Formulary and Managed Entry Subgroup
Ulipristal acetate (Esmya®) for intermittent treatment of uterine fibroids

RAG List Status
Ulipristal acetate (Esmya®) is classified as follows:
- GREEN following specialist initiation for intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age who are not eligible for surgery
- RED for treatment of moderate to severe symptoms of uterine fibroids prior to surgery. GPs should not prescribe for this indication.

What is it?
Ulipristal acetate is an orally-active selective progesterone receptor modulator licensed for the management of uterine fibroids.

NICE Guidance
There is no published NICE guidance on the management of fibroids or use of ulipristal acetate. NICE clinical guideline NG88: Heavy menstrual bleeding: assessment and management gives recommendations on the management of fibroids, but does not deal specifically with ulipristal acetate.

When should GPs be asked to prescribe?
GP will only prescribe when a specialist has confirmed the diagnosis of uterine fibroids, carried out an initial check of liver function and prescribed an initial 3 month course of ulipristal. The specialist should inform the GP of the treatment initiation and provide follow-up information.

Preparations available
Ulipristal acetate (Esmya®) 5 mg tablets

Dosage and Administration
Initiation of the drug is from a specialist clinic at a dose of 5 mg once daily, to be taken with or without food. Each course may last up to 3 months.

Up to 3 further courses may be initiated by the GP only if symptoms return, and provided:
- No more than a total of 4 courses are given (including the initial course started by the specialist)
- Appropriate liver monitoring is carried out (see below)
At the earliest, additional courses should start during the first week of the second menstruation following completion of the previous course. The treating physician should explain to the patient the requirement for treatment free intervals. See below for full treatment algorithm.

Contraindications
- Hypersensitivity to the active substance or to any of the excipients listed (refer to SPC).
- Pregnancy and breastfeeding.
- Genital bleeding of unknown etiology or for reasons other than uterine fibroids.
- Uterine, cervical, ovarian or breast cancer.
- Underlying hepatic disorder.

Cautions
- Concomitant use of progestogen-only pills, a progestogen-releasing intrauterine device or combined oral contraceptive pills is not recommended (see section 4.5). Although a majority of women taking a therapeutic dose of ulipristal acetate have anovulation, a non hormonal contraceptive method is recommended during treatment.

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Endometrial changes. Changes in the histology of the endometrium may be observed in patients treated with ulipristal acetate. These changes are reversible after treatment cessation and should not be mistaken for endometrial hyperplasia. See below for monitoring requirements.

Bleeding pattern. Treatment usually results in a significant reduction in menstrual blood loss, or in amenorrhea within the first 10 days of treatment. Should excessive bleeding persist, patients should notify their physician. Menstrual periods generally return within 4 weeks after the end of each 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.

Renal impairment is not expected to significantly alter the elimination of ulipristal acetate. Use is not recommended for patients with severe renal impairment unless the patient is closely monitored.

Hepatic injury has been reported in post-marketing surveillance. Liver monitoring must be performed on a regular basis, as described below. Patients who develop transaminase levels (ALT or AST) > 3 times the upper limit of normal during treatment should stop treatment and be closely monitored.

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

What are the main side-effects?
The most commonly reported adverse reactions with ulipristal acetate are amenorrhea and endometrial thickening. See the SPC for full details of the side effect profile. There have been post-marketing reports of hepatic injury associated with Esmya. All patients should be advised to seek urgent medical attention if they develop any symptoms or signs of liver injury (such as tiredness, yellowing of the skin, darkening of the urine, nausea and vomiting). Any serious adverse events, including liver injury, should be reported to the Yellow Card Scheme (www.mhra.gov.uk/yellowcard).

Drug Interactions

- Co-administration with moderate or potent CYP3A4 inhibitors (e.g. erythromycin, grapefruit juice, verapamil, ketoconazole, ritonavir, itraconazole, clarithromycin) is not recommended.
- Co-administration with CYP3A4 inducers (e.g. rifampicin, rifabutin, carbamazepine, oxcarbazepine, phenytoin, fosphenytoin, phenobarbital, primidone, St John’s wort, efavirenz, nevirapine) is not recommended.
- Hormonal contraceptives and progestogens are likely to reduce ulipristal acetate efficacy by competitive action on the progesterone receptor. Ulipristal acetate may also affect the action of combined hormonal contraceptives, progestogen-only contraceptives and progestogen-releasing devices. Therefore concomitant use with these products is not recommended.
- Ulipristal acetate may inhibit P-glycoprotein (P-gp), and therefore reduce metabolism of P-gp substrates (e.g. dabigatran etexilate, digoxin, fexofenadine). It is therefore recommended that co-administration of ulipristal acetate and P-gp substrates should be separated in time by at least 1.5 hours.
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Monitoring
- Response to treatment after each 3 month course
- Side effects
- Confirmation that menstruation has returned after each 3 month course.
- Bleeding pattern (see below)
- Ultrasound at 12 months (see above under endometrial changes)

Liver function monitoring is to be carried out in all women treated with Esmya:
- Before initiation of each treatment course. Do not initiate treatment in women with baseline alanine transaminase (ALT) or aspartate aminotransferase (AST) more than 2-times the upper limit of normal (ULN)
- During the first 2 treatment courses – perform liver function tests every month
- Whenever clinically indicated during subsequent treatment courses
- 2-4 weeks after completion of each treatment course
Stop Esmya treatment and closely monitor women with ALT or AST more than 3-times ULN; consider the need for specialist hepatology referral

References
- MHRA Drug Safety Update. Esmya (ulipristal acetate) and risk of serious liver injury: new restrictions to use and requirements for liver function monitoring before, during, and after treatment. 24 August 2018.
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Specialist confirms uterine fibroids diagnosis with associated symptoms
- Specialist ensures that patient is eligible for ulipristal (see NTS recommendation)
- Specialist performs baseline liver monitoring tests and prescribes initial 3 month course of ulipristal.
- Specialist informs GP of treatment and provides follow up information

GP to monitor liver function
- Before initiation of each treatment course
- During the first 2 treatment courses
- Whenever clinically indicated during subsequent treatment courses
- 2-4 weeks after completion of each treatment course.
Stop treatment and closely monitor women with ALT or AST more than 3-times ULN; consider the need for specialist hepatology referral

GP review after initial 3 month course
Assess symptom control (heavy menstrual bleeding, abdominal pressure/pain), patient satisfaction, tolerability.

Good response
GP prescribes second and subsequent 3 month courses if clinically appropriate, and if patient is still symptomatic.
Ulipristal can be given for up to 4 total courses.
Symptoms and continuing need should be assessed following each course. Allow 1 menstrual bleed after initial 3 month course and start ulipristal during the next menstrual bleed.
Stop treatment if symptom control is achieved, patient wishes to become pregnant, or reaches menopause. Additional courses to be given only if symptoms return

Sub-optimal response or side effects
Consider second 3 month course if patient feels they may still benefit or stop therapy and refer back to specialist for alternative therapy or surgery
Allow 1 menstrual bleed after initial 3 month course and start ulipristal during the next menstrual bleed

Poor response/Treatment stopped
Refer back to Specialist if no improvement or if treatment is stopped due to side effects or abnormal ultrasound at 12 months.

Symptoms return following a total of 4 intermittent courses
Refer back to specialist.