Scottish Medicines Consortium
Providing advice about the status of all newly licensed medicines
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micronised progesterone vaginal capsules 200mg (Utrogestan Vaginal®)
SMC No (935/13)

Besins Healthcare (UK) Ltd

07 April 2017

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 NHS Scotland. The advice is summarised as follows:

ADVICE: following a full submission

micronised progesterone (Utrogestan Vaginal®) is accepted for use within NHS Scotland.

Indication under review: in women for supplementation of the luteal phase during Assisted Reproductive Technology (ART) cycles.

In women receiving luteal support during ART cycles, micronised progesterone 200mg vaginal capsules administered three times daily were non-inferior to another progesterone preparation administered vaginally with respect to ongoing pregnancy rate at the end of the 12th week of gestation.

This advice takes account of the benefits of a Patient Access Scheme (PAS) that improves the cost-effectiveness of micronised progesterone (Utrogestan Vaginal®). This advice is contingent on the continuing availability of the PAS in Scotland or a list price that is equivalent or lower.

Overleaf is the detailed advice on this product.

Chairman
Scottish Medicines Consortium

Indication

In women for supplementation of the luteal phase during Assisted Reproductive Technology (ART) cycles.[1]

Dosing Information

600mg per day administered intravaginally in three divided doses from the day of embryo transfer (ET) until at least the seventh week of pregnancy and no later than the 12th week of pregnancy.[1]

Product availability date

July 2013

Summary of evidence on comparative efficacy

Assisted reproductive technology (ART) includes *in vitro* fertilisation (IVF) and intracytoplasmic sperm injection (ICSI). Progesterone is a natural progestogen, the main hormone of the corpus luteum and the placenta. During ART cycles the luteal phase is shortened, reducing the chance of successful embryo implantation and pregnancy.[2] Progesterone is in established use to support the luteal phase of ART cycles.

The key clinical evidence was from a phase III, randomised, controlled, open-label, non-inferiority study[3] comparing micronised progesterone 200mg capsules (Utrogest®) with progesterone 8% vaginal gel (Crinone®) in 430 women with a history of infertility undergoing IVF. Women were recruited to the study if they had an indication for IVF / ICSI; had successful transfer of two or three embryos; presented for the first ART (i.e. first treatment cycle of either conventional IVF or ICSI); were aged ≥18 years and ≤35 years; and had a normal cervical cytological smear result within the previous 12 months.[3] Patients were assessed for eligibility but there were no strict instructions regarding pre-treatment, which included pituitary down-regulation with a gonadotrophin-releasing hormone (GnRH) agonist, ovarian stimulation with human menopausal gonadotropin (hMG) or follicle-stimulating hormone (FSH) before oocyte retrieval (OCR) and embryo transfer (ET). Following successful ET patients were randomised to either micronised progesterone 200mg capsules administered vaginally three times daily (n=218) or progesterone 8% vaginal gel twice daily (n=212) beginning on the evening of ET and continued for ten weeks (12th week of gestation), if pregnant.

The primary endpoint was on-going pregnancy at the end of the 12th week of gestation in the intent-to-treat (ITT) population.[3] Twenty-five percent (55/218) of patients in the micronised progesterone 200mg capsules group and 22% (47/212) of patients in the progesterone 8% vaginal gel group were reported as having an on-going pregnancy at or beyond 12 weeks gestation,[3] a difference of 3.1% (95% confidence interval [CI]: −6.5% to 12%).[4] In the per protocol (PP) population, 26% (55/208) of patients in the micronised progesterone 200mg vaginal capsules group and 24% (47/197) of patients in the progesterone 8% vaginal gel group were reported as having an on-going pregnancy at or beyond 12 weeks gestation, a difference of 2.6% (95% CI: -7.2 to 12%).[4]

The odds ratio (calculated in the per protocol population) for an intact pregnancy at the end of the 12th week of gestation was 1.19 (90% CI: 0.73 to 1.83). Non-inferiority was demonstrated at the pre-specified margin of 10% difference.

Rates of implantation and abortion and number and reason for withdrawal from the study were reported as secondary outcomes. These are shown in Table 1 below:

Table 1: Secondary outcomes

Variable	Micronised progesterone 200mg vaginal capsules	Progesterone 8% vaginal gel
Number of transfers	218	212
Number of embryos transferred	489	481
Number of implantations (% per transferred embryos)	72 (15%)	57 (12%)
Number of abortions/missed abortions (% of clinical pregnancies)	10 (18%)	9 (19%)

Similar proportions of patients withdrew from study treatment: 75% (163/218) of patients in the micronised progesterone 200mg vaginal capsule group and 78% (165/212) of patients in the progesterone 8% vaginal gel group.[3] The main reason for withdrawal in both groups was pregnancy failure: 70% (153/218) and 71% (150/212) respectively which represented 94% and 91% of all treatment discontinuations. Reasons other than pregnancy failure were observed in 10 patients and 15 patients in the micronised progesterone 200mg vaginal capsule and progesterone 8% vaginal gel groups; these patients were excluded from the per protocol population.

More than 90% of patients rated overall tolerability of the study medicines as either “very good” or good”. There was a statistically significant difference in both tolerability and acceptance in favour of micronised progesterone vaginal capsules compared with progesterone 8% vaginal gel.[4]

Summary of evidence on comparative safety

During the pivotal study, the frequency of adverse events (AEs) was similar between the treatment groups: with 24 AEs reported in 9.6% (21/218) of patients in the micronised progesterone 200mg vaginal capsules group and 26 AEs in 9.9% (21/212) of patients in the progesterone 8% vaginal gel group. Three of 24 AEs and 7/26 AEs in the respective groups were considered related to the use of the study medicine, predominantly local discomfort or vaginal discharge. Only one serious AE was reported, jugular vein thrombosis, which occurred in a patient receiving micronised progesterone vaginal capsules.[3] AEs led to discontinuation of study treatment in 0.9% (2/218) of patients in the micronised progesterone 200mg vaginal capsules group and 2.4% (5/212) of patients in the progesterone 8% vaginal gel group.

Summary of clinical effectiveness issues

Progesterone is an essential hormonal regulator of normal female reproductive function.[4] In IVF, progesterone is necessary to increase endometrial receptivity for implantation of an embryo. Once an embryo is implanted, progesterone acts to maintain the pregnancy. The National Institute for Health and Care Excellence (NICE) recommends progesterone for luteal phase support after IVF treatment for a maximum treatment duration of eight weeks; after this point it is expected the placenta secretes sufficient progesterone to maintain the pregnancy.[3] There are a number of other vaginal progesterone preparations licensed for luteal phase support; progesterone 8% vaginal gel (Crinone®)[5], progesterone 100mg vaginal tablets (Lutigest®)[6], and progesterone 400mg pessaries (Cyclogest®).[7] Intramuscular progesterone preparations, Gestone® and Lubion®, are also licensed for this indication but vaginally administered preparations are considered the most appropriate comparators for this submission (Lubion® is licensed for use in women who are unable to use or tolerate vaginal preparations). Clinical experts consulted by SMC report that Crinone® and Cyclogest® are the most commonly used treatments currently.

The key study[3] found similar rates of on-going pregnancy at the end of the 12th week of gestation in patients undergoing ART with micronised progesterone 200mg capsules (Utrogest®) vaginally three times a day or progesterone 8% vaginal gel (25% and 22%) and non-inferiority was considered demonstrated.[3] Fewer patients were recruited than originally intended, however sensitivity analysis using conservative estimates indicated that non-inferiority was maintained. The study used progesterone 200mg capsules intended for oral administration (Utrogest®), however these are the same as the commercially available progesterone 200mg vaginal capsules (Utrogestan Vaginal®). The comparator (Crinone®) was administered twice daily in the study, and so the relative efficacy versus the licensed dose (of once daily) is unclear. Patients aged >35 years were not included in the study, so there are no data in older patients undergoing ART. The study was conducted in Germany and patients had two or three embryos implanted. Practice may differ in Scottish fertility centres. In addition, it was of insufficient duration to determine the effect on live birth rate.

There are no direct comparative data against the other relevant comparators Cyclogest® and Lutigest®. The submitting company conducted a systematic literature review for all relevant evidence on the efficacy and safety of vaginal progesterone for luteal phase support during ART cycles. A total of seventeen studies, conducted in Europe[8-16], Asia[17-20], US[21, 22], and South America,[23, 24] were included in the review. The study described in the comparative efficacy section[3] was identified as the pivotal study for this submission. With the exception of three studies, all were undertaken in specialist reproductive or infertility clinics, [15, 16, 23], and the majority were conducted at a single site. The age of the patients was broadly similar across studies; however there were fewer woman aged >40 years and indeed they were excluded from some studies.[8, 10, 11, 13, 15-17] A variety of interventions and comparisons were reported across the studies; specifically: Utrogestan Vaginal®, Crinone 8%®, Progestan®, Endometrin®, Duphaston®, Cyclogest®, Prometrium®, and Pregnyl®. Five studies[10, 11, 15, 23, 24] reported Utrogestan Vaginal® as being the intervention of interest. There was significant variation in the posology of the agents utilised across the studies in terms of both dosage and frequency of administration. The primary outcome measure also varied: clinical pregnancy rate was reported in six studies[13, 16, 18, 22-24]; on-going pregnancy rate in seven studies[8, 10-12, 15, 17, 21]; patient satisfaction/adverse events in two studies[19, 20]; expected live birth rate in one study[14] and delivery rate in another.[9] None of the studies reported a significant difference in efficacy or safety between the intervention and comparator and the

submitting company concluded that vaginally administered formulations of progesterone could be considered to be equivalent. It was noted that the Cochrane review[2] of luteal phase support for assisted reproduction cycles also made this assumption.

Utrogestan Vaginal® would provide an alternative choice of vaginal progesterone in this indication. There is variation in the dosing and administration schedules of alternative formulations: Utrogestan Vaginal® 200mg vaginal capsules and Lutigest® 100mg vaginal tablets are administered three times daily compared with Crinone® 8% vaginal gel which is administered once daily and Cyclogest® 400mg pessaries which are administered twice daily.[1, 5-7] Compliance with a three times daily regimen may be a potential concern, however women receiving ART are likely to be highly motivated.[22]

Summary of comparative health economic evidence

The company submitted a cost- minimisation analysis comparing Utrogestan Vaginal® to Crinone®, Lutigest® and Cyclogest®, for the treatment of women requiring luteal phase support during ART cycles. Based on SMC expert responses, the comparators appear to be appropriate. The time horizon in the analysis reflected the duration of treatment of the medicines as defined by the summary of product characteristics (SPC). Patients were treated with Utrogestan Vaginal® for 34 days, Crinone® and Lutigest® for 30 days and Cyclogest® for 38 days. The company conducted a simple model in Excel®, which was used to incorporate the per-day cost associated with each treatment, as well as scenario analyses which varied the duration of treatment.

The clinical data used to support the assumption of comparable efficacy between treatments were taken from the pivotal study which compared Utrogestan Vaginal® three times daily to twice daily Crinone®.[3] Based on this analysis, Utrogestan Vaginal® was considered to demonstrate comparable efficacy to Crinone®. It should be noted that there are no direct study data comparing Utrogestan Vaginal® capsules to the other relevant comparators. As such a systematic literature review was used to support the assumption of comparable efficacy.

Only medicines acquisition costs were included in the analysis. Administration and monitoring costs were assumed to be the same for all treatments, and therefore were not included in the analysis. No medicines wastage was assumed in the base case.

The base case results and key sensitivity analyses are presented in Table 2 below.

Table 2: Base case results and key sensitivity analyses

Analysis	Utrogestan Vaginal® Total Cost	Incremental cost versus Crinone® (once daily)	Incremental cost Crinone® (twice daily)	Incremental cost Versus Cyclogest®	Incremental cost vs Lutigest® using list price for Lutigest®
Base case	£102.00	£40.34	-£21.32	£36.34	£18.43
Treatment for one month (Drug wastage assumed)	£105	£43.34	-£18.32	£53.16	£7.50
Treatment initiated at Oocyte removal to 7 weeks (Drug wastage assumed)	£126	£33.51	-£28.15	£61.20	£9.00

Treatment initiated at Oocyte removal to 8 weeks (Drug wastage assumed)	£147	£54.51	-£37.98	£69.24	£10.50

A Patient Access Scheme (PAS) was submitted by the 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 which reduced the list price of Utrogestran®. SMC would wish to present the with-PAS cost-effectiveness estimates that informed the SMC decision. However, owing to the commercial in confidence concerns regarding the PAS, SMC is unable to publish these results. As such, only the without-PAS figures can be presented. The base case results with the PAS indicated Utrogestan Vaginal® was a cost-effective treatment option.

A PAS discount is in place for the comparator Lutigest® and when an estimate of the PAS was included and used for decision-making, Utrogestan Vaginal® became less cost-effective. SMC is unable to present the results provided by the company which used an estimate of the PAS price for Lutigest® due to commercial confidentiality and competition law issues.

The weaknesses with the analysis are as follows:

- There are no direct study data comparing Utrogestan Vaginal® to the alternative progesterone formulations other than Crinone®. Therefore, comparable efficacy is based on a systematic literature review. In addition there were a number of issues surrounding the pivotal study which may introduce further uncertainty, for example the dose used for Crinone® was unlicensed.

- There is some uncertainty surrounding the appropriate treatment duration upon which to base the analysis. According to the Utrogestan Vaginal® SPC, the advised treatment duration is between 7 to 12 weeks. One SMC expert has indicated that that treatment for luteal phase support is likely to be provided for the first trimester of pregnancy (12 weeks).

Despite the weaknesses outlined above, the economic case has been demonstrated.

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

Summary of patient and public involvement

No Patient Group Submission was received.

Additional information: guidelines and protocols

The National Institute for Health and Care Excellence (NICE) published clinical guideline 156 (CG156) Fertility problems: assessment and treatment in February 2013. The guidance recommends that women should be offered progesterone for luteal phase support following IVF but that human chronic gondatrophin (hCG) should not be offered routinely as it is associated with an increased likelihood of ovarian hyperstimulation syndrome (OHSS). Furthermore, the guidance recommends that available evidence does not support the continuation of any treatment for luteal support beyond eight weeks' gestation.

Additional information: comparators

Other vaginal progesterone preparations including: progesterone 8% vaginal gel (Crinone®); progesterone 400mg pessaries (Cyclogest®); progesterone 100mg vaginal tablets (Lutigest®)

Cost of relevant comparators

Drug	Dose Regimen	Cost per course (£)
Micronised progesterone 200mg vaginal capsule (Utrogestan Vaginal®)	**200mg three times daily from the day of embryo transfer until at least the 7th week of pregnancy and not later than the 12th week of pregnancy**	**105 to 210**
progesterone 100mg vaginal tablets (Lutigest®)	100mg three times daily for 30 days	84
progesterone 400mg pessaries (Cyclogest®)	400mg twice daily for 38 days	66
progesterone 8% vaginal gel (Crinone®)	90mg once daily for 30 days	62

Doses are for general comparison and do not imply therapeutic equivalence. Costs from eVadis on 06/12/17. Costs do not take any patient access schemes into consideration.

Additional information: budget impact

The submitting company estimated there would be 1,078 patients eligible for treatment with micronised progesterone 200mg vaginal capsules in all years 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.**

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This assessment is based on data submitted by the applicant company up to and including 16 March 2017.

**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.