Ulipristal acetate 5mg tablets *(Esmya®)*

(AMBER with Share Care)

Shared Care Guidelines: For the **intermittent treatment** of moderate to severe symptoms of uterine fibroids in adult women of reproductive age who are not eligible for surgery

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AREAS OF RESPONSIBILITY FOR THE SHARING OF CARE

This shared care agreement outlines suggested ways in which the responsibilities for managing the prescribing of medicine name and indication shared between the specialist and general practitioner (GP). 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 between the specialist, GP and patient. 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 with the condition are under regular specialist follow-up, which provides an opportunity to discuss drug therapy.

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

RESPONSIBILITIES and ROLES

	Specialist responsibilities
1	Initiate treatment and provide a 3 month cycle.
2	U+Es, renal function and LFTs to be checked prior to initiation. Do not start Esmya treatment if levels of alanine transaminase (ALT) or aspartate aminotransferase (AST) are > 2 times the upper limit of normal (ULN) (isolated or in combination with bilirubin > 2 x ULN)
3	Discuss the benefits and side effects of treatment with the patient, whilst also taking the time to explain the requirement for **3 month breaks** in between **3 month cycles**.
4	Advise the GP on the duration of treatment and number of courses/cycles to be prescribed, and when to stop the treatment or consult with the specialist.
5	Ask the GP whether he or she is willing to participate in shared care, and agree with the GP as to who will discuss the shared care arrangement with the patient.
6	Advise the patient If they experience symptoms associated with liver problems (nausea, vomiting, feeling ill, lack of appetite, weakness, upper abdominal pain, yellowing of the skin/eyes) then they must stop treatment and seek medical attention immediately.
7	Supply GP with summary within 14 days of a hospital out-patient review or in-patient stay.
8	Review concurrent medications for potential interaction prior to initiation of Ulipristal. Ensure the patient is using a compatible contraceptive.
9	Review the patient annually with an ultrasound to monitor for endometrial thickening (ultrasound to be performed after resumption of menstruation during an off-treatment period).
10	Review the patient's condition and monitor response to treatment during the first 3 month cycle and also annually.
11	Report adverse events to the MHRA
12	Ensure that clear backup arrangements exist for GPs to obtain advice and support.
13	Stop treatment in patients whose ALT or AST levels are > 3 x ULN

	General Practitioner responsibilities
1	Reply to the request for shared care as soon as practicable.
2	Prescribe medicine at the dose recommended after the first 3 month cycle, ensuring the patient has a 3 month break in-between cycles.
3	Perform liver function tests monthly during the first two treatment courses and 2 to 4 weeks after treatment has stopped.
4	Refer promptly to specialist when any loss of clinical efficacy is suspected (e.g. worsening of disease-related symptoms, new symptoms suggestive of disease recurrence or progression) or intolerance to therapy occurs.
5	If a patient shows signs or symptoms compatible with liver injury (nausea, vomiting, right hypochondrial pain, anorexia, asthenia, jaundice, etc.) investigated immediately (including liver function tests) and referral back to specialist.
6	Patients who develop transaminase levels > 2 times the upper limit of normal during treatment should stop treatment

	and be referred back to the specialist
7	Review any new concurrent medications for potential interactions
8	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 after 2 months of treatment.
9	Stop treatment on the advice of the specialist.
10	Report adverse events to the specialist and MHRA.

	Patient's role
1	Report to the specialist or GP if he or she does not have a clear understanding of the treatment.
2	Share any concerns in relation to treatment with medicine, especially if it fails to control symptoms and excessive bleeding persists or if there is an unexpected bleeding pattern.
3	Stop treatment and seek urgent medical attention immediately in relation if experiencing symptoms associated with liver problems (nausea, vomiting, feeling ill, lack of appetite, weakness, upper abdominal pain, yellowing of the skin/eyes)
4	Understand that the medicine should be taken as a 3 month cycle/course followed by a 3 month break before starting a second course/cycle. It is not to be taken continuously.
5	Report any adverse effects to the specialist or GP whilst taking the medicine.

BACK-UP ADVICE AND SUPPORT

Contact details RUH	Telephone No.	Bleep:	Fax:	Email address:
Specialist: Mrs Qureshi	07801023653			aysha.qureshi@nhs.net
Hospital Pharmacy Dept:	01225 824640			

Advice to the patient:

1. **Missed dose** -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.

2. **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, the patient should report back to the GP. (Investigation of the endometrium including endometrial biopsy should be performed in order to exclude other underlying conditions, including endometrial malignancy.)

SUPPORTING INFORMATION

Summary of condition and licensed indications.

The medicine is indicated for:

- For the intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age who are not eligible for surgery
- For the pre-operative treatment of moderate- to-severe symptoms of uterine fibroids in adult women of reproductive age. *Please note, this indication is RED on local formularies and GPs should not be asked to prescribe for this indication.*

Treatment Aims (Therapeutic plan)

A symptomatic fibroid is one causing, usually multiple, symptoms including heavy menstrual bleeding / menorrhagia or abnormal uterine bleeding / menorrhagia; pain accompanying heavy bleeding / dysmenorrhoea; pressure symptoms due to volume of the fibroid pressing on pelvis organs (pressure on bladder, bowel and pain during intercourse / dyspareunia). Fibroid impacting on quality of life, including tiredness due to anaemia.

Ulipristal acetate 5mg exerts a specific and direct effect on the endometrium, stopping bleeding, and a direct action on fibroids, reducing their size probably via a number of mechanisms including inhibition of cell proliferation and

induction of apoptosis and with intermittent treatment, resorption / restructuring of extracellular matrix. Recent data demonstrates that with intermittent use, each three month course of treatment with Ulipristal has a consistent and rapid impact on the multiple symptoms of fibroids and progressively shrinks fibroids with associated improvements in quality of life.

Three patient groups are suitable for use of Esmya® as follows:

1.) **Peri-menopausal patients.** Patients who have significant menorrhagia and a large uterine size (which means they are not suitable for coil fitting or ablation) and the patient is nearly menopausal. It is envisaged this would avoid surgery (hysterectomy) in these patients.
2.) **Younger patients with fibroids who wish to maintain their fertility to have children**. Such patients may not be ready to have children or may be undecided. If these patients have very large fibroids and hence uterus size, coil fitting or ablation won't work. Hence Esmya® would be a good option to treat as a bridging therapy.
3.) **Patients with co-morbidities or not wanting surgery**. E.g. patients with very high BMI where the surgical risk is high.

Treatment Schedule (including dosage and administration)

One 5mg tablet to be taken orally once a day for up to 3 months. Treatment should be started during the first week of a menstrual cycle. Tablets should be taken with or without food. Re-treatment courses should start at the earliest during the first week of the second menstruation following the previous treatment course completion.

Each treatment course should not exceed 3 months; this should be followed by a 3 month treatment free duration before the next 3 month treatment course is started.

Repeated intermittent treatment has been studied for up to 4 intermittent treatment courses. Hence the maximum total duration is 4 courses over a 2 year period.

Contra-indications and precautions for use

1. Is contra-indicated in women with underlying liver disorders
2. Hypersensitivity to the active substance or to any of the excipients.
3. Pregnancy and breastfeeding.
4. Genital bleeding of unknown etiology or for reasons other than uterine fibroids, e.g. Uterine, cervical, ovarian or breast cancer.
5. Pregnancy should be precluded prior to initiation.

Cautions and Special Recommendations

Renal impairment

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

Hepatic impairment (amended Oct 2018)

Requirements for liver function monitoring

• Liver function tests should be performed before starting each treatment course, monthly during the first 2 treatment courses, and 2-4 weeks after stopping treatment.

• Do not start Esmya treatment if levels of alanine transaminase (ALT) or aspartate aminotransferase (AST) are > 2 times the upper limit of normal (ULN) (isolated or in combination with bilirubin > 2 x ULN)

• Stop treatment in patients whose ALT or AST levels are > 3 x ULN.

Asthma patients

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

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.

Side-effects

The most common finding in clinical trials was amenorrhea (79.2%), which is considered as a desirable outcome for the patients.

The most frequent adverse reaction was **hot flush**. The vast majority of adverse reactions were mild and moderate (95.0%), did not lead to discontinuation of the medicinal product (98.0%) and resolved spontaneously.

Endometrial thickening
In 10-15% of patients, thickening of the endometrium (> 16 mm by ultrasound or MRI at end of treatment) was observed with ulipristal acetate by the end of the first 3-month treatment course. In subsequent treatment courses, endometrial thickening was less frequently observed (4.9% and 3.5% of patients by the end of second and fourth treatment course, respectively). The endometrial thickening reverses when treatment is stopped and menstrual periods resume.

In addition, reversible changes to the endometrium are denoted 'Progesterone Receptor Modulator Associated Endometrial Changes' (PAEC) and are different from endometrial hyperplasia. If hysterectomy or endometrial biopsy specimens are sent for histology, then the pathologist should be informed that the patient has taken ulipristal acetate

Headache
Mild or moderate severity headache was reported in 5.8% of patients.

Ovarian cyst

Functional ovarian cysts were observed during and after treatment in 1.0% of patients and in most of the cases spontaneously disappeared within a few weeks.

Uterine haemorrhage

Patients with heavy menstrual bleeding due to uterine fibroids are at risk of excessive bleeding, which may require surgical intervention. A few cases have been reported during ulipristal acetate treatment or within 2-3 months after ulipristal acetate treatment was stopped.

Refer to the SPC for a full list of adverse effects.

Medicine name was launched in February 2012 and no longer has black triangle (▼) status. Serious suspected reactions (even if well recognised or causal link uncertain) should be reported to the MHRA.

Monitoring

Liver function tests should be performed before starting each treatment course, monthly during the first 2 treatment courses, and 2-4 weeks after stopping treatment.

Do not start Esmya treatment if levels of alanine transaminase (ALT) or aspartate aminotransferase (AST) are > 2 times the upper limit of normal (ULN) (isolated or in combination with bilirubin > 2 x ULN)

Stop treatment in patients whose ALT or AST levels are > 3 x ULN

GP to Perform liver function tests monthly during the first two treatment courses and 2 to 4 weeks after treatment has stopped.

Drug Interactions
Hormonal contraceptives
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 progestogens are likely to reduce ulipristal acetate efficacy by competitive action on the progesterone receptor. In addition, Ulipristal acetate may interfere with the action of hormonal contraceptive products (progestogen only, progestogen releasing devices or combined oral contraceptive pills) and progestogen administered for other reasons. Therefore concomitant administration of medicinal products containing progestogen is not recommended. Medicinal products containing progestogen should not be taken within 12 days after cessation of ulipristal acetate treatment. A non-hormonal contraceptive method is recommended during treatment.

CYP3A4 inhibitors

Co-administration of potent CYP3A4 inhibitors (e.g. **ketoconazole, ritonavir, nefazodone**) may lead to greater increases in plasma levels of ulipristal acetate. Co- administration of moderate or potent CYP3A4 inhibitors and ulipristal acetate is not recommended.

CYP3A4 inducers

Patients receiving concomitant CYP3A4 inducers may have reduced plasma levels of ulipristal acetate. Concomitant use of ulipristal acetate and potent CYP3A4 inducers (e.g. **rifampicin, rifabutin, carbamazepine, oxcarbazepine, phenytoin, fosphenytoin, phenobarbital, primidone, St John´s wort, efavirenz, nevirapine, long term use of ritonavir**)) is not recommended.

P-gp substrates

In vitro data indicate that ulipristal acetate may be an inhibitor of P-gp at clinically relevant concentrations in the gastrointestinal wall during absorption. Thus, co- administration of ulipristal acetate may increase the plasma levels of concomitant medicinal products that are substrates of P-gp. It is therefore recommended that co- administration of ulipristal acetate and P- gp substrates (e.g. **dabigatran etexilate, digoxin, fexofenadine**) should be separated in time by at least 1.5 hours.

Cost

At current prices, one year's treatment (2 x 3 months) with medicine at the dose is £733.69 (28=£114.13).

References

1. **Ulipristal Summary of Product Characteristics accessed via http://www.medicines.org.uk/EMC/medicine/26068/SPC**
2. **Courtoy et al. Fertil, 2015 104:426–34. http://dx.doi.org/10.1016/j.fertnstert.2015.04.025**
3. **Donnez J, Donnez O, Matule D, Ahrendt H-J, Hudecek R, Zatik J, et al. Long-term medical management of uterine fibroids with ulipristal acetate Fertil Steril, 2015; http://dx.doi.org/10.1016/j.fertnstert.2015.09.032**
4. **MHRA Drugs Safety Alert Feb 2018 https://www.gov.uk/government/news/esmya-no-new-treatment-courses-prescribed-until-further-notice Feb 2018**

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Document details

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