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HPRA DRUG SAFETY NEWSLETTER

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In this Edition

Xofigo (radium-223 dichloride) – New restrictions for use

The European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (*PRAC*) has now concluded its review of Xofigo used in the treatment of prostate cancer. Information about this review and the temporary measures introduced to protect public health (advising against use of Xofigo in combination with abiraterone and prednisone/prednisolone) was previously provided in the HPRA Drug Safety Newsletter *Edition 85* and *Edition 86* and in a Direct Healthcare Professional Communication (DHPC) issued by the Marketing Authorisation Holder (MAH) following approval by the HPRA in late 2017/early 2018. The concluded review has now recommended further restrictions on the use of Xofigo. These are based on an association between the use of Xofigo and an increased risk of fractures and the observation of a possible increased risk of death in a clinical trial investigating Xofigo in combination with abiraterone acetate and prednisone/prednisolone in patients with asymptomatic or mildly asymptomatic castration-resistant prostate cancer.

This randomised, double blind, placebo controlled phase III trial (ERA-223), showed that there was an increased incidence of fractures (28.6% vs 11.4%), a possible reduction in median overall survival (30.7 months vs 33.3 months, HR 1.195, 95% confidence interval (CI) 0.950 - 1.505, p=0.13) and a possible increased risk of radiological non-bone progression (HR 1.376 [95% CIs 0.972, 1.948], p=0.07) among patients receiving Xofigo in combination with abiraterone acetate plus prednisone/prednisolone (n=401) compared to patients receiving placebo in combination with abiraterone acetate plus prednisone/prednisolone (n=405). An increased fracture risk was found particularly in patients with a medical history of osteoporosis and in patients with fewer than six bone metastases.

In another randomised, double blind, placebo controlled phase III trial (ALSYMPCA), a statistically significant overall survival benefit of treatment with Xofigo could not be demonstrated in the subgroups of patients with fewer than six metastases (HR for radium-223 to placebo 0.901; 95% CI [0.553 - 1.466], p=0.674) or a baseline total alkaline phosphatase (ALP) <220 U/L (HR 0.823 95% CI 0.633-1.068, p=0.142), indicating that efficacy may be diminished in patients with a low level of osteoblastic activity from their bone metastases.

Arising from an evaluation of these data, the following restrictions and risk minimisation measures will apply to the use of Xofigo:

Advice to Healthcare Professionals

- Xofigo is restricted to use as monotherapy or in combination with luteinising hormone releasing hormone (LHRH) analogue for the treatment of adult patients with metastatic castration-resistant prostate cancer (mCRPC), symptomatic bone metastases and no known visceral metastases, in progression after at least two prior lines of systemic therapy for mCRPC (other than LHRH analogues), or ineligible for any available systemic mCRPC treatment.
- As per previous communications, the use of Xofigo in combination with Zytiga (abiraterone acetate) and prednisone/prednisolone remains contraindicated. In addition, Xofigo should not be initiated in the first five days following the last dose of Zytiga (abiraterone acetate) and prednisone/prednisolone. Subsequent cancer treatments should not be initiated for at least 30 days after the last administration of Xofigo.
- Xofigo is not recommended in patients with a low level of osteoblastic bone metastases and in patients with only asymptomatic bone metastases. It is also not recommended in combination with other systemic active cancer therapies other than LHRH analogues.

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- Xofigo should only be used in patients with mildly symptomatic bone metastases if the benefits are expected to outweigh the known risks, considering that high osteoblastic activity is likely to be required for treatment benefit.
- Prior to initiating therapy with Xofigo, an assessment of the patient's bone status (e.g. by scintigraphy, bone mineral density measurement) and risk of fractures (e.g. osteoporosis, fewer than six bone metastases, medication increasing fracture risk, low body mass index) should be performed. Monitoring should continue for at least 24 months. If patients are at a high risk of suffering a fracture, then treatment should only be started if the benefits are expected to outweigh the known risks. Concurrent use of bisphosphonates or denosumab has been found to reduce the incidence of fractures and such preventative measures should be considered before starting or resuming treatment with Xofigo.
- The Marketing Authorisation Holder (MAH) (i.e. the licence holder) for Xofigo has been requested to conduct studies and a trial in order to further characterise the safety and efficacy of Xofigo and further understand the mechanisms responsible for the increased risk of fracture and possible risk of increased mortality.
- The approved product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) will be updated with this information shortly and a Direct Healthcare Professional Communication (DHPC) has been circulated by the MAH.

Key Message

An increase in the incidence of deaths and fractures in patients with chemotherapy-naïve metastatic castration-resistant prostate cancer receiving radium-223 dichloride was observed in a trial where Xofigo was used in combination with abiraterone acetate (Zytiga) and prednisone/prednisolone. The combination used in this study is now contraindicated.

The use of Xofigo is now restricted to monotherapy or in combination with LHRH analogue for the treatment of adult patients with mCRPC, symptomatic bone metastases, and no known visceral metastases, who are in progression after at least two prior lines of systemic therapy for mCRPC (other than LHRH analogue), or ineligible for any available systemic mCRPC treatment.

Xofigo is not recommended in patients with a low level of osteoblastic bone metastases and in patients with only asymptomatic bone metastases. It is also not recommended in combination with systemic cancer therapies other than LHRH analogues.

In mildly symptomatic patients, the benefit of treatment should be carefully assessed against its risks, considering that high osteoblastic activity is likely to be required for treatment benefit.

Report any suspected adverse reaction to the HPRA via the usual methods (www.hpra.ie).

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

Varenicline (Champix) – Product Information Update – Reports of Transient Loss of Consciousness

Varenicline (Champix) is authorised for use throughout the EU for the treatment of smoking cessation in adults. Having considered the available evidence from reports of adverse reactions and in the available literature with regards the risk of loss of consciousness, following a signal, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has recommended that the product information for varenicline should be updated regarding the risk of transient loss of consciousness.

The review considered that an association between varenicline and loss of consciousness could not be ruled out, with the association plausible biologically, in that the nicotinic receptors that varenicline is a partial agonist of are known to be involved in both excitatory and inhibitory neurotransmission. Therefore varenicline could potentially stimulate the receptors to release either one. Furthermore dose-dependent behavioural effects were observed in data from non-clinical studies.

The product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) is being updated to reflect the risk of transient loss of consciousness. Sections 4.7 (Effects on ability to drive and use machines) and 4.8 (Undesirable effects) of the SmPC will include this updated information, with this information reflected in sections 2 and 4 of the PL. Patients taking varenicline should be instructed to seek medical attention if they experience signs and symptoms of loss of consciousness.

Key Message

Reports of transient loss of consciousness in association with the smoking cessation medication varenicline (Champix) has resulted in its product information (SmPC and PL) being updated in the coming months.

Report any suspected adverse reactions to the HPRA via the usual methods (www.hpra.ie).

Further information on varenicline (Champix) is available on www.hpra.ie and www.ema.europa.eu

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Oral Methotrexate – Updates to Product Information

Oral methotrexate* is indicated for the treatment of active rheumatoid arthritis, adult psoriasis and in a number of oncological indications, with differing treatment regimens for the respective indications, with a once weekly dosing regimen for non-oncological indications (see individual Summaries of Product Characteristics (SmPCs) available on www.hpra.ie).

Methotrexate is a known teratogen, with use contraindicated in pregnancy and lactation. Following a recent review of the available literature at EU level, the product information (Summary of Product Characteristics (SmPC) and package leaflet (PL)) for oral methotrexate is currently being updated to better reflect current scientific knowledge and to accurately differentiate between the clear requirements for risk minimisation in exposed women of child-bearing potential and those in men as a precautionary measure to exclude a potential residual risk.

Women must not become pregnant while taking methotrexate and effective contraception should be used throughout treatment and for at least six months after treatment cessation. Prior to therapy commencing, women of child bearing potential should be fully informed of the risks of malformations associated with methotrexate and pregnancy should always be excluded with certainty, e.g. a pregnancy test. Women should be counselled appropriately regarding pregnancy prevention and planning. If pregnancy does occur during treatment or in the 6 months after treatment finishes, medical advice should be given regarding the risk of harmful effects. Since it is not known if methotrexate is present in semen and as a precautionary measure, it is advised that male patients taking methotrexate, and their female partners, are recommended to use reliable contraception during treatment with methotrexate and for six months after treatment finishes.

The SmPC will also outline that methotrexate effects on fertility appear to be reversible after discontinuation of therapy in most cases. The product information will also be updated to reflect the most up to date information on the risks associated with becoming pregnant while taking methotrexate including the need for patient counselling on pregnancy prevention, information about observed malformations and medical advice in the event of pregnancy.

The Health Products Regulatory Authority (HPRA) would like to take this opportunity to remind healthcare professionals of the need for vigilance when prescribing, dispensing and/or counselling patients in relation to methotrexate. For rheumatology and dermatology indications, methotrexate should be administered as a **once weekly dose only**. Patients and/or carers should be informed of the risks associated with an overdose and of the importance of adhering to once weekly dosing. For these indications, it is also suggested that the day of intake should be specified on the prescription and dispensing label. Medication errors resulting in inadvertent overdose due to daily intake of a weekly dose have been reported in Ireland and elsewhere. These reports have included cases of serious adverse reactions, some of which resulted in a fatal outcome, particularly due to the haematological toxicity of methotrexate, but also as a result of pulmonary toxicity.

Key Message

The product information (SmPC and PL) for oral methotrexate is being updated to reflect current knowledge in relation to use in women of child bearing potential and also use in men.

Patients and/or carers should be informed of the risk of overdose due to erroneous daily intake of the weekly dose and should be advised to contact a healthcare professional promptly, if they consider an error in dosing has occurred.

Please report any suspected adverse reactions to the HPRA via the usual methods (www.hpra.ie).

**Further details on methotrexate products are available on www.hpra.ie*

Adverse Reaction Reporting – Update

The HPRA continues to place great emphasis on encouraging and promoting the submission of adverse reaction reports associated with the use of medicines from its stakeholders. These reports are important to signal potential safety issues from medicines in use and ultimately to assist the HPRA in monitoring the safety of medicines on the Irish market.

During 2017, the HPRA received a total of 4,402 new adverse reaction reports occurring in Ireland associated with the use of human medicines. This represents a 35% increase in overall reporting rates compared with 2016 as a result of changes to reporting requirements across the EU, for marketing authorisation holders (MAH) and national competent authorities (NCA), which came into effect on 22nd November 2017.

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In the context of the changed reporting requirements, some 76% of all adverse reaction reports received by the HPRA in 2017 were notified by MAHs. The remaining reports were received directly from patients/consumers and healthcare professionals including pharmacists, doctors and nurses. The online reporting system, available to healthcare professionals and patients / consumers, accounted for 47% of reports submitted directly to the HPRA throughout the year and the increasing use of this reporting option is greatly welcomed.

Medicines subject to additional monitoring accounted for 26% of the reports submitted during 2017. Such medicines are identifiable by a black inverted triangle which is included on the accompanying package leaflet (PL) and the summary of product characteristics (SmPC). Healthcare professionals and patients are particularly encouraged and reminded to report all adverse reactions associated with the use of these medicines and the HPRA would like to acknowledge the submission of reports for these medicines.

Information collected through spontaneous adverse reaction reporting systems is an important method of monitoring medicines safety in normal clinical practice, by increasing knowledge about known adverse reactions and also by acting as an early warning system for the identification of previously unrecognised adverse reactions. Such information is one of the tools used by the HPRA in its ongoing safety evaluation of marketed medicines and contributes to the identification of medicines where a change in their authorisation status is required such as the addition of warnings and precautions for use, restriction in usage or rarely withdrawal from the marketplace.

There are several options in place for reporting suspected adverse reactions to the HPRA, as follows:

- By following the links ('Report an Issue' tab) to the online reporting options accessible from the HPRA website homepage (www.hpra.ie);
- Using the downloadable report form also accessible for the HPRA website, which may be completed manually and submitted to the HPRA via 'freepost';
- Using the traditional 'yellow card' report, which also utilises a freepost system. 'Yellow cards' are available from the HPRA Pharmacovigilance department on request;
- By telephone to the HPRA Pharmacovigilance section (01 676 4971).

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

PRODUCT	SAFETY ISSUE
Esmya (ulipristal acetate)	New contraindication, requirements for liver monitoring and restricted indication for Esmya
Zinbryta (Daclizumab beta)	Cases of immune-mediated encephalitis
Xofigo (radium 223 dichloride)	New restrictions on use due to increased risk of fracture and trend for increased mortality
Hydroxyethylstarch (HES) Solutions	New measures to reinforce existing restrictions due to increased risk of renal dysfunction and mortality in critically ill or septic patients
Spinraza (nusinersen)	Hydrocephalus not related to meningitis or bleeding reported
Keytruda (pembrolizumab)	Restriction of indication for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin containing chemotherapy
Tecentriq (atezolizumab)	Restriction of indication for the treatment of locally advanced or metastatic urothelial carcinoma in adults who are not eligible for cisplatin-containing chemotherapy
Darunavir/cobicistat	Increased risk of treatment failure & increased risk of mother to child transmission of HIV infection due to low exposure values during the second and third trimesters of pregnancy.

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

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