New Medicine Assessment

Prasterone (Intrarosa®) 6.5 mg pessary for the treatment of vulvar and vaginal atrophy in postmenopausal women having moderate to severe symptoms.

Recommendation: BLACK

Prasterone was only compared to placebo in clinical studies which makes comparison with currently used treatments for vulvar and vaginal atrophy in postmenopausal women having moderate to severe symptoms difficult.

The EMA public assessment report states “clinical efficacy as demonstrated in the clinical trials was modest” and that “the safety profile of prasterone is still uncertain”.

Summary of clinical supporting evidence

The efficacy profile of Prasterone (dehydroepiandrosterone (DHEA)) is based on two placebo-controlled phase III studies. Although local oestrogens are the “standard” vulvar and vaginal atrophy (VVA) treatment in this population (postmenopausal women), no active comparator group was included in the study design and this point was not sufficiently justified. From the main pivotal studies ERC-231 and ERC-238, a slight placebo effect was observed on the primary endpoints (parabasal and superficial cell, vaginal pH). However, this placebo effect was more important than expected in the study ERC-238 compared to ERC-231. Regarding the 4th co primary outcome which is the clinical parameter in both phase III studies (dyspareunia), there was a clear improvement of this parameter (decrease in severity score of dyspareunia) with the placebo at the end of treatment period compared to baseline in both studies. This placebo effect on dyspareunia is probably related to the excipients (lubricant-like). Although the change versus baseline in the DHEA group was more important than the change versus baseline in the placebo group, the clinical relevance of this effect over placebo is unknown. Also, the frequency of intercourse in the efficacy population is unknown.

The phase III pivotal studies ERC–231 and ERC-238 were conducted in Canada and in USA. There were no European women exposed to the drug. Given the cultural dimension related to menopause and sexual activities, comparability between Canadian/US women and European women can be questioned as a different perception of the benefit in European women cannot be excluded.

Details of Review

Name of medicine (generic & brand name): Prasterone (Intrarosa®)
Strengths and forms: 6.5 mg pessary
Dose and administration: The recommended dose is 6.5 mg prasterone (one pessary) administered once daily, at bedtime.
BNF therapeutic class / mode of action: Genito-urinary system / Vaginal and vulval conditions
Licensed indication(s): [1]

Intrarosa is indicated for the treatment of vulvar and vaginal atrophy in postmenopausal women having moderate to severe symptoms.

Proposed use: As per licensed indication

Course and cost:

One 6.5mg pessary, once daily.

28 pessaries – NHS indicative price = £15.94 (information from company)

Annual cost assuming one pessary daily = £207.79

Current standard of care/comparator therapies: [2]

- Vagifem® 10µg vaginal tablets – cost of 24 tablets = £16.72

Annual cost (assuming one tablet daily for two weeks then one tablet twice weekly thereafter) = £79.42

- Ovestin® cream 15g = £4.45

Annual cost assuming wastage and one applicator dose daily for 2 weeks, then decrease to twice weekly thereafter) = £17.80

- Estring® vaginal ring – cost = £31.42

Annual cost (inserted every 3 months) = £125.68

Relevant NICE and other guidance: [3]

NICE guideline NG23 - Menopause: diagnosis and management

Urogenital atrophy

1.4.9 Offer vaginal oestrogen to women with urogenital atrophy (including those on systemic HRT) and continue treatment for as long as needed to relieve symptoms.

1.4.10 Consider vaginal oestrogen for women with urogenital atrophy in whom systemic HRT is contraindicated, after seeking advice from a healthcare professional with expertise in menopause.

1.4.11 If vaginal oestrogen does not relieve symptoms of urogenital atrophy, consider increasing the dose after seeking advice from a healthcare professional with expertise in menopause.

1.4.12 Explain to women with urogenital atrophy that:

symptoms often come back when treatment is stopped adverse effects from vaginal oestrogen are very rare they should report unscheduled vaginal bleeding to their GP.

1.4.13 Advise women with vaginal dryness that moisturisers and lubricants can be used alone or in addition to vaginal oestrogen.

1.4.14 Do not offer routine monitoring of endometrial thickness during treatment for urogenital atrophy.

Disease Background and Current treatment options

Vulvovaginal atrophy (VVA) is a common and underreported condition associated with decreased oestrogenisation of the vaginal tissue. Symptoms include dryness, irritation, soreness, and dyspareunia with urinary frequency, urgency, and urge incontinence. It can occur at any time in a woman's life cycle, although more commonly in the postmenopausal phase, during which the prevalence is close to 50%.[4] During menopause, the ratio of the three vaginal epithelial cell types (parabasal, intermediate, and superficial) changes. The proportion of these vaginal cell types is categorised by the vaginal maturation index (VMI). The VMI provides an objective assessment of vaginal hormone response as well as overall hormonal

environment. Increasing progression from parabasal to superficial epithelial cells is a characteristic of increasing oestrogenisation of the vaginal tissue.

Treatment goals for VVA include alleviating symptoms, reversing or minimising the physiologic changes, and improving quality of life for the patient. There are:

- Non-hormonal treatments: A number of over-the-counter (OTC) vaginal moisturiser and lubricant products are considered first-line non-hormonal treatments for vaginal dryness. This option can be appropriate for women concerned about hormone use, those with minimal physiologic changes or symptoms, or those who are not candidates for oestrogen treatment.
- Hormonal treatments: Local, low-dose oestrogen preparations to be applied vaginally are considered first-line pharmacologic treatment (Royal College of Obstetricians and Gynaecologists Guideline Menopause and Hormone Replacement). The guideline further states: "There is no evidence that local vaginal oestrogen treatment is associated with significant risks". These preparations include: Vagifem® 10 mg (estradiol tablets for vaginal application), Estring® (estradiol in vaginal ring) and Ovestin® (estriol cream for vaginal application).

Treatment should be reviewed at least annually, with special consideration given to any symptoms of endometrial hyperplasia or carcinoma.

Summary of efficacy data in proposed use:

The clinical efficacy of prasterone on the symptoms and signs of vulvovaginal atrophy (VVA) has been evaluated in 6 clinical studies performed in Canada and the USA. Within the 6 studies, there were two pivotal 12-week efficacy studies (ERC-231 and ERC-238) which support the proposed indication. The pivotal efficacy studies were performed in postmenopausal women who have self-identified moderate to severe (MS) dyspareunia (pain at sexual activity) as their most bothersome symptom (MBS) of VVA.

In addition, the clinical programme includes one 7-day PK study (ERC–213), one dose-response study (ERC-210), and one placebo-controlled efficacy study performed with a different (reduced) regimen (ERC-234).

The study ERC–230 was an open-label long term (52 weeks) safety study in which efficacy parameters were only regarded as secondary endpoints.

Please see table below:

Study ID	No of centers	Design	Posology	Study objective	Subj / arm randomized/ completed	Duration	Gender, median age	Diagnosis Incl criteria	Primary endpoint
ERC-213 (Ph I PK study)	1	Random, DB, placebo controlled	Placebo, DHEA: 6.5, 13 and 23.4 mg	DHEA and metabolites serum level. PK parameters	40 in total 10/10 each arm	7 days	F Median age: 62	Postmenopausal women with vaginal atrophy	PK parameters
ERC-210 (Ph II) Dose – response study	8	Random, DB, placebo controlled	Placebo, DHEA: 3.25 mg, 6.5 mg and 13 mg	Dose - response	54/48 53/48 56/52 54/51	12 weeks	F Median age: 58	Postmenopausal women with vaginal atrophy	4 co- primary (vaginal maturation index*, vaginal pH, improvement in MBS)
ERC–231 (Ph III pivotal).	33	Random, DB, placebo controlled	Placebo, DHEA: 3.25 mg and 6.5 mg	Confirm efficacy on symptoms and signs of VA	81/72 87/74 87/76	12 weeks	F Median age: 59	Postmenopausal women with VVA, dyspareunia as MBS	4 co- primary (vaginal maturation index*, vaginal pH and dyspareunia)
ERC–238 (Ph III, pivotal).	38	Random, DB, placebo controlled	Placebo, DHEA: 6.5 mg	Confirm efficacy on dyspareunia as MBS	182/171 376/356	12 weeks	F Median age: 59	Postmenopausal women with VVA, dyspareunia as MBS	4 co- primary (vaginal maturation index*, vaginal pH and dyspareunia)
ERC–234 (Ph III).	42	Random, DB, placebo controlled	Placebo, DHEA: 3.25 mg and 6.5 mg	Confirm efficacy on vaginal dryness. **Different regimen**	152/130 148/128 150/125	12 weeks	F Median age: 58	Postmenopausal women with VVA, dryness as MBS	4 co- primary (vaginal maturation index*, vaginal pH and vaginal dryness)
ERC–230 (Ph III long term safety)	41	Open-label	DHEA: 6.5 mg	Long-term safety	521/435	52 weeks	F Median age: 58	Postmenopausal women with VVA symptom(s) (mild to severe)	Safety parameters

*: percentage of superficial cells and parabasal cells

Main Studies

Pivotal study ERC–231: DHEA against Vaginal Atrophy (Placebo-Controlled, Double-Blind and Randomized Phase III Study of 3-Month Intravaginal Prasterone (dehydroepiandrosterone - DHEA)).

This was a Phase III, placebo-controlled, double-blind and randomized study to confirm the efficacy of daily intravaginal administration of a 0.25% (3.25 mg) prasterone and 0.50% (6.5 mg) prasterone suppositories for 12 weeks compared to placebo in postmenopausal women. Women were randomized between 3 treatment arms in a 1:1:1 ratio. The study was divided into two phases, namely a screening period of 4 to 6 weeks followed by a treatment period of 12 weeks.

Subject population was postmenopausal women (non-hysterectomized or hysterectomized), between 40 and 75 years of age, having ≤5% of superficial cells on vaginal smear, a vaginal pH above 5 and having self-identified moderate to severe vaginal pain associated with sexual activity (dyspareunia) as their MBS of VVA. 210 evaluable participants (70 subjects to be treated with each dose of prasterone or placebo) were planned to be enrolled. A total of 255 subjects were enrolled in the study.

Women were instructed to apply one intravaginal ovule (suppository, pessary) containing placebo (0%), 0.25% (3.25 mg) prasterone or 0.50% (6.5 mg) prasterone daily before bedtime (usually evening) during12 weeks.

Primary objective was to confirm the efficacy of daily intravaginal administration of prasterone on the symptoms and signs of vaginal atrophy in postmenopausal women suffering from moderate to severe pain at sexual activity (dyspareunia) as their MBS of VVA at baseline.

Secondary objectives were to evaluate the efficacy on arousal/lubrication, subjective arousal, desire, pain at sexual activity, satisfaction and orgasm using the female sexual function index (FSFI) questionnaire as well as to examine the tolerance to local administration of prasterone.

The four co-primary endpoints compared to placebo were:

1. A statistically significant decrease in percentage of parabasal cells.
2. A statistically significant increase in percentage of superficial cells.
3. A statistically significant decrease in vaginal pH.
4. A statistically significant improvement of moderate to severe dyspareunia self-identified by subjects as the most bothersome VVA symptom to her at screening and at baseline (Day 1).

Self-assessment of the other symptoms of vulvar and vaginal atrophy associated with menopause were evaluated by a questionnaire but were not co-primary objectives:

- Vaginal dryness (none, mild, moderate or severe) and
- Vaginal and/or vulvar irritation/itching (none, mild, moderate or severe)

Secondary efficacy variables included: dryness and irritation as symptoms of vaginal atrophy, observations at vaginal examination related to local tolerance to prasterone (vaginal secretions, vaginal epithelial integrity, vaginal epithelial surface thickness, vaginal colour, menopause-specific quality of life questionnaire (MENQOL), Female Sexual Function Index (FSFI), and safety variables, vital signs.

464 subjects were screened and 255 were enrolled and randomized to this study. 222 subjects have completed the study. Among the 33 subjects who prematurely discontinued from study treatment, 15 subjects discontinued early as they did not meet the inclusion criteria (vaginal maturation index, vaginal pH and/or vulvovaginal atrophy symptom).

The ITT population (all subjects who have received at least one dose of study drug (based on diary) with a baseline (Day 1) evaluation meeting the entry criteria) is the primary analysis population of efficacy analyses and includes a total of 237 subjects with 77, 79 and 81 subjects in the placebo, 0.25% and 0.50% prasterone groups, respectively. The ITT population is composed of postmenopausal women aged 58.84 ± 0.38 years (mean ± standard error of the mean (SEM)) and includes 93% of White Caucasian, 5% of Black or African American, 1%

Asian and 1% other race while the ethnicity of 94% of this population is not Hispanic or Latino. In this population, 63% had an hysterectomy and 33% had undergone an ovariectomy prior to the study.

The Per Protocol (PP) Population consists of a subset of 204 subjects of the ITT population that completed the study through the time points of 12 weeks with no major protocol violations considered to compromise efficacy data. Subjects in this population have received at least 90% of the required number of applications of study treatment, based on the subject diary data. The PP population is a supportive population for efficacy data analysis.

Outcomes

Effect on parabasal cells

- Placebo had no effect on the percentage of parabasal cells at week 12 of the treatment.
- The 3.25 mg prasterone decreased the % of parabasal cells from 65.72 ± 4.56% at baseline to 31.76 ± 3.78% at 6 weeks ($p<0.0001$ over placebo) and 28.43±3.62% at 12 weeks ($p<0.0001$ vs placebo).
- The 6.5 mg decreased the % of parabasal cells from 65.05 ± 4.63% at baseline to 26.31 ± 3.38% ($p<0.0001$ versus placebo) at 6 weeks and 17.65 ± 2.87% at 12 weeks ($p<0.0001$ vs placebo).

Effect on superficial cells

- There was a slight increase in the % of superficial cells in the placebo group from 0.73 ± 0.15% at baseline to 1.13 ± 0.24% ($p=0.028$ versus baseline) and 1.64 ± 0.33% ($p=0.004$ versus baseline) at 6 and 12 weeks, respectively.
- In the group who received daily 3.25 mg prasterone, the % of superficial cells increased from 0.68 ± 0.13% at baseline to 4.33 ± 0.50 ($p<0.0001$ versus placebo) and 5.43 ± 0.57% ($p<0.0001$ versus placebo) at 6 and 12 weeks, respectively.
- In the group who received a daily dose of 6.5 mg prasterone, the % of superficial cells increased from 0.68 ± 0.12% at baseline to 5.11 ± 0.57% ($p<0.0001$ versus placebo) and 6.30 ± 0.59% ($p<0.0001$ versus placebo) at 6 and 12 weeks, respectively.

Effect on vaginal pH

- A slight decrease was observed in the placebo group.
- with 3.25 mg prasterone, the pH decreased from 6.48 ± 0.07 pH units at baseline to 5.81 ± 0.10 ($p=0.0008$ vs placebo) and 5.70 ± 0.11 ($p<0.0001$ versus placebo) at 6 and 12 weeks, respectively.
- with 6.5 mg prasterone, the pH decreased from 6.47 ± 0.07 at baseline to 5.52 ± 0.10 ($p<0.0001$ vs placebo) at 6 weeks and then to 5.43 ± 0.10 ($p<0.0001$ versus placebo) at 12 weeks.

Effect on dyspareunia

Women were enrolled on the basis of having pain at sexual activity considered as most bothersome symptom. The self-reported symptom score takes the following values: none, mild, moderate or severe to be analysed using values of 0, 1, 2 or 3, respectively. All subjects must have this symptom at screening and Day 1 graded as 2 or 3.

- In the placebo group, there was a decrease in the severity score of dyspareunia from 2.58 at baseline to 1.87 and 1.71 at 6 and 12 weeks, respectively ($p<0.0001$ versus baseline at both time intervals).
- At the 3.25 mg dose, the severity score of dyspareunia decreased from 2.56 at baseline to 1.86 (NS versus placebo) and 1.54 (NS versus placebo) at 6 and 12 weeks, respectively.
- At the 6.5 mg dose, the severity score of dyspareunia decreased from 2.63 ± 0.05 at baseline to 1.63 ± 0.13 ($p=0.066$ versus placebo) and 1.36 ± 0.12 ($p=0.013$ versus placebo) at 6 and 12 weeks, respectively. An improvement of 0.40 severity score unit was thus observed or a 46% improvement over placebo ($p=0.013$ versus placebo).

Study ERC–238: Intravaginal prasterone (DHEA) against vulvovaginal atrophy associated with menopause: a placebo controlled double blind and randomized phase III study.

The subject population was postmenopausal women (non-hysterectomized or hysterectomized), between 40 and 80 years of age, having ≤5% of superficial cells on vaginal smear, a vaginal pH above 5 and having self-identified moderate to severe vaginal pain associated with sexual activity (dyspareunia) as their MBS of VVA at baseline (Day 1).

Study ERC-231 indicated that the appropriate prasterone dose was 6.5mg (0.50%).

ERC -238 was a confirmatory efficacy study performed with the selected 6.5mg (0.50%) prasterone dose.

Women were randomized in a 2:1 ratio between the 0.50% prasterone and placebo groups.

The treatment duration was 12 weeks.

Primary objectives

To confirm the efficacy of intravaginal prasterone on moderate to severe (MS) pain at sexual activity (dyspareunia) as most bothersome symptom (MBS) of VVA due to menopause and to collect further data on subjects exposed to intravaginal prasterone at the dose or dose range believed to be efficacious in order to meet the ICH E1 guideline requirement so that the "total number of individuals treated with the investigational drug, including short-term exposure, will be about 1500."

Secondary objectives

- Examine the tolerance to intravaginal administration of DHEA;
- Investigate a possible influence of treatment on the male partner;
- Evaluate the efficacy on the other two symptoms of VVA (dryness and irritation/itching);
- Evaluate the efficacy on arousal/lubrication, subjective arousal, desire, satisfaction and orgasm by the Female Sexual Function Index (FSFI) questionnaire according to the indicated priority design;
- Obtain information on the usability of the applicator used to insert the medication.

The four co-primary endpoints compared to placebo are:

- A statistically significant decrease in percentage of parabasal cells;
- A statistically significant increase in percentage of superficial cells;
- A statistically significant decrease in vaginal pH; and
- A statistically significant improvement of moderate to severe dyspareunia self-identified by subjects as the most bothersome VVA symptom to her at screening and at baseline (Day 1).

Secondary efficacy endpoints:

Self-assessment of the other symptoms of VVA associated with menopause were evaluated by a questionnaire but were not co-primary objectives:

- Vaginal dryness (none, mild, moderate or severe); and
- Vaginal and/or vulvar irritation/itching (none, mild, moderate or severe)

558 subjects were enrolled and randomized to this study in a 2:1 ratio. A total of 527 subjects (94%) have completed the study (prasterone = 356 and Placebo = 171).

The intent-to-treat (ITT) population, which consists of all subjects who have received at least one dose of study drug (based on the diary card) with a baseline (Day 1) evaluation meeting the study entry criteria, is the primary analysis population of efficacy analyses and includes a total of 482 subjects with 157 and 325 women in the placebo and 0.50% prasterone groups, respectively.

The Per Protocol (PP) Population consists of a subset of 373 subjects (prasterone = 254 and Placebo = 119) of the ITT population that completed the study through the time point of 12

weeks with no major protocol violations considered to compromise efficacy data. Subjects in this population have received at least 90% of the required number of applications of study treatment, based on the subject diary data and they have valid data entry at Week 12 for the 4 co-primary efficacy endpoints (superficial and parabasal cells, pH and pain at sexual activity).

Outcomes

Effect on parabasal cells

There was a slight effect of intravaginal placebo on the percentage of parabasal cells. At baseline, percentage of parabasal cells was 51.66 ± 3.00%, and decreased to:

- 42.35 ± 2.73% ($p<0.0001$ versus baseline) at week 6
- 39.68 ± 2.68% ($p<0.0001$ versus baseline) at week 12

With the daily 6.5 mg (0.50%) intravaginal prasterone, the % of parabasal cells decreased from 54.25 ± 2.14% at baseline to:

- 14.72 ± 1.09% ($p<0.0001$ versus placebo) at 6 weeks
- 12.74 ± 1.02% ($p<0.0001$ versus placebo) at 12 weeks

Effect on superficial cells

Percentage of superficial cells increased slightly in the ITT placebo group of 157 women from 1.04 ± 0.11% at baseline to:

- 2.60 ± 0.27% ($p<0.0001$ versus baseline) at week 6
- 2.78 ± 0.27% ($p<0.0001$ versus baseline) at week 12

In the group who received daily 6.5 mg prasterone, the % of superficial cells increased from 1.02 ± 0.08% at baseline to:

- 11.71 ± 0.61% ($p<0.0001$ versus placebo) at week 6
- 11.22 ± 0.56% ($p<0.0001$ versus placebo) at week 12

Effect on vaginal pH

A relatively small decrease was observed in the placebo group. Vagina pH decreased from 6.32 ± 0.05 pH units at baseline to:

- 6.06 ± 0.07 ($p<0.0001$ versus baseline) at 6 weeks
- 6.05 ± 0.07 ($p<0.0001$ versus baseline) at 12 weeks

In the dose group of 6.5mg prasterone, the pH decreased from 6.34 ± 0.04 at baseline to:

- 5.47 ± 0.05 ($p<0.0001$ versus placebo) at 6 weeks
- 5.39 ± 0.05 ($p<0.0001$ versus placebo) at 12 weeks

Effect on dyspareunia (as MBS)

In the ITT placebo group, (N=157), the severity score of dyspareunia decreased from 2.56 ± 0.04 units at baseline to

- 1.61 ± 0.08 at 6 weeks
- 1.50 ± 0.08 unit at 12 weeks, ($p<0.0001$ versus baseline at both time intervals).

With the daily 6.5 mg (0.50%) prasterone dose (N=325), the severity score of dyspareunia decreased from 2.54 ± 0.03 units at baseline to:

- 1.41 ± 0.06 ($p=0.036$ versus placebo) at 6 weeks
- 1.13 ± 0.05 ($p=0.0002$ versus placebo) at 12 weeks

An improvement of 0.35 point in the severity score unit was thus observed or a 33% improvement over placebo ($p=0.0002$ versus placebo).

Summary of safety data

The safety population consisted of 1,542 women exposed to the 0.25%, 0.50% or 1.0% intravaginal prasterone in studies ERC-210, ERC-213, ERC-230, ERC-231, ERC-234 and ERC-238 and 474 women who received placebo. There were 1,196 women exposed to the 0.5% dose including 435 women exposed up to 52 weeks. More than 300 biopsies were available after week 52 to assess endometrial safety.

As Prasterone's metabolites are mainly androgens which could have an action on cardiovascular system and oestrogens (to a lesser degree) which could be involved in thromboembolic events and development of hormonal cancers, women with history of thromboembolic accident, cancer (including hormonal cancer), cardiac failure or coronary heart disease and hypertension (>140/90 mmHg) were excluded from the studies.

Only treatment-emergent adverse events (TEAEs) reported up to week 16 were analysed in the summary of safety.

Regarding long-term data, TEAEs observed up to week 52 are globally the same than those observed at week 16. However, several serious AEs occurred during ERC-230 (52 weeks study) which were not previously reported at week 16: hypertension, breast cancer, breast hyperplasia, ovarian cancer, cervical/uterine polyps.

No death was reported during clinical trials.

However, the safety profile of prasterone is still uncertain and this is reflected in the sections of the SPC covering contraindications and special warnings and precautions for use.

The contraindications / special warnings and precautions for use, are comparable to those for other HRT preparations.

A careful appraisal of the risks and benefits should be reassessed at least every 6 months and prasterone should only be continued as long as the benefit outweighs the risk

Table of Adverse events for Prasterone (Intrarosa®)

Incidence of Event	Adverse Event
Common (≥1/100 to <1/10)	Application site discharge, Abnormal Pap smear (mostly ASCUS or LGSIL), Weight fluctuation
Uncommon (≥ 1/1,000 to < 1/100)	Cervical/ uterine polyps, Breast mass (benign)

Prasterone is metabolised into oestrogenic compounds. The following risks have been associated with systemic HRT and apply to a lesser extent for oestrogen products for vaginal application of which the systemic exposure to the oestrogen remains within the normal postmenopausal range. However, they should be considered in case of long term or repeated use of this product.

Breast cancer risk

- An up to 2-fold increased risk of having breast cancer diagnosed is reported in women taking combined oestrogen-progestagen therapy for more than 5 years.
- Any increased risk in users of oestrogen-only therapy is substantially lower than that seen in users of oestrogen-progestagen combinations.
- The level of risk is dependent on the duration of use

Ovarian cancer

Use of oestrogen-only or combined oestrogen-progestogen HRT has been associated with a slightly increased risk of having ovarian cancer diagnosed

Risk of venous thromboembolism

HRT is associated with a 1.3-3-fold increased relative risk of developing venous thromboembolism. The occurrence of such an event is more likely in the first year of using HRT

Risk of ischaemic stroke

- The use of oestrogen-only and oestrogen + progestogen therapy is associated with an up to 1.5 fold increased relative risk of ischaemic stroke. The risk of haemorrhagic stroke is not increased during use of HRT.
- This relative risk is not dependent on age or on duration of use, but as the baseline risk is strongly age-dependent, the overall risk of stroke in women who use HRT will increase with age

Strengths and limitations of the evidence:

Strengths:

- Large number of subjects in trials

Limitations:

- No active comparator in trials
- Short trial duration
- No European subjects
- Reproducibility of the results (cell count) is questionable as no secondary confirmatory assessment conducted (ERC-231)
- No validation of questionnaire relating to dyspareunia (ERC-231)
- No information on frequency of intercourse in the efficacy population set (ERC-231 / 238)
- The percentages of subjects with an improvement in their dyspareunia symptom at week 12 were not statistically different between placebo and Intrarosa groups (ERC-231)
- The size effect observed with placebo was more important than expected in ERC-238

Prescribing and risk management issues:

For the treatment of postmenopausal symptoms, Intrarosa should only be initiated for symptoms that adversely affect quality of life. In all cases, a careful appraisal of the risks and benefits should be reassessed at least every 6 months and Intrarosa should only be continued as long as the benefit outweighs the risk.

Commissioning considerations:

Comparative unit costs

Drug	**Example regimen**	**Pack cost**	**Cost per patient per year (ex VAT)**
Intrarosa® 6.5mg pessary	**One pessary administered once daily, at bedtime.**	**£15.94**	**£207.22**
Vagifem® 10µg vaginal tablets	Use one tablet daily for two weeks then one tablet twice weekly thereafter	£16.72*	£79.42
Ovestin® cream 15g	one applicator dose daily for 2 weeks, then decrease to twice weekly thereafter	£4.45*	£17.80 (assuming wastage)
Estring® vaginal ring	Insert every 3 months	£31.42*	£125.68

*Costs as per Drug Tariff April 2019
This table does not imply therapeutic equivalence of drugs or doses.

Anticipated patient numbers and net budget impact:

Vaginal atrophy occurs in the majority of postmenopausal women, but not all will be symptomatic. Large cohort studies have reported the prevalence of vaginal dryness in women from 27% to 55% and dyspareunia from 32% to 41%. Using data from ePACT2, it is estimated that approximately 14,000 patients are already being treated with existing vaginal hormonal products (Vagifem®, Ovestin® and Estring®).

For the 12 months February 2018-January 2019 please see below the following spend across the Lancashire NHS footprint

- Vagifem® NIC = £169,089
- Ovestin® NIC = £18,721
- Estring® NIC = £4,556
- **Total spend = £192,366**

The cost of Intrarosa® for 1000 patients for 6 months = £103,610, for 12 months = £207,220 therefore, there is a significant cost implication if Intrarosa® were to be prescribed in preference / in addition to the three currently prescribed preparations.

Associated additional costs or available discounts:

None identified

Productivity, service delivery, implementation:

N/A

Innovation, need, equity:

N/A

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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References

[1] Prasterone (intrarosa) SPC https://www.medicines.org.uk/emc/product/9986 (accessed April 2019)

[2] Drug Tariff April 2019 http://www.drugtariff.nhsbsa.nhs.uk/#/00690997-DB/DB00690405/Part%20VIIIA%20products%20E

[3] NICE NG 23 Menopause: diagnosis and management https://www.nice.org.uk/guidance/ng23

[4] Intrarosa EPAR https://www.ema.europa.eu/en/documents/assessment-report/intrarosa-epar-public-assessment-report_en.pdf