Medicines Adverse Reactions Committee

Meeting date	**8 March 2018**	Agenda item	3.2.6
Title	**Ulipristal acetate and drug induced liver injury**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Active constituent Ulipristal acetate	**Medicines** **Esmya 5 mg tablets**	**Sponsors** Pharmacy Retailing (NZ) Ltd trading as Healthcare Logistics	
Funding	Not funded		
Previous MARC meetings	Ulipristal acetate has not been discussed previously		
International action	The EMA is currently reviewing Esmya (ulipristal acetate) for the treatment of uterine fibroids and liver injury – 1 December 2017: The EMA has started a review of the medicine Esmya (ulipristal acetate) used to treat uterine fibroids. This follows four reports of serious liver injury, three of which ended in liver transplantation, in patients treated with the medicine. The PRAC will make a recommendation to the CHMP in March 2018.		
Schedule	Prescription medicine		
Usage data	Two patients have been treated with Esmya in New Zealand		
Advice sought	**The Committee is asked to advise whether:** – the evidence is strong enough to suggest an association between ulipristal acetate and liver injury – the proposed update to the data sheet and patient information leaflet is sufficient – any communication to healthcare professionals is required other than MARC's Remarks in *Prescriber Update*.		

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1.0 PURPOSE

In December 2017, the European Medicines Agency (EMA) announced that they had started a review of Esmya (ulipristal acetate) [1]. This followed four reports of serious liver injury, three of which ended in liver transplantation, in patients treated with the medicine.

The purpose of this paper is to review the available information on the possible risk of drug induced liver injury with ulipristal acetate.

2.0 BACKGROUND

2.1 Esmya (ulipristal acetate)

The active substance in Esmya, ulipristal acetate, is a synthetic derivative of progesterone (see comparison of structures in Figure 1) [2]. It is an orally active selective progesterone receptor modulator that acts via high affinity binding to the human progesterone receptor.

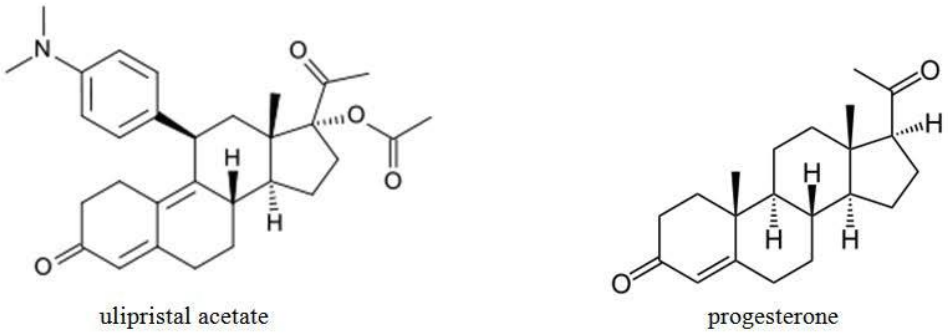

Figure 1: Chemical structures of ulipristal acetate and progesterone

Ulipristal acetate works by attaching to the targets on cells (receptors) that the hormone progesterone normally attaches to, preventing progesterone from having its effect.

Ulipristal acetate exerts a direct effect on the endometrium and a direct action on fibroids reducing their size through inhibition of cell proliferation and induction of apoptosis.

Esmya was first authorised in the European Union in 2012 for the treatment of moderate to severe symptoms of uterine fibroids (ie, non-cancerous (benign) tumours of the womb) in women who have not reached menopause [1]. It is used for up to three months before women undergo surgery to remove the fibroids. The three-month course can be repeated with breaks between each course.

Esmya was approved in New Zealand on 7 December 2017 for the intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age [3].

In some countries, ulipristal acetate is also indicated for emergency contraception [2]. ellaOne was approved in the European Union in 2009 for emergency contraception within 120 hours (five days) of unprotected sexual intercourse or contraceptive failure.

There are no ulipristal acetate containing products approved in New Zealand that are indicated for emergency contraception.

Comments: *Esmya (ulipristal acetate) was recently approved in New Zealand.*

The Australian sponsor of Esmya has confirmed that, following an investigation, all packs supplied in New Zealand have been accounted for. There have only been two patients who have been treated with Esmya in New Zealand, originating from one prescriber, both of which have finished a course of therapy. The physician has been advised of the recommendations of the EMA and has agreed to postpone the second course of therapy until a final outcome is known.

As Esmya is not promoted in New Zealand as yet, the Australian sponsor does not expect any new patients to begin therapy. To prevent an unlikely event of a new patient commencing therapy, a temporary hiatus of sales by the distributor has been implemented.

2.2 Drug induced liver injury

Liver injury can develop following the use of many drugs [4].

Drug induced liver injury can be classified in several ways, including by its clinical presentation (hepatocellular injury, cholestatic injury, or mixed injury), the mechanism of hepatotoxicity (predictable or idiosyncratic), and the histologic findings (eg, hepatitis, cholestasis, and steatosis).

Many patients with drug induced liver injury are asymptomatic and are only detected because of laboratory testing. Patients with acute drug induced liver injury who are symptomatic may report malaise, low-grade fever, anorexia, nausea, vomiting, right upper quadrant pain, jaundice, acholic stools, or dark urine. In addition, patients with cholestasis may have pruritus. In severe cases, hepatic encephalopathy may develop, indicating acute liver failure. Patients with chronic drug induced liver injury may go on to develop significant fibrosis or cirrhosis and have signs and symptoms associated with cirrhosis or hepatic decompensation (eg, jaundice, palmar erythema, and ascites).

Making a diagnosis of drug induced liver injury can be difficult. It depends on obtaining a careful drug use history and ruling out other potential causes of liver injury.

The primary treatment for drug induced liver injury is withdrawal of the offending drug and monitoring to ensure the liver tests normalize.

Recovery will occur in the majority of patients with drug induced liver injury once the offending medication is stopped.

Comments:

A searchable database of drugs, herbal medications, and dietary supplements associated with drug-induced liver injury has been developed by the National Institutes of Health called LiverTox (available at https://livertox.nlm.nih.gov/). Esmya is not listed in the LiverTox database.

2.3 Summary of the PRAC review

In December 2017, the EMA announced that it had started a review of Esmya (ulipristal acetate) [1]. See section 1.0 for further information.

In January 2018, the EMA announced that, as a temporary measure while the review is ongoing, the PRAC had recommended regular liver monitoring for women taking Esmya for uterine fibroids [5]. All women taking Esmya should have a liver function test at least once a month during treatment. If the test is abnormal (liver enzyme levels more than two times the upper limit of normal), the healthcare professional should stop treatment and closely monitor the patient. Liver tests should be repeated two to four weeks after stopping treatment. The PRAC is also recommending that no new patients should be started on Esmya and no patients who have completed a course of treatment should start another one for the time being.

No cases of serious liver injury have been reported with ellaOne and there are no concerns with this medicine at this time [6].

Comments:

Any information published by the EMA after this report has been circulated will be presented verbally at the meeting, if available.

In Australia, the Therapeutic Goods Administration is awaiting the outcome of the PRAC review before making a decision about any regulatory action.

2.4 Data sheets

2.4.1 New Zealand – Esmya [3]

Indications:

Ulipristal acetate is indicated for intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age.

Dose:

The treatment consists of one tablet of 5 mg to be taken once daily for treatment courses of up to three months each. Tablets may be taken with or without food.

Treatments should only be initiated when menstruation has occurred:

- The first treatment course should start during the first week of menstruation.
- Re-treatment courses should start at the earliest during the first week of the second menstruation following the previous treatment course completion.

The treating physician should explain to the patient the requirement for treatment free intervals.

Special populations (of interest for this paper):

Hepatic impairment: No dose adjustment is recommended for patients with mild hepatic impairment. In the absence of specific studies, ulipristal acetate is not recommended in patients with moderate or severe hepatic impairment unless the patient is closely monitored.

Comments:

As with the United Kingdom and Australian data sheets, there is no information on drug induced liver injury or hepatic disorders in the current New Zealand data sheet.

3.0 INFORMATION PROVIDED BY THE COMPANY

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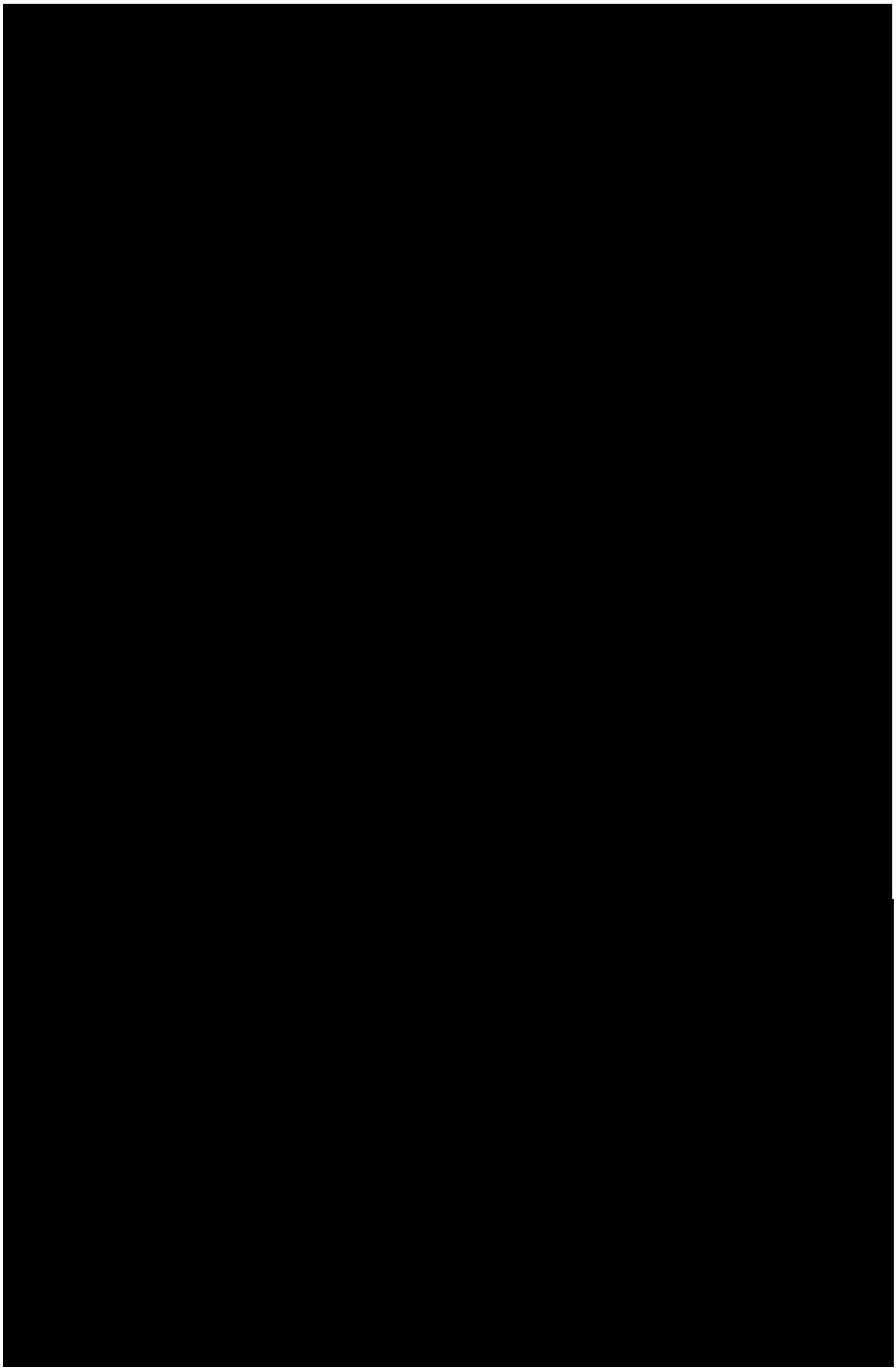

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4.0 DISCUSSION AND CONCLUSIONS

Esmya was approved in New Zealand on 7 December 2017 and to date only two patients have been treated. To prevent an unlikely event of a new patient commencing therapy, a temporary hiatus of sales by the distributor has been implemented.

The marketing authorisation holder in Europe [redacted]

[redacted]

Given the strength of the evidence at the present time, monitoring of liver function may be sufficient to manage this potential risk.

5.0 ADVICE SOUGHT

The Committee is asked to advise whether:

- the evidence is strong enough to suggest an association between ulipristal acetate and liver injury
- the proposed update to the data sheet and patient information leaflet is sufficient
- any communication to healthcare professionals is required other than MARC's Remarks in *Prescriber Update*.

6.0 ANNEXES

1. Gedeon Richter. 2017. *Responses to PRAC Request (November 2017)*.
2. Gedeon Richter. 2016. *EU Risk Management Plan – Esmya v15.1 (22 June 2016)*.
3. Gedeon Richter. 2017. *Periodic Safety Update Report No. 8 (24 April 2017)*.

7.0 REFERENCES

1. European Medicines Agency. 2017. *Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 27-30 November 2017 – PRAC starts review of Esmya for treatment of uterine fibroids*. URL: www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2017/11/news_detail_002863.jsp&mid=WC0b01ac058004d5c1 (accessed 9 February 2018).
2. Australian Government Department of Health Therapeutic Goods Administration. 2015. *Australian Public Assessment Report for ulipristal acetate – Proprietary product name: EllaOne*. URL: www.tga.gov.au/sites/default/files/auspar-ulipristal-acetate-150904.pdf (accessed 9 February 2018)
3. Pharmacy Retailing (NZ) Ltd trading as Healthcare Logistics. 2017. *Esmya New Zealand data sheet*. URL: www.medsafe.govt.nz/profs/Datasheet/e/esmyatab.pdf (accessed 9 February 2018).
4. Larson AM. 2017. *Drug-induced liver injury*. UpToDate Database (accessed 15 February 2018).
5. European Medicines Agency. 2018. *Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 8-11 January 2018 – Women taking Esmya for uterine fibroids to have regular liver tests while EMA review is ongoing*. URL: www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/01/news_detail_002881.jsp&mid=WC0b01ac058004d5c1 (accessed 9 February 2018).
6. European Medicines Agency. 2018. *Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 5-8 February 2018 – Women taking Esmya for uterine fibroids to have regular liver tests while EMA review is ongoing*. URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2018/02/news_detail_002901.jsp&mid=WC0b01ac058004d5c1 (accessed 9 February 2018).