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Montelukast – Reminder of risk of neuropsychiatric reactions and product information update

The European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) recently completed a periodic review of the available safety data in association with the orally active leukotriene reception antagonist, montelukast*.

Montelukast is indicated for use in the prophylaxis and treatment of asthmatic conditions and neuropsychiatric reactions including nightmares, insomnia, somnambulism, anxiety, agitation aggressive behaviour or hostility, depression and psychomotor hyperactivity are known to occur, albeit, infrequently in association with its use. This information is described in the currently approved product information (Section 4.8 of Summary of Product Characteristics (SmPC)) and healthcare professionals are advised to be alert for the occurrence of neuropsychiatric reactions occurring amongst patients treated with montelukast and to communicate this risk to patients and carers.

The recently completed review considered cases of dysphemia which have been reported in association with montelukast. The majority of these cases involved the paediatric population, especially young children less than five years of age. Based on review of this data, an association between montelukast and dysphemia as well as other closely related speech disorders cannot be excluded.

Advice to Healthcare Professionals

- Healthcare professionals are reminded of the risk of neuropsychiatric reactions associated with montelukast, and should make patients/carers aware of the possibility of experiencing these symptoms.
- Patients/carers should be advised to notify their healthcare professional immediately if such symptoms are experienced.
- Prescribers should evaluate the risks and benefits of continuing treatment if such symptoms occur.
- A general warning will be added to the product information (SmPC and Package Leaflet (PL)), as a risk minimisation measure, to further increase the understanding and awareness related to the occurrence of neuropsychiatric events, which may occur during treatment with montelukast.

Key Message

Montelukast is known to be associated with neuropsychiatric reactions and these are described in the currently approved product information.

Healthcare professionals and patients should be alert for the occurrence of neuropsychiatric reactions with montelukast.

The product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) for montelukast will be amended shortly to update the existing warnings regarding the risk of neuropsychiatric reactions.

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

* *Products currently authorised include Singulair and montelukast. Further details are available at www.hpra.ie*

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

Modafinil-containing medicines – potential risk of congenital malformations when administered during pregnancy

The European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) recently completed a review of the available data regarding the risk of congenital malformations in the offspring of women treated with modafinil* during pregnancy.

Modafinil is indicated in adults for the treatment of excessive sleepiness associated with narcolepsy with or without cataplexy.

Reports of major congenital malformations including congenital heart defects, hypospadias and orofacial clefts for which a causal relationship with modafinil was considered possible have been received from the Nuvigil® and Provigil® registry, in addition to reports from other spontaneous sources.

The Nuvigil® and Provigil® registry, a prospective, observational study in the United States, was established to characterise the pregnancy and foetal outcomes associated with modafinil exposure from six weeks prior to conception and/or during pregnancy (NCT01792583). Major birth defects are the primary endpoint of the registry and major structural and functional birth defects identified in the perinatal period through 12 months of life are collected and classified. The Pregnancy Registry Advisory Committee (RAC) adjudicates cases within the registry and provides annual reports.

Interim data ascertained from the 2018 Annual Registry report revealed that the rate of major congenital malformations was approximately 15%, compared to 3%[1] in the general population. Therefore, modafinal should not be used in women who are pregnant and should not be used in women who may become pregnant unless they are using effective contraception.

Advice to Healthcare Professionals

- Modafinil should not be used during pregnancy.
- Women of childbearing potential must use effective contraception during, and for 2 months after stopping, treatment with modafinil.
- Healthcare Professionals should ensure that all female patients of childbearing potential are informed of and fully understand the following:
  - The potential risk to a foetus associated with modafinil use during pregnancy.
  - That modafinil should not be used during pregnancy.
  - The need to use effective contraception during treatment with and for 2 months after stopping modafinil. As modafinil may reduce the effectiveness of oral contraception, alternative or concomitant methods of contraception are required.
  - The need to discuss other treatment options with their doctor if planning a pregnancy before stopping contraception.
- Non-pharmacological treatment options including behaviour modifying measures, sleep hygiene, and scheduled daytime naps should be preferred during pregnancy.

Key Message

Based on post-marketing reports received as part of a pregnancy registry conducted in the US, in addition to reports from other spontaneous sources, the use of modafinil during pregnancy is suspected to cause congenital malformations.

Modafinil should not be used in women who are pregnant and should not be used in women of childbearing potential unless they are using effective contraception.

A Direct Healthcare Professional Communication (DHPC) was circulated by MAHs for formulations of modafinil (following approval by the HPRA) in June 2019 and is available from the HPRA website.

The product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) for modafinil will be amended shortly to include an updated warning reflecting the current understanding of the risk of congenital malformations in the offspring of women treated with modafinil during pregnancy.

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

* *Products currently authorised in Ireland include Modafinil, Prosentio and Provigil. Further details are available at www.hpra.ie.*

Reference

1. *Canfield MA, Honein MA, Yuskiv N, et al. National estimates and race/ethnic-specific variation of selected birth defects in the United States, 1999–2001. Birth Defects Research (Part A) 2006; 76:747–56*

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

RoActemra® (tocilizumab) – rare risk of serious hepatic injury including acute liver failure requiring transplantation

Tocilizumab* is an interleukin inhibitor indicated for the treatment of:

- rheumatoid arthritis (RA),
- giant cell arteritis (GCA) in adult patients (subcutaneous formulation only),
- polyarticular juvenile idiopathic arthritis (pJIA) in patients 2 years of age and older
- systemic juvenile idiopathic arthritis (sJIA), and
- chimeric antigen receptor (CAR) T-cell-induced severe or life-threatening cytokine release syndrome (CRS) in patients 2 years of age and older (intravenous formulation only).

Tocilizumab is known to cause transient or intermittent mild to moderate elevation of hepatic transaminases, with increased frequency when used in combination with potentially hepatotoxic drugs (e.g. methotrexate).

A recent cumulative review of data from clinical trials, non-interventional studies, spontaneous reports, and the published literature identified 8 cases of tocilizumab-related, drug-induced liver injury worldwide, including acute liver failure, hepatitis, and jaundice. These events occurred between 2 weeks to more than 5 years after initiation of tocilizumab with median latency of 98 days. Two cases of acute liver failure required liver transplantation. Based on data from clinical trials, events of serious liver injury are considered to be rare and the benefit-risk profile of tocilizumab in the approved indications remains favourable.

In RA, GCA, pJIA and sJIA patients, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) should be monitored every 4 to 8 weeks for the first 6 months of treatment, followed by every 12 weeks thereafter. The currently approved prescribing information does not recommend treatment with tocilizumab in patients with elevated ALT or AST above 5-times upper limit of normal (ULN). Caution should continue to be exercised when considering initiation of tocilizumab treatment in patients with ALT or AST above 1.5-times ULN.

Recommended dose modifications (reduction, interruption or discontinuation) of tocilizumab due to liver enzyme abnormalities remain unchanged and healthcare professionals are reminded to refer to the guidance in the approved product information.

Please note that these updates do not apply to the indication for treatment of cytokine release syndrome (CRS).

Advice to Healthcare Professionals

- Serious cases of drug-induced liver injury, including acute liver failure, hepatitis and jaundice, in some cases requiring liver transplantation, have been observed in patients treated with tocilizumab. The frequency of serious hepatotoxicity is considered rare.
- Advise patients to immediately seek medical help if they experience signs and symptoms of hepatic injury.
- ALT and AST should be monitored every 4 to 8 weeks for the first 6 months of treatment, followed by every 12 weeks thereafter in patients with rheumatological indications.
- Caution should be exercised when considering treatment initiation in patients with ALT or AST higher than 1.5-times ULN. Treatment is not recommended in patients with ALT or AST higher than 5-times ULN.
- If liver enzyme abnormalities are identified, dose modifications (reduction, interruption or discontinuation) of tocilizumab may be necessary. The recommended dose modifications remain unchanged (see guidance in the approved product information).
- Educational Materials that include a healthcare professional guide and dosing guide as well as a patient alert card and patient guide are available from the HPRA website (www.hpra.ie).

Key Message

Serious cases of drug-induced liver injury, including acute liver failure, hepatitis and jaundice, in some cases requiring liver transplantation, have been observed in patients treated with tocilizumab.

Patients should be advised to immediately seek medical help if they experience signs and symptoms of hepatic injury.

Caution should be exercised when considering treatment initiation in patients with ALT or AST higher than 1.5-times ULN. ALT and AST should be monitored every 4 to 8 weeks for the first 6 months of treatment, followed by every 12 weeks thereafter.

A Direct Healthcare Professional Communication (DHPC) was circulated by the MAH (following approval by the HPRA) in June 2019 and is available from the HPRA website.

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

* *The product currently authorised is RoActemra®. Further details are available at www.hpra.ie.*

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

Febuxostat – Increased risk of cardiovascular death and all-cause mortality in patients treated with febuxostat in the CARES study

Febuxostat* is a non-purine selective inhibitor of xanthine oxidase and at a dose of 80mg and 120mg, is indicated for treatment of chronic hyperuricaemia in conditions where urate deposition has already occurred. Furthermore, febuxostat 120mg is indicated for the prevention and treatment of hyperuricaemia in adult patients undergoing chemotherapy for haematological malignancies at intermediate to high risk of tumour lysis syndrome (TLS).

Treatment with febuxostat should be avoided in patients with pre-existing major cardiovascular disease (for example, myocardial infarction, stroke or unstable angina) unless no other treatment options are appropriate. Findings from a phase IV clinical study (the CARES study) in patients with gout and a history of major cardiovascular disease show a higher risk for cardiovascular-related death and for all-cause mortality in patients assigned to Febuxostat than in those assigned to allopurinol.

The CARES study

The phase IV CARES (Cardiovascular safety of febuxostat and allopurinol in patients with gout and cardiovascular comorbidities) study was a multicentre, randomised, double-blind, non-inferiority trial that recruited patients with gout and a history of major cardiovascular disease from the USA, Canada and Mexico[1].

The primary endpoint in the study was time to first occurrence of major adverse cardiovascular events (MACE), a composite of non-fatal myocardial infarction, non-fatal stroke, cardiovascular death and unstable angina with urgent coronary revascularisation. The endpoints were analysed according to the intention-to-treat (ITT) analysis including all subjects who were randomized and received at least one dose of double-blind study medication.

Overall 56.6% of patients prematurely discontinued trial treatment and 45% of patients did not complete all trial visits. In total, 6,190 patients were followed for a median of 32 months and the median duration of exposure was 728 days for patients in febuxostat group (n=3,098) and 719 days in allopurinol group (n=3,092).

The primary MACE endpoint occurred at similar rates in the febuxostat and allopurinol treatment groups (10.8% versus 10.4% of patients, respectively; hazard ratio 1.03, 95% confidence interval [CI] 0.87–1.23).

In the analysis of the individual components of MACE (secondary endpoint), the incidence of cardiovascular deaths was significantly higher in the group assigned to febuxostat than in the group assigned to allopurinol (4.3% versus 3.2%, respectively; hazard ratio 1.34, 95% CI 1.03–1.73). The rate of all-cause mortality was also higher in patients assigned to febuxostat than in those assigned to allopurinol (7.8% versus 6.4% respectively; hazard ratio 1.22, 95% CI 1.01–1.47), which was mainly driven by the higher rate of cardiovascular deaths in the febuxostat group. For other findings of the trial[1].

In Europe, the phase IV FAST (Febuxostat vs Allopurinol Streamlined Trial) study is evaluating the cardiovascular safety of Febuxostat and allopurinol in patients with chronic symptomatic hyperuricaemia and at least one additional CV risk factor. The study is currently ongoing and results are expected in 2020.

Advice to Healthcare Professionals

- Febuxostat is recommended for chronic hyperuricaemia or gout when allopurinol is not tolerated or contraindicated.
- Patients with pre-existing major cardiovascular disease, should not be treated with Febuxostat, unless no other treatment options are appropriate.

Key Message

Based on results from the CARES study, patients with gout and a history of major cardiovascular disease, have a significantly higher risk for all-cause mortality and for cardiovascular related death if treated with Febuxostat compared to patients treated with allopurinol.

The product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) for febuxostat will be updated to reflect the CARES study results and to include recommendations for prescribers.

A Direct Healthcare professional Communication (DHPC) was circulated by the MAH, following approval by the HPRA, in June 2019.

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

* *Further details on febuxostat are available at www.hpra.ie.*

Reference

1. *White WB, et al. CARES investigators. Cardiovascular safety of febuxostat or allopurinol in patients with gout. N Engl J Med 2018; 378:1200-10*

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

Darzalex▼ (daratumumab) – Risk of Hepatitis B reactivation

Darzalex▼ (daratumumab) is authorised for use across EU as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma and as part of combined chemotherapy regimens for the treatment of newly diagnosed adult patients with multiple myeloma who are ineligible for the autologous stem cell transplant, or who have received at least one prior therapy.

A recent cumulative review of data from clinical trials and post-marketing cases, by the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC), has identified reports of hepatitis B reactivation (HBV) in patients treated with daratumumab. Most of these cases were considered non-serious, although fatal HBV reactivation cases have been reported in clinical trials and in the post-marketing setting.

Nearly all cases have been observed in the first six months of treatment with daratumumab and, in some patients, treatment was continued once HBV reactivation was controlled with antiviral medication. In patients treated with daratumumab who experienced HBV reactivation, observed risk factors included previous autologous stem cell transplant (ASCT), concurrent and/or prior immunosuppressive therapy, and in patients who live in, or who have immigrated from regions of high HBV prevalence.

It is acknowledged that the role of daratumumab therapy in the reported cases is confounded by the underlying medical condition given that patients with multiple myeloma are immunosuppressed. Some of the patients were also receiving concomitant medications associated with viral reactivation. However, a causal association cannot be ruled out and the product information (SmPC and PL) has been updated to reflect the new safety information.

Advice to Healthcare Professionals

- All patients should be screened for HBV before initiation of treatment with daratumumab. Patients currently being treated with daratumumab and for whom HBV serology is unknown should also be tested for HBV.
- Patients with positive HBV serology should be monitored for clinical and laboratory signs of HBV reactivation during treatment, and for at least six months after treatment finishes. Experts in the treatment of HBV should be consulted, as necessary.
- If patients experience HBV reactivation, treatment with daratumumab should be stopped and experts in the treatment of HBV infection should be consulted.
- Resumption of daratumumab treatment in patients whose HBV reactivation is adequately controlled should be discussed with physicians and experts in the treatment of HBV.

Key Message

Hepatitis B reactivation (HBV) has been reported in patients treated with Darzalex (daratumumab).

Healthcare professionals should be alert to the possibility of HBV reactivation, with patients screened and monitored appropriately before, during and following treatment.

The product information (Summary of Product Characteristics (SmPC) and Package Leaflet (PL)) for Darzalex was updated in June 2019 in relation to these safety warnings and is available from the HPRA website.

A Direct Healthcare Professional Communication (DHPC) was circulated by the MAH (following approval by the HPRA) in June 2019 and is available from the HPRA website.

This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions to the HPRA via the available options (www.hpra.ie).

* *The product currently authorised is Darzalex. Further details are available at www.hpra.ie.*

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

PRODUCT	SAFETY ISSUE
Elmiron (pentosane polysulfate sodium)	Risk of pigmentary maculopathy
Febuxostat	Increased risk of cardiovascular death and all-cause mortality in patients treated with febuxostat in the CARES study
RoActemra (tocilizumab)	Rare risk of serious hepatic injury including acute liver failure requiring transplantation
Darzalex (daratumumab)	Risk of reactivation of hepatitis B virus

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

HPRA
An tÚdarás Rialála Táirgí Sláinte
Health Products Regulatory Authority