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HPRA DRUG SAFETY
NEWSLETTER

86TH EDITION

In this Edition

Esmya 5mg Tablets (Ulipristal acetate) – important new warnings of serious liver injury and recommendations for liver monitoring

An EU-wide review of Esmya has been initiated following reports of serious liver injury in patients being treated with Esmya (5mg tablet). Esmya is an orally-active synthetic selective progesterone receptor modulator which is authorised for the pre-operative and intermittent treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age for treatment courses of up to three months each. A small number of cases of serious liver injury, including some cases of acute liver failure leading to transplantation, have been reported in patients being treated with Esmya within the EU. The Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) has accordingly recommended temporary measures for use of Esmya, as outlined below, to minimise potential risk to patients, whilst the more comprehensive review of the benefits and hepatic risks is ongoing.

A Direct Healthcare Professional Communication (DHPC) was circulated by the Marketing Authorisation Holder (MAH) following approval by the HPRA in in February 2018. Following the completion of the ongoing review, the HPRA, in conjunction with our European counterparts, will communicate further and provide updated guidance for patients and healthcare professionals. In the meantime, the following recommendations on use and monitoring requirements apply:

Advice to Healthcare Professionals

- Do not initiate Esmya in new patients or restart in patients who have completed a previous treatment course.
- Monitor liver function at least monthly in patients who are currently being treated with Esmya and repeat 2-4 weeks after stopping treatment.
- If any patient develops signs or symptoms consistent with liver injury, check transaminase levels immediately.
- Stop Esmya treatment if a patient develops transaminase levels greater than 2 times the upper limit of normal (ULN) and closely monitor them.
- Discuss the risk and symptoms of liver injury (nausea, vomiting, right hypochondrial pain, anorexia, asthenia, jaundice etc.) with patients and advise them to contact their doctor immediately if any symptoms are experienced.

  Please report any suspected adverse reactions associated with use of Esmya to the HPRA using the usual methods (www.hpra.ie).

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Key Message

While an EU wide review of new information on liver safety is ongoing, no new patients should be initiated on treatment with Esmya. Patients who have previously completed a treatment course with Esmya should not be re-initiated.

For patients who are currently on a treatment course with Esmya, liver function should be monitored at least monthly and again 2-4 weeks after treatment cessation.

If there is evidence of hepatic injury (transaminases >2 time ULN), treatment with Esmya should be stopped immediately and patients monitored closely.

Patients on Esmya treatment should be advised what to look out for and also to contact their doctor immediately if any signs or symptoms of hepatic injury develop.

Further information is available on www.hpra.ie and www.ema.europa.eu

Xofigo (radium-223 dichloride) – Contraindicated in combination with Zytiga (abiraterone acetate) and prednisone/prednisolone

The European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) has recommended a contraindication regarding use of Xofigo in combination with abiraterone acetatre (Zytiga) and prednisone/prednisolone. This recommendation follows the review of preliminary data from an ongoing clinical trial which shows an increased risk of death and fractures. In this study 34.7% of patients treated with the combination of Xofigo, Zytiga and prednisone/prednisolone died, compared with 28.2% of patients given placebo, Zytiga and prednisone/prednisolone. Fractures have also occurred more frequently with the Xofigo combination than the placebo combination (26% versus 8.1%).

Pending conclusion of the review and to allow a thorough assessment of the available data, this contraindication is being introduced to protect public health. Xofigo is currently approved for the treatment of men with castration-resistant prostate cancer, symptomatic bone metastases and no known visceral metastatic disease.

Information about this review and advising against use of Xofigo in combination with abiraterone and prednisone/prednisolone was previously provided in the HPRA Drug Safety Newsletter Edition 85 and in a Direct Healthcare Professional Communication (DHPC) issued by the Marketing Authorisation Holder (MAH) following approval by the HPRA.

Advice to Healthcare Professionals

- Use of Xofigo in combination with Zytiga (abiraterone acetate) and prednisone/prednisolone is now contraindicated.
- Any patients treated with this combination should have their treatment stopped and reviewed.
- The safety and efficacy of Xofigo in combination with second generation androgen receptor antagonists such as Xtandi (enzalutamide) have not been established.
- These medicines can continue to be used separately, in line with their approved Summary of Product Characteristics (SmPC).

The PRAC will further evaluate the data from this study as well as other available data to fully assess any further impacts on the authorised use of Xofigo.

Key Message

Preliminary data from an ongoing clinical trial indicates an increased death rate and fracture rate for patients receiving Xofigo in combination with abiraterone acetate (Zytiga) and prednisone/prednisolone versus those receiving placebo in combination with abiraterone acetate and prednisone/prednisolone.

Healthcare professionals are advised that the use of Xofigo in combination with abiraterone acetate and prednisone/prednisolone to treat patients with metastatic castration-resistant prostate cancer is now contraindicated while a full review is ongoing.

Further information is available on www.ema.europa.eu

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Mycophenolate – Updated contraceptive advice for male patients

Mycophenolate mofetil (and its active metabolite mycophenolic acid) is an immunosuppressive agent indicated in combination with ciclosporin and corticosteroids for the prophylaxis of acute transplant rejection in patients receiving allogeneic renal, cardiac or hepatic transplants. As highlighted in the HPRA Drug Safety Newsletter edition 72 in 2015, mycophenolate-containing medicines are teratogenic and genotoxic, known to cause miscarriage (45-49%) and congenital malformations (23-27%) when used in pregnant women and are therefore contraindicated in women of child-bearing potential, not using effective contraception. While the available clinical evidence does not indicate an increased risk of malformations or miscarriage in pregnancies where the father was taking mycophenolate-containing medicines, a risk cannot be fully excluded. As a precautionary measure for male patients, it is now recommended that male patients, or their female partners should use reliable contraception during treatment with mycophenolate-containing medicines and for at least 90 days after discontinuation.

Following a recent EU-wide review by the European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) of non-clinical and clinical data in relation to men fathering a child while being treated with mycophenolate-containing medicines, the recommendations based on the available evidence at that time have been updated, as outlined below.

Advice to Healthcare Professionals

Advice for Male Patients

- The available clinical evidence does not indicate an increased risk of malformations or miscarriage in pregnancies where the father was taking mycophenolate-containing medicines. However mycophenolate mofetil is genotoxic and therefore a risk cannot be fully excluded.
- It is recommended that male patients or their female partners should use reliable contraception during treatment with mycophenolate-containing medicines and for at least 90 days after discontinuing treatment.
- Prescribers should discuss with male patients planning to have children the implications of both immunosuppression and the effect of prescribed medications on the pregnancy.

Reminder of Existing Advice for Female Patients

- The risks and subsequent recommendations for female patients are unchanged. Mycophenolate-containing medicines remain contraindicated in women of childbearing potential who are not using reliable contraception and in pregnant women, unless there are no suitable alternatives to prevent transplant rejection.
- Women of child bearing potential should use two reliable forms of contraception simultaneously before beginning treatment; during therapy and for six weeks following discontinuation of therapy.
- A negative pregnancy test is required prior to commencing treatment with mycophenolate-containing medicines in order to exclude unintended pregnancy.
- Repeat pregnancy tests should be performed as clinically indicated if, for example, there are concerns about contraceptive failure or gaps in contraception.
- Patients should be instructed not to stop treatment but to consult their physician immediately should pregnancy occur.
- The product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) will be updated shortly and a Direct Healthcare Professional Communication (DHPC) has been circulated by the Marketing Authorisation Holder.
- Updated educational materials for healthcare professionals will be made available shortly.

Key Message

There is an increased risk of congenital malformations and spontaneous abortions associated with mycophenolate containing medicines in comparison with other immunosuppressive medicines.

Male patients taking mycophenolate-containing medicines or their partners should use reliable contraception during treatment and for 90 days after finishing treatment.

Women of child bearing potential should use at least one form of reliable contraception before starting treatment, during treatment and for six weeks after stopping treatment. Two forms of contraception are preferred.

Please report any suspected adverse reactions associated with mycophenolate-containing medicines to the HPRA via the usual methods (www.hpra.ie).

**Further details on Cellcept and Myfortic products are available on www.hpra.ie*

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Oral Retinoids – Outcome of EU review and updated warnings

The European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) has concluded a review of retinoid-containing medicinal products*. Following a review of the available data which included published literature and post-marketing reports of suspected adverse reactions, the PRAC has recommended updating the measures for pregnancy prevention and warnings on the possible risk of neuropsychiatric disorders such as depression and anxiety.

Advice to Healthcare Professionals

Teratogenicity

- Oral retinoids are known to be teratogenic and must not be used during pregnancy.
- The oral retinoids acitretinoin, alitretinoin and isotretinoin must be used in accordance with the conditions of a Pregnancy Prevention Plan (see below) for all women of child bearing potential.
- The updated educational materials, which are developed by the Marketing Authorisation Holder and approved by the HPRA, should be used to facilitate discussions with female patients prior to prescribing oral retinoids.
- As a precaution, topical retinoids are contraindicated in pregnancy and in women planning a pregnancy. The currently available data show that systemic exposure is negligible following topical application however a precautionary approach is advisable and therefore their use is contraindicated.
- A pregnancy prevention plan was not considered necessary for oral retinoids used to treat certain cancers (e.g. tretinoin) because of the circumstances for use in these indications, where current measures are considered appropriate for pregnancy prevention.

Neuropsychiatric disorders

- Depression, depression-aggravated anxiety and mood alterations have been reported rarely in patients treated with oral retinoids.
- From review of the available evidence, it has not been possible to identify a clear increase in the risk of psychiatric disorders in people who take oral retinoids compared to those who do not. However taking into account that patients with severe skin disorders are at an increased risk of psychiatric disorders, it is recommended that patients taking oral retinoids are advised of the possibility of experiencing changes in mood and behaviour and that they should speak to their doctor and a family member if this occurs.
- All patients treated with oral retinoids should be monitored for signs of depression and referred for appropriate treatment if necessary. Special attention should be paid to patients with a history of depression. A risk of psychiatric disorders with topical retinoids is considered unlikely following a review of the available data.

Pregnancy Prevention Programme for Oral Retinoids

A pregnancy prevention programme for oral retinoids has been in place for a number of years. Following the EU wide review, the programme will now be harmonised and streamlined to provide clear and concise information for both healthcare professionals and patients. The conditions of the pregnancy prevention programme require prescribers to ensure that every female patient understands that:

- Oral retinoids are highly likely to harm a baby exposed to them in utero and should not be taken during pregnancy.
- Use of oral retinoids indicated for skin conditions (i.e. acitretin, alitretinoin and isotretinoin) in female patients of childbearing potential should be in accordance with the Pregnancy Prevention Programme.
- Effective contraception must be used without interruption for at least one month before initiating therapy, throughout treatment, and for one month after stopping treatment.
- Regular follow up with the prescribing doctor is required, ideally monthly, along with regular pregnancy testing.
- If the patient becomes pregnant or thinks that she is pregnant, she should discontinue her medication immediately and consult her prescribing doctor immediately.

* Retinoid-containing medicinal products are available in oral and topical form and are used to treat conditions mainly those affecting the skin such as various forms of acne, severe chronic hand eczema unresponsive to corticosteroids, severe forms of psoriasis and keratinisation disorders. Tretinoin is indicated for the treatment of acute promyelocytic leukaemia (APL).

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Key Message

Oral retinoids are teratogenic and should not be used during pregnancy.

Oral retinoids should only be used in accordance with the conditions of a Pregnancy Prevention Programme for women of child bearing potential.

All patients taking oral retinoids should be advised of the risk of experiencing changes in mood and/or behaviour during treatment and should seek help if these symptoms are experienced. Patients with a history of depression are at increased risk.

A Direct Healthcare Professional Communication (DHPC) will be circulated by the MAH, following approval by the HPRA, to relevant healthcare professionals.

Please report any suspected adverse reactions associated with use of oral retinoids to the HPRA via the usual methods (www.hpra.ie).

**Further information on isotretinoin, acitretin, alitretinoin and tretinoin is available from www.hpra.ie and www.ema.europa.eu/ema*

Zinbryta (daclizumab beta) – EMA recommends immediate suspension and recall

The European Medicines Agency (EMA) has recommended the immediate suspension of the marketing authorisation for Zinbryta (daclizumab beta) following reports of serious inflammatory brain disorders worldwide, including encephalitis and meningoencephalitis, some of which resulted in a fatal outcome. A product recall from pharmacies and hospitals in Ireland is underway.

Advice to Healthcare Professionals

- Do not start any new patients on Zinbryta.
- Patients currently being treated with Zinbryta should be stopped and switched to alternative treatment as soon as possible.
- Patients whose treatment have been stopped should be monitored at least monthly, and more frequently as clinically indicated, for up to six months after the last dose of Zinbryta.

A risk of unpredictable and potentially fatal immune-mediated liver injury occurring in association with Zinbryta and for up to six months after stopping treatment was communicated previously via a Direct Healthcare Professional Communication, issued by the marketing authorisation holder (MAH) (following approval by the HPRA) in July and November 2017, and an article was included in the HPRA Drug Safety Newsletter Edition 85 at that time.

As the available evidence also indicates that Zinbryta could be linked to other immune-mediated disorders, such as blood dyscrasias, thyroiditis or glomerulonephritis, the EMA will complete its review and will publish the outcome of its final evaluation

It is estimated that over 8,000 patients have been treated with Zinbryta worldwide, with a very small number of patients treated in Ireland.

Key Message

The marketing authorisation for Zinbryta (daclizumab beta) has been suspended by the European Medicines Agency (EMA) with immediate effect.

A Direct Healthcare Professional Communication (DHPC) has been issued by the Marketing Authorisation Holder (MAH) following approval by the HPRA.

Further information on daclizumab beta (Zinbryta) is available from www.hpra.ie and www.ema.europa.eu

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

PRODUCT	SAFETY ISSUE
Esmya (ulipristal acetate)	Restrictions on the use of Esmya 5mg tablets and important new warnings of serious liver injury and recommendations for liver monitoring
Ocaliva (obeticholic acid)	Reinforced differential dosing recommendations for Ocaliva in PBC patients with moderate and severe hepatic impairment
Buccolam (midazolam)	Risk of inhalation/ingestion of tip cap of prefilled plastic syringes
Mycophenolate mofetil (MMF)/mycophenolic acid (MPA)	Amended recommendations for contraception
Zinbryta (daclizumab beta)	Marketing authorisation suspended in the European Union

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

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