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HPRA DRUG SAFETY NEWSLETTER

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In this Edition

Reminder - Oral methotrexate and risk of unintentional overdose due to medication errors

The Health Products Regulatory Authority (HPRA) would like to remind healthcare professionals of the need for vigilance when prescribing, dispensing and/or counselling patients in relation to methotrexate.

Oral methotrexate* is indicated in the treatment of active rheumatoid arthritis, adult psoriasis and in a number of oncological indications, with differing dosage regimens for the respective indications (Summary of Product Characteristics (SmPCs) available on www.hpra.ie).

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. Reports of medication errors have occurred in a range of areas, including prescribing and administration errors (mainly for hospitalised patients), to errors in self-administration (by patients at home, either inadvertently, or by misunderstanding the medication schedule). The HPRA would like to remind healthcare professionals of the need for vigilance when prescribing, dispensing, administering and counselling patients and/or carers in relation to methotrexate, particularly following initiation of treatment, a change in the dose, or in circumstances where therapy is re-started.

The HPRA previously highlighted the risk of inadvertent overdose due to medication errors associated with methotrexate and the recommendations to reduce *(HPRA Drug Safety Newsletter Edition 47)* this risk following an EU review of this issue completed in 2012. The product information (SmPC and Package Leaflet (PL)) was updated at that time to emphasise the need for adherence to once weekly dosing and to strengthen existing warnings regarding the risk of overdose. The Pharmaceutical Society of Ireland (PSI) also updated and re-issued its *guidance* to support safe dispensing of methotrexate around that time.

Advice to Healthcare Professionals

- Cases of overdose, sometimes fatal, due to erroneous daily instead of weekly intake of methotrexate have been reported.
- Methotrexate, for dermatology and rheumatology indications, should be taken as a single once weekly dose.
- Healthcare professionals should ensure that the patient and/or their carer understand the prescribed therapy, including the dose and frequency, with any treatment changes highlighted. Great care should be taken to give and repeat clear instructions on dosage.
- Patients and/or carers should be encouraged to read the Package Leaflet (PL) provided with their methotrexate and to discuss any concerns with a relevant healthcare professional.
- Patients and/or carers should be informed of the potential risks of serious adverse reactions in the case of overdose and of the signs and symptoms of toxicity.
- Any adverse reactions suspected to be related to a medication error with methotrexate should be notified to the HPRA in the usual way.

Key Message

- Methotrexate for oral use for rheumatology and dermatology indications should be taken once a week only.
- 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.

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

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Tecfidera (dimethyl fumarate) – New measures to minimise the risk of Progressive Multifocal Leukoencephalopathy (PML)

Following an EU review, the European Medicines Agency (EMA) recently advised that Healthcare Professionals and patients should be informed of new measures regarding enhanced monitoring surrounding stopping treatment to further minimise the risk of progressive multifocal leukoencephalopathy (PML) associated with Tecfidera (dimethyl fumarate). Tecfidera is authorised for use across the EU for treatment of adult patients with relapsing remitting multiple sclerosis.

Lymphopenia is a known and common side effect with Tecfidera. Three unconfounded cases of PML have occurred so far with Tecfidera in the setting of prolonged (over 6 months) severe lymphopenia. PML is an opportunistic infection caused by John-Cunningham (JC) virus, which may result in severe disability or even be fatal.

Advice to Healthcare Professionals

- Prior to initiating treatment with Tecfidera, a complete blood count including a lymphocyte count should be performed and a baseline MRI scan should be available (usually within 3 months) as a reference. After starting therapy, complete blood counts including lymphocytes should be performed every 3 months.
- If during treatment with Tecfidera the lymphocyte count drops below 0.5x109/L for more than 6 months, the benefit-risk of continued treatment with Tecfidera should be re-considered in the context of other therapeutic options available. Clinical factors and evaluation of any laboratory and imaging investigations could be included as part of this re-consideration. If Tecfidera is discontinued, the lymphocyte count should be closely monitored until recovery.
- PML can only occur in the presence of JC virus infection. If an anti-JC virus antibody test is done, it should be considered that the influence of lymphopenia on the accuracy of such tests has not been studied in patients treated with Tecfidera. Doctors should also note that a negative antibody test (in the presence of normal lymphocyte counts) does not preclude the possibility of subsequent JC virus infection.
- During treatment with Tecfidera, the need for further MRI scans should be considered in accordance with national and local recommendations. MRI imaging may be considered as part of increased vigilance in patients considered at increased risk of PML. In case of clinical suspicion of PML, MRI should be performed immediately for diagnostic purposes.
- If therapy is continued in patients with severe prolonged lymphopenia, these patients should be considered at increased risk for PML and should be monitored closely for signs and symptoms of new neurological dysfunction (e.g. motor dysfunction, cognitive or psychiatric symptoms).
- In case PML is suspected, treatment with Tecfidera should be withheld immediately and further evaluations performed.
- No studies have been performed evaluating the efficacy and safety of Tecfidera when switching patients from other disease-modifying therapies to Tecfidera. The contribution of prior immunosuppressive therapy to the development of PML in patients treated with Tecfidera is unknown. When switching patients from other disease-modifying therapy to Tecfidera, the half-life and mode of action of the other therapy must be considered in order to avoid an additive immune effect whilst at the same time reducing the risk of disease reactivation.

Key Message

- Patients should have complete blood counts, including lymphocytes, performed before initiating Tecfidera and then every three months. A baseline reference MRI should be available (usually within 3 months) prior to initiation and patients/carers counselled on the risk of PML.
- Consider interrupting Tecfidera in patients with lymphocyte counts below 0.5x109/L persisting for more than 6 months (i.e. severe prolonged lymphopenia) due to a possible increased risk of PML. Where treatment is discontinued, these patients should be monitored until lymphocytes levels return to normal.
- If treatment is continued in patients with severe prolonged lymphopenia, enhanced vigilance for PML is recommended including reminding patients/carers of the risk, monitoring for signs and symptoms or appearance of new neurological dysfunction (e.g. motor dysfunction, cognitive or psychiatric symptoms) along with considering the need for further MRI imaging as part of increased vigilance for PML, in accordance with national and local recommendations.
- If PML is suspected, stop treatment with Tecfidera immediately and investigate appropriately.
- A Direct Healthcare Professional Communication (DHPC) has been circulated by the Marketing Authorisation Holder (MAH) to the relevant healthcare professionals and is available from the HPRA website (www.hpra.ie). The product information (SmPC and PL) will be updated in line with these recommendations.
- All suspected adverse reactions associated with Tecfidera should be reported to the HPRA (www.hpra.ie).

** Further details on Tecfidera are available at www.hpra.ie and http://www.ema.europa.eu/ema/*

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Related Recommendations Apply to other fumarate medicines:

The EMA also reviewed cases of PML which occurred with two other fumarate-containing medicines, Fumaderm and Psorinovo, used to treat psoriasis. Related recommendations have been issued. Fumaderm is a nationally-authorised medicine, marketed in Germany to treat psoriasis; it contains the active substances dimethyl fumarate and ethyl hydrogen fumarate salts. Psorinovo is available as a compounded fumarate preparation in the Netherlands. Neither of these products are authorised for use in Ireland. Further information on the restrictions and recommendations concerning this product are available on the EMA website at http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2015/10/news_detail_002423.jsp&mid=WC0b01ac058004d5c1

EU Review concludes that evidence does not support that HPV vaccines cause CRPS or POTS

The European Medicines Agency (EMA) has recently published the outcome of a detailed scientific review of the evidence surrounding reports of two syndromes, complex regional pain syndrome (CRPS) and postural orthostatic tachycardia syndrome (POTS) in individuals given HPV vaccines.

The EMA's Pharmacovigilance Risk Assessment Committee (PRAC) concluded by consensus that the evidence did not support a causal link between either CRPS or POTS and HPV vaccines.

As part of the system for monitoring the safety of medicinal products, the Health Products Regulatory Authority (HPRA) has a spontaneous reporting system by which patients/consumers and healthcare professionals can report suspected adverse reactions through various reporting options. All reports of suspected adverse reactions received by the HPRA are anonymised before being routinely transmitted to the EMA's adverse reaction database (known as EudraVigilance) for inclusion in global signal detection activities.

The PRAC thoroughly reviewed all available data and analyses regarding CRPS and POTS from clinical trials and post-marketing safety data. It also took account of the scientific literature, data from Eudravigilance (the EMAs adverse reaction data base) and studies submitted by Member States including Denmark, as well as information from Japan. In addition, detailed information submitted voluntarily by the public and patient groups, including those from Ireland was considered as part of the review. The PRAC also sought advice from a group of experts in this field.

Symptoms of CRPS and POTS may overlap with other conditions, making diagnosis difficult in both the general population and vaccinated individuals. The review found no evidence that the overall rates of these syndromes in vaccinated individuals were different from expected rates in these age groups, even taking into account possible underreporting. The PRAC noted that some symptoms of these syndromes may overlap with chronic fatigue syndrome (CFS, also known as myalgic encephalomyelitis or ME). Many of the reports considered in the review have features of CFS and some patients had diagnoses of both POTS and CFS. Results of a large study that showed no link between HPV vaccine and CFS were therefore particularly relevant.

The PRAC concluded that there was no reason to recommend changes to the way the vaccines are used or to amend the current product information. The review recognised that more than 80 million girls and women worldwide have now received these vaccines and in some European countries they have been given to 90% of the age group recommended for vaccination. Use of these vaccines is expected to prevent many cases of cervical cancer (cancer of the neck of the womb, which is responsible for tens of thousands of deaths in Europe each year) and various other cancers and conditions caused by HPV.

The PRAC's recommendations were endorsed by consensus by the Committee for Medicinal Products for Human Use (CHMP). The CHMP' s position will now be passed to the European Commission for a final, legally binding, decision which will be applicable in all Member States.

The HPRA will, as with all medicines, continue to carefully monitor the safety of these vaccines.

http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2015/11/news_detail_002436.jsp&mid=WC0b01ac058004d5c1

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

PRODUCT	SAFETY ISSUE
CellCept (mycophenolate mofetil)	Serious risk of teratogenicity-important new pregnancy prevention advice for women and men.
Reminyl (galantamine hydrobromide)	New warning on the risk of serious skin reactions, Stevens-Johnson syndrome and acute generalised exanthematous pustulosis.
Xalkori (crizotinib)	Inclusion of a new warning regarding cardiac failure.
Tecfidera (dimethyl fumarate)	New measures to minimise the risk of PML – enhanced monitoring and stopping rules.

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

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