Petraglia, D. Hornung, C. Seitz, T. Faustmann, C. Gerlinger, S. Luisi, L. Lazzeri, T. Strowitzki. Reduced pelvic pain in women with endometriosis: efficacy of long-term dienogest treatment.	Arch Gynaecol Obstet 2012: 285; 167-173
Dienogest vs leuprolide		
AU19	T.Strowitzki, J.Marr, C.Gerlinger, T.Faustmann, C.Seitz. Dienogest is as effective as leuprolide acetate in treating the painful symptoms of endometriosis: a 24 week, randomized, multicentre, open-label trial.	Human Reproduction 2010: 25(3);633-641
Non-randomised or open label studies		
A02266	G. Köhler, T.A. Faustmann, C. Gerlinger, C. Seitz, A.O. Mueck. A dose-ranging study to determine the efficacy and safety of 1, 2, and 4 mg of dienogest daily for endometriosis	International Journal of Gynecology and Obstetrics 2010: 108;21-25
Caruso 2015	S. Caruso, M. Iraci, S. Cianci, E. Casella, V. Fava, A. Cianci. Quality of life and sexual function of women affected by endometriosis-associated pelvic pain when treated with dienogest.	J Endocrinol Invest 2015: 38;1211-1218
Momoeda 2009	M. Momoeda, T. Harada, N. Terakawa, T. Aso, M. Fukunaga, H. Hagino and Y. Taketani. Long-term use of dienogest for the treatment of endometriosis	Journal of Obstetrics and Gynaecology Research December 2009: 35(6);1069-1076
Ebert 2017	A.D. Ebert, L. Dong, M. Merz, B. Kirsch, M. Francuski, B. Bottcher , H. Roman, P. Suvitie. O. Hlavackova, K. Gude, C. Seitz. Dienogest 2 mg Daily in the Treatment of Adolescents with Clinically Suspected Endometriosis: The VISanne Study to Assess Safety in ADOlescents (NCT01283724)	J Pediatric and Adolescent Gynecology 2017: 30(5);560-567
Pooled analyses		
Strowitzki 2015	T. Strowitzki, T. Faustmann, C. Gerlinger, U. Schumacher, C. Ahlers, C. Seitz. Safety and tolerability of dienogest in endometriosis: pooled analysis from the European clinical study program	International Journal of Women's Health 2015: 7;393-401

Source: Tables 6 and 7, pp24-26 of the submission.

6.13 The key features of the included studies are summarised in Table 4.

Table 4: Key features of the included evidence

Trial	N	Design/ duration	bias	Treatment	Patient population	Outcome(s)
dienogest vs. placebo						
A32473	198	P3, MC, R, DB 12 weeks	Low	Dienogest 2 mg D or placebo	18-45y, Endometriosis^ EAPP VAS ≥30mm	1: EAPP (VAS) and analgesic use 2: B&B score, QoL (SF-36)
A39700 (A32473 Extension)	168	P3, MC, OL, single arm 52 weeks	High	Dienogest 2 mg D	From A32473	1: EAPP (VAS) 2: uterine bleeding pattern
dienogest vs leuprolide acetate						
AU19	248	P3, MC, R, OL 24 weeks	High	Dienogest 2 mg D or LA 3.75 mg Q4W	18-45y, Endometriosis^	1: EAPP (VAS) 2: VAS Score, B&B, QoL (SF-36), safety (BMD)
Non-randomised or open label studies						
A02266	68	P2, MC, R, OL 24 weeks	High	Dienogest 1 mg, 2 mg or 4 mg D	Mean 27.6-33.5y, Mild to moderate endometriosis^	1: endometriosis stage (rAFS) 2: dysmenorrhea, dyspareunia, pelvic pain, menstrual pain, safety (tolerability, bleeding pattern)
Caruso 2015	92*†	OL 6 months	High	Diengoest 2mg D Control (NSAIDs)	18-37y, Chronic pelvic pain with diagnosis of endometriosis†	1: EAPP (VAS), QoL (SF-36)
Momoeda 2009	135	OL 52 weeks	High	Dienogest 2mg (1 mg BiD)	≥20y (range 21-47 years), Visually diagnosed (including CT/ultrasound) with subjective symptoms	1: Safety (bleeding pattern, BMD), global improvement of symptoms, lower abdominal pain VAS
Ebert 2017	111	MC, OL 52 weeks	High	Dienogest 2mg D	12-18y, Clinically suspected or laproscopically proven endometriosis	1: BMD 2: EAPP (VAS), B&B
Strowitzki 2015	332[a]	Pooled analysis of Kohler 2010, Strowitzki 2010a, Strowitzki 2010, Petraglia 2012	Unclear	As above	As above	Safety (AEs, bleeding pattern, BMD)

Source: Tables 6 and 7, pp24-26 of the submission.

AE = adverse event; BMD = bone mineral density; B&B = Biberoglu and Behrman (pelvic pain, dysmenorrhea, dypspareunia and signs pelvic tenderness and induration); DB = double blind; EAPP = Endometriosis associated pelvic pain score; LA=leuprolide acetate; MC = multi-centre; NSAIDs = non-steroidal anti-inflammatory drugs; OL = open label; QoL = quality of life; R = randomised; rAFS = revised classification of the American Fertility Society; renamed the American Society for Reproductive Medicine; VAS = Visual analogue scale; BiD = twice daily; D = daily; Q4W = every 4 weeks;

^ histologically proven endometriosis determined at diagnostic laparoscopy.

* of the 92 women enrolled 38 (41.3%) refused hormonal treatment.

† Transvaginal ultrasound was performed to rule out rectal endometriosis, deep endometriosis, ovarian endometrioma, adenomyosis.

[a] 514 women were included from the four studies, of which 332 were treated with dienogest 2 mg daily for 12 and 65 weeks.

6.14 A32473 and AU19 were multicentre, randomised trials in women with endometriosis. In A32473, patients received either dienogest or placebo during double-blind treatment for 12 weeks, whereas in AU19 patients received open-label dienogest or leuprolide acetate for 24 weeks. Study A39700 was an extension of A32473, in which patients who completed the double-blind treatment (without major protocol

violation) were eligible to receive open-label dienogest for up to 53 weeks (total 65 weeks including 12 weeks in A32473). Of the total patients randomised (N=198) in A32473, 188 (94.9%) completed the double-blind treatment and 168 (84.8%) entered the extension study A39700 and was included in the full analysis set (FAS). AU19 was designed to demonstrate non-inferiority of dienogest vs leuprolide acetate for EAPP on the visual analogue scale (VAS), with a pre-specified non-inferiority margin of 15 mm on VAS based on the per protocol set (PPS). PPS included all randomised patients without major protocol deviations. Supportive analysis was also conducted in the FAS, which included all randomised patients receiving at least one unit of study drug and had at least one observation after dosing.

6.15 Study A02266, Caruso 2015, Momoeda 2009 and Ebert 2017 were all open-label studies of dienogest treatment in women with endometriosis. Study A02266 was a dose-ranging study in which patients were randomised to three dose levels of dienogest (1, 2 and 4 mg) for 24 weeks. In Caruso 2015, patients who consented received 6 months treatment with dienogest and those who refused dienogest continued their previous non-steroidal anti-inflammatory drugs (NSAIDs), which constituted the control group. In Momoeda 2009 and Ebert 2017, patients received dienogest for 52 weeks.

6.16 The dose regimens across all the included studies were generally consistent with the PI, with the exception of Study A02266, which also included treatment arms dosed with daily dienogest 1 mg or 4 mg, and patients in Momoeda 2009 received dienogest 1 mg twice daily. Except for Ebert 2017, the included studies enrolled premenopausal women aged above 18 or 20 years with endometriosis. Ebert 2017 included eligible adolescent girls post-menarche aged 12-18 years with suspected endometriosis. All studies reported patient-reported outcome measures for endometriosis-associated pain using either VAS or subjective improvement categories (Study A02266 and Momoeda 2009) as the primary or secondary outcomes.

6.17 The risk of bias in the A32473 trial was considered low whereas for the risk of bias in the other studies were considered to be high due to the nature of the design, being open-label (A39700, AU19, A02266, Caruso 2015, Momoeda 2009, Ebert 2017) or single arm non-comparative (A39700, Momoeda 2009, Ebert 2017).

6.18 Baseline patient characteristics were generally balanced across treatment arms for A32473/A39700 extension and AU19 in terms of age, pelvic pain VAS and analgesic medication for endometriosis. In AU19, it was noted that more patients in the dienogest arm (12.2%) had 'very severe' total symptom and severity signs compared to the leuprolide acetate arm (6.3%) at screening. However, between the studies, more patients enrolled in A32473/A39700 (71%) had severity stage III-IV endometriosis than AU19 (42.9-47.5%), based on the revised classification of the American Fertility Society (rAFS; rename the American Society for Reproductive Medicine).

6.19 It was unknown whether there were important differences across the supportive studies in terms of diagnosis, severity and duration of disease, and prior and concomitant treatments due to lack of comparable information. Based on available information, there were some differences in the patient characteristics owing in part to differences in the eligibility criteria in terms of age (younger in Ebert 2017), endometriosis diagnosis (more clinically suspected in Ebert 2017) and disease severity (mild to moderate in A02266).

Comparative effectiveness

6.20 According to clinical guidelines, the main goal of treatment for endometriosis is to reduce symptoms, which is mainly pain. The clinical outcomes reported in the submission were reduction in endometriotic lesions (assessed by laparoscopy), change in EAPP (assessed by VAS), change in Biberoglu and Behrman (B&B) severity profile and quality of life assessment using the SF-36 survey and or global clinical impression scale.

6.21 The VAS consists of a straight line 100 mm in length with verbal anchors at either end representing a continuum of pain intensity. The VAS is validated for many pain indications and has been used in numerous studies specifically designed to evaluate pelvic pain associated with endometriosis.

6.22 The B&B scale, which is widely used in clinical trials, consists of a rating (0 = none; 1 = mild; 2 = moderate; 3 = severe) based on the patient's self-assessment of pain and on the gynaecological palpation finding of the attending physician. Higher numbers indicate greater severity of endometriosis.

6.23 Table 5 presents the change from baseline in EAPP VAS score in A32473, Study A39700, AU19 and Ebert et al 2017.

Table 5: Improvement (reduction) from baseline in EAPP VAS (in mm)

	Dienogest Mean (SD)	Placebo Mean (SD)	Leuprolide Mean (SD)	Difference (95% CI)
A32473, dienogest v placebo, 12 wks	27.4 (22.9)‡	15.1 (16.4)‡	-	**12.27 (6.40, 18.14)** ‡
A39700 Ext, dienogest, 65 wks	43.2 (21.7)†		-	-
AU19, dienogest v leuprorelin, 24 wks	40.2 (32.0)*	-	41.8 (28.6)*	1.6 (-6.42, 9.58)
Ebert 2017 dienogest, 48 wks	55.3^			

Source: table compiled for information in submission p38, 43

Bold text indicates statistical significance.

EAPP=endometriosis-associated pelvic pain; FAS=full analysis set; LA=leuprorelin acetate; PPS=per protocol set; VAS=visual analogue scale; wk=week

‡ *mean (SD) for FAS from submission. Strowitzki et al 2010a did not report SD. Difference in mean VAS score for PPS was 13.2 (7.3, 19.2).*

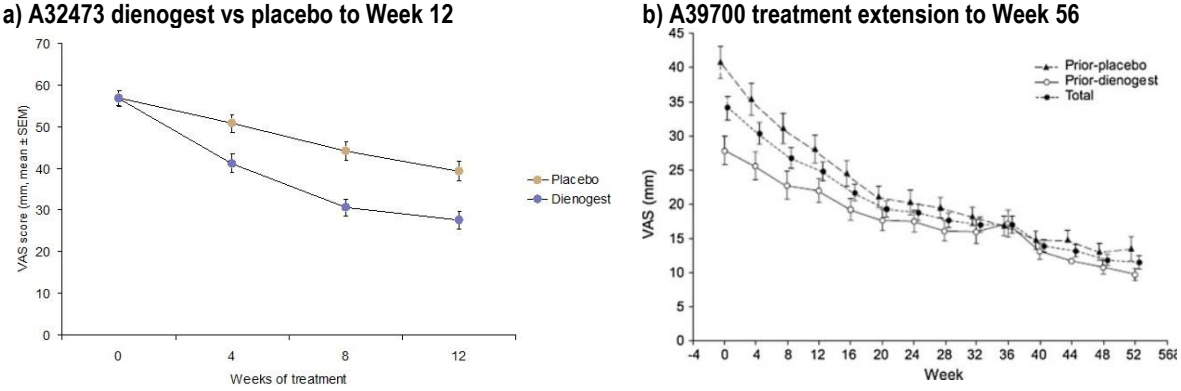
* *mean VAS score for PPS was 47.5 (28.8) dienogest group, 46.0 (24.8) in the LA group and treatment difference 1.5 (-9.26, 6.25).*

† *mean EAPP VAS reduction over the total treatment period of 65 weeks (i.e 12 wks placebo -controlled plus 53 wks open-label extension).*

^ *Calculated from mean EAPP VAS at baseline of 64.3 mm (SD 19.1 mm) and mean VAS score at Week 48 of 9.0 mm (SD 13.9 mm).*

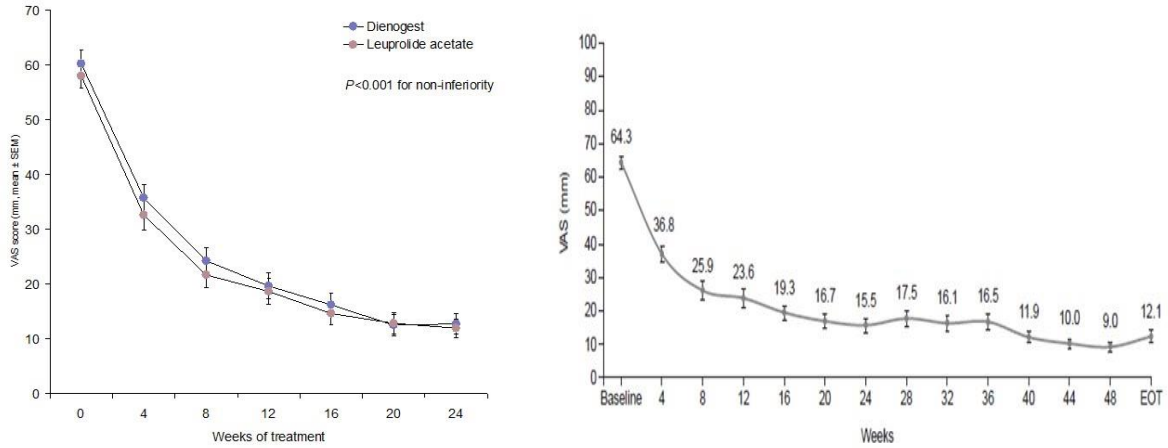
6.24 Figure 2 presents the change in EAPP VAS in A32473 during the placebo-controlled treatment to Week 12 and A39700 open-label extension for 53 weeks. Figure 3 presents the change in EAPP VAS in AU19 to Week 24 and Ebert 2017 (in adolescents) to Week 52.

Figure 2: Change in EAPP VAS score (mm, mean±SE) in studies A32473 and A39700 (FAS)
a) A32473 dienogest vs placebo to Week 12 **b) A39700 treatment extension to Week 56**



Source: Figure 6, p31 and Figure 7, p33 of the submission and Petraglia 2012.
EAPP=endometriosis-associated pelvic pain; FAS=full analysis set; VAS=visual analogue scale;

Figure 3: Change in EAPP VAS score (mm, mean±SE) in study AU19 and Ebert 2017
a) AU19 dienogest vs leuprelide acetate to Week 24 b) Ebert 2017 dienogest to Week 52 (aged 12-18 years) (PPS)



Source: Figure 8, p3 if the submission and Strowitzki 2010 and Ebert 2017.
EAPP=endometriosis-associated pelvic pain; LA=leuprolide acetate; PPS=per protocol set; VAS=visual analogue scale;

6.25 The results demonstrated improvement (reduction) from baseline in the mean EAPP VAS across the treatment arms. In A32473, there was statistically significantly greater improvement in the mean EAPP VAS at Week 12 in the dienogest group than in placebo. Patients treated with open-label dienogest in extension study A39700 showed continued improvement in EAPP VAS to Week 65. The results in the full analysis set (FAS, p<0.0001) was consistent with the per protocol set (PPS, p<0.0001). In the extension study A39700, the reduction in EAPP was sustained during the treatment period.

6.26 In AU19, there was no difference between dienogest and leuprolide acetate in the improvement from baseline in EAPP VAS at Week 24. The submission stated that non-inferiority was demonstrated between dienogest and leuprolide acetate based on the prespecified non-inferiority margin of 15 mm (p<0.0001).

6.27 The submission also presented other outcomes in A32473 and AU19. Further, patients treated with dienogest showed a trend towards reduction in analgesic medication use

(difference: 0.74 tablets/28 days; 95%CI: -1.4, 2.9) and improvement in total symptom and sign severity on B&B scale (pelvic pain, dysmenorrhea and dyspareunia) compared to placebo at Week 12. In AU19, B&B total score was similar between dienogest and leuprolide acetate groups at Week 24.

6.28 Across the supportive studies, Ebert 2017 showed improvement (reduction) in mean (SD) EAPP VAS of 64.3 (19.1) mm at baseline to 36.8 (26.1) mm at Week 4 and 9.0 (13.9) mm at Week 48. The proportion of responders (reduction from baseline in VAS score ≥30%) was 81.0% at Week 24. In Caruso 2015, patients treated with dienogest 2 mg daily showed improvement from baseline after 3-6 months in pelvic pain VAS, compared to no change in the control group. Momoeda 2009 showed increased global improvement in subjective symptoms during menstruation and reduction in lower abdominal pain and lumbago mean (SD) VAS at Week 24 (-22.5 (32.1) and -16.5 (28.4) mm, respectively) and 52 (-28.4 (29.9) and -19.8 (28.2) mm, respectively). In A02266, patients treated with dienogest 2 mg showed reduction from baseline at Week 24 in disease severity as measured by rAFS staging based on laparoscopy ($p < 0.001$) and improvement in rates of endometriosis symptoms (pelvic pain, dysmenorrhea, dyspareunia and premenstrual pain).

6.29 For patient reported outcomes, A32473 showed that treatment with dienogest had greater improvement on clinical global impressions (CGI) assessed by physicians and patients compared to placebo. While there were differences in two of the eight domains of SF-36 (pain and role limitation due to emotional problems), there was no difference between groups in mental and physical summary scale score after 12 weeks. In AU19, the dienogest group showed greater numerical improvement from baseline in SF-36 (mental and physical summary scale score) compared to leuprolide acetate group after 24 weeks. Caruso 2015 showed dienogest group had significant improvement in some QoL domains (physical function, physical role, bodily pain, general health and social function) at 3 months and all domains of SF-36 at 6 months compared to the control (NSAIDs) group. Momoeda 2009 reported dienogest treatment improved one of the eight SF-36 domains (bodily pain) from baseline after 24 weeks and 52 weeks and Ebert 2017 reported improvement on the endometriosis health profile (EHP-30) questionnaire all domains (pain, control and powerlessness, emotional well-being, social support and self-image) after 52 weeks.

6.30 With its PSCR, the sponsor provided the CSR of study A32473 to support the statement in the submission that more patients treated with dienogest in A32473 had reductions in EAPP VAS ≥50% and ≥75% without increase of concomitant pain medication compared to placebo (37.3% vs 19.8% and 18.6% vs 7.3%, respectively) at Week 12.

Comparative harms

6.31 Table 6 summarises the key adverse events (AEs) in the dienogest 2 mg group pooled across four studies (A32473, A39700, AU19 and A02266) and comparator group of placebo (A32473) and leuprolide acetate (AU19). Mean dienogest treatment duration across the four studies was 39.8 weeks.

Table 6: Frequently reported adverse events (≥3%) in pooled dienogest group (A32473, A39700, AU19, A02266), compared to placebo (A32473) and leuprolide acetate (AU19)

	Dienogest^ (N=332)	Placebo (N=96)[a]	Leuprolide acetate (N=128)[b]
AEs leading to discontinuation	15 (4.5%)	1 (1.0%)	5 (3.9%)
Adverse event (MedDRA preferred term)			
Headache	30 (9.0%)	5 (5.2%)	25 (19.5%)
Acne	17 (5.1%)	NR	6 (4.7%)
Nausea	14 (4.2%)	1 (1.0%)	NR
Weight increased	12 (3.6%)	NR	5 (3.9%)
Breast discomfort	18 (5.4%)	1 (1.0%)	NR
Depressed mood	17 (5.1%)	2 (2.1%)	11 (8.6%)
Flatulence	10 (3.0%)	NR	NR
Hot flush	9 (2.7%)	0 (0.0%)	9 (7.0%)
Loss of libido	5 (1.5%)	NR	8 (6.3%)
Vaginal dryness	2 (0.6%)	NR	9 (7.0%)

Source: Table 14, p 53 of the submission and Strowitzki 2015, Strowitzki 2010a (A32473), Strowitzki 2010b (AU19).

^ pooled safety of dienogest 2 mg group from four studies (A32473 (12 weeks), A39700 (65 weeks), AU19 (24 weeks) and A02266 (24 weeks)). Number of pooled patients is not equal to the sum of the individual dienogest 2 mg groups as patients in extension study A39700 were enrolled from A32473 and 87 of 168 patients had prior dienogest in A32473.

a The incidence of most frequent AEs (i.e. at least 2% patients) in the placebo group as reported by Strowitzki 2010a (A32473). The submission reported incidence of headache as 3 (3.1%) and none for acne, weight gain, depression and flatulence, which could not be verified.

b The incidence of most frequent AEs (i.e. at least 4% patients) in the leuprolide acetate group as reported by Strowitzki 2010b (AU19). The submission reported incidence of headache as 27 (21.1%) and hot flush as 8 (6.3%) from Strowitzki 2015 and incidence of nausea 3 (2.3%), weight gain 6 (4.7%), depression 3 (2.3%) and flatulence 1 (0.8%), which could not be verified.

6.32 Across the four studies, the incidence of AEs leading to discontinuation was low but numerically higher in the dienogest group compared to placebo (up to 12-65 weeks), and was similar compared to leuprolide acetate group (up to 24 weeks). AEs were generally mild or moderate in intensity. The most frequently reported AEs included headaches, acne, nausea, weight gain, breast discomfort and depressed mood. In Ebert 2017, the incidence of AEs in adolescent patients treated with dienogest 2 mg daily to Week 52 was generally consistent with the pooled analyses. In Momoeda 2009, for patients treated with dienogest 2 mg (1 mg twice daily dosing) to Week 52, the most frequently reported AEs included metrorrhagia (71.9%), headaches (18.5%) and constipation (10.4%); the majority of metrorrhagia (84.5%) and other AEs were mild to moderate in severity.

6.33 Additional data showed there was minimal change in lipid parameters and moderate reductions in plasma oestrogen with dienogest treatment. In AU19, patients treated with dienogest experienced fewer incidence of hypoestrogenic symptoms (such as hot flush, vaginal dryness, decreased libido and sleep disorder) compared to leuprolide acetate treatment. Further continuing treatment with dienogest decreased the frequency and intensity of bleeding irregularities. A32473 showed there was no difference between dienogest and placebo groups in bleeding pattern over 12 weeks. The mean (and median) number of bleeding/spotting days, number and duration of bleeding/spotting episodes decrease over time with treatment, and there was no difference between dienogest vs placebo group to Week 12. However, in AU19 there was higher rates of amenorrhea in leuprolide acetate group (due to hypoestrogenic effect) compared to dienogest group and there was numerically greater reduction in

the number of bleeding/spotting days and episodes and duration of episodes in the leuprolide acetate group compared to dienogest group to Week 24.

6.34 The submission stated that treatment with dienogest was not associated with a reduction in BMD. In Study AU19, for women whose measurements were available at screening and final visit there was significant difference between dienogest and leuprolide acetate (p=0.003) in the mean change in BMD of the lumbar spine at Week 24. The mean (SD) percentage change in lumbar BMD in the dienogest group (n=21) showed an increase of 0.25% (2.77%) compared to leuprolide acetate group (n=29) -4.04% (4.84%). Change in BMD was not reported in A32473/39700. The TGA delegate summary (2009) of dienogest for treatment of endometriosis noted the key trials (A32473 and AU19) provided short term results at 12-24 weeks and there was a lack of data on the effect of dienogest on BMD, which impacts on the duration of treatment considered safe.

6.35 Across the supportive evidence, Momoeda 2009 showed that patients treated with dienogest had significant reductions from baseline in BMD of the lumbar at Week 24 and Week 52 (n=43, mean (SD) change in BMD was -1.6% (2.4%) and -1.7% (2.2%), respectively). In Ebert 2017, adolescent patients with suspected endometriosis who received treatment with dienogest showed reduction from baseline in lumbar BMD at Week 52/end of dienogest treatment (EOT) (n=103, mean (SD) change in BMD -1.2% (2.3%)). However, in the subgroup (n=60) with reduction in BMD at Week 52/EOT, follow-up measurements 6 months post-treatment showed partial recovery of lumbar BMD (mean (SD) change from baseline: -2.3% at Week 52/EOT, -0.6% at 6 months after Week 52/EOT).

6.36 An independent search conducted during the evaluation to identify safety of longer-term use of dienogest for endometriosis found four non-comparative, observational studies (Seo 2017[28], Kim 2021[29], Park 2023[30], Maiorana 2024[31]), with treatment durations ranging from at least 52 weeks to 8 years. Overall, the studies generally showed a reduction from baseline in BMD after 6 months to 3 years of dienogest treatment. Seo 2017 reported significant reduction in BMD at the lumbar and femur neck after 6 months and 12 months post-operative dienogest treatment, however there was no difference in BMD after 2 years compared to after 1 year of treatment. Kim 2021 also showed significant reduction in BMD at the lumbar and femur neck after

[28] Seo JW, Lee DY, Yoon BK, Choi D. Effects of long-term postoperative dienogest use for treatment of endometriosis on bone mineral density. Eur J Obstet Gynecol Reprod Biol. 2017 May; 212:9-12. doi: 10.1016/j.ejogrb.2017.03.011.

[29] Kim SE, Lim HH, Lee DY, Choi D. The Long-Term Effect of Dienogest on Bone Mineral Density After Surgical Treatment of Endometrioma. Reprod Sci. 2021 May;28(5):1556-1562. doi: 10.1007/s43032-020-00453-7.

[30] J C Park, D J Kim, P-320 Change of bone mineral density after long-term use of dienogest with calcium and vitamin D supplementation after surgical treatment of endometrioma, Human Reproduction, Volume 38, Issue Supplement_1, June 2023, dead093.678, https://doi.org/10.1093/humrep/dead093.678.

[31] Maiorana A, Maranto M, Restivo V, Gerfo DL, Minneci G, Mercurio A, Incandela D. Evaluation of long-term efficacy and safety of dienogest in patients with chronic cyclic pelvic pain associated with endometriosis. Arch Gynecol Obstet. 2024 Feb;309(2):589-597. doi: 10.1007/s00404-023-07271-7.

3 years of dienogest treatment. Maiorana 2024 reported that osteopenia was found in 27.6% patients who had received dienogest for >15 to 108 months. Park 2023 reported there was a reduction in BMD at the femur and lumbar spine, which were not significant, in 15% and 62.5% patients respectively, treated with dienogest for mean duration of 41.3 months (range 24-101 months).

Benefits/harms

6.37 The submission did not present comparative efficacy or safety data to allow for quantitative comparison of the benefits and harms of treatment between dienogest and a nominated comparator. Accordingly, a benefits/harms table was not presented.

Clinical claim

6.38 The submission did not make a direct clinical claim.

6.39 The submission described treatment with dienogest was superior in effectiveness compared to placebo in terms of the EAPP VAS and quality of life measures in patients with endometriosis pain. Dienogest has favourable safety and tolerability profile, with no impact to BMD over 24 weeks.

6.40 The clinical claim for effectiveness vs placebo may be supported by the evidence presented in the submission, however the claim of favourable safety may not be adequately supported, given treatment with dienogest was associated with higher incidence of AEs compared to placebo and evidence comparing longer-term treatment was limited. Supportive evidence and available literature also showed that patients treated with dienogest experienced BMD loss after 24-52 weeks. On balance, it may be more appropriate to claim inferior safety.

6.41 The submission also provided evidence that indicate dienogest was non-inferior in effectiveness and has favourable safety compared to leuprolide acetate. Given leuprorelin acetate is not the treatment most likely to be replaced by dienogest in the requested setting, this information is less relevant for the requested restrictions.

6.42 The ESC noted that no clinical claim was made.

6.43 The ESC advised that endometriosis affects a high proportion of women and can be debilitating[32]. The ESC considered that providing women access to more options for the treatment of endometriosis was important, in particular for women who are not able to use estrogen-based treatment. The ESC advised that the request to list dienogest on the basis of clinical efficacy and safety was reasonable. However, the ESC emphasised that the submission did not clearly define the place of therapy for dienogest compared to other progestogens nor sufficiently demonstrate that

[32] *Around 1 in 7 (14%) women born in 1973–1978 were estimated to have been diagnosed with endometriosis by age 44–49 and women in the 1989–95 cohort who had turned 31, 9.2% were estimated to have been diagnosed with endometriosis compared with 6.9% of women born in 1973–78 at this age. Australian Longitudinal Study on Women's Health; Australian Institute of Health and Welfare, Endometriosis Web Report, www.aihw.gov.au/reports/chronic-disease/endometriosis-in-australia/contents/summary*

dienogest offers advantage over PBS listed progestogens used for the treatment of endometriosis.

6.44 The pre-PBAC response provided 5 letters of support for the PBS listing of dienogest – one letter each from Family Planning Australia and the Pelvic Pain Foundation of Australia and 3 from individual clinicians. These letters supported the unmet need from a clinical practice perspective that listing dienogest on the PBS would address. Input from Family Planning Australia noted that dienogest *"*is the only progesterone only therapy which is effective for managing endometriosis with once daily dosing which improves therapeutic adherence. Overall, there is a lack of PBS-listed oral progesterone only treatments which limit options for Australians who live with common co-morbidities such as migraine disorder or prior venous thrombo-embolism that precludes the COCP as a clinically-safe option." The Pelvic Pain Foundation of Australia noted in its input that "Currently available progestogen medications do not suit the needs of all patients, and dienogest (Visanne) offers another option for women who do not tolerate other progestogens" and that "Dienogest (Visanne) can suppress endometriosis lesions in women who plan surgery but wait sometimes long periods of time on hospital waiting lists. Where dienogest (Visanne) is particularly effective, it may reduce the need for surgery"

6.45 In the pre-PBAC response the sponsor stated on further review of the literature, to the sponsor's knowledge, dienogest (Visanne) is the only hormonal treatment of endometriosis to date with the largest (over 25,000 women across six European countries) real-world, non-interventional study published (Visanne Post-approval Observational Study (VIPOS)) (Heinemann et al., 2020; Moehner et al., 2020; Moehner et al., 2021; Becker et al., 2021a; Becker et al., 2021b) demonstrating long-term (7 years) effective use for treatment management of endometriosis compared to existing PBS listed treatments.

6.46 The PBAC considered that overall there was insufficient evidence provided to demonstrate superior effectiveness and safety compared to PBS listed oral progestogens that may be used for endometriosis. However, based on the clinical input received for this submission the PBAC considered the dienogest offered a therapeutic advantage for some patients.

Economic analysis

6.47 The submission did not provide an economic model for evaluation.

Drug cost/patient/year: $[redacted]

6.48 The annual cost of treatment was calculated to be $[redacted] (based on the DPMQ of $[redacted]).

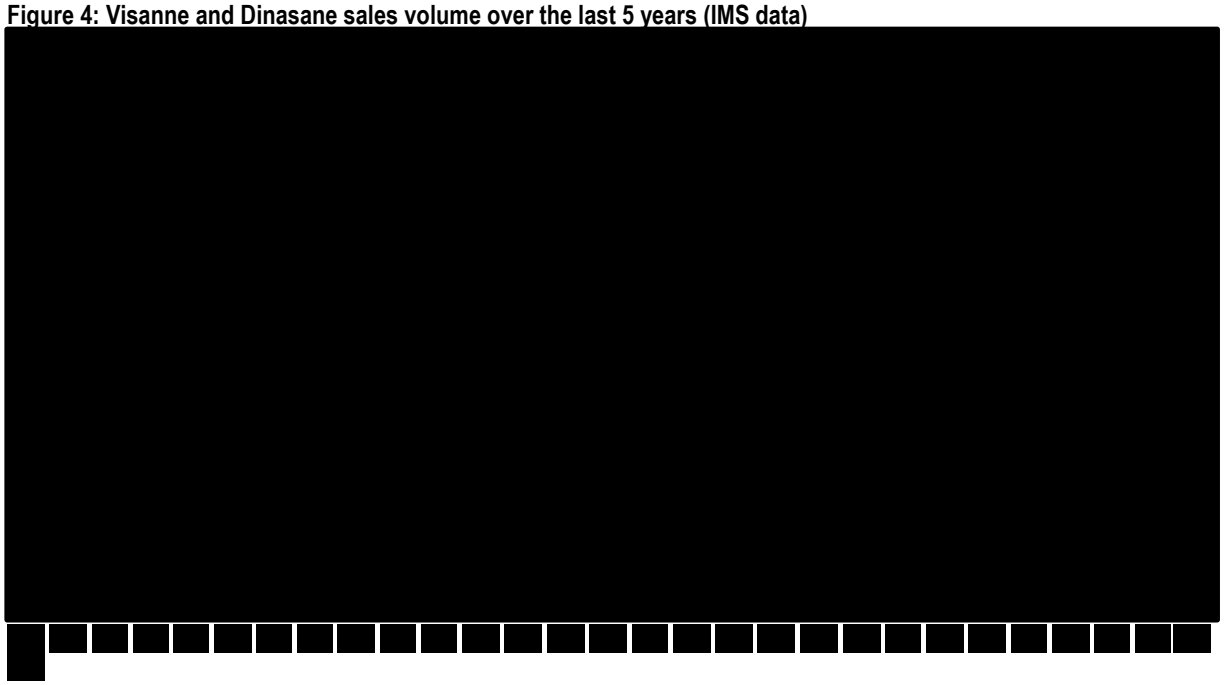
Estimated PBS usage & financial implications

6.49 This submission was not considered by DUSC.

6.50 The submission used a modified epidemiological approach based on the sales volume of dienogest (Visanne) in the private market, and assuming a *small* proportion of patients is expected to switch from PBS oral medroxyprogesterone.

6.51 The submission noted sales volume of dienogest (Visanne) had slowed since the availability of generic brand (Dinasane) (Figure 4). This is a market share issue; the data demonstrate that the total dienogest market has continued to increase. The dienogest market as a whole is relevant for PBS use.

Figure 4: Visanne and Dinasane sales volume over the last 5 years (IMS data)



6.52 The key inputs in the financial analysis are summarised in Table 7.

Table 7: Key inputs for financial estimates

Parameter	Value applied and source	Comment
Current dienogest market	Visanne ex-manufacturer sales (source: IMS) Year 1 – [redacted] [1] Year 2 – [redacted] [1] Year 4 – [redacted] [1] Year 5 – [redacted] [1] Year 6 – [redacted] [1] Year 7 – [redacted] [2]	Likely underestimated. Patients currently prescribed generic dienogest (Dinasane brand) were not accounted for in the estimation of patients migrating from non-PBS supply. These patients would conceivably switch to PBS should dienogest be listed. The dienogest (Visanne) market projection in the submission assumes an [redacted]% market share decreasing to [redacted]%. Accounting for 100% of the dienogest market projection would add [redacted] [1] patients in Year 1 increasing to [redacted] [1] additional patients in Year 6.
Annual growth rate of dienogest market	[redacted]% (average moving annual total ex-manufacturer sales; source: IMS)	Uncertain. The growth rate may not account for the effect that PBS-subsidised access may have on uptake, particularly in Year 1. The submission presented a sensitivity analysis of cost to PBS assuming 10% growth.
Cumulative switch patients	Small number of patients of patients anticipated to switch from oral medroxyprogesterone (source: *unclear*) Year 1 – [redacted] [3] Year 2 – [redacted] [3] Year 3 – [redacted] [3] Year 4 – [redacted] [3] Year 5 – [redacted] [3] Year 6 – [redacted] [3]	Likely underestimated. The submission did not provide justification for the estimated proportion of switch from oral medroxyprogesterone. The submission did not account for switch from other PBS products such as norethisterone; while due to data limitations, this results in an underestimate of the potential switch population.
Total Treated patients	[redacted] [1] patients in Year 1 increasing to [redacted] [2] in Year 6. (projected Visanne patients + projected oral medroxyprogesterone patients)	Likely underestimated given issues above.
Grandfathered patients	[redacted] [1] patients	The submission incorrectly identified patients prescribed dienogest (Visanne) on the private market as grandfathered patients. As the requested listings are for unrestricted PBS listings and patients currently using these products will be able to access these if PBS-listed, no Grandfather arrangements would be required.
Dose/duration	120 months (10 years)/ 2 mg daily	Dosing was appropriate. However, the duration of treatment proposed in financial estimates is not consistent with the durations of treatment presented in clinical evidence.
Offsets from other therapies	Cumulative patients switching from oral medroxyprogesterone (source: unclear) Year 1 – [redacted] [3] Year 2 – [redacted] [3] Year 3 – [redacted] [3] Year 4 – [redacted] [3] Year 5 – [redacted] [3] Year 6 – [redacted] [3]	The submission did not nominate a comparator therapy. The submission noted other therapies that were listed that may be used for the treatment of endometriosis. The submission did not account for switching from other PBS products such as norethisterone; while this may be due to data limitations, this also resulted in an underestimate of the potential population switching from other therapies.

Source: Compiled from information on p100 of the submission.

The redacted values correspond to the following ranges:

[1] *500 to < 5,000*

[2] *5,000 to < 10,000*

[3] *< 500*

6.53 The submission assumed that all patients currently prescribed dienogest privately will transition to PBS subsidised supply. It was reasonable to assume that all patients prescribed dienogest privately would transition to PBS subsidised treatment.

6.54 A growth rate of 8% from the current moving annual total growth of dienogest was applied to each year (along with the percentage of medroxyprogesterone patients switching therapy). This did not account for any market growth as a result of a PBS listing and was therefore likely underestimated, particularly in Year 1. The submission presented a sensitivity analysis using 10% growth.

6.55 The submission did not account for patients switching from the generic brand of dienogest 2 mg (Dinasane). The evaluation noted that the generic brands of dienogest, APX-dienogest and dienogest-STR have entries in the Australian Register of Therapeutic Goods, however it is not known if these brands are currently marketed in Australia. The dienogest market as a whole is relevant for PBS use. It would be reasonable to assume that all patients prescribed the generic brand dienogest would transition to PBS-listed dienogest (Visanne), if recommended. Based on the market data (see Figure 3), 500 to < 5,000 packs of Dinasane were sold in November 2023. While this was not dispensing data, using the submission's logic for the brand name dienogest (Visanne), then 500 to < 5,000 packs of Dinasane can be assumed as approximately 500 to < 5,000 patients. It was noted that 2023 annual sales was missing data from January 2023.

6.56 Estimation of patients swapping from other therapies was limited to a small number of patients prescribed oral medroxyprogesterone acetate. A summary of the number of patients treated with oral medroxyprogesterone is presented in Table 8. It would be reasonable to expect that a proportion of patients prescribed oral norethisterone may swap to dienogest.

Table 8: Patients treated with medroxyprogesterone acetate 10 mg tablets for endometriosis

Year	Patients
2021	[1]
2022	[1]
2023	[1]
2024	[2]

Source: PBS data provided by DUSC. Date of extraction: 2 May 2024. Data extracted from 1 January 2021 to 31 March 2024 Data for PBS item codes: 2722G and 13928C

The redacted values correspond to the following ranges:

[1] 5,000 to < 10,000

[2] 500 to < 5,000

6.57 The submission identified norethisterone and goserelin to be available on the PBS for the treatment of endometriosis, despite this, these medicines were not included in the financial impact analysis. The exclusion of goserelin from the financial impact analysis was reasonable given it is usually reserved as a later line therapy to dienogest. While it was acknowledged that the submission had excluded norethisterone due to data limitations, nonetheless, it meant the estimated population may not reflect the entire population for which dienogest may be prescribed. The extent of this underestimation was uncertain.

6.58 The submission assumed a duration of treatment of 120 months (10 years) for all patients. The submission assumed that treatment with dienogest would be chronic (continuous over a 10-year duration of treatment).

6.59 The predicted use of dienogest (Visanne) and the financial implications associated with the proposed listing are summarised in Table 9.

Table 9: Estimated use and financial implications

	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Estimated extent of use						
Number of patients treated	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][1]	[redacted][2]
Number of scripts dispensed[a]	[redacted][3]	[redacted][3]	[redacted][4]	[redacted][4]	[redacted][5]	[redacted][5]
Estimated financial implications of dienogest						
Cost to PBS less copayments	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]
Cost to RPBS less copayments	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]
Estimated financial implications for medroxyprogesterone						
Cost to PBS less copayments	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]	-$[redacted][7]
Cost to RPBS less copayments	-	-	-	-	-	-$[redacted][7]
Net financial implications						
Net cost to PBS	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]
Net cost to RPBS	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]
Net cost to PBS/RPBS	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]	$[redacted][6]

Source: Tables 44, 45, 47 & 48, pp100-101 of the submission

The redacted values correspond to the following ranges:

[1] 500 to < 5,000

[2] 5,000 to < 10,000

[3] 40,000 to < 50,000

[4] 50,000 to < 60,000

[5] 60,000 to < 70,000

[6] $0 to < $10 million

[7] net cost saving

6.60 The total cost to the PBS/RPBS of listing dienogest (Visanne) was estimated to be $0 to < $10 million in Year 6 and a total of $10 million to < $20 million in the first 6 years of listing.

6.61 Cost offsets from PBS therapies were likely underestimated as they relied on the switch assumptions. The submission stated that only < 500 patients would switch from medroxyprogesterone 10 mg tablets (pack of 100) in the first year (increasing to < 500 patients in year 6 accumulatively).

6.62 It was noted that elements of potential utilisation were not addressed in the submission's estimates:

- Potential product preference for dienogest compared to current PBS-listed options to determine likely patient switching to dienogest if it is PBS listed as requested.

6.63 Overall, the estimated cost to the PBS/RPBS was likely underestimated due to the submission not including the whole dienogest private market, not accounting for any growth with transition to PBS, and using conservative switch assumptions.

6.64 In the PSCR, the sponsor provided sensitivity analyses to account for 10% market growth, switching from generic dienogest, [redacted]% to [redacted]% oral medroxyprogesterone patient

switch and [redacted]% norethisterone patient switch. The sponsor stated that the cumulative total of all sensitivity analyses shows that the cost of listing dienogest on the PBS will not exceed $0 to < $10 million the first year to $0 to < $10 million in year 6.

6.65 The ESC noted the sensitivity analysis for the financial estimates, but considered the growth rate assumptions were still underestimated. The ESC advised that the private price for dienogest is likely a barrier to current use and expected it would be used more widely if listed on the PBS.

6.66 The ESC noted that it was not clear whether patients with adenomyosis were include in the utilisation estimates. The ESC considered that adenomyosis would likely be encompassed by the requested PBS listing.

6.67 Overall, the ESC considered that there was uncertainty in the utilisation of dienogest (Visanne) should it be listed on the PBS and that the costs were likely underestimated.

Committee-In-Confidence information

6.68 [redacted]

End Committee-In-Confidence information

7 PBAC Outcome

7.1 The PBAC recommended the listing of dienogest on the PBS as an Authority Required (STREAMLINED) listing for the treatment of endometriosis on the basis that it would be cost effective with a price premium over medroxyprogesterone due to therapeutic advantages for some women.

7.2 The PBAC noted the public health benefit of PBS-subsidised access to effective treatment options for endometriosis. The PBAC considered that there was a clinical need for access to effective medicines to manage endometriosis, in particular for women who are not able to use estrogen-based treatment. The PBAC recalled from its December 2022 consideration of the Stocktake of PBS subsidised medicines available for endometriosis and related conditions that the use of dienogest 2 mg for the treatment of endometriosis is supported by clinical guidelines.

7.3 The PBAC considered that clinical trial evidence provided in the submission supported the clinical efficacy of dienogest for improving pelvic pain and quality of life outcomes in patients with endometriosis. The PBAC considered that the information from the clinical trial comparing dienogest and leuprorelin acetate was less relevant for the requested restrictions.

7.4 The PBAC noted that no comparator was nominated in the submission. The PBAC noted the paucity of data available and considered that it was unlikely that an improved analysis would be forthcoming.

7.5 The PBAC considered that dienogest had comparable efficacy to oral medroxyprogesterone for the treatment of endometriosis, in terms of improvements in pelvic pain scores and quality of life outcomes. The PBAC noted the comments from the clinician in sponsor hearing regarding the current clinical use of dienogest and the potential benefits because of its mechanism of action. The PBAC noted the input from consumers describing the positive impact of dienogest, particularly its effectiveness in reducing pain, but also in reducing other symptoms of endometriosis. The PBAC noted the inputs from Family Planning Australia, the Pelvic Pain Foundation of Australia and individual clinicians provided in the sponsor's pre-PBAC response supporting the unmet need from a clinical practice perspective that PBS access to dienogest would address.

7.6 The PBAC noted the price requested for dienogest was higher than that of other oral progestogens listed on the PBS that may be used for the treatment of endometriosis. The PBAC noted that in its PSCR, the sponsor had cited evidence that dienogest was superior to oral medroxyprogesterone for the treatment of endometriosis in some circumstances. Overall, the PBAC considered that a claim of superiority was not supported by the evidence provided. However, after giving consideration to the clinical inputs provided for this submission, the PBAC was satisfied that dienogest offers a therapeutic advantage for some patients over other progestogens currently listed on the PBS, including for women with endometriosis that have not responded

or who are unable to tolerate currently listed oral progestogen therapies. The PBAC noted the clinical advice provided regarding the mechanism of action of dienogest and that its ovarian activity, in addition to uterine activity, can provide benefits for fertility preservation compared to oral norethisterone and medroxyprogesterone. The PBAC considered that a price premium over medroxyprogesterone was justified. The PBAC considered that dienogest would be acceptably cost-effective at the requested price.

7.7 The PBAC considered that the financial and utilisation estimates were uncertain and likely underestimated, despite the adjustments made in the PSCR. However, in the context of the clinical need, the PBAC advised the listing of dienogest would result in a relatively modest cost to the PBS. The PBAC recommended that the Department of Health and Aged Care undertake a utilisation review of PBS listed medicines that may be used for the treatment of endometriosis when 2 years of data post-listing of dienogest are available.

7.8 The PBAC considered dienogest is suitable for inclusion in the PBS medicines for prescribing by nurse practitioners as continuing therapy only.

7.9 Dienogest should not be exempt from the Early Supply Rule as it currently applies to medroxyprogesterone acetate 10 mg.

7.10 The PBAC recommended that dienogest should not be treated as interchangeable on an individual patient basis with any other drugs, according to s101(3BA) of the *National Health Act 1953*.

7.11 The PBAC found that the criteria prescribed by the *National Health (Pharmaceuticals and Vaccines – Cost Recovery) Regulations 2022* for Pricing Pathway A were not met. Specifically the PBAC found that in the circumstances of its recommendation for dienogest:

a) The treatment is not expected to provide a substantial and clinically relevant improvement in efficacy, or reduction of toxicity over alternative therapies;

b) The treatment is not expected to address a high and urgent unmet clinical need due to availability of other treatments;

c) It was not necessary to make a finding in relation to whether it would be in the public interest for the subsequent pricing application to be progressed under Pricing Pathway A because one or more of the preceding tests had failed.

7.12 The PBAC noted that this submission is not eligible for an Independent Review as it received a positive recommendation.

Outcome:
Recommended

8 Recommended listing

8.1 Add new item:

MEDICINAL PRODUCT medicinal product pack		PBS item code	Max. qty packs	Max. qty units	№.of Rpts	Available brands
DIENOGEST						
Dienogest 2 mg tablet, 28		NEW	1	28	5	Visanne
Restriction Summary / Treatment of Concept:						
	Category / Program: GENERAL – General Schedule (Code GE)					
	Prescriber type: ☒Medical Practitioners ☒Nurse Practitioners					
	Restriction type: ☒ Authority Required (STREAMLINED)					
	Administrative Advice: **Continuing Therapy Only:** For prescribing by nurse practitioners as continuing therapy only, where the treatment of, and prescribing of medicine for, a patient has been initiated by a medical practitioner. Further information can be found in the Explanatory Notes for Nurse Practitioners.					
	Condition: Endometriosis					
	Indication: Endometriosis					

These restrictions may be subject to further review. Should there be any changes made to the restriction the sponsor will be informed.

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised through the Pharmaceutical Benefits Scheme (PBS) in Australia. It considers applications regarding the listing of medicines on the PBS and provides advice about other matters relating to the operation of the PBS in this context. A PBAC decision in relation to PBS listings does not necessarily represent a final PBAC view about the merits of the medicine or the circumstances in which it should be made available through the PBS. The PBAC welcomes applications containing new information at any time.

10 Sponsor's Comment

Bayer welcomes the outcome for Visanne. Visanne is an established off-patent product which is currently privately available to Australian women. Bayer made submission to the PBAC in response to stakeholder interest in providing an alternative treatment for women with endometriosis through the Pharmaceutical Benefits Scheme (PBS).

Bayer is committed to advancing women's health by providing solutions for her different reproductive needs and advocating for equitable access.