Guideline on Prescribing of Gonadorelin (GnRH) Analogues and Progesterone Receptor Modulators in treatment of Endometriosis, Uterine Fibroids (including pre-op use) or prior to Endometrial Ablation

1. BACKGROUND

Endometriosis is a chronic condition characterised by growth of endometrial tissue in sites other than the uterine cavity. The commonest symptom of endometriosis is pain, usually manifesting as dysmenorrhoea or dyspareunia and non-cyclic pelvic pain and sub-fertility. Gonadorelin analogues, also known as Gonadotrophin Releasing Hormone (GnRH) analogues are used in the treatment of endometriosis. Administration of these agents produces an initial phase of stimulation; continued administration is followed by a down regulation of gonadotrophin releasing hormone receptors thereby reducing the release of gonadotrophins (FSH and LH). This in turn leads to inhibition of androgen and oestrogen production.

Endometrial ablation is a modern surgical treatment for menorrhagia after medical methods have failed to control symptoms. There are many methods by which the endometrium can be ablated or resected but the majority benefit from the endometrium being as thin as possible prior to surgery. Gonadorelin analogues give excellent endometrial suppression with a single dose administered prior to menstruation a month before surgery.

Uterine fibroids are the most common benign tumours in women of reproductive age. Common symptoms include menorrhagia and anaemia, but uterine fibroids can also cause pelvic pain, dysmenorrhoea and pressure effects which can affect quality of life and fertility. Gonadorelin analogues and Ulipristal (which is a progesterone receptor modulator) can be used pre-operatively to reduce volume of fibroids and suspend menstruation, or as an intermittent treatment in patients in who wish to avoid surgery or are unsuitable for surgery.

Other unlicensed indications

Gonadorelin analogues are also used for treatment of other conditions either whilst waiting surgery or where surgery is not an option. These include chronic pelvic pain; premenstrual syndrome where other treatments have failed; severe menstrual disorders in the peri-menopausal period. Where treatment is continued for more than six months, add back hormonal therapy (e.g. combined HRT or tibilone) should be prescribed to reduce risk of trabecular bone density loss.

This document provides guidance on prescribing and of gonadorelin analogues amd progesterone receptor modulators for these indications. Treatment will normally be initiated by GP following assessment and recommendation from specialist.
2. INDICATION
See sections 1 & 3

3. DOSE / DURATION

Treatment with Gonadorelin analogues:

Patients should be prescribed a licensed treatment, where available, with the lowest acquisition cost.

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Trade name</th>
<th>Dose for:</th>
<th>Endometrial ablation dose</th>
<th>Uterine fibroids dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goserelin</td>
<td>Zoladex®</td>
<td>Endometriosis, chronic pelvic pain*, PMS, severe menstrual disorders*</td>
<td>3.6mg single dose</td>
<td>3.6mg every 28 days**</td>
</tr>
<tr>
<td>Leuporelin</td>
<td>Prostap SR DCS®</td>
<td>3.75 mg every 28 days OR 11.25 every 3 months</td>
<td>3.75mg single dose</td>
<td>3.75mg every 28 days**</td>
</tr>
<tr>
<td>Triptorelin</td>
<td>Decapeptyl SR®</td>
<td>3mg every 28 days OR 11.25mg every 3 months</td>
<td>Not licensed</td>
<td>3mg every 28 days</td>
</tr>
<tr>
<td>Gonapeptyl Depot®</td>
<td>3.75mg every 28 days</td>
<td>Not licensed</td>
<td></td>
<td>3.75mg every 28 days**</td>
</tr>
</tbody>
</table>

* unlicensed indications ** licensed for pre-op treatment of uterine fibroids only

Injection sites should be changed each time.
No dosage adjustments are required for renal or hepatic impairment or in the elderly.

Treatment with progesterone receptor modulators (Ulipristal, Esmya®)

Ulipristal acetate is a selective progesterone receptor modulator which acts on progesterone receptors in myometrial and endometrial tissue and inhibits ovulation without causing large effects on estradiol levels or antiglucocorticoid activity.

Ulipristal is recommended for

- pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age (as second line pre-operative treatment in patients in whom gonadorelin analogues are not appropriate or not tolerated, due to side effect profile.)
- intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age (as first line treatment for patients who wish to avoid surgery or for whom surgery is not appropriate)

Dose is 5mg daily (orally).
See Section 4 for use in renal and hepatic impairment.

Duration of Treatment with Gonadorelin analogues:

- Endometriosis: Continue every 4 weeks or 3 months for up to 6 months. Repeat courses should not be administered due to the concern of reduced bone mineral
density. Initial dose can be given at any time of the menstrual cycle but some manufacturers advise first dose to be given within first 5 days of cycle for optimal effect.

- Endometrial ablation: Given as a single dose in the week before a period, 5-6 weeks prior to ablation surgery.

- Uterine fibroids: Continue every 4 weeks for a minimum of 3 months. Treatment can be continued for up to 6 months if advised by specialist. Initial dose can be given at any time of the menstrual cycle but some manufacturers advise first dose to be given within first 5 days of cycle for optimal effect.

- Chronic pelvic pain: Continue every 4 weeks or 3 monthly until surgery, or where surgery is not an option - duration and supplementary treatment to be advised by specialist

- Severe menstrual disorders in perimenopausal period, PMS: Duration and supplementary treatment to be advised by specialist

**Duration of Treatment with Treatment with progesterone receptor modulators (Ulipristal, Esmya®)**

Ulipristal can be taken for treatment courses of up to 3 months (duration may be shorter if patient was initiated on gonadorelin analogues and switched to ulipristal due to intolerable side effects. Ulipristal should be initiated within first 7 days of cycle.

**Further intermittent treatment courses can be prescribed up to a total of four courses. Repeated courses should be started during first week of second menstruation following previous treatment course completion.**

4. **CONTRAINDICATIONS**

- Known hypersensitivity to treatment or any of the excipients.
- Pregnancy and breastfeeding. There is a theoretical risk of abortion and foetal abnormality. Non-hormonal methods of contraception should be used during therapy.
- Clinically manifest osteoporosis

**Additional contraindications for Ulipristal**

- genital bleeding of unknown aetiology or for reasons other than uterine fibroids; uterine, cervical, ovarian or breast cancer;
- severe renal impairment (GFR < 30ml/minute/1.73m²)
- moderate to severe hepatic impairment.
5. DRUG INTERACTIONS

Interactions for Gonadorelin analogues:
Drugs which raise the prolactin levels should not be used at the same time as they may reduce the level of LHRH receptors in the pituitary.

Interactions for Ulipristal:
- P-gp substrates – ulipristal may inhibit P-gp substrates in the gastrointestinal wall during absorption e.g. digoxin, dabigatran, fexofenadine – separate administration times by 1.5 hours
- CYP3A4 inhibitors – may increase plasma level of ulipristal e.g. macrolides, azole antifungals, ritonavir, verapamil, diltiazem
- CYP3A4 inducers – may reduce plasma level of ulipristal e.g. carbamazepine, Phenobarbital, phenytoin, rifampicin, St John’s Wort

6. ADVERSE EFFECTS

Gonadorelin analogues
Skin rashes have been reported but are generally mild and occasionally local reactions such as mild bruising at the injection site can occur.

Pharmacological effects include hot flushes, sweating and loss of libido: headaches, mood changes including depression, vaginal dryness and change in breast size have also been noted, although this is highly unlikely to occur with the single dose used prior to endometrial ablation. During early treatment, some women may experience vaginal bleeding of variable duration and intensity. This occurs usually in the first month after starting treatment and probably represents oestrogen withdrawal bleeding and is expected to stop spontaneously. Serum oestradiol concentrations will be initially enhanced if the first injection is administered during the follicular phase of the menstrual cycle but levels become suppressed approximately 21 days after the first depot injection if it is given immediately prior to menstruation. This produces endometrial thinning and will result in amenorrhoea in the vast majority of patients.

Rarely some women may enter the menopause during treatment and do not resume menses on cessation of treatment.

Prolonged use of more than 6 months may cause a loss in bone mineral density in women and should be used with caution in women with known metabolic bone disease

Ulipristal
Most common side effects (>1 in 10) are amenorrhea, hot flush and endometrial thickening.
N.B. If the endometrial thickening persists within 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.

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 consultant. Menstrual periods will generally return within 4 weeks after the end of the treatment course.
Ulipristal is an intensively monitored drug (black triangle drug), as such any possible adverse effects (including any considered not to be serious) relating to treatment should be reported via the yellow card scheme (www.yellowcard.gov.uk).

Details of contraindications, cautions, drug interactions and adverse effects listed for all drugs above are not exhaustive. For further information always check with BNF www.bnf.org.uk or SPC (www.medicines.org.uk).

7. MONITORING

Additional monitoring for repeated intermittent courses of ulipristal

In case of repeated intermittent treatment, periodic monitoring of the endometrium is recommended. This includes annual ultrasound to be performed after resumption of menstruation during off-treatment period. Annual follow up scan will be arranged by specialist team.

If endometrial thickening is noted, which persists after return of menstruations during off-treatment periods or beyond 3 months following the end of treatment courses, and/or an altered bleeding pattern is noted investigation including endometrial biopsy should be performed in order to exclude other underlying conditions, including endometrial malignancy.

8. INFORMATION TO PATIENT

Patients should be informed of risks and benefits of treatment, including

- Common adverse effect
- Need for non hormonal contraceptive
- Importance of compliance for successful surgery
- For unlicensed indications, patients should be informed that treatment is unlicensed and given sufficient information to allow them to make an informed decision, as per GMC guidance.
- For ulipristal - Reduction of menstrual blood loss or amenorrhea within 10 days of treatment – if excessive bleeding persists following initiation patient should inform clinic
- For ulipristal – Inform patient of the need for treatment free intervals (next course can start in first week of second menstruation following previous treatment course)

APPROVAL PROCESS

<table>
<thead>
<tr>
<th>Written by:</th>
<th>Marie Miller, Interface Pharmacist</th>
</tr>
</thead>
<tbody>
<tr>
<td>Update:</td>
<td>Oct 2015</td>
</tr>
<tr>
<td>Consultation process:</td>
<td>Mr Oboh, Clinical Lead for Gynaecology, HEY</td>
</tr>
<tr>
<td>Approved by:</td>
<td>Medicines Management Interface Group</td>
</tr>
<tr>
<td>Ratified by:</td>
<td>HERPC Nov 2015</td>
</tr>
<tr>
<td></td>
<td>Approved Hull CCG, ERY CCG (July 16)</td>
</tr>
<tr>
<td>Review date:</td>
<td>Nov 2018</td>
</tr>
</tbody>
</table>