



# Drug Information Bulletin

*Drug Information Centre (DIC)*

*Indian Pharmaceutical Association*

*Bengal Branch*

*Tele fax: 033 24612776, E-mail: [ipabengal.dic@gmail.com](mailto:ipabengal.dic@gmail.com)*

*Web Site: <http://www.ipabengal.org>*

*Contact: 09830136291*

*&*

*Regulatory Affairs Division (RAD), IPA*

**10<sup>th</sup>  
Year**

**Volume: 10**

**Number: 20**

**1<sup>st</sup> January 2017**

## *Content*

- *Editorial*
- *New Drug: Ulipristal acetate for fibroids*
- *Etoricoxib Reduced initial dose recommendation for rheumatoid arthritis and ankylosing spondylitis*
- *Levetiracetam Only to be used with dosing syringe provided with package to avoid accidental overdose*
- *Ondansetron Assessing potential harm to the foetus: insufficient information*
- *Report: Drug approvals, ROI low in 2016*
- *Studies shed light on extensive brain damage in infants with congenital Zika*
- *Highlights of 68<sup>th</sup> IPC*

## *Editorial*

Access to high cost medicines are a problem round the world especially in the low and middle income countries. Low health care budget and absence or low coverage of Health Insurance makes the situation more complex. Respective governments have taken measures for innovations and framed various legislation to make high priced medicines more accessible. India has taken several steps for Universal Health care by introducing new initiatives like- Unorganized Workers Social Security Act (2008), Rashtriya Swasthya Bima Yojana (RSBY), National Rural Health Mission (NRHM), National Urban Health Mission (NUHM) for overall development of the health care system. Several other steps have also been taken to make medicines more accessible like- Pradhan Mantri Jan Aushadhi Scheme. Greater number of drugs, including high priced medicines have been included under the price control mechanism, through which price of the medicines are monitored by the National Pharmaceutical Pricing Authority (NPPA) under the Department of Pharmaceuticals, Government of India. Several state Governments have taken up innovative projects to improve accessibility to high cost medicines. Government of India has also utilized flexibilities of IPR provisions in case of public health care exigencies by granting compulsory licensing making life saving medicines affordable. In the innovation part the Government of India declared the policy "Make in India". Hope this programme will be successful in case of innovation.



**Dr. Subhash C. Mandal**  
**Editor**

**E mail: [subhash.mandaldr@gmail.com](mailto:subhash.mandaldr@gmail.com)**  
**Mob. 9830136291**

## New Drug: Ulipristal acetate for fibroids

Approved indication: fibroids  
Esmya  
5 mg tablets

Ulipristal acetate is a progesterone receptor modulator that has previously been approved as a postcoital contraceptive.<sup>1</sup> 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.<sup>2-5</sup> 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.<sup>2</sup>

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.<sup>3</sup>

### 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.<sup>4</sup>

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 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.<sup>6</sup> 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.<sup>5</sup>

### 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.<sup>3</sup> 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.<sup>4,6</sup>

### 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, 5 mg is the approved dose in Australia.

### References

1. Ulipristal acetate. Aust Prescr 2016;39:228-9.
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.
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.
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.
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.
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.

Ref. Australian Prescriber

## **Etoricoxib Reduced initial dose recommendation for rheumatoid arthritis and ankylosing spondylitis**

The MHRA has recommended that the starting dose for treatment of rheumatoid arthritis or ankylosing spondylitis with etoricoxib is reduced to 60 mg once daily, with the option to increase to a maximum of 90 mg once daily if necessary. Etoricoxib is indicated for the symptomatic relief of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and the pain and signs of inflammation associated with acute gouty arthritis. Etoricoxib is also indicated for the short-term treatment of moderate pain associated with dental surgery. Following an EU-wide review in 2008 of the benefits and risks of etoricoxib, the marketing authorisation holder was required to conduct clinical trials to assess the efficacy and safety of etoricoxib 60 mg once daily for the treatment of rheumatoid arthritis and ankylosing spondylitis including comparison with etoricoxib 90 mg. From these trials, there is evidence that the 60-mg dose is effective in rheumatoid arthritis and ankylosing spondylitis. However, for some patients, the 90-mg dose will be more efficacious, although it is not possible to predict which patients might benefit from the higher dose. Reference: Drug Safety Update, MHRA, Volume 10, issue 3:1, October 2016 Ref. ([www.gov.uk/mhra](http://www.gov.uk/mhra))

## **Levetiracetam Only to be used with dosing syringe provided with package to avoid accidental overdose**

The EMA has recommended measures to ensure safe use of levetiracetam (Keppra® and generics) oral solution to avoid medication errors and the risk of overdose. Parents and carers should only use the syringe provided with the package to measure the dose of levetiracetam. The packages and labels will be colour-coded to indicate the volume of the bottle, the volume of the dosing syringe, and the age range of the patient that the medicine should be used for. Levetiracetam is a medicine for the

treatment of epilepsy. Cases of accidental overdose have been reported with levetiracetam oral solution; the majority of cases occurred in children aged between 6 months and 11 years. Most of the cases occurred when the medicine was used with an incorrect dosing syringe (e.g. a 10 ml syringe was used instead of a 1 ml one, leading to a 10-fold overdose), or because of a misunderstanding by the caregiver about how to properly measure the dose. Levetiracetam overdose often has no symptoms, but it may cause sleepiness, agitation, difficulty breathing and coma. Reference: Press release, EMA, 14 October 2016 ([www.ema.europa.eu](http://www.ema.europa.eu))

## **Ondansetron Assessing potential harm to the foetus: insufficient information**

Health Canada is working with the Drug Safety and Effectiveness Network to further investigate the extent of ondansetron (Zofran®) use during pregnancy and the risk to the foetus. Health Canada has requested that manufacturers submit information they may have regarding birth defects and use of ondansetron during pregnancy. Ondansetron is indicated for nausea and vomiting associated with cancer treatment or surgery. It is not authorized in Canada to treat nausea and vomiting with ondansetron during pregnancy. Health Canada carried out a safety review to assess the risk of birth defects with the use of ondansetron. At the time of the review, Health Canada had received 14 reports of birth defects in the newborn babies of mothers treated with ondansetron. In four of these reports, there was insufficient information on the time of exposure of ondansetron during pregnancy. In two other reports, ondansetron was given after the organs of the fetus were already developed. In the remaining eight reports, ondansetron was given to the mother at the stage the organs were developing. In these eight reports, a link between birth defects and ondansetron could not be ruled out. Information about the medical history of the mother, including additional medications she may have been taking, and exposure time were lacking. There were no patterns of birth defects. Findings from published scientific studies were

inconsistent and inconclusive. There were concerns with study design, and the majority had a number of limitations such as use of concomitant medications. The findings from animal studies have not established that ondansetron can cause birth defects. Available information were not sufficient to establish a link between the use of ondansetron during pregnancy and the risk of birth defects. Health Canada will continue to monitor safety information involving the use of ondansetron.

Reference: Summary Safety Review, Health Canada, 16 November 2016 ([www.hc-sc.gc.ca](http://www.hc-sc.gc.ca))

#### **Report: Drug approvals, ROI low in 2016**

A Deloitte report found that only 19 new drugs have been approved in the US so far this year and a total of 22 approvals are projected by year's end, far below 2015's 45 approvals and 41 in 2014. Deloitte says returns on investment for drugmakers worldwide are falling -- at just 3.7% this year, down from 2010's high of 10.1%.

Ref. [Reuters](#)

#### **Studies shed light on extensive brain damage in infants with congenital Zika**

A Brazilian study in The New England Journal of Medicine showed that 42% of infants whose mothers were infected with the Zika virus had brain scans suggesting severe brain damage and other physical symptoms, while another study in the Journal of the American Medical Association found that 6% of 442 pregnancies with possible Zika infections had birth defects, none of whom were born to mothers infected in the second or third trimesters. CDC researchers also reported in Emerging Infectious Diseases that the virus was present in the placenta for up to seven months after the mother contracted the virus and persisted for weeks in newborns' brains after birth.

Ref. The New York Times



Mr. Veeramani, President 68<sup>th</sup> Indian Pharmaceutical Congress addressing gathering



HRD Minister of Andhra Pradesh addressing during inaugural session of 68<sup>th</sup> Indian Pharmaceutical Congress at Visakhapatnam



Dr. V.S.V. Rao addressing in 68<sup>th</sup> Indian Pharmaceutical Congress at Visakhapatnam

#### **DISCLAIMER:**

The Newsletter intends to provide updated and reliable information on medicines and other related issues in an attempt to equip healthcare professionals to take informed decision in recommending medicines to the patients. However, they are encouraged to validate the contents. None of the people associated with the publication of the Newsletter nor the organization shall be responsible for any liability for any damage incurred as a result of use of contents of this publication. The brand names of medicines, if mentioned, are for illustration only and the Newsletter does not endorse them.