Ulipristal (Esmya®) 5mg tablets for the intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women.

The New Therapies Subgroup discussed the above at its meeting on 17<sup>th</sup> May 2016. The recommendation of this subgroup is as follows:* 

<table>
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<tr>
<th>Drug/Indication</th>
<th>The New Therapies Subgroup of the GMMMG considered the use of ulipristal (Esmya®) 5mg tablets for the intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women.</th>
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<tbody>
<tr>
<td>Recommendation</td>
<td>The group recommends use as per the licensed indication for those patients who wish to preserve their fertility, peri-menopausal women and those who are not fit enough to undergo surgery and where other therapies have failed or are not suitable.</td>
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<td></td>
<td>NB For those patients with fibroids less than 3 cm in diameter which are causing no distortion of the uterine cavity other pharmaceutical treatment options should be tried first. i.e. tranexamic acid or non-steroidal anti-inflammatory drugs (NSAIDs) or combined oral contraceptives (COCs), Mirena® coil or injected long-acting progestogens.</td>
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<td>According to set criteria ulipristal was deemed to be high priority for funding in the patient group described only.</td>
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<td>Clinical Trial Data – Efficacy</td>
<td>The efficacy of repeated treatment courses of ulipristal 5mg once daily was evaluated in two phase III studies assessing up to four courses of intermittent 3-month treatment, with heavy menstrual bleeding and other symptoms associated with uterine fibroids. The pivotal PEARL IV study demonstrated that 73% of patients on the licensed dose of ulipristal achieved the secondary outcome of controlled bleeding and approximately 50% of patients were in amenorrhea after the fourth treatment course. Ulipristal 10mg daily also led to a reduction in fibroid volume and there was further reduction with successive treatment courses, with no evidence of rapid rebound regrowth. Women reported substantial improvements in pain and QoL scores during treatment.</td>
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<td>Clinical Trial Data – Safety</td>
<td>The most frequently reported adverse event was headache The majority were mild or moderate in intensity. Other commonly reported side effects (≥2%) in PEARL III and/or IV studies included hot flushes, nasopharyngitis, abdominal pain, influenza, breast pain/tenderness/discomfort, nausea, fatigue and pelvic pain. Overall, adverse reactions were less frequent in subsequent treatment</td>
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courses than during the first one, with no increase in frequency of any adverse event over time. Some women who obtain symptomatic relief (e.g. less bloating and discomfort due to reduced fibroid size and better energy due to less heavy bleeding) might be inclined to use ulipristal persistently without a break. Continued use poses a risk since intermittent use allows/induces a type of withdrawal bleed, which should offset any developing endometrial hyperplasia. The SPC indicates that each treatment cycle should not be longer than 3 months as the effect on endometrium is unknown if continued longer. Periodic monitoring of the endometrium (e.g. with annual ultrasound) is recommended with repeated intermittent treatment with ulipristal. (see SPC)

<table>
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<tr>
<th>Cost Effectiveness/Affordability</th>
<th>Ulipristal costs £342.39 for 12 weeks supply. Managing appropriate patients with ulipristal may avoid the need for a hysterectomy in some patients and therefore there may be some potential cost savings associated with this. The cost of one hysterectomy (national tariff cost) is ~£3322 per patient per procedure.</th>
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<tbody>
<tr>
<td>Patient perspective</td>
<td>Intermittent treatment with ulipristal has the potential to avoid surgery/other invasive procedures or allow less invasive procedures. This could be beneficial for the above patient group with symptomatic fibroids. This new treatment option will be especially welcomed by those patients who wish to preserve their fertility or for those unsuitable for surgery. Patients should be counselled on the need to have a break between courses and that treatment will be stopped if they are no longer symptomatic.</td>
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<tr>
<td>Commissioning impact</td>
<td>Ulipristal is currently “red” on the Interface list as, until now, treatment was intended to be short term in advance of surgery according to the marketing authorisation at the time. However, there is some primary care prescribing (0-10 items per quarter). The RAG status in conjunction with this New Therapies recommendation for this additional marketing authorisation will be reviewed at Interface subgroup. Commissioners should review the number of hysterectomies carried out in future years and compare with prescribing rates of this drug.</td>
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</table>

* * This recommendation is valid unless it is has been superseded by a NICE TA or national guidance. The recommendation will only be reviewed when there is substantial new data that may change the initial recommendation. For recommendations that are >24 months old please note that there may be new data available and this should be checked prior to prescribing.

▼ Newly marketed drugs and vaccines are intensively monitored for a minimum of two years, in order to confirm the risk / benefit profile of the product. Healthcare professionals are encouraged to report all suspected adverse drug reactions regardless of the severity of the reaction.

References available on request.
Ulipristal for intermittent treatment for women with symptomatic uterine fibroids - protocol for use.

Specialist confirms uterine fibroids diagnosis with associated symptoms
- Specialist ensures that patient is eligible for ulipristal (see NTS recommendation)
  - Specialist prescribes initial 3 month course of ulipristal.
  - Specialist informs GP of treatment and provides follow up information

GP review after initial 3 month course
Assess: Symptom control (heavy menstrual bleeding, abdominal pressure/pain), Patient satisfaction, Tolerability.

Good response
GP prescribes second 3 month course if necessary and patient is still symptomatic.
Allow 1 menstrual bleed after initial 3 month course and start ulipristal during the next menstrual bleed.
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.

Intermittent Courses can continue to be prescribed if symptoms persist
Ulipristal can be given for up to 4 courses, symptoms and continuing need should be assessed following each course.
Stop treatment if symptom control is achieved, patient wishes to become pregnant or reaches menopause.
If symptoms return following 4 intermittent courses then refer back to specialist.

Report adverse events to the specialist and MHRA
Dosage and Administration:
- 5 mg orally once daily for up to 3 months
- Treatment should be started during the first week of a menstrual cycle.
- Treatments should only be initiated when menstruation has occurred
- The first treatment course should start during the first week of menstruation.
- Re-treatment course should start at the earliest during the first week of the second menstruation following the previous treatment course completion however patients should be reviewed for continuing need after each treatment course.
- The treating physician should explain to the patient the requirement for treatment free intervals.
- If a patient misses a dose and is more than 12 hours the patient should not take the missed dose.

Monitoring required:
- 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 below under endometrial changes)

Contraception:
Concomitant use of progestogen-only pills, a progestogen-releasing intrauterine device or combined oral contraceptive pills is not recommended. Despite the majority of women taking ulipristal having anovulation, a non-hormonal contraceptive method is recommended during treatment.

Bleeding pattern:
After the initial reduction in bleeding or amenorrhea, if an altered persistent or unexpected bleeding pattern occurs (eg inter-menstrual bleeding), investigation of the endometrium including endometrial biopsy should be performed in order to exclude other underlying conditions, including endometrial malignancy.

Endometrial Changes:
Periodic monitoring of the endometrium is recommended. This includes annual ultrasound scan to be performed after resumption of menstruation during off-treatment period. Reversible thickening of the endometrium may occur during treatment. If it persists beyond 3 months following the end of treatment and return of menstruations, and/or an altered bleeding pattern is noted, this may need to be investigated as per usual clinical practice.

Refer back to specialist if
- Poor or no response
- Treatment stopped because of side effects
- Abnormal ultrasound at 12 months
- Symptoms return after completing the full 4 x 3 month courses
**Drug interactions:**

The following are not recommended:

- Moderate CYP3A4 inhibitors (e.g. **erythromycin, grapefruit juice, verapamil**)
- Potent CYP3A4 inhibitors (e.g. ketoconazole, ritonavir, nefazodone, itraconazole, telithromycin, **clarithromycin**)
- Potent CYP3A4 inducers (e.g. rifampicin, rifabutin, carbamazepine, oxcarbazepine, phenytoin, fosphenytoin, phenobarbital, primidone, St John’s wort, efavirenz, nevirapine, long term use of ritonavir)

- Ulipristal acetate may interfere with the action of hormonal contraceptive products. Medicinal products containing progestogen should not be taken within 12 days after cessation of ulipristal treatment.

For more information please see manufacturer’s summary of product characteristics

[https://www.medicines.org.uk/emc/medicine/26068](https://www.medicines.org.uk/emc/medicine/26068)