Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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progesterone 100mg vaginal tablets (Lutigest®) SMC No. (1185/16)

Ferring Pharmaceuticals Ltd

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The Scottish Medicines Consortium (SMC) has completed its assessment of the above product and advises NHS Boards and Area Drug and Therapeutic Committees (ADTCs) on its use in Scotland. The advice is summarised as follows:

ADVICE: following a full submission

progesterone (Lutigest®) is accepted for use within NHS Scotland.

Indication under review: Luteal support as part of an assisted reproductive technology (ART) treatment program for infertile women.

In women receiving luteal phase support during ART cycles, progesterone (Lutigest®) 100mg vaginal tablets administered three times daily were non-inferior to another progesterone preparation administered vaginally with respect to ongoing pregnancy rates at four to six weeks gestation and live birth rates.

This advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of progesterone 100mg vaginal tablets. This advice is contingent on the continuing availability of the patient access scheme in Scotland or a list price that is equivalent or lower.

Overleaf is the detailed advice on this product.

Chairman,
Scottish Medicines Consortium

Indication

Luteal support as part of an assisted reproductive technology (ART) treatment program for infertile women.

Dosing Information

Progesterone 100mg vaginal tablet administered vaginally three times daily starting at oocyte retrieval. Administration should be continued for 30 days, if pregnancy has been confirmed.

Product availability date

6 January 2015

Summary of evidence on comparative efficacy

Progesterone, a naturally occurring steroid secreted by the ovary, placenta, and adrenal gland, is necessary to increase endometrial receptivity for implantation of an embryo following in vitro fertilisation (IVF). Once an embryo is implanted, progesterone acts to maintain the pregnancy.[1]

Evidence of efficacy comes from a randomised, open-label (assessor-blinded), phase III, non-inferiority study conducted in women aged 18 to 42 years with a history of infertility who were undergoing IVF. Patients were required to have a body mass index (BMI) ≤34kg/m^2 and a baseline follicle stimulating hormone (FSH) level ≤15IU/L. The study allowed use of fresh embryos only. No more than three cleaving embryos were transferred (day 3 after retrieval) and no more than two blastocytes (day 5 after retrieval). Patients received pre-treatment which involved screening, gonadotropin-releasing hormone (GnRH) agonist down-regulation, ovarian stimulation human chorionic gonadotropin (hCG) administration and oocyte retrieval. On completion of the pre-treatment phase patients were randomised equally to progesterone 100mg twice daily, progesterone 100mg three times daily (licensed dose) or progesterone 8% gel once daily, all administered vaginally for up to 10 weeks. Patients were stratified by age according to the Society for Assisted Reproductive Technology categories (<35, 35 to 37, 38 to 40, and 41 to 42 years) and FSH level at baseline (<10IU/L and 10 to 15IU/L).[2]

The primary outcome was 'ongoing pregnancy', defined as presence of detectable foetal heart motion, at approximately four to six weeks gestation, confirmed by transvaginal ultrasound by an assessor blinded to treatment allocation. A step-down procedure was used for statistical analyses; if non-inferiority was demonstrated for the progesterone 100mg three times daily group versus progesterone 8% gel group, then the progesterone 100mg twice daily group was compared with progesterone 8% gel group. A similar step-down procedure was used for the other pregnancy endpoints.[2]

'Ongoing pregnancy' occurred in 42% (171/404) of patients in the progesterone 100mg three times daily group, 39% (156/404) in the progesterone 100mg twice daily group and 42% (170/403) in the progesterone 8% gel group. The lower bound of the 95% confidence interval (CI) for the difference between progesterone 100mg three times daily and progesterone 8% gel group was -6.7% and non-inferiority (using a 10% margin) was demonstrated. The lower bound of the 95% CI for the difference between progesterone 100mg twice daily (unlicensed dose) and progesterone 8% gel group was -10.3%; non-inferiority was not demonstrated.[2]

Secondary endpoints included 'biochemical pregnancy' (serum pregnancy test) assessed at 14 ± 5 days, 'clinical pregnancy' (defined as presence of an intrauterine gestational sac) confirmed at 14 ± 5 days after a second positive biochemical pregnancy test, and live births. Results for these endpoints are included in table 1 for the licensed dose of progesterone 100mg vaginal tablets and comparator.

Table 1: Secondary endpoints in ITT population

Endpoint	Progesterone 100mg three times daily	Progesterone 8% gel	Lower bound of 95% CI for difference
Biochemical pregnancy; % (n/N)	56% (225/404)	53% (212/403)	-3.8%
Clinical pregnancy; % (n/N)	45% (183/404)	43% (174/403)	-4.7%
Live birth rate; % (n/N)	38% (154/404)	38% (153/403)	-6.5%

CI=confidence interval

A supportive study of exploratory, randomised, phase IV design, recruited women aged 18 to 42 years with a documented history of infertility and a BMI of 18 to 34kg/m^2. It aimed to compare treatments for ovarian stimulation (not discussed further) and also to compare vaginal progesterone (100mg twice or three times daily [n=84]) versus intramuscular (IM) progesterone (50mg once daily [n=81]) for luteal phase support. Patients were treated with progesterone for 10 weeks or until negative pregnancy test. The proportion of women with 'ongoing pregnancy' was 44% in the vaginal progesterone group and 47% in the IM progesterone group. Biochemical pregnancy and clinical pregnancy results were consistent between treatment groups.[3]

Summary of evidence on comparative safety

In the pivotal study, adverse events were reported in 54% (217/404) of patients in the progesterone 100mg three times daily group and 52% (210/403) of patients in the progesterone 8% gel group. Adverse events that were considered probably related to treatment occurred in 1.2% (5/404) and 1.0% (4/403) of patients in the progesterone 100mg three times daily and progesterone 8% gel groups respectively. There were no serious adverse events considered to be related to treatment.[2]

The most frequently reported adverse events in the progesterone 100mg three times daily and progesterone 8% gel groups respectively were post-oocyte pain (25% and 25%), abdominal pain (11% and 15%), nausea (7.2% and 7.7%), ovarian hyperstimulation syndrome (4.2% and 4.5%), and headache (2.0% and 2.2%).[2]

The rate of foetal abnormalities in the progesterone 100mg three times daily group was higher than in the progesterone 8% gel group, which may in part be explained by higher systemic exposure of progesterone in the former group.[4] Of the 404 patients treated with progesterone 100mg three times daily, there were seven cases of foetal anomalies. However, the rate is comparable with the event rate described in the general population, although the total exposure is too low to allow conclusions to be drawn.[1]

Summary of clinical effectiveness issues

There are four other progesterone preparations licensed for luteal phase support during ART cycles.[5-9] Clinical experts consulted by SMC report the use of progesterone 8% vaginal gel once daily, progesterone pessaries 400mg twice daily and some use of progesterone 50mg to 100mg administered IM from two to three times weekly up to daily.

In the pivotal study progesterone 100mg three times daily was non-inferior to progesterone 8% gel for the primary endpoint of 'ongoing pregnancy' and for secondary endpoints including live birth rate, in a patient population where most were aged <35 years (mean age was 33 years) and had baseline FSH <10 IU/mL (86% with FSH < 10IU/ml). Non-inferiority was not demonstrated for progesterone 100mg twice daily group and so the three times daily dose was licensed. The non-inferiority margin of 10% was considered large.[4] Endpoints were achieved in highest proportions of patients in the subgroup aged <35 years and lowest in patients aged 41 to 42 years. The proportion of patients who were followed up to live births and how missing data were handled was unclear.[2]

The study has some limitations which may impact on its generalisability. The treatment duration in the study was for up to 10 weeks. However the summary of product characteristics for progesterone 100mg vaginal tablets states that it should be continued for 30 days.[1,2] The 30-day treatment duration was proposed, during regulatory approval, to be in line with progesterone 8% vaginal gel. Additionally, plasma progesterone levels were similar for the two formulations.[5] The study allowed transfer of fresh embryos only,[3] although clinical experts consulted by SMC considered the study results for progesterone were generalisable to luteal phase support with frozen embryo transfer. Patients in the study had a mean of 2.4 embryos transferred into the uterus; UK guidance recommends a maximum of two embryos dependent upon the clinical circumstances. It is unclear if the pregnancy and live birth rates observed in the study would be replicated in Scottish practice.[3,10]

The submitting company did not present any comparative efficacy data (direct or indirect) for the licensed dose of progesterone 100mg vaginal tablets versus progesterone 400mg pessaries, which have recently been licensed for luteal phase support and were used off-label prior to this. In the supportive study, pregnancy rates were similar for vaginal progesterone compared with IM progesterone.[4] Furthermore, in a Cochrane review to assess luteal phase support provided to sub-fertile women undergoing ART, the route of progesterone administration did not appear to be associated with outcomes.[11]

Progesterone 100mg vaginal tablets are administered three times daily compared to progesterone 8% vaginal gel administered once daily and progesterone 400mg pessaries administered twice daily.[1, 5, 9] Compliance with a three times daily regimen is unlikely to be an issue given that women receiving ART are likely to be highly motivated.[4] In a questionnaire survey of vaginal (100mg two or three times daily) and daily progesterone IM injections given for luteal phase support, women found vaginal progesterone administration more convenient and easy to administer and overall were more satisfied with the route compared to women who received IM progesterone.[12]

The optimum duration of luteal support is still to be established although recent NICE guidance recommends a maximum treatment duration of eight weeks.[10] The summaries of product characteristics state a duration of treatment of 30 days for progesterone 100mg vaginal tablets and 8% gel, 38 days for progesterone 400mg pessaries, and 8 to 12 weeks for IM progesterone.[1, 5, 7-9]

In the Cochrane review, a comparison of long versus short duration of progesterone administration showed no evidence of differences in ongoing pregnancy and live birth rates, although results for clinical pregnancy were inconsistent.[11]

Summary of comparative health economic evidence

The submitting company presented a cost-minimisation analysis which compared progesterone 100mg vaginal tablets against progesterone 8% vaginal gel, progesterone 400mg pessaries, and IM progesterone. The patient population considered in the economic analysis was infertile women receiving luteal phase support as part of an assisted reproductive technology (ART) treatment programme.

A decision-analytic model was developed in order to evaluate the cost-effectiveness of progesterone 100mg vaginal tablets versus the comparators. In terms of model structure patients entered the model at initiation of treatment and then proceeded to embryo transfer, biochemical pregnancy, clinical pregnancy, on-going pregnancy and birth at various time points throughout the analysis. Patients who did not report embryo transfer, biochemical pregnancy, clinical pregnancy or on-going pregnancy discontinued treatment. The base case analysis assumed patients were treated with progesterone 100mg vaginal tablets and progesterone 8% vaginal gel for 30 days. Patients initiated to progesterone 400mg pessaries, and IM progesterone were treated for 38 days and 56 days respectively. The analysis used a time horizon of 10 months.

The company referenced the pivotal study and a systematic Cochrane review in order to support the equivalence of the different progesterone regimes in terms of clinical outcomes. The clinical outcomes referenced by the company included biochemical pregnancy rate, clinical pregnancy rate, ongoing pregnancy rate and live birth rate. The company also referenced the view of Scottish advisers to support the equivalence of the medicines in terms of live births. The economic analysis used values for each of the efficacy parameters listed above in order to estimate the proportion of patients who continued or discontinued treatment in the analysis. The values for the clinical outcomes were taken from the pivotal study.

The analysis focused on the medicine cost only for each comparator. Costs associated with administration, monitoring, hospitalisation, healthcare professional visits, tests, procedures, concomitant medications and managing adverse events were assumed to be same for all comparators and therefore excluded from the analysis.

The base case result indicated that the cost of progesterone 100mg vaginal tablets was £64. Progesterone 8% vaginal gel, progesterone 400mg pessaries, and IM progesterone were estimated to cost £47, £46 and £87 respectively. The company provided a scenario analysis where microgenised progesterone was included in the evaluation which generated a cost of £75 for the medicine.

The economic analysis was most sensitive to the following changes:

Scenario	Progesterone 100mg vaginal tablets	Progesterone 8% vaginal gel	Progesterone 400mg pessaries	IM progesterone
Duration of treatment 8 weeks with exception of IM progesterone (10 weeks) if pregnancy confirmed	£94	£70	£59	£102
Duration of treatment 10 weeks if pregnancy confirmed	£110	£81	£68	£102
Duration of treatment 16 days	£43	£32	£27	£40
Less frequent administration of IM progesterone (2 x/week)	£64	£47	£46	£44

A Patient Access Scheme (PAS) was proposed by the submitting company and was assessed by the Patient Access Scheme Assessment Group (PASAG) as acceptable for implementation in NHS Scotland. Under the PAS, a simple discount was offered on the price of the medicine.

With the PAS, progesterone 100mg vaginal tablets became a cost-effective treatment option.

The main weaknesses were:

- The economic analysis used different treatment durations for each medicine included in the analysis. However, initial SMC expert responses indicated that there was no clear evidence to suggest that the different preparations would be associated with different duration of treatment. In addition, it did not appear the evidence base presented by the company was able to demonstrate equivalent efficacy for the comparators at the various durations of treatment. However, following discussions at the New Drugs Committee (NDC) the treatment durations used in the base case analysis were considered appropriate as they reflected the licensed treatment duration for each medicine.
- The company suggested that the pivotal study and the Cochrane review supported the equivalent efficacy of the medicines included in the analysis in terms of biochemical pregnancy rate, clinical pregnancy rate, ongoing pregnancy rate and live birth rate. However, it was unclear whether actual data were available to support equivalence in relation to all comparators and efficacy outcomes referenced above. The company subsequently provided additional clarification and data to support the assumption of equivalent efficacy of the medicines under review. Following discussions at the NDC, the data presented by the company were considered sufficiently robust to support a cost-minimisation analysis.

Despite the above uncertainties the economic case has been demonstrated.

*Other data were also assessed but remain commercially confidential.**

Summary of patient and public involvement

A patient group submission was not made.

Additional information: guidelines and protocols

NICE published clinical guideline 156; Fertility problems: assessment and treatment, in February 2013. It recommends offering progesterone to women for luteal phase support after IVF treatment. It also notes that the evidence does not support continuing any form of treatment for luteal phase support beyond eight weeks gestation. hCG should not routinely be offered to women for luteal phase support after IVF treatment because of the increased likelihood of ovarian hyperstimulation syndrome.[10]

Additional information: comparators

Progesterone 8% vaginal gel once daily, progesterone pessaries 400mg twice daily and some use of progesterone 50 to 100mg IM up to once daily.

Cost of relevant comparators

Drug	Dose Regimen	Cost per course (£)
Progesterone vaginal tablets	**100mg three times daily for 30 days**	**84**
Progesterone for injection	50mg IM twice weekly up to once daily for up to 8 weeks*	72 to 252
Progesterone pessaries	400mg twice daily for 38 days	66
Progesterone 8% vaginal gel	90mg once daily for 30 days	62

Doses are for general comparison and do not imply therapeutic equivalence. Costs from DM&D and eVadis on 23 June 2016. Costs do not take any patient access schemes into consideration.
*NICE recommends maximum duration of treatment with progesterone of eight weeks.
NB: the comparators listed in the table have not been reviewed by SMC as they predate SMC or have recently been licensed.

Additional information: budget impact

The company estimated there would be 3,647 patients eligible for treatment with progesterone 100mg vaginal tablets in year 1, increasing to 4,250 patients in year 5 year, to which confidential estimates of treatment uptake were applied.

SMC is unable to publish the with-PAS budget impact due to commercial in confidence issues. A budget impact template is provided in confidence to NHS health boards to enable them to estimate the predicted budget with the PAS.

*Other data were also assessed but remain commercially confidential.**

References

The undernoted references were supplied with the submission. Those shaded in grey are additional to those supplied with the submission.

1. Progesterone 100mg vaginal tablets (Lutigest®) summary of product characteristics. Ferring Pharmaceuticals Ltd. . Electronic Medicines Compendium, wwwmedicinesorguk/emc/ Last updated October 2014.
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3. Miller C, Zbella E, Webster B et al. Clinical comparison of ovarian stimulation and luteal support agents in patients undergoing GnRH antagonist IVF cycles. Journal of Reproductive Medicine. 2013;58:153-60.
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5. Progesterone 8% vaginal gel (Crinone®) summary of product characteristics. Merck. Electronic Medicines Compendium, wwwmedicinesorguk/emc/ Last updated March 2015.
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7. Progesterone 50mg/mL for injection (Gestone®) summary of product characteristics. Nordic Pharma Limited. . Electronic Medicines Compendium, wwwmedicinesorguk/emc/ Last updated August 2007.
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10. National Institute for Health and Care Excellence. Fertility problems: assessment and treatment (clinical guideline 156). 2013.
11. van der Linden M, Buckingham K, Farquhar C ea. Luteal phase support for assisted reproduction cycles. Cochrane Database of Systematic Reviews. 2015;Issue 7. Art. No.: CD009154. DOI: 10.1002/14651858.CD009154.pub3.
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This assessment is based on data submitted by the applicant company up to and including 11 August 2016.

**Agreement between the Association of the British Pharmaceutical Industry (ABPI) and the SMC on guidelines for the release of company data into the public domain during a health technology appraisal: http://www.scottishmedicines.org.uk/About_SMC/Policy_statements/Policy_Statements*

Drug prices are those available at the time the papers were issued to SMC for consideration. SMC is aware that for some hospital-only products national or local contracts may be in place for comparator products that can significantly reduce the acquisition cost to Health Boards. These contract prices are commercial in confidence and cannot be put in the public domain, including via the SMC Detailed Advice Document. Area Drug and Therapeutics Committees and NHS Boards

are therefore asked to consider contract pricing when reviewing advice on medicines accepted by SMC.

Patient access schemes: A patient access scheme is a scheme proposed by a pharmaceutical company in order to improve the cost-effectiveness of a drug and enable patients to receive access to cost-effective innovative medicines. A Patient Access Scheme Assessment Group (PASAG, established under the auspices of NHS National Services Scotland reviews and advises NHS Scotland on the feasibility of proposed schemes for implementation. The PASAG operates separately from SMC in order to maintain the integrity and independence of the assessment process of the SMC. When SMC accepts a medicine for use in NHS Scotland on the basis of a patient access scheme that has been considered feasible by PASAG, a set of guidance notes on the operation of the scheme will be circulated to Area Drug and Therapeutics Committees and NHS Boards prior to publication of SMC advice.

Advice context:

No part of this advice may be used without the whole of the advice being quoted in full.

This advice represents the view of the Scottish Medicines Consortium and was arrived at after careful consideration and evaluation of the available evidence. It is provided to inform the considerations of Area Drug & Therapeutics Committees and NHS Boards in Scotland in determining medicines for local use or local formulary inclusion. This advice does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgement in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.