

In this Edition

- Ulipristal acetate 5mg (Esmya) for uterine fibroids – suspension of marketing authorisation during ongoing review of liver injury risk
- Paracetamol – reminder to prescribers on risk of hepatotoxicity in patients with risk factors
- Durvalumab (Imfinzi[▼]) – risk of myasthenia gravis
- Rivaroxaban (Xarelto) – not for use as thromboprophylaxis in patients who have recently undergone transcatheter aortic valve replacement
- Selective Serotonin Reuptake Inhibitors (SSRI) and Serotonin-norepinephrine reuptake inhibitors (SNRI) – persistent sexual dysfunction after drug withdrawal
- Direct Healthcare Professional Communications published on the HPRA website since the last Drug Safety Newsletter

Ulipristal acetate 5mg (Esmya) for uterine fibroids – suspension of marketing authorisation during ongoing review of liver injury risk

The European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) has recommended the temporary suspension of the marketing authorisation for ulipristal acetate 5mg (Esmya) while a safety review into the risk of serious liver injury is ongoing. Ulipristal acetate 5mg (Esmya) is currently approved in the EU for one treatment course of pre-operative treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age, and for intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age who are not eligible for surgery. Ulipristal acetate is also authorised as a 30mg single-dose medicine for emergency contraception (ellaOne and other trade names). This suspension and safety review does not affect the 30mg ulipristal acetate emergency contraceptive and to date, there is no concern regarding a risk of liver injury associated with use of ulipristal acetate in these circumstances. In accordance with the PRAC recommendation, batches of Esmya have been recalled from pharmacies and this recall is going to patient level, pending completion of the safety review.

In 2018, the PRAC finalised a review of ulipristal acetate 5mg (Esmya), which was initiated due to reports of serious hepatic injury, including four cases requiring liver transplantation. To minimise this rare, but serious risk of hepatic injury, the use of ulipristal 5mg (Esmya) was restricted, product information was updated, recommendations for regular liver function tests (before and during treatment, and stopping treatment immediately in case of raised liver enzyme levels) were issued and educational materials to assist healthcare professionals were made available. However, in December 2019, the EMA was informed of a new case of serious liver injury leading to liver transplantation following treatment with ulipristal acetate 5mg (Esmya), despite adherence to the new risk minimisation measures implemented in 2018. In light of this the PRAC has initiated a new review into the risk of liver injury. Following approval by the HPRA, a [DHPC](#) has been distributed by the licence holder for ulipristal acetate 5mg (Esmya). Further information and updated recommendations will be communicated following the conclusion of the review. Ulipristal acetate 5mg (Esmya) must not be used while the current PRAC review is ongoing, and the measures outlined below must be followed:

Advice to Healthcare Professionals

- Ulipristal acetate 5mg (Esmya) must not be initiated in any new patients.
- Patients currently being treated should stop taking ulipristal acetate (Esmya) for uterine fibroids.
- Contact your patients currently on treatment with ulipristal acetate 5mg (Esmya) for uterine fibroids as soon as possible, and stop their treatment.

- Advise your patients to immediately report signs and symptoms of liver injury (such as nausea, vomiting, right hypochondrial pain, anorexia, asthenia, jaundice), which could occur after stopping treatment.
- Liver function tests should be performed within 2-4 weeks after treatment has stopped.
- Batches of Esmya have been recalled from pharmacies and this recall is going to patient level.

Key Message

Ulipristal acetate 5mg (Esmya) is temporarily withdrawn from the market during an ongoing review into the risk of serious liver injury and should not be initiated in new patients.

For patients on treatment with ulipristal acetate 5mg (Esmya) the treatment must be stopped and liver monitoring should be performed within 2-4 weeks of treatment cessation.

This suspension and safety review does not affect the 30mg ulipristal acetate emergency contraceptive (ellaOne and other trade names) and to date, there is no concern regarding a risk of liver injury with ulipristal acetate used in these circumstances.

All reports of suspected adverse reactions should be reported to the HPRA via the available methods (www.hpra.ie).

* Further details on Ulipristal acetate 5mg (Esmya) are available at www.hpra.ie and www.ema.europa.eu.

Paracetamol – reminder to prescribers on risk of hepatotoxicity in patients with risk factors

Healthcare professionals are reminded of the known potential for hepatotoxicity in association with paracetamol, even at doses within the normal therapeutic range, in patients who are at particular risk of such adverse effects. Patients at increased risk of hepatotoxicity include patients who are underweight (adults or adolescents <50kg) or of low body mass index, malnourished, dehydrated, those with chronic alcoholism, co-existing renal or hepatic impairment, concomitantly taking hepatotoxic drugs and those with conditions that may predispose to glutathione deficiency or depletion. For some patients considered to be at higher risk, a lower starting dose, a reduction in dose and/or a reduced frequency of dosing may be appropriate. As some of these risk factors may change during the course of an illness (e.g. malnourishment, weight loss, dehydration), healthcare professionals should take into consideration any emerging or changing risk factors and maintain an awareness that these may warrant a dose adjustment when prescribing or administering paracetamol.

Durvalumab (Imfinzi[▼]) – risk of myasthenia gravis

Imfinzi^{▼*} (durvalumab) is a monoclonal antibody that acts as an “immune checkpoint inhibitor” by selectively blocking the interaction of programmed cell death ligand-1 (PD-L1) with PD-1 and CD80, thereby enhancing antitumour immune responses and increasing T-cell activation. Imfinzi is indicated for the treatment of locally advanced, unresectable non-small cell lung cancer (NSCLC) in adults whose tumours express PD-L1 on $\geq 1\%$ of tumour cells and whose disease has not progressed following platinum-based chemoradiation therapy.

The European Medicines Agency’s Pharmacovigilance Risk Assessment Committee (PRAC) recently reviewed the risk of myasthenia gravis associated with Imfinzi, considering the relevant available information from spontaneous reports and the published literature. Evidence for a potential causal relationship between Imfinzi treatment and development of myasthenia gravis was provided in a number of the spontaneous reports identified by the PRAC, some of which resulted in a fatal outcome. Myasthenia gravis was reported in less than 1% of patients treated with durvalumab monotherapy in clinical trials.

Immune checkpoint inhibitors such as durvalumab are known to generate a wide range of immune-mediated adverse reactions. The PRAC noted that several literature articles describe the potential mechanism of action by which durvalumab may induce myasthenia gravis, while also highlighting that treatment with several other immune checkpoint inhibitors is known to be associated with myasthenia gravis.

The PRAC concluded that there is a risk of myasthenia gravis associated with Imfinzi treatment. The product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) for Imfinzi has been updated to reflect this risk.

Advice to Healthcare Professionals

- Myasthenia gravis is an immune-mediated adverse reaction which has been reported in patients undergoing treatment with Imfinzi (durvalumab).
- Patients should be monitored for signs and symptoms of myasthenia gravis and managed as recommended in the product information, which may involve withholding the dose for up to 12 weeks and treatment with high-dose prednisone followed by a taper on improvement.
- If there are signs of muscular weakness or respiratory insufficiency, treatment with Imfinzi should be permanently discontinued.

Key Message

Myasthenia gravis is a rare immune-mediated adverse reaction to treatment with Imfinzi (durvalumab).

Patients should be monitored for signs of myasthenia gravis and managed as recommended in the product information.

If there are signs of muscular weakness or respiratory insufficiency, treatment with Imfinzi should be permanently discontinued.

The product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) for Imfinzi has been updated to reflect the risk of myasthenia gravis associated with treatment.

All reports of suspected adverse reactions should be reported to the HPRa via the available methods (www.hpra.ie).

* Further details on Imfinzi are available at www.hpra.ie and www.ema.europa.eu.

Rivaroxaban (Xarelto) – not for use as thromboprophylaxis in patients who have recently undergone transcatheter aortic valve replacement

The Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) undertook a review of data concerning the risk of all-cause mortality, thromboembolic and bleeding events in patients treated with rivaroxaban* after transcatheter aortic valve replacement (TAVR). It should be noted that treatment with rivaroxaban is not currently recommended for patients with prosthetic valves.

The review was undertaken in light of findings from a phase III clinical study (GALILEO), which was prematurely terminated in 2018. The GALILEO study was a randomised, open label, multicentre trial to evaluate clinical outcomes after successful TAVR in patients without an established indication for oral anticoagulation. Patients were randomised to either a rivaroxaban-based anticoagulation strategy (rivaroxaban 10 mg once daily and acetylsalicylic acid (ASA) 75-100 mg once daily for 90 days followed by maintenance with rivaroxaban 10 mg once daily) or an antiplatelet-based strategy (clopidogrel 75 mg and ASA 75-100 mg once daily for 90 days followed by maintenance with ASA). An increase in all-cause mortality, thromboembolic and bleeding events in patients treated with rivaroxaban after TAVR was identified, as previously highlighted in the [90th Edition](#) of the HPRa's Drug Safety Newsletter.

The PRAC review considered the final results of the GALILEO study, as well as available evidence from other randomised clinical trials and spontaneous reports. The PRAC concluded that rivaroxaban should not be used for thromboprophylaxis in patients having recently undergone TAVR, and recommended an update to the Summary of Product Characteristics (SmPCs) of rivaroxaban-containing medicines regarding use of rivaroxaban in patients with prosthetic valves, which is not an approved indication. In addition, the PRAC considered that the benefit-risk balance for rivaroxaban, for the currently-approved indications as listed in the approved product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)), remains positive.

Advice to Healthcare Professionals

- Rivaroxaban is not authorised for thromboprophylaxis in patients with prosthetic heart valves, including patients who have recently undergone TAVR, and should not be used in these patients. Rivaroxaban should be used for the currently-approved indications as listed in the approved product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)).

Key Message

A clinical trial found an increase in all-cause mortality, thromboembolic and bleeding events in patients randomised to a rivaroxaban-based anticoagulation strategy compared with an antiplatelet-based strategy after successful TAVR.

Rivaroxaban is not authorised for thromboprophylaxis in patients with prosthetic heart valves, including patients who have undergone TAVR, and should not be used in these patients.

The Summary of Product Characteristics (SmPCs) for rivaroxaban-containing medicines have been updated to reflect that rivaroxaban should not be used for thromboprophylaxis in patients who have recently undergone TAVR.

The benefit-risk balance for rivaroxaban remains positive for the currently-approved indications as listed in the approved product information.

All reports of suspected adverse reactions should be reported to the HPRA via the available methods (www.hpra.ie).

* Rivaroxaban-containing medicines include Xarelto and Rivaroxaban Rowex. Further details are available at www.hpra.ie and www.ema.europa.eu.

Selective Serotonin Reuptake Inhibitors (SSRI) and Serotonin-norepinephrine reuptake inhibitors (SNRI) – persistent sexual dysfunction after drug withdrawal

The European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) has reviewed the available evidence from the EMA database of adverse reactions (EudraVigilance), along with evidence from the literature, information from social media and cumulative data reviews for selective serotonin reuptake inhibitors (SSRI) and serotonin-norepinephrine reuptake inhibitors (SNRI) medicinal products. Following this review, the PRAC considered that the product information for SSRI and SNRI medicinal products should be amended to warn about the possibility of sexual dysfunction, which may persist following discontinuation of these medicinal products. SSRI and SNRI containing medicinal products include citalopram, escitalopram, fluvoxamine, fluoxetine, paroxetine, sertraline (SSRIs) and duloxetine, venlafaxine, desvenlafaxine, and milnacipram (SNRIs). The PRAC also examined the evidence relating to clomipramine and vortioxetine, however based on the available data no update of the product information for medicinal products containing these active substances was considered warranted at this time.

Advice to Healthcare Professionals

- The product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL) for SSRI and SNRI containing medicines will be updated to advise of the possibility of the occurrence of sexual dysfunction which may persist despite discontinuation of the medicinal product.

Key Message

Selective serotonin reuptake inhibitors (SSRIs)/serotonin-norepinephrine reuptake inhibitors (SNRIs) may cause symptoms of sexual dysfunction.

There have been reports of long-lasting sexual dysfunction where the symptoms have continued despite discontinuation of SSRIs/SNRIs.

All reports of suspected adverse reactions should be reported to the HPRA via the available methods (www.hpra.ie).

Direct Healthcare Professional Communications published on the HPRA website since the last Drug Safety Newsletter

PRODUCT	SAFETY ISSUE
Esmya	Esmya 5mg Tablets (Ulipristal acetate) for uterine fibroids not to be used during ongoing review of liver injury risk
Xeljanz	Increased risk of venous thromboembolism and increased risk of serious and fatal infections XELJANZ (tofacitinib)
Picato	Suspension of the marketing authorisation due to risk of skin malignancy
Lemtrada	LEMTRADA (alemtuzumab) - Restricted indication, additional contraindications and risk minimisation measures
Implanon NXT	Update to the insertion and removal instructions to minimise the risks of neurovascular injury and implant migration of Implanon NXT – etonogestrel 68mg, implant for subdermal use
Increlex	Risk of benign and malignant neoplasia of INCRELEX 10mg/ml Solution for Injection (mecasermin)
Methotrexate	Recommendations to avoid potentially fatal dosing errors when using Methotrexate for inflammatory diseases
Cyproterone acetate*	Restrictions in use of cyproterone acetate due to risk of meningioma

* Due to the unprecedented logistical limitations as a result of the current COVID-19 pandemic which have impacted on the marketing authorisation holder's (MAH – i.e. the company which holds a licence for a medicine) capacity to print and distribute the Direct Healthcare Professional Communication (DHPC) for cyproterone acetate in hard copy format to healthcare professionals at this time, a copy of the full text is appended to this DSN, with a link to the electronic version available on the HPRA website at the above link.

Access to current versions of product information

Healthcare professionals are reminded that SmPCs for all products currently authorised in Ireland are accessible on the HPRA website (www.hpra.ie). The HPRA advises healthcare professionals not to retain printed versions of Summary of Product Characteristics (SmPC) documents. As these documents are subject to frequent content updates, including changes to safety and dose related information, we recommend that you visit our website as necessary to access the most up-to-date versions.

Correspondence/Comments should be sent to the Pharmacovigilance Section, Health Products Regulatory Authority, contact details below.

5 Kevin O'Malley House, Earlsfort Centre, Earlsfort Terrace, Dublin 2, Ireland.
T: +353 1 676 4971 E: medsafety@hpra.ie www.hpra.ie



April 2020

Direct Healthcare Professional Communication

Restrictions in use of cyproterone acetate due to risk of meningioma

Dear Healthcare Professional,

Bayer Limited, in agreement with the European Medicines Agency and the Health Products Regulatory Authority (HPRA) would like to inform you of the following:

Summary

- **The occurrence of meningiomas (single and multiple) has been reported in association with the use of cyproterone acetate, primarily at doses of 25 mg/day and above.**
- **The risk of meningioma increases with increasing cumulative doses.**
- **Use of cyproterone acetate is contraindicated in patients with a meningioma or a history of meningioma.**
- **Patients should be monitored for meningiomas in accordance with clinical practice.**
- **If a patient treated with cyproterone acetate is diagnosed with meningioma, treatment must be permanently stopped.**
- **For reduction of drive in sexual deviations in men, cyproterone acetate 100 mg can be used when other interventions are considered inappropriate.**
- **The use of cyproterone acetate for the following indication remains unchanged: inoperable prostate cancer**

Background on the safety concern

Therapeutic indications in men (100 mg) include antiandrogen treatment in inoperable carcinoma of the prostate and reduction of the sex drive in sexual deviations.

Meningioma is a rare tumour which forms from the meninges. Clinical signs and symptoms of meningioma may be unspecific and may include changes in vision, hearing loss or ringing in the ears, loss of smell, headaches that worsen with time, memory loss, seizures or weakness in extremities.



The association of high dose (50 mg/day) CPA with meningioma was first described in 2008 and the SmPC of CPA-containing products with a strength of 10 mg and above was updated with a contraindication of (a history) of meningioma and a warning regarding the risk of meningioma. Recently, results from a French epidemiological cohort study showed a cumulative dose-dependent association between cyproterone acetate and meningioma.¹ This study was based on data from the French Health insurance (CNAM) and included a population of 253,777 women using 50 - 100 mg cyproterone tablets. The incidence of meningioma treated with surgery or radiotherapy was compared between women exposed to high-dose cyproterone acetate (cumulative dose ≥ 3 g) and women who were slightly exposed to cyproterone acetate (cumulative dose < 3 g). A cumulative dose-response relationship was demonstrated.

Cumulative dose of cyproterone acetate	Incidence rate (in patient-years)	HR _{adj} (95% CI) ^a
Slightly exposed (<3 g)	4.5/100,000	Ref.
Exposed to ≥ 3 g	23.8/100,000	6.6 [4.0-11.1]
12 to 36 g	26/100,000	6.4 [3.6-11.5]
36 to 60g	54.4/100,000	11.3 [5.8-22.2]
more than 60 g	129.1/100,000	21.7 [10.8-43.5]

^a Adjusted based on age as a time-dependent variable and oestrogen at inclusion

A cumulative dose of 12 g for example can correspond with one year of treatment with 50 mg/day for 20 days each month.

In view of these data, treatment with cyproterone acetate 50 mg and 100 mg should be restricted to situations where alternative treatments or interventions are unavailable or considered inappropriate in all indications, except prostate carcinoma. Also, the lowest possible effective dose should be used.

Cyproterone acetate (1 and 2 mg) in combination with ethinylestradiol (EE)/estradiol valerate (EV) is indicated for the treatment of moderate to severe acne related to androgen-sensitivity (with or without seborrhoea) and/or hirsutism, in women of reproductive age, for the treatment of acne after topical therapy or systemic antibiotic treatments have failed and not in combination with other hormonal contraceptives. No new safety concern regarding a risk of meningioma associated to the use of low dose CPA/EE and CPA/EV products could be identified. However, as the risk of meningioma increases with increasing cumulative doses of cyproterone acetate, low dose combination products are now contraindicated in patients with meningioma or history of meningioma.



Call for reporting

Healthcare professionals are encouraged to report adverse events in patients taking CPA-containing products via HPRAs Pharmacovigilance, website: www.hpra.ie. Reports of suspected adverse reactions can also be made to Bayer Limited, contact details below.

Company contact point

If you have any questions, or if you require any further information, please contact the medical information service by email

Info.ireland@bayerhealthcare.com or phone +353 1 216 3300.

Yours faithfully,

A handwritten signature in black ink that reads "Tristan P. Cooper".

Dr Tristan P. Cooper
Medical Director
Bayer Ltd

List of literature references

Weill A et al. (2019 Jun). Exposition prolongée à de fortes doses d'acétate de cyprotérone et risque de méningiome chez la femme. Paris: ANSM.

https://www.anism.sante.fr/var/anism_site/storage/original/application/b632fbd0387cd9e80a8312469ed52d2a.pdf