NEW DRUGS

Ulipristal acetate

Aust Prescr 2016;39:230-1
http://dx.doi.org/10.18773/austprescr.2016.091

Approved indication: fibroids

Esmya (Vifor Pharma)
5 mg tablets
Australian Medicines Handbook section 17.1.3

Ulipristal acetate is a progesterone receptor modulator that has previously been approved as a postcoital contraceptive.[1] As progesterone promotes the growth of uterine fibroids, blocking its receptor may reduce their size. The dose used for this indication can inhibit ovulation and lead to amenorrhoea which will be of benefit to women who have heavy menstrual bleeding related to their fibroids.

Treatment should begin in the first week of a menstrual period. The single daily dose is rapidly absorbed. There is extensive metabolism involving cytochrome P450 3A4. Ulipristal should therefore not be taken with inducers of this enzyme, such as carbamazepine, phenytoin and St John's wort, or with inhibitors such as erythromycin. The half-life of ulipristal is about 38 hours with most of the metabolites being excreted in the faeces. No studies have been done in women with impaired hepatic or renal function.

The approval of ulipristal for the treatment of fibroids appears to have been mainly based on four trials (see Table).[2-5] PEARL I and II were short term while PEARL III and IV studied repeated courses of treatment.

Single three-month course

PEARL I enrolled women with anaemia as a result of heavy periods related to fibroids. These women were planning to have surgical treatment. There was a placebo group of 48 women, while 96 were randomised to take ulipristal 5 mg and 98 to take ulipristal 10 mg. After 13 weeks, bleeding was significantly reduced in more than 90% of the women taking ulipristal compared with 19% of the placebo group. Amenorrhoea was reported by 73% of the women taking ulipristal 5 mg and by 82% of those taking 10 mg. Only 6% of the placebo group had amenorrhoea. MRI showed that the median total fibroid volume had decreased by 21% with ulipristal 5 mg and by 12% with 10 mg while there had been a 3% increase in the volume measured in the placebo group.[2]

PEARL II enrolled 307 women with heavy bleeding who were eligible for surgical treatment of their fibroids. In this trial daily ulipristal was compared to monthly injections of leuprorelin, an agonist of gonadotrophin-releasing hormone. After 13 weeks, bleeding had been controlled in 90% of the women who took ulipristal 5 mg and 98% of those taking 10 mg. It was also controlled in 89% of the women given leuprorelin. These differences showed ulipristal was not inferior to leuprorelin, but leuprorelin had a greater effect on fibroid size. The total volume of the three largest fibroids in each patient was reduced by a median of 36% with ulipristal 5 mg, 42% with ulipristal 10 mg and by 53% with leuprorelin.[3]

Repeated courses

In PEARL III 209 women with heavy bleeding and at least one fibroid took open-label ulipristal 10 mg for three months. This was followed by double-blind treatment with norethisterone or a placebo for 10 days. The women could then opt to repeat this regimen up to three times giving a total of up to four courses. The primary outcome of the study was amenorrhoea. This was achieved by 79% of the women after the first course of ulipristal. Among the 107 women who had four courses of treatment, 90% had amenorrhoea. The three largest fibroids, seen on ultrasound scans, shrunk by a median of 45% after one course and 72% after four courses. In the women who took norethisterone, menstruation resumed more rapidly and blood loss was less than in the placebo group.[4]

PEARL IV had a similar study population and also had amenorrhoea as a primary end point. The 451 women were randomised to take ulipristal 5 mg or 10 mg in 12-week courses. The interval between each course

Table **Efficacy of ulipristal in women with fibroids**

Trial	Total number of patients	Duration of treatment	Proportion of patients with amenorrhoea after treatment			
			Ulipristal 5 mg	Ulipristal 10 mg	Placebo	Leuprorelin
PEARL I[2]	242	13 weeks	73%	82%	6%	–
PEARL II[3]	307	13 weeks	75%	89%	–	80%
PEARL III[4]	209	Four 12–week courses (107 women)	–	90%	–	–
PEARL IV[5]	451	Four 12–week courses (291 women)	63%	73%	–	–

depended on the timing of menstruation. At the end of each of the first two treatment courses 62% of the women taking 5 mg and 73% of those taking 10 mg had amenorrhoea.[6] For patients who completed the protocol of four treatment courses the corresponding figures were 63% and 73%. After four treatment courses the three largest fibroids seen on ultrasound had reduced in volume by around 72% in both groups.[5]

Safety

The common adverse effects of ulipristal include headache, nausea and abdominal pain. The actions of ulipristal may cause some women to experience hot flushes. In the comparison with leuprorelin approximately 25% of the women taking ulipristal had at least one hot flush compared with 65% of those taking leuprorelin.[3] Ulipristal causes changes in the endometrium. This is one reason for having intermittent courses of therapy. An annual ultrasound is recommended. If there is persistent thickening of the endometrium, a biopsy may be indicated to exclude malignancy. Some women will develop ovarian cysts.

Although ulipristal at the recommended dose will suppress ovulation in most women, others will still be at risk of pregnancy. A non-hormonal contraceptive is recommended during treatment. If pregnancy occurs there is little information about the effects of ulipristal on the fetus. It is contraindicated in pregnancy and lactation.

The effect of repeated courses on fertility is uncertain. For most women menstruation resumes within a month of stopping ulipristal.[4,6]

Conclusion

The role of ulipristal will be determined by each patient's problems. While surgery will remove fibroids, this may not be appropriate for women planning a future pregnancy. It is possible that ulipristal could reduce the size of the fibroids to enable less invasive surgery. For women who do not want surgery more research will be needed on repeated courses of ulipristal.

Although a 10 mg dose was studied in the trials (see Table), 5 mg is the approved dose in Australia.

T T manufacturer provided additional useful information

REFERENCES

1. Ulipristal acetate. Aust Prescr 2016;39:228-9. http://dx.doi.org/10.18773/austprescr.2016.082
2. Donnez J, Tatarchuk TF, Bouchard P, Puscasiu L, Zakharenko NF, Ivanova T, et al.; PEARL I Study Group. Ulipristal acetate versus placebo for fibroid treatment before surgery. N Engl J Med 2012;366:409-20. http://dx.doi.org/10.1056/NEJMoa1103182
3. Donnez J, Tomaszewski J, Vázquez F, Bouchard P, Lemieszczuk B, Baró F, et al.; PEARL II Study Group. Ulipristal acetate versus leuprolide acetate for uterine fibroids. N Engl J Med 2012;366:421-32. http://dx.doi.org/10.1056/NEJMoa1103180
4. Donnez J, Vázquez F, Tomaszewski J, Nouri K, Bouchard P, Fauser BC, et al. Long-term treatment of uterine fibroids with ulipristal acetate. Fertil Steril 2014;101:1565-73.e18. http://dx.doi.org/10.1016/j.fertnstert.2014.02.008
5. Donnez J, Donnez O, Matule D, Ahrendt HJ, Hudecek R, Zatik J, et al. Long-term medical management of uterine fibroids with ulipristal acetate. Fertil Steril 2016;105:165-73.e4. http://dx.doi.org/10.1016/j.fertnstert.2015.09.032
6. Donnez J, Hudecek R, Donnez O, Matule D, Arhendt HJ, Zatik J, et al. Efficacy and safety of repeated use of ulipristal acetate in uterine fibroids. Fertil Steril 2015;103:519-27.e3. http://dx.doi.org/10.1016/j.fertnstert.2014.10.038

The Transparency Score (T) is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the European Medicines Agency (www.ema.europa.eu) and the Therapeutic Goods Administration (www.tga.gov.au/industry/pm-austpar.htm)..

EDITORIAL OFFICE

For general correspondence such as Letters to the Editor, contact the Editor.

Postal The Editor
Australian Prescriber
PO Box 104
DEAKIN WEST 2600

Telephone (02) 6202 3100

Fax (02) 6282 6855

Email info@australianprescriber.com

Website nps.org.au/australianprescriber

Twitter @AustPrescriber

SUBSCRIPTIONS

Australian Prescriber is published every two months online. All content is accessible free of charge in full text at nps.org.au/australianprescriber. New drugs are published between issues as they become available.

An email alert can be sent to you when *Australian Prescriber* publishes new material. Subscribe or update your details at nps.org.au/australianprescriber

For back issues, and copies of the Anaphylaxis wallchart and Switching-antidepressants poster, email info@australianprescriber.com