Pending CCG approval

NHS
Pan Mersey
Area Prescribing Committee

ULIPRISTAL ACETATE 5mg tablets (Esmya®)

The Pan Mersey Area Prescribing Committee recommends the prescribing of ULIPRISTAL ACETATE tablets (Esmya®), by physicians experienced in the diagnosis and treatment of uterine fibroids, in line with the prescribing criteria defined below

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Following an EU-wide review of the safety profile of Esmya®, new restrictions to use and requirements for liver function monitoring before, during, and after treatment have been introduced. Full details can be found in the MHRA Drug Safety Update (August 2018)[1].

Indication

Esmya is now indicated for[2]:

- The intermittent treatment of moderate to severe symptoms of uterine fibroids in women of reproductive age who are not eligible for surgery (see prescribing information for more details).
- One treatment course of pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.

NICE makes the following recommendations regarding the use of ulipristal acetate[3]:

- Offer ulipristal acetate (up to 4 courses) to women with heavy menstrual bleeding and fibroids ≥3cm in diameter and a haemoglobin ≤102g.
- Consider ulipristal acetate (up to 4 courses) to women with heavy menstrual bleeding and fibroids ≥3cm in diameter and a haemoglobin ≥102g.

Liver function monitoring[1-3]

- Before initiation of each treatment course: perform liver function tests (LFT). **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 first two treatment courses: perform LFT every month.
- For further treatment courses: perform LFT once before each new treatment course and when clinically indicated.
- At the end of each treatment course: perform LFTs after 2-4 weeks
- **Stop Esmya treatment and closely monitor women with ALT or AST more than 3-times ULN and consider the need for specialist hepatology referral.**

Note: Patients who are not eligible for treatment under this statement may be considered on an individual basis where their GP or consultant believes exceptional circumstances exist that warrant deviation from the rule of this policy. In this situation, follow locally defined processes.

SUPPORTING INFORMATION

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Effectiveness[2,4,5]

The efficacy of fixed doses of ulipristal acetate 5mg and unlicensed 10mg once daily was evaluated in two Phase 3 randomised, double-blind, 13 week studies recruiting patients with very heavy menstrual bleeding associated with uterine fibroids.

PEARL I was double-blind placebo controlled and showed that ulipristal was superior to placebo in reducing menstrual bleeding and fibroid size.

PEARL II evaluated ulipristal against the active comparator GnRH analogue leuprorelin, and showed that ulipristal was non-inferior to monthly injections of leuprorelin acetate for controlling uterine bleeding.

Evidence for intermittent courses:

The main evidence comes from one pivotal study that evaluated the efficacy of repeated treatment courses fixed doses of ulipristal 5mg or unlicensed 10mg.

PEARL IV was phase III, double-blind, randomised, controlled and demonstrated that 73% of patients on 5mg ulipristal achieved the secondary outcome of controlled bleeding after the fourth treatment course. The primary outcome of amenorrhoea at the end of all four individual treatment courses was achieved in approximately half of evaluable patients receiving 5mg ulipristal.

Safety[1,2]

Contraindications to treatment with Esyma® are:

- Pregnancy and breastfeeding
- Genital bleeding of unknown origin or for reasons other than uterine fibroids
- Uterine, cervical, ovarian or breast cancer
- Underlying hepatic disorder
- Hypersensitivity to ulipristal or any of the excipients

Esyma is contraindicated in women with underlying liver disease. Regular LFT monitoring is required as outlined on page 1.

The most common adverse effect associated with Esmya was hot flush. The vast majority of adverse effects were mild to moderate and did not require discontinuation of treatment. Consult the SPC for full adverse effect profile.

Pregnancy

Pregnancy should be precluded before initiating treatment. Patients should be advised to use a non-hormonal contraceptive method during treatment. Progesterone-only pills, a progestogen-releasing intrauterine device or combined oral contraceptive pills are not recommended.

Cost[6]

For a three month course, excluding VAT:

Ulipristal orally 5mg daily £342

Goserelin 3.6mg s/c injection monthly £195

Leuprorelin 3.75mg s/c or IM injection monthly £192

Triptorelin 3mg IM injection monthly £207

Triptorelin 3.75mg s/c or IM injection monthly £245

Prices from http://dmd.medicines.org.uk, January 2018.

Patient factors[2]

No dosage adjustment is required in patients with renal impairment. Use in patients with severe renal impairment is not recommended unless the patient is closely monitored.

Concomitant use of moderate (e.g. erythromycin, grapefruit juice, verapamil) or potent (e.g. ketoconazole, ritonavir, itraconazole, clarithromycin) CYP3A4 inhibitors with ulipristal is not recommended.

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

Use of ulipristal in women with severe asthma controlled by oral corticosteroids is not recommended.

Prescribing information

Treatment consists of one 5mg tablet to be taken once a day for treatment courses of up to 3 months. The first treatment course should be initiated during the first week of menstruation. In women who are eligible for repeat courses, re-treatment courses should start, at the earliest, during the first week of the second menstruation following the completion of the previous course. Repeated treatment has been studied up to 4 intermittent courses. The prescribing specialist should explain the requirement for treatment-free intervals to the patient. Patients should be informed to notify their specialist should excessive bleeding persist beyond 10 days of commencing treatment.

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Implementation notes

- **Prescribing and monitoring responsibility must be retained by the specialists. Requests should not be made for primary care to take over the care or monitoring of patients.**
- Prescribers must discuss with women the rare risk of liver damage and the need for regular monitoring during treatment.
- Advise women to seek urgent medical attention if they develop any signs or symptoms of liver disease.
- Pharmacists should provide the new patient card to women when dispensing Esmya®.
- Any suspected adverse drug reactions should be reported on Yellowcard without delay.
- Specialists prescribing and monitoring Esmya® should ensure that they have read the Physician's Guide

References

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4. Scottish Medicines Consortium. Ulipristal acetate 5mg tablet (Esmya®); January 2013. Accessed 26 November 2018 at: http://www.scottishmedicines.org.uk/files/advice/ulipristal_acetate_Esmya_FINAL_January_2013_Amended_080213_for_website.pdf
5. Scottish Medicines Consortium. Ulipristal acetate 5mg tablet (Esmya®); January 2016. Accessed 26 November 2018 at: http://www.scottishmedicines.org.uk/files/advice/ulipristal_acetate_Esmya_FINAL_January_2016_for_website.pdf
6. eMC Dictionary of Medicines and Devices Browser. Accessed January 2018 at: http://dmd.medicines.org.uk