AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

Evidence summary report for a limited assessment

Progesterone (Prometrium®) 400 mg soft vaginal capsules

Indication
Prevention of miscarriage in women presenting with bleeding in the first trimester of pregnancy and have a history of recurrent miscarriages.

Company
Besins Healthcare UK Ltd

Background
Miscarriage in the UK is defined as the loss of a pregnancy before 24 weeks gestation and affects one in five pregnancies. Miscarriage can cause excessive bleeding, infection, and complications associated with surgical treatment, as well as substantial psychological harm, including anxiety, depression, and post-traumatic stress disorder (PRISM). Recurrent miscarriage is generally defined as the loss of three or more pregnancies and can stem from a variety of factors (RCOG). These include genetic, anatomical, hormonal, autoimmune and lifestyle-related causes although the cause is not known in about 50% of cases (ESHRE). Recurrent miscarriage affects around 1 in 100 women (RCOG).

The most common sign of miscarriage is vaginal bleeding. However, this is relatively common in early pregnancy; up to 25% of all pregnancies experience bleeding in the first trimester but half will continue normally (Coomarasamy et al., 2020).

Progesterone is essential for the establishment and maintenance of a pregnancy. Withdrawal of progesterone in early pregnancy typically results in a miscarriage, and antiprogesterone drugs are powerful inducers of abortion. The central role of progesterone in early pregnancy led clinicians and researchers to hypothesize that progesterone deficiency could be a cause of some miscarriages, although early trials were small and methodologically weak, producing heterogenous and unreliable results (Coomarasamy et al., 2020).

Two large multicentre, double-blind, placebo-controlled, randomised trials, PROMISE and PRISM, were conducted, predominantly in the UK, to investigate whether treatment with progesterone (formulated as micronised vaginal suppositories) would increase the rates of live births and newborn survival among women with unexplained recurrent miscarriage. The results of these trials have informed guidelines for the clinical management of women presenting with bleeding in the first trimester with a history of recurrent miscarriage. Until June 2025, no licensed progesterone product for this indication has been available in the UK and treatment was with micronised vaginal progesterone products licensed for other indications and used off-label for this patient population (NG126).

Guidance and recommendations
The NICE guideline NG126: Ectopic pregnancy and miscarriage: diagnosis and initial management was updated in 2021 to include the recommendation that vaginal

micronised progesterone 400 mg twice daily should be offered to women with an intrauterine pregnancy confirmed by a scan, if they have vaginal bleeding and have previously had a miscarriage, and should be continued until 16 completed weeks of pregnancy if a fetal heartbeat is confirmed. The guideline states that this recommendation was made as there is good evidence that this medication increases the number of live births in women with early pregnancy bleeding and a previous miscarriage. NICE acknowledges that this recommendation will increase the use of progestogens to prevent miscarriage but this is cost-effective, and that the recommendation will standardise the preparation of progesterone used to treat threatened miscarriage.

The Royal College of Obstetricians and Gynaecologists green-top guideline no. 17: Recurrent miscarriage (June 2023) states that progestogen supplementation should be considered in women with recurrent miscarriage who present with bleeding in early pregnancy (for example 400 mg micronised vaginal progesterone twice daily at the time of bleeding until 16 weeks of gestation). The European Society of Human Reproduction and Embryology (ESHRE) also updated their guideline on the management of recurrent pregnancy loss in 2022 to conditionally recommend that vaginal progesterone may improve live birth rate in women with 3 or more pregnancy losses and vaginal blood loss in a subsequent pregnancy.

The submitting company advises AWTTC that Prometrium® for its licensed indication is made available in England via NHS England commissioning as NICE has determined that appraisal is unnecessary. This is because the discounted price agreed between the applicant company and NHS England will likely lead to a net budget saving when compared to established off-label treatments. Prometrium® was accepted for use in NHS Scotland following an abbreviated submission in December 2025.

A simple Wales Patient Access Scheme (WPAS) for Prometrium® has been accepted making it available to NHS Wales at the same price as in England and Scotland.

Technology

Prometrium® is indicated for the prevention of miscarriage in women presenting with bleeding in the first trimester of pregnancy and have a history of recurrent miscarriages. The recommended dose is 400 mg twice a day (morning and night). Treatment should be initiated during the first trimester of pregnancy, at first sign of vaginal bleeding and should continue to the 16th week of gestation.

Prometrium® is not licensed for any other indications.

Marketing authorisation date: 12 July 2024

Criteria for limited assessment

The Scrutiny Panel reviewed the company request for the assessment of Prometrium® and considered that it was suitable for a limited assessment via the Licensed One Wales Medicines Assessment Group (LOWMAG). They cited the following reasons for this decision:

- This is the first licensed progesterone product for this patient group and will replace off-label preparations used in NHS Wales.
- There is national clinical guidance from NICE and the Royal College of Obstetricians and Gynaecologists available recommending use of vaginal progesterone products for this indication.
- The clinical effectiveness and cost-effectiveness have been sufficiently established from published clinical and economic studies according to NICE in the development of their guidelines.
- It is available to patients in both England and Scotland.
- It is expected that Prometrium® will be cost-saving in comparison to off-label products currently used for this indication.

The AWMSG Scrutiny Panel agreed that as the case for clinical effectiveness is established it does not warrant further review. Therefore, the limited assessment should give an overview of current use, equity of access and budget impact only.

Comparator(s) and place in pathway

Micronised vaginal progesterone products licensed for other indications are currently used off-label in this patient population in accordance with published clinical guidelines (NG126). Access to Prometrium® would provide a licensed treatment option.

Comparators are the following micronised vaginal progesterone products currently used off-label for this indication; Utrogestan® 200 mg vaginal capsules and Cyclogest® 400 mg pessaries.

Budget impact

Prometrium® is costed at the WPAS price of [commercial in confidence information removed]. for a pack of 15 x 400 mg vaginal capsules. The recommended dose is 400 mg twice a day. Both off-label comparators are costed at list price; Utrogestan® is £21 for a pack of 21 x 200 mg vaginal capsules and Cyclogest® is £12.96 for a pack of 15 x 400 mg pessaries. Dosing for the off-label comparators is the same as for Prometrium®.

The company estimates for the budget impact is given in Table 1. The company have estimated the prevalence of women presenting with bleeding in the first trimester of pregnancy and have a history of recurrent miscarriage as 1% of the number of live births recorded for Wales in 2023; this assumption is based on advice provided to AWTTC from a clinical expert in NHS Wales that 1% of all pregnancies may require progesterone for bleeding after previous recurrent miscarriage. An incidence of 3 additional patients per year is assumed from Years 2-5. The eligible patient population has then been reduced by 20% on the assumption derived from specialist opinion sought by the company, that there is 80% uptake of progesterone treatment in eligible patients; this resulting sub-group population has been used as the basis for their budget impact calculations. Treatment with progesterone should be initiated within the first 12 weeks of pregnancy as soon as bleeding occurs and continued until the start of week 16 (SPC). The company has used a treatment period of 16 weeks (112 days) with 400 mg twice daily dosing for Prometrium® and comparators. It has been assumed that comparator use is split evenly between Utrogestan® and

Cyclogest®. A 20% discontinuation rate has also been assumed for each product. The company estimate that the market share of Prometrium® would be 20% in Year 1, due to a likely delay in switching from off-label comparators, rising to 90% by Year 5. All cost estimates exclude VAT.

Table 1. Company model: summary acquisition costs for Prometrium® in NHS Wales

	Year 1	Year 2	Year 3	Year 4	Year 5
Number of eligible patients	**274**	**277**	**280**	**282**	**285**
Subpopulation of eligible patients (indication under consideration)	219	221	224	226	228
Uptake of new medicine (%)	20%	50%	75%	80%	90%
Number of patients receiving new medicine allowing for discontinuations	35	89	134	145	164
Medicine acquisition costs in a market without new medicine	£41,310	£41,724	£42,141	£42,562	£42,988
Medicine acquisition costs in a market with new medicine	¶¶	¶¶	¶¶	¶¶	¶¶
Net medicine acquisition costs	¶¶	¶¶	¶¶	¶¶	¶¶

¶¶: commercial in confidence figure removed

Critique of company BI model

- AWTTC agree that Prometrium® offers a cost-saving treatment option for this indication.
- Table 1 reports medicine acquisition costs only. Other resource use is not included (e.g. monitoring costs and costs associated with adverse events). Administration costs were equally applied to both the comparator and off-label progesterone products and provided as a separate table. As these costs are the same, they have no material impact on the net cost of the treatment and are not considered further.
- AWTTC broadly agrees with estimated eligible patient numbers. A clinical expert from NHS Wales confirms that 1% of all pregnancies may require progesterone therapy for bleeding after previous recurrent miscarriage which aligns with the RCOG estimate that 1% of women experience recurrent miscarriage. ONS data for Wales indicates there were 38,811 conceptions in 2022 of which 30.1% led to a legal abortion. Of the 27,129 remaining

pregnancies, AWTTC estimate that 271 women per year may be eligible for treatment with Prometrium®. However, AWTTC question why the eligible population under the licensed indication has subsequently been reduced by 20% as there is no reason given why this proportion would not be eligible for treatment.

- Due to how pregnancy length is calculated, treatment with progesterone would not start until at least week 4 when pregnancy can be confirmed. Therefore, calculations should be based on a shorter maximum treatment length of 12 weeks (84 days).
- A discontinuation rate of 20% has been applied to each progesterone treatment. However, as treatment is for less than a year's duration, applying this factor means that, in effect, an additional proportion of patients has been removed from the treatment population. Taking this and the 20% reduction already applied means that about a third of eligible patients have been removed from the company BI model. AWTTC acknowledge that, unfortunately, some women will still miscarry before 16 weeks gestation despite treatment with progesterone; the PRISM study showed that for women with three or more previous miscarriages and pregnancy bleeding, the live birth rate was 78% after progesterone treatment. However, there is no data available to inform what the average length of progesterone treatment is for this population which would take into account discontinuations throughout the treatment course.
- AWTTC considers that the company predicted displacement of off-label progesterone with Prometrium® may be conservative especially in the first few years. Prompt adoption in NHS Wales of a licensed and cost-saving product over off-label alternatives would be reasonable to expect.
- Use of the two off-label comparator products is assumed to be equal. This is a reasonable assumption to inform the BI model although one is significantly more expensive.

To take into account the critique points raised above, Table 2 gives a simplified AWTTC budget impact overview per year; this considers medicine acquisition costs only as administration costs and other costs are assumed to be the same for all progesterone products. A 12-week treatment course for the full eligible population with no discontinuations and full displacement of the off-label comparators is assumed. As it is not possible to ascertain the proportion of patients currently prescribed each off-label progesterone product, comparator costs below are given for all patients receiving either Utrogestan® or Cyclogest® and for 50% receiving each. All costs exclude VAT.

Table 2. Acquisition costs associated with use of Prometrium® per year in Wales in comparison to off-label progesterone products

	Year 1 and subsequent years
Number of eligible patients	271
Prometrium® acquisition cost	¶¶
Off-label comparator acquisition costs	
100% Utrogestan®	£91,056
100% Cyclogest®	£39,154
50% Utrogestan® / 50% Cyclogest®	£65,105
Minimum net acquisition cost of Prometrium® in comparison to off-label comparators	¶¶
Maximum net acquisition cost of Prometrium® in comparison to off-label comparators	¶¶
¶¶: commercial in confidence figure removed	

Prescribing Prometrium® to all eligible patients will result in a predicted cost-saving of between [commercial in confidence information removed] per year depending on the comparator displaced and assuming eligible patient numbers remain relatively stable.

Impact on health and social care services

No additional impact expected. No additional monitoring is required for the use of Prometrium® in comparison to currently used off-label progesterone products above that routinely offered to women presenting with bleeding and with a history of recurrent miscarriage.

Patient factors

The company highlight that a significant burden of disease and substantial impact to patient quality of life is associated with miscarriage (Quenby et al, 2021). Miscarriage can be detrimental to both psychological and physical health (Lok & Neugebauer, 2007, Quenby et al, 2021). There are wider socio-economic impacts resulting from time off work, reduced productivity and social withdrawal, with a corresponding increased utilisation of healthcare services including fertility and mental health support (Quenby et al, 2021). There can also be a significant impact on partner quality of life (Obst et al, 2021). The company consider that recurrent miscarriage is inconsistently treated due to the uneven application of, and access to, guidance and treatment options and that access to a licensed progesterone treatment option will address these issues.

Clinicians in Wales report that a licensed progesterone product for this indication, and which may be cost-saving, would be a welcome alternative to the current off-label progesterone treatments currently offered.

Equality impact assessment

AWTTC have completed an Equality and Health Impact Assessment in parallel with each development stage of the project. This follows the five ways of working for public bodies, and work to achieving the wellbeing goals, outlined in the Well-Being of Future Generations (Wales) Act 2015.

It is not expected that Prometrium® will have a potential negative impact on people based on the protected characteristics of the Equality Act 2010. We may expect a positive impact on women who are pregnant and who are presenting with bleeding in the first trimester of pregnancy and have a history of recurrent miscarriages.

This report should be cited as: All Wales Therapeutics and Toxicology Centre. Evidence status report for a limited assessment. Progesterone (Prometrium®) 400 mg soft vaginal capsules. Reference number: 6820. March 2026.