Dorset Medicines Advisory Group

SHARED CARE GUIDELINE FOR THE USE OF ULIPRISTAL ACETATE (ESMYA®) IN THE TREATMENT OF MODERATE TO SEVERE SYMPTOMS OF UTERINE FIBROIDS IN ADULT WOMEN OF REPRODUCTIVE AGE

INDICATION

Ulipristal (Esmya®) is licensed for the pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age. It is also indicated for intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.

Ulipristal acetate (Esmya®) is an orally active synthetic selective progesterone receptor modulator characterised by a tissue-specific partial progesterone antagonist effect.

Traffic Light Categorisation
Esmya is categorised as an amber drug with shared care when used for intermittent treatment of moderate to severe symptoms of uterine fibroids; secondary care should provide the first course (usually 3 months of treatment and at least one month treatment free); it is recommended that treatment is initiated in a specialist setting by relevant clinicians with experience in gynaecology and the management of fibroids (medical and surgical management). The patient's GP can provide up to a further two courses of treatment before it is recommended the patient is referred back to secondary care for ultrasound scan, assessment of treatment efficacy and review of ongoing treatment plan. For full prescribing information on Esmya® see the SPC (Link).

Pre-operative treatment of moderate to severe symptoms of uterine fibroids holds a red status and must be supplied from secondary care.

AREAS OF RESPONSIBILITY FOR SHARED CARE

This shared care agreement outlines suggested ways in which the responsibilities for managing the prescribing of ulipristal (Esmya®) can be shared between the specialist setting and the patient's GP (if different). GPs are invited to participate. If the GP is not confident to undertake these roles, then he or she is under no obligation to do so. In such an event, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist. If a specialist asks the GP to prescribe this drug, the GP should reply to this request as soon as practicable.

Sharing of care assumes communication. The intention to share care is usually explained to the patient by the doctor initiating treatment. It is important that patients are consulted about treatment and are in agreement with it.

Patients taking ulipristal acetate should remain under follow-up in secondary care, where it is expected that response to treatment will be assessed.

The doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use.

REFERRAL AND INITIATION

Specialist Responsibilities	
1	Initiate and prescribe treatment with ulipristal acetate for the first course of therapy
2	Where prescribed, review the patient 3 months post initiation of treatment to determine next treatment steps
3	To ask the GP whether he or she is willing to participate in shared care. Requests to GPs should be made in writing and must include appropriate information to allow an informed decision to be made.
4	Discuss the benefits and side effects of treatment with the patient, whilst also taking time to explain the requirement for treatment free intervals

Specialist Responsibilities	
5	Advise the GP on the duration of treatment and number of courses to be prescribed, when to stop treatment or consult with the specialist.
6	To review the patient at 12 months post initiation of ulipristal treatment and at least annually thereafter to include ultrasound scan following resumption of menstruation during an off-treatment period. Communicate the details of this review to the patient's GP.
7	Report adverse events to the MHRA, the Company and GP.
8	Ensure that clear arrangements exist for GPs to obtain advice and support.
9	Ensure details for follow up are communicated to both the patient and the patient's GP.
10	Ask the GP whether he or she is willing to participate in shared care, and discuss the shared care arrangement with the patient.

General Practitioner Responsibilities	
1	Reply to the request for shared care as soon as practicable.
2	Prescribe ulipristal acetate at the dose recommended and for the duration specified.
3	Do not continue to prescribe ulipristal for more than 3 courses per year unless the patient has undergone secondary care review as detailed above and the details of the review have been noted and where necessary actioned.
4	Report to and seek advice from the specialist on any aspect of patient care that is of concern to the GP and may affect treatment e.g. if symptoms continue or if menstruation fails to be suppressed during treatment.
5	Refer back to specialist as per agreed treatment plan, if the patient's condition deteriorates, loss of efficacy or intolerance occurs.
6	Stop treatment on the advice of the specialist or immediately if an urgent need to stop treatment arises.
7	Report adverse events to the specialist, MHRA and company
8	To check for possible drug interactions when newly prescribing or stopping concurrent medication.

Patient's role (or that of carer)	
1	Report to the specialist or GP if he or she does not have a clear understanding of the treatment.
2	Attend appropriate consultant and GP appointments.
3	Share any concerns in relation to treatment with Esmya
4	Use written and other information supplied with the medication
5	Seek help if suffering suspected side-effects, or otherwise unwell.

SUPPORTING INFORMATION

Monitoring

Dosage and Administration[1]

One 5mg tablet to be taken orally once daily, with or without food for a treatment course up to 3 months.

Treatments should only be initiated when menstruation has occurred:
- The first treatment course should start during the first week of menstruation.
- Re-treatment courses should start at the earliest during the first week of the second menstruation following the previous treatment course completion.

If a patient misses a dose, the patient should take ulipristal acetate as soon as possible. If the dose was missed by more than 12 hours, the patient should not take the missed dose and simply resume the usual dosing schedule.

The clinician initiating treatment must explain to the patient the requirement for treatment free intervals.

Contraindications

- Hypersensitivity to the active substance or to any of the excipients.
- Pregnancy and breastfeeding.
- Genital bleeding of unknown aetiology or for reasons other than uterine fibroids. Uterine, cervical, ovarian or breast cancer.

Cautions

Endometrial changes

Ulipristal acetate has a specific pharmacodynamic action on the endometrium. Increase in thickness of the endometrium may occur. If the endometrial thickening persists beyond 3 months following the end of treatment and return of menstruations, this may need to be investigated as per usual clinical practice to exclude underlying conditions, including endometrial malignancy. Changes in the histology of the endometrium may be observed in patients treated with ulipristal acetate. These changes are reversible after treatment cessation. These histological changes are denoted as “Progesterone Receptor Modulator Associated Endometrial Changes” (PAEC) and should not be mistaken for endometrial hyperplasia.

Bleeding pattern

Patients should be informed that treatment with ulipristal acetate usually leads to a significant reduction in menstrual blood loss or amenorrhea within the first 10 days of treatment. Should the excessive bleeding persist, patients should notify their physician. Menstrual periods will generally return within 4 weeks after the end of the treatment course.
If, during repeated intermittent treatment, after the initial reduction in bleeding or amenorrhea, an altered persistent or unexpected bleeding pattern occurs, such as inter-menstrual bleeding, investigation of the endometrium including endometrial biopsy should be performed in order to exclude other underlying conditions, including endometrial malignancy.

Asthma

Use in women with severe asthma insufficiently controlled by oral glucocorticoids is not recommended

Contraception

Concomitant use of progestagen-only pills, a progestagen-releasing intrauterine device or combined oral contraceptive pills is not recommended. Although a majority of women taking a therapeutic dose of ulipristal acetate have anovulation, a non-hormonal contraceptive method is recommended during treatment.

Renal impairment

No dose adjustment is recommended in patients with mild or moderate renal impairment. In the absence of specific studies, ulipristal acetate is not recommended in patients with severe renal impairment unless the patient is closely monitored.

Hepatic impairment

No dose adjustment is recommended for patients with mild hepatic impairment. In the

absence of specific studies, ulipristal acetate is not recommended in patients with moderate or severe hepatic impairment unless the patient is closely monitored.

Side effects
The most frequent adverse reactions reported were hot flush and headaches.

Interactions

Ulipristal acetate is not recommended for patients receiving P-glycoprotein (P-gp) substrates (e.g. dabigatran etexilate, digoxin)

Co-administration of moderate or potent CYP3A4 inhibitors and ulipristal acetate is not recommended e.g. cimetidine, erythromycin, verapamil

Concomitant use of ulipristal acetate and potent CYP3A4 inducers (e.g. rifampicin, carbamazepine, phenytoin, St John´s wort) is not recommended.

Ulipristal acetate has a steroid structure and acts as a selective progesterone receptor modulator with predominantly inhibitory effects on the progesterone receptor. Thus hormonal contraceptives and progestagens are likely to reduce ulipristal acetate efficacy by competitive action on the progesterone receptor. Therefore concomitant administration of medicinal products containing progestagen is not recommended for up to 12 days post cessation of ulipristal acetate treatment.

This list is not exhaustive. The manufacturer's summary of product characteristics (SPC) and the most current edition of the British National Formulary should be consulted for full information on contra-indications, warnings, side-effects and drug interactions.

Drug costs:
Ulipristal acetate 5mg tablets x28 £114.13 as at November 2015[2]

References
1. Esmya® summary of product characteristics available at http://www.medicines.org.uk/emc/medicine/26068 Accessed December 2015

2. Joint Formulary Committee. *British National Formulary* (online). London: BMJ Group and Pharmaceutical Press; Electronic edition. Accessed on 1/12/15 via http://www.medicinescomplete.com/