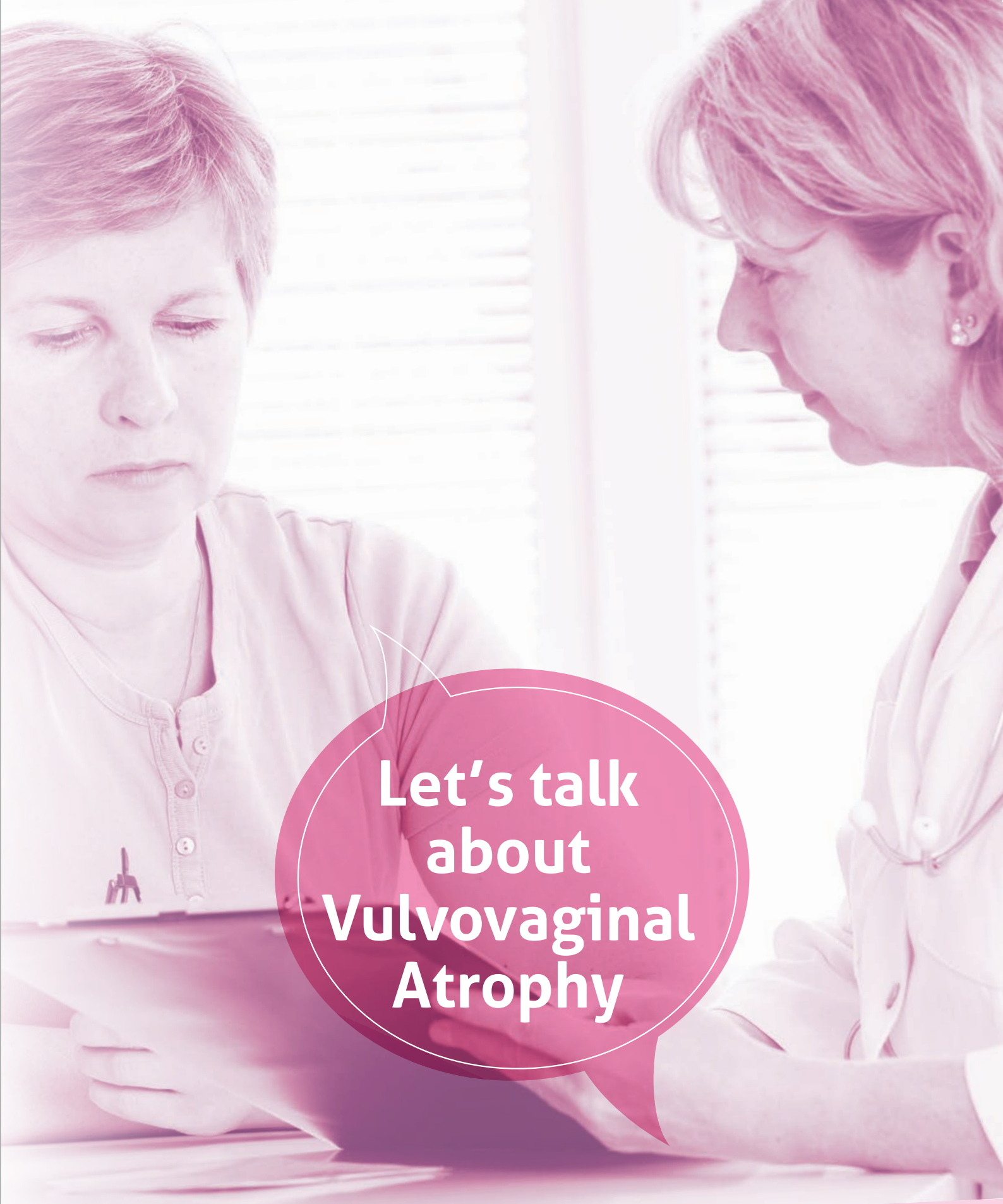

Let's talk about Vulvovaginal Atrophy

Prescribing information can be found on back cover

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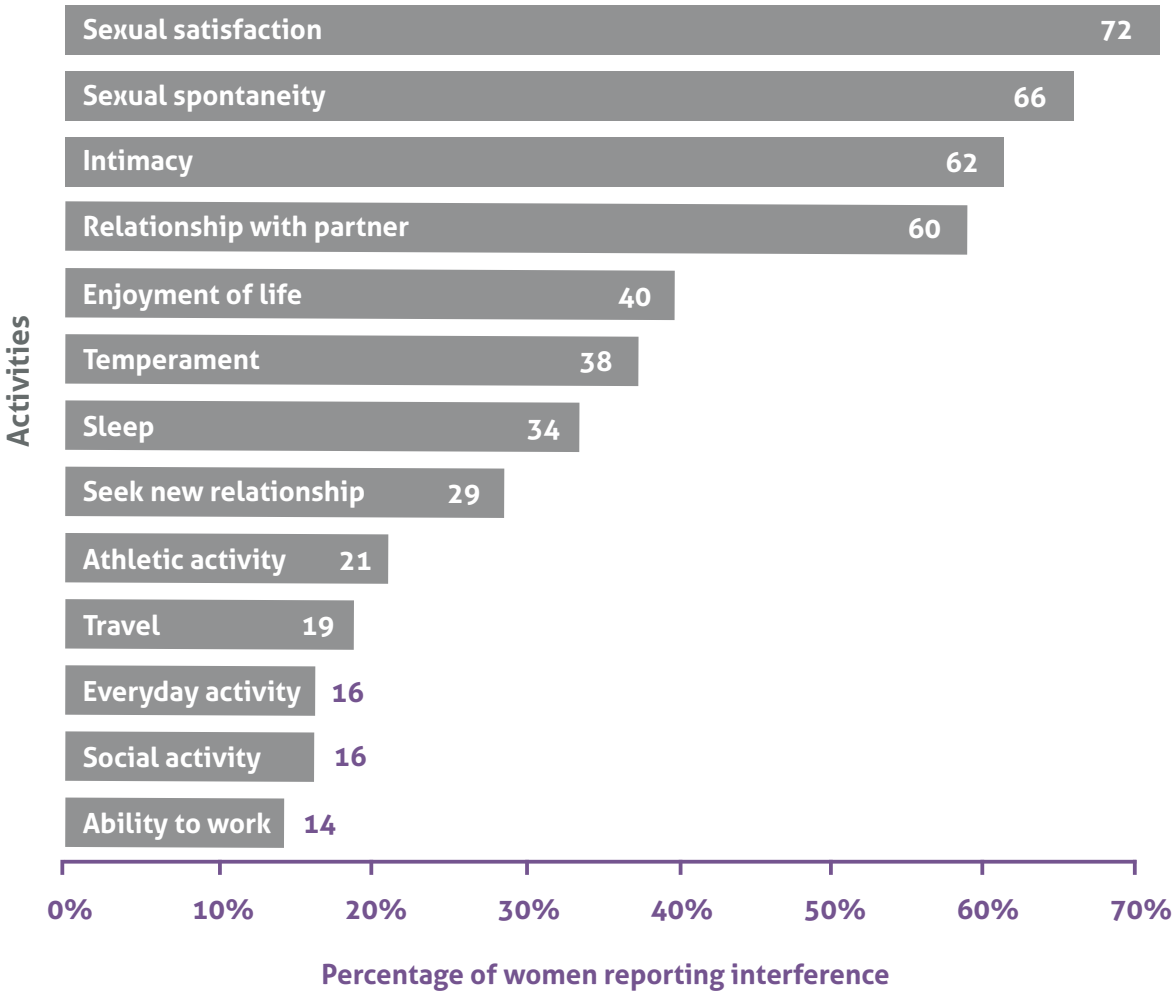
FACTS ABOUT VULVOVAGINAL ATROPHY (VVA)

- More than half of all post-menopausal women will experience symptoms associated with vaginal and urogenital tissue atrophy resulting from loss of estrogen stimulation[1]
- Symptoms of VVA can include vaginal dryness, burning and irritation, lack of lubrication, dyspareunia, dysuria, urinary urgency[2] and recurrent urinary tract infections (in up to 20% of women)[3]
- In a recent European survey of 3,768 postmenopausal women reported that VVA symptoms had most impact on aspects related to sexual satisfaction and spontaneity, the ability to be intimate and the ability to establish a trusted relationship with partners *(Figure 1)*[4]

Figure 1. Interference of symptoms of VVA with sexual life and other activities[4]



Impact for patients:

- The impact of VVA on the quality of life of many women is profound but underestimated[3]
- As more women are spending a significant proportion of their lives in the postmenopausal period, understanding the diagnosis and treatment of VVA must develop in synchrony with this growing unmet need[3]
- The discussion of symptoms with HCPs seems the most critical factor for diagnosis and treatment of VVA but there is an inadequacy of fluent communication related to VVA symptoms between patients and healthcare professionals (HCPs) - only 10% of HCPs initiate a discussion on VVA symptoms[4]

VAGINAL ESTROGENS FOR VVA

Why And When To Use Intravaginal Estrogens?

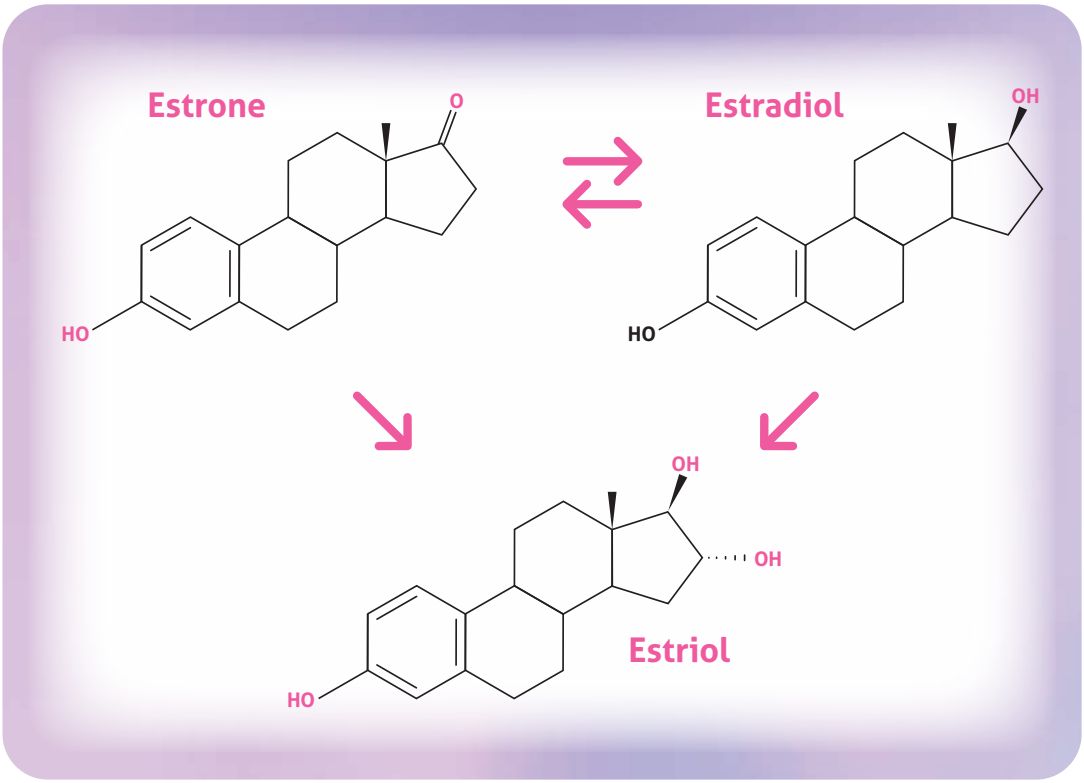
- Following the publication of a study of some 100,000 women with breast cancer[5] the Medicines and Healthcare Products Regulatory Agency (MHRA) has confirmed the risk of breast cancer increases during use of all types of hormone replacement therapy (HRT), except vaginal estrogens, and that an excess risk of breast cancer persists for longer after stopping HRT than previously thought[6]
- For urogenital symptoms, manage according to the specific symptom:
    - For women with urogenital atrophy offer low-dose vaginal oestrogen
    - Continue treatment for as long as needed to relieve symptoms (NICE CKS)[7]

What Differentiates Intravaginal Estrogen Preparations?

Which estrogen?

- Estradiol is the principle estrogen secreted by the ovaries premenopausally - secreted estradiol is oxidised reversibly to estrone, and both can be converted irreversibly to estriol *(see Figure 2)*[8]

Figure 2. Interconversion of the three naturally occurring estrogens



- Vaginal preparations containing estradiol and estriol are clinically effective

  Additionally:

  - estriol has been shown *in vitro* to be 80 times less potent at the oestrogen receptors than oestradiol
  - Blissel contains a low (50mcg) dose of estriol per application[9]

Which formulation?

- Patient acceptability and preference is an important aspect of local estrogen therapy since long-term treatment is likely to be necessary[10]
- Patients often consider pessaries and creams unhygienic and both forms are associated with leakage, often necessitating the use of some form of sanitary protection[10]
- Blissel® delivers an ultra-low dose of estriol (50 micrograms/g) in a strongly hydrating, clear, aqueous mucoadhesive gel administered using a single reusable dose-marked applicator[9, 11]

Table 1. Intravaginal Estrogen Preparations[12]

Product	Active	Formulation	Estrogen Dose Per Application	NHS List Price	Applications per Pack	Cost Per Application
Blissel® Gel	Estriol 50mcg/g	Gel	50 mcg per 1g applicator-dose	£18.90	30	£0.63
Vagifem® Tablets	Estradiol 10mcg	Vaginal tablet	10 mcg per tablet-dose	£16.72	24	£0.70
Gynest® Cream	Estriol 100mcg/g	Cream	500 mcg per 5ml applicator-dose	£24.98	16	£1.56
Ovestin® Cream	Estriol 1000mcg/g	Cream	500 mcg per 0.5g applicator-dose	£4.45	30	£0.15
Imvaggis® Pessaries	Estriol 30mcg	Pessary	30 mcg per pessary dose	£13.38	24	£0.56

Blissel®

ESTRIOL 50 micrograms/g VAGINAL GEL

References

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2. Palma F. *et al.*, Maturitas. 2016; 83: 40-44
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5. Collaborative Group on Hormonal Factors in Breast Cancer. Lancet. 2019; 394: 1159–68
6. https://www.gov.uk/drug-safety-update/hormone-replacement-therapy-hrt-further-information-on- the-known-increased-risk-of-breast-cancer-with-hrt-and-its-persistence-after-stopping (Accessed October 2019)
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12. https://apps.nhsbsa.nhs.uk/DMDBrowser/DMDBrowser.do

NOTES

BLISSEL® (ESTRIOL 50 micrograms/1g) VAGINAL GEL

PRESCRIBING INFORMATION: Please refer to Summary of Product Characteristics (SmPC) before prescribing. **ACTIVE INGREDIENT:** 1g vaginal gel contains 50 micrograms estriol. **INDICATIONS:** Local treatment of vaginal dryness in postmenopausal women with vaginal atrophy. **DOSAGE AND ADMINISTRATION:** Use the lowest effective dose for the shortest duration. **Treatment initiation or reinstitution:** One applicator-dose per day for 3 weeks at bedtime. Only initiate local estrogen therapy for symptoms that adversely affect quality of life. Take a complete personal and family medical history. Use this, and the contraindications and warnings for use, to guide physical (including pelvic and breast) examination. Treat vaginal infections before starting therapy. **Maintenance treatment:** One applicator-dose twice weekly at bedtime. Evaluate treatment continuation after 12 weeks. Conduct periodic check-ups and investigations, adapted to the individual, including mammography, in accordance with accepted screening practices. Advise of breast changes that should be reported. Appraise the risks and benefits at least annually and continue only if the benefit outweighs the risk. Administer a missed dose as soon as remembered. Skip doses 12 hours or more overdue and administer the next dose at the normal time. **Administration:** Apply into vagina using dose-marked applicator in accordance with instructions in the information leaflet. **CONTRAINDICATIONS:** Known, past or suspected breast cancer, known or suspected estrogen dependent malignant tumour, undiagnosed genital bleeding, untreated endometrial hyperplasia, previous idiopathic or current venous thromboembolism, active or recent arterial thromboembolic disease, known thrombophilic disorders, acute liver disease or a history of liver disease as long as liver function tests have failed to return to normal, porphyria, hypersensitivity to the active substance or to any of the excipients. **SPECIAL WARNINGS AND PRECAUTIONS**: Do not combine with estrogen preparations for systemic treatment. Risk of endometrial hyperplasia and carcinoma in oral treatment solely with estrogen is dependent on treatment duration and estrogen dose. Increased risk of endometrial hyperplasia or uterine cancer has not been attributed to treatment with estriol by vaginal use; if continued treatment is required periodic revisions are recommended, with special consideration to symptoms suggestive of endometrial hyperplasia or endometrial malignancy. Investigate breakthrough bleeding or spotting occurring at any time on therapy to exclude endometrial malignancy. Caution in women who have undergone hysterectomy because of endometriosis, especially if there is residual endometriosis. Increased risk of certain types of cancer (in particular uterine, ovarian and breast cancer),venous thromboembolism, stroke and coronary artery disease associated with systemic hormone replacement treatment. Blissel vaginal gel administered locally is not expected to increase the risk of cancer, VTE, stroke and coronary artery disease. Generally recognised risk factors for VTE include a personal history or family history, severe obesity (BMI > 30 kg/m^2) and systemic lupus erythematosus . No consensus about the possible role of varicose veins in VTE. Close supervision is recommended in these patients. Estrogens with systemic effects may cause fluid retention or increase of plasma triglycerides. Therefore, careful observation of patients with heart diseases or impaired renal function or with pre-existing hypertriglyceridemia during the first weeks of treatment is recommended. No systemic effects expected with local treatment using a low dose estriol vaginal gel. Careful observation in severe renal insufficiency as levels of circulating estriol may be increased. Close supervision of patients with current, previous, or where the condition has been aggravated during pregnancy, or previous hormone treatment: Leiomyoma or endometriosis, risk factors for thromboembolic disorders or estrogen-dependent tumours, hypertension, liver disorders, diabetes mellitus with or without vascular involvement, cholelithiasis, migraine or (severe) headache, systemic lupus erythematosus, history of endometrial hyperplasia,epilepsy,asthma,otosclerosis. Intravaginal applicator may cause minor local trauma, especially in women with serious vaginal atrophy. Discontinue immediately if a contraindication is discovered and in cases of jaundice or deterioration in liver function,significant increase in blood pressure, new onset of migraine-type headache or pregnancy. **INTERACTIONS:** No interaction studies have been performed. No clinically relevant interactions expected. **FERTILITY, PREGNANCY, LACTATION:** Not indicated during pregnancy. Withdraw treatment immediately if pregnancy occurs. No data available on exposed pregnancies. Not indicated during lactation. **DRIVING:** No influence on ability to drive and use machines. **UNDESIRABLE EFFECTS: Very common:** None. **Common:** Pruritus genital, application site pruritus, pruritus. Consult SmPC in relation to less common side effects. **PHARMACEUTICAL PRECAUTIONS:** Store below 25°C. **LEGAL CATEGORY:** POM.

Product	NHS List Price	Pack Size	Marketing Authorisation Number
Blissel	£ 18.90	30g	PL 20663/0003

MARKETING AUTHORISATION HOLDER: Italfarmaco S.A., San Rafael 3, 28108 Alcobendas (Madrid), Spain. Marketed in the UK by Flynn Pharma Limited, Hertlands House, Primett Road, Stevenage, Herts, SG1 3EE, Tel: 01438 727822, E-mail: medinfo@flynnpharma.com.

Adverse events should be reported. Reporting forms and information can be found at https://yellowcard.mhra.gov.uk/. Adverse events should also be reported to Flynn Pharma Ltd. Medical Information: Tel 01438 727822, E-mail medinfo@flynnpharma.com.

Information about this product, including adverse reactions, precautions, contraindications and method of use can be found at http://www.medicines.org.uk/emc/. **DATE OF REVISION OF PRESCRIBING INFORMATION:** May 2019.

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