New Medicine Assessment

Dienogest

Recommendation: Amber 0 for the following indications:

Treatment of endometriosis.

Following specialist recommendation, when combined oral contraceptives and progestogen-only oral contraceptives have proved ineffective or are not tolerated by the patient.

Summary of supporting evidence:

- Studies have shown dienogest significantly reduces pain related to endometriosis, vs placebo.
- A systematic review and meta- analysis has shown comparable efficacy and tolerability of dienogest vs COC, with the exception of dyspareunia which was reduced significantly in the COC treatment groups.
- A systematic review of dienogest vs GnRH agonists concluded that they were comparable in controlling symptoms associated with endometriosis.
- There is an absence of data comparing dienogest to other oral progestogen options.
- The most frequently cited adverse effect of progestins is spotting/irregular bleeding whilst those receiving comparator interventions most often reported hot flushes.
- Treatment selection is strongly led by patient choice, so the greater the range of treatment options available the wider the patient choice. Oral treatment options may remain important for women post-surgery as endometrial tissue often grows back.
- Treatment choice may differ if fertility is a priority. Dienogest is not a contraceptive, but will inhibit ovulation in the majority of patients.
- Any hormonal contraception needs to be stopped prior to initiation of dienogest. If contraception is required, non-hormonal methods of contraception should be used (e.g. barrier method).
- Two new oral treatment options have recently been approved by NICE: Relugolix–estradiol–norethisterone and Linzagolix. These are more expensive than dienogest.
- In adolescents dienogest has been associated with a decrease in lumbar bone mineral density (BMD), followed by partial recovery after treatment discontinuation. It is unknown if BMD decrease in this population will reduce peak bone mass and increase the risk for fracture in later life.
- Dienogest is significantly less expensive that the GnRH agonists and the newer gonadotrophin-releasing hormone (GnRH) receptor antagonists.
- Dienogest is more expensive than other progestogens and COCs.

Details of Review

Name of medicine (generic & brand name)**:**

Dienogest (Available as brands Dimetrum® and Sawis®, and as generics)

Strength(s) and form(s):

Tablets 2mg

Dose and administration:

For oral use.

One tablet daily without any break, taken preferably at the same time each day with some liquid as needed. The tablet can be taken with or without food.

Tablets must be taken continuously without regard to vaginal bleeding. When a pack is finished the next one should be started without interruption.

Treatment can be started on any day of the menstrual cycle.

Any hormonal contraception needs to be stopped prior to initiation of Dimetrum. If contraception is required, non-hormonal methods of contraception should be used (e.g. barrier method).[1]

BNF therapeutic class / mode of action:

Progestogen.

Dienogest is a nortestosterone derivative that has a progestogenic effect in the uterus, reducing the production of estradiol and thereby suppressing endometriotic lesions.[2]

Licensed indication(s):

Treatment of endometriosis.

Proposed use (if different from, or in addition to, licensed indication above):

Licensed indication.

Course and cost:

28 x 2mg tablets = £20.50 = cost/patient/month

Available as 28 and 84 tablet packs.

Prices as per drug tariff June 2025

Current standard of care/comparator therapies:

NICE recommended management[3]

- Analgesia (including for neuropathic pain)
- Hormonal – Combined oral contraceptive or progestogen
- Drugs affecting gonadotrophins (as an adjunct to surgery for 3 months)
- Surgical
- Combination of above

L&SC formulary[4]

Hormonal [Green]:

- Medroxyprogesterone acetate
- Norethisterone
- Desogestrel (Unlicensed indication)
- Combined Hormonal Oral Contraceptives (COCs)

Drugs affecting gonadotrophins [Amber 0]:

- Goserelin
- Leuprorelin
- Triptorelin
- NICE TA1057: Relugolix–estradiol–norethisterone acetate (Ryeqo ®)
- [NICE TA1067: Linzagolix (June 2025) – requires hormonal add-back therapy alongside]

Relevant NICE guidance:

NG73: Endometriosis: diagnosis and management

QS172: Endometriosis

Background and context

Endometriosis is the growth of endometrial-like tissue outside the uterus. Endometriosis is a condition affecting women mainly of reproductive age and, although its exact cause is unknown, it is an oestrogen-dependent condition and is associated with menstruation. Endometriosis is typically associated with symptoms such as pelvic pain, painful periods and subfertility. Women with endometriosis report pain, which can be frequent, chronic and severe, as well as tiredness, more sick days, and a significant physical, sexual, psychological and social impact. Endometriosis is an important cause of subfertility and this can also have a significant effect on quality of life.[5]

Management options for endometriosis include drug treatment and surgery. Most drug treatments for endometriosis work by suppressing ovarian function and are contraceptive. Surgical treatment aims to remove or destroy endometriotic lesions. The choice of treatment depends on the woman's preferences and priorities in terms of pain management and fertility.[5]

In 2024 the Royal College of Obstetricians and Gynaecologists announced a call to action to address critical gynaecology wait times.[6] In January 2025, 582744 people were on the gynaecology waiting list in England.[7] Treatment options are required for patients awaiting surgical intervention.

Summary of evidence

Summary of efficacy data in proposed use:

NICE Endometriosis[3] (2024)

Offer hormonal treatment (for example, the combined oral contraceptive pill or a progestogen) to women with suspected, confirmed or recurrent endometriosis.

Systematic review and meta-analysis – Diengogest vs COC[8] (2025)

This systematic review and meta-analysis aims to compare efficacy and tolerability data between dienogest and combined oral contraceptives (COC) in patients taking hormonal therapy for endometriosis treatment in order to inform evidence-based guidelines.

A total of four randomized control trials and one observational study were included, showing

moderate risk at bias assessment. Meta-analysis did not show any statistical difference in improving pelvic pain after treatment [CI 95% (−1.45–1.17);I2 = 86%; p = 0.84]. In contrast, dyspareunia after treatment was significantly lower in the COC group [CI 95% (0.64–1.33); I2 = 0%; p < 0.00001]. No statistical difference was found in terms of vaginal bleeding [OR = 0.88; CI 95% (0.39–1.96); I2 = 41%;p = 0.75], nausea and vomiting [OR = 0.51; CI 95% (0.16–1.63); I2 = 67%; p = 0.26],headache [OR = 0.91; CI 95% (0.38–2.21); I2 = 59%; p = 0.84], hot flushes [OR = 1.16;CI 95% (0.54–2.48); I2 = 0%; p = 0.71], and hair loss [OR = 1.69; CI 95% (0.52–5.53);I2 = 46%; p = 0.39]. Treatment discontinuation rate was similar between groups.

Dienogest is comparable to COC in terms of efficacy and tolerability. The therapeutic choice should be based on the patient's preference, clinical history, and experience.

Systematic review – Progestins for pain[9] (2025)

Systematic review investigating the analgesic efficacy of progestins compared to any comparator interventions for individuals with the three specified gynaecological conditions - endometriosis, fibroids and pre-menstrual syndrome. The primary search identified 1220 potentially eligible RCTs of which 21 were ultimately included; 19 RCTs related to endometriosis, two related to fibroids and zero related to PMS.

In 18 of the 19 studies concerning endometriosis, progestins produced a statistically significant reduction in pain, further, in five instances progestins were more efficacious in reducing pain than comparator interventions.

- Two studies comparing daily dienogest to placebo found dienogest to significantly reduce pain compared to placebo. One of these, a 2018 trial conducted in China, found that women who received dienogest daily (n=126) compared to placebo (n=129) experienced significantly reduced endometriosis-associated pelvic pain (EAPP).
- A 2010 multi-centre trial (n=33) conducted in Germany, Italy, and Ukraine compared the efficacy of dienogest (n=102) versus placebo (n=96) in reducing EAPP. VAS score reductions were significantly greater among women in the dienogest arm.

The most frequently cited adverse effect of progestins was spotting/irregular bleeding whilst those receiving comparator interventions most often reported hot flushes; cited in 12 and seven studies respectively.

Systematic review – Dienogest vs GnRH analogues [10] (2015)

Nine randomized trials were included. Dienogest 2 mg/day was superior to placebo in reducing pelvic pain (27.4 versus 15.1 mm, P < 0.0001), with similar results to buserelin, leuprorelin, leuprolide acetate and triptorelin, in controlling symptoms associated with endometriosis. Dienogest 2 mg/day was effective in reducing endometriotic lesions (11.4 ± 1.71-3.6 ± 0.95, P < 0.001). The extended therapy with dienogest 2 mg/day also showed an improvement in pelvic pain after 24-52 weeks (-22.5 ± 32.1 and -28.4 ± 29.9 mm, respectively) with tolerable side effects.

Dienogest should be considered as an alternative for controlling symptoms related to endometriosis. Nevertheless, in this systematic review, no studies were found comparing dienogest with first-line therapy, such as progestins and estrogen-progestogen combinations, which are proved to be effective in the treatment of endometriosis, are less expensive, and also can be used for contraception.

Comparative study - Dienogest after surgery[11] (2018)

A total of 285 women were diagnosed as endometriosis by laparoscopy between 2011 and 2015.

Patients were grouped into no treatment (*n* = 83), treatment with dienogest (*n* =130) and treatment with levonorgestrel-releasing intrauterine system (LNG-IUS) (*n* =72) after laparoscopic surgery. The changes of the pain scores were checked at 6, 12 and 24 months after the surgery.

At 6 and 12 months, the median pain scores in treatment (dienogest and LNG-IUS) groups were significantly lower than control group. Both treatment groups had significantly lower recurrence rate than control group (3.8% and 9.7%, respectively, vs 32.5%, *P* =0.001). No significant difference was found in the recurrence rate between the two treatment groups (*P* =0.461). Patients in the LNG-IUS group showed lower rate of discontinuation due to complication (27.8%) than those in dienogest group (35.6%, *P* =0.010).

LNG-IUS treatment in the patients with endometriosis is effective for postoperative pain control and preventing recurrence, however, the LNG-IUS group is older, it is difficult to compare the efficacy between dienogest and LNG-IUS in present study.

Prospective randomized trial – Dienogest after surgery[12] (2018)

To compare the efficacy and safety of dienogest (DNG) with depot leuprolide acetate (LA) in patients with recurrent pelvic pain following laparoscopic surgery for endometriosis. Two hundred and forty-two patients with recurrent pelvic pain following laparoscopic surgery for endometriosis were given dienogest (2 mg/day, orally) or depot LA (3.75 mg/4 weeks, intramuscularly) for 12 weeks.

There was highly significant reduction in pelvic pain, back pain and dyspareunia in both groups with mean of difference in dienogest group (28.7 ± 5.3, 19.0 ± 4.3 and 20.0 ± 3.08 mm, respectively) and in LA group (26.2 ± 3.01, 19.5 ± 3.01 and 17.9 ± 2.9 mm, respectively).

The most frequent drug-related adverse effects in dienogest group were vaginal bleeding and weight gain (64.5 and 10.8%, respectively) which were significantly higher than LA group (21.5 and 3.3%, respectively). While the most frequent drug-related adverse effects in LA group were hot flushes and vaginal dryness (46.3 and 15.7%, respectively) which were significantly higher than dienogest group (15.7 and 3.3%, respectively).

Daily dienogest is as effective as depot LA for relieving endometriosis-associated pelvic pain, low back pain and dyspareunia. In addition, dienogest has acceptable safety, tolerability and lower incidence of hot flushes. Thus, it may offer an effective and well-tolerated treatment in endometriosis.

Open label study - Dienogest in adolescents[13] (2017)

A 52-week, open-label, single-arm study in 21 study centers, in 6 European countries. Adolescents aged 12 to younger than 18 years with clinically suspected or laparoscopically confirmed endometriosis given Dienogest 2 mg once daily.

The primary end point was relative change in lumbar spine (L2-L4) bone mineral density (BMD) measured using dual-energy x-ray absorptiometry. A key secondary end point was change in endometriosis-associated pain assessed using a visual analogue scale. Of 120 patients screened 97 (87.4%) completed the study. Mean lumbar BMD at baseline was 1.1046 (SD, 0.1550) g/cm^2. At the end of dienogest treatment (EOT; defined as at 52 weeks or premature study discontinuation), mean relative change in BMD from baseline was -1.2% (SD, 2.3%; n = 103). Follow-up measurement 6 months after EOT in the subgroup with decreased BMD at EOT (n = 60) showed partial recovery in lumbar BMD (mean change from baseline: -2.3% at EOT, -0.6% 6 months after EOT). Mean endometriosis-associated pain score was 64.3 (SD, 19.1) mm at baseline and decreased to 9.0 (SD, 13.9) mm by week 48.

In adolescents with suspected endometriosis, dienogest 2 mg for 52 weeks was associated with a decrease in lumbar BMD, followed by partial recovery after treatment discontinuation.

Endometriosis-associated pain was substantially reduced during treatment. Because bone accretion is critical during adolescence, results of the VISanne study to assess safety in ADOlescents (VISADO) study highlights the need for tailored treatment in this population, taking into account the expected efficacy on endometriosis-associated pain and an individual's risk factors for osteoporosis.

European Society of Human Reproduction and Embryology - Guideline[14] (2022)

NB. The Royal College of Obstetricians and Gynaecologists guideline on endometriosis has been archived and they signpost to the ESHRE and NICE guidance.

It is recommended to prescribe women progestogens to reduce endometriosis associated pain. The Guideline Development Group recommends that clinicians take the different side effect profiles of progestogens into account when prescribing them.

Cochrane: Endometriosis[15] (2014)

Seventeen systematic reviews published in *The Cochrane Library* were included. All the reviews were high quality. The quality of the evidence for specific comparisons ranged from very low to moderate. Five systematic reviews reported on medical treatment using ovulation suppression. There was no consistent evidence of a difference in effectiveness between oral contraceptives and goserelin, estrogen plus progestogen and placebo, or progestogens and placebo, though in all cases the relevant evidence was of low or very low quality.

Canadian Agency for Drugs and Technologies in Health[16] (2012)

The Canadian Drug Expert Committee (CDEC) recommends that dienogest be listed for the management of pelvic pain associated with endometriosis in patients for whom one or more less costly hormonal options are either ineffective or cannot be used.

Reasons for the Recommendation:

1. In two randomized controlled trials (RCTs) included in the systematic review, dienogest was superior to placebo (study A32473), and non-inferior to leuprolide (study AU19), in reducing pelvic pain in patients with endometriosis.

2. At the submitted price, the daily drug cost of dienogest is less than all alternatives with a Health Canada indication for the treatment or hormonal management of endometriosis, with the exception of generic injectable medroxyprogesterone. Dienogest is more costly than combined hormonal contraceptives.

Summary of safety data:

[See *Summary of efficacy data in proposed use* for additional safety data.]

Canadian Agency for Drugs and Technologies in Health[16] (2012)

• The proportion of patients experiencing serious adverse events in the trials was low. Serious adverse events were numerically higher with dienogest than with leuprolide in study AU19 (4.2% versus 0.8%, respectively). No serious adverse event was reported in study A32473.

• The proportion of patients with adverse events was 68% versus 74% for dienogest and leuprolide acetate, respectively, in study AU19 and 33% versus 26% for dienogest and placebo, respectively, in study A32473.

• Withdrawal due to adverse events was relatively infrequent and the incidence was similar

between treatment arms in the included trials.

Summary of product characteristics[1]

Contraindications

• Active venous thromboembolic disorder

• Arterial and cardiovascular disease, past or present (e.g. myocardial infarction, cerebrovascular accident, ischemic heart disease)

• Diabetes mellitus with vascular involvement

• Presence or history of severe hepatic disease as long as liver function values have not returned to normal

• Presence or history of liver tumours (benign or malignant)

• Known or suspected sex hormone-dependent malignancies

• Undiagnosed vaginal bleeding

• Hypersensitivity to the active substance or to any of the excipients

Special warnings and precautions for use

- As dienogest is a progestogen-only preparation it can be assumed that the special warnings and precautions for use of progestogen-only preparations are also valid.
- Changes in bone mineral density (BMD)

Interaction with other medicinal products

Inducers or inhibitors of CYP3A4 may affect the progestogen drug metabolism.

Undesirable effects

Undesirable effects are more common during the first months after the start of treatment with 2 mg dienogest, and subside with continued treatment. There may be changes in bleeding pattern, such as spotting, irregular bleeding or amenorrhea. The following undesirable effects have been reported in users of 2 mg dienogest. The most frequently reported undesirable effects under treatment with 2 mg dienogest are headache (9.0%), breast discomfort (5.4%), depressed mood (5.1 %) and acne (5.1 %).

In addition, the majority of patients treated with 2 mg dienogest experience changes in their menstrual bleeding pattern.

For a full list of ADRs, please see the product SPC.

Strengths and limitations of the evidence:

Strengths

- Dienogest is an established treatment option globally, although it is not formulary locally.
- Several systematic reviews have shown dienogest to be superior to placebo in reducing pain related to endometriosis, and comparable to other established therapies.
- Dienogest is generally well tolerated, with a similar side effect profile to other progestogens.
- National and European guidance supports the use of progestogens for endometriosis, but do not differentiate between the available options.
- Additional oral treatment options may help to resolve issues with the 6-month licensing of GnRH agonists for endometriosis, prescribing beyond this time period is unlicensed and can result in patients being required to travel to hospital for injections.
- Dienogest is significantly less expensive that the GnRH agonists and the newer

gonadotrophin-releasing hormone (GnRH) receptor antagonists.

Limitations

- There is an absence of data comparing dienogest to other oral progestogen options.
- Multiple hormonal treatment options are already available, with established efficacy and side effects profiles.
- Two new oral treatment options have recently been approved by NICE.
- Reduction in bone mineral density may occur in adolescents treated with dienogest.
- Dienogest is more expensive than other progestogens and COCs.

Summary of evidence on cost effectiveness:

Medicine	Strength/formulation	Cost/patient/month
Dienogest	28 x 2mg tablets	£20.50
Medroxyprogesterone acetate	90 x 10mg tablets	£22.16
Norethisterone	10(2x5mg) – 25(5x5mg) mg daily	£14.10 - £35.25
Desogestrel (unlicensed indication)	84 x 75mcg tablets	£0.70
Combined Hormonal Contraceptives	Multiple brands and strengths e.g.	*Microgynon 30* approx. £0.90 *Yasmin* approx. £5
Goserelin	3.36mg syringe	£70.00
Leuprorelin	Prostap SR DCS® 3.75 mg Prostap 3 DCS® 11.25 mg	£75.24
Triptorelin	Decapeptyl® SR 11.25mg Decapeptyl® SR 3mg 3 mg Gonapeptyl Depot® 3.75 mg	£69 - £81.69
Relugolix–estradiol–norethisterone acetate (Ryeqo ®)	28 x 40mg/1mg/0.5mg tablets	£72.00
Surgery	Major, Laparoscopic or Endoscopic, Upper Genital Tract Procedures, average national cost range	£2500 - £4500 per procedure 2023/24 National Cost Collection data

Prescribing and risk management issues:

- The majority of patients treated with 2 mg dienogest experience changes in their menstrual

bleeding pattern.
- Any hormonal contraception needs to be stopped prior to initiation of dienogest. If contraception is required, non-hormonal methods of contraception should be used (e.g. barrier method).

Commissioning considerations:

Innovation, need and equity implications of the intervention:
Due to extensive waiting lists, increasing numbers of women are living with the symptoms of endometriosis whilst waiting for surgery. This medication is another treatment option for this cohort.
Financial implications of the intervention:
It is not anticipated that approval of this medicine would increase prescribing for patients with endometriosis, but it is likely that some patients on other treatments may be switched to dienogest. If the existing treatment option is less expensive that dienogest then the switch would incur a cost to the ICB (= £dienogest - £existing treatment). Patients requiring contraception will be likely to choose an alternative treatment option to dienogest.
Service Impact Issues Identified:
Approval of this treatment may help to reduce extensive gynaecology waiting lists and reduce surgical waiting lists.
Equality and Inclusion Issues Identified:
None identified.
Cross Border Issues Identified:
Pan Mersey has a Grey position for dienogest (no application received). **GMMMG** has no position for dienogest. **Airedale NHS Trust** has an Amber RAG position for dienogest, following specialist recommendation for endometriosis. **Leeds** has an Amber 1 (suitable for GP prescribing following specialist recommendation) RAG position for dienogest.
Legal Issues Identified:
None identified.
Media/ Public Interest:
None identified.

Grading of evidence (based on SORT criteria):

Levels	Criteria	Notes
Level 1	Patient-oriented evidence from: • high quality randomised controlled trials (RCTs) with low risk of bias • systematic reviews or meta-analyses of RCTs with consistent findings	High quality individual RCT= allocation concealed, blinding if possible, intention-to-treat analysis, adequate statistical power, adequate follow-up (greater than 80%)
Level 2	Patient-oriented evidence from: • clinical trials at moderate or high risk of bias • systematic reviews or meta-analyses of such clinical trials or with inconsistent findings • cohort studies • case-control studies	
Level 3	Disease-oriented evidence, or evidence from: • consensus guidelines • expert opinion • case series	Any trial with disease-oriented evidence is Level 3, irrespective of quality

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