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HPRA DRUG SAFETY NEWSLETTER

110TH EDITION

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Janus Kinase inhibitors (JAKi) – Recommendations to mitigate risks of malignancy, major adverse cardiovascular events, serious infections, venous thromboembolism and mortality when used in the treatment of chronic inflammatory disorders

The EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has recommended measures to minimise the risk of a number of serious adverse reactions considered to be class effects of certain Janus kinase (JAK) inhibitors used in the treatment of several chronic inflammatory disorders. The recommendations apply to Cibinqo (abrocitinib), Jyseleca (filgotinib), Olumiant (baricitinib), Rinvoq (upadacitinib) and Xeljanz (tofacitinib).*

The recommendations have been made following a review of available data by PRAC, including the final results from a clinical trial (study A3921133)[1] of Xeljanz (tofacitinib) and preliminary findings from an observational study (B023)[2] involving Olumiant (baricitinib). Findings from study A3921133 have shown an increased incidence of malignancy, major adverse cardiovascular events (MACE), serious infections, venous thromboembolism (VTE) and mortality in patients with rheumatoid arthritis (RA) 50 years of age or older with at least one additional cardiovascular risk factor using tofacitinib compared to TNF-alpha inhibitors. Preliminary findings from observational study B023 have also suggested an increased risk of MACE and VTE in patients with RA treated with baricitinib, compared with those treated with TNF-alpha inhibitors.

Previous recommendations for Xelijanz (tofacitinib)

Following a previous review of interim results from study A3921133[1] in 2020, PRAC recommended tofacitinib should be used with caution in patients with known risk factors for VTE due to a dose dependent increased risk of VTE including pulmonary embolism (PE) and deep vein thrombosis (DVT). Additionally, the use of tofacitinib twice daily for maintenance treatment in patients with ulcerative colitis with known VTE risk factors was no longer recommended, unless there was no suitable alternative treatment. Recommendations also included that due to an increased risk of infections, patients older than 65 years of age should be treated with tofacitinib only when there is no suitable

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alternative treatment. Educational materials for patients and healthcare professionals were updated accordingly to include a warning about VTE in the prescriber's brochure and treatment checklists as well as the patient alert card.

Following the further evaluation of data from the completed study A3921133, a Direct Healthcare Professional Communication (DHPC) was distributed in March 2021 informing that data suggested a higher risk of MACE and malignancies (excluding non-melanoma skin cancer (NMSC)) with tofacitinib as compared to patients treated with a TNF-alpha inhibitor. In July 2021 an updated DHPC was circulated, informing healthcare professionals of an increased incidence of myocardial infarction, lung cancer, and lymphoma observed in completed study A3921133 with tofacitinib compared to TNF-alpha inhibitors, along with the recommended updates for the product information. The educational materials for tofacitinib were again updated accordingly at that time.

Updated PRAC recommendations for class of JAKi approved in treatment of chronic inflammatory disorders

The findings from study A3921133 have been considered in the most recent PRAC review, encompassing all JAKi used to treat chronic inflammatory disorders, together with the premliminary findings from the observational study (B023) involving another JAKi, Olumiant (baricitinib). Following this latest review of all available evidence, the PRAC has now concluded that these safety findings apply to all approved uses of the JAKi Cibinqo (abrocitinib), Jyseleca (filgotinib), Olumiant (baricitinib), Rinvoq (upadacitinib) and Xeljanz (tofacitinib) in chronic inflammatory disorders (rheumatoid arthritis, psoriatic arthritis, juvenile idiopathic arthritis, axial spondyloarthritis, ulcerative colitis, atopic dermatitis and alopecia areata).

The PRAC has recommended that these medicines should only be used if no suitable treatment alternatives are available in patients:

- 65 years of age and older,
- with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors,
- who are current or past long-time smokers,
- with malignancy risk factors (e.g. current malignancy or history of malignancy).

The PRAC also recommended that these medicines should be used with caution in patients with VTE risk factors other than those listed above including previous VTE, patients undergoing major surgery, immobilisation, use of combined hormonal contraceptives or hormone replacement therapy and inherited coagulation disorder.

If treatment with a JAKi is needed in patients with risk factors for serious adverse reactions, a lower dose may be recommended, depending on the medicine, the indication and individual patient characteristics.

In addition to the above measures, periodic skin examination is now also recommended for all patients.

Healthcare professionals should discuss these risks with their patients.

Product information** and educational materials for Cibinqo, Olumiant, Rinvoq and Jyseleca will now be updated with the new recommendations and warnings. The warnings in the product information and educational materials for Xeljanz will also be revised.

JAKi used in the treatment of myeloproliferative disorders, including Jakavi (ruxolitinib) and Inrebic (fedratinib) did not fall within the scope of this review. The review also did not cover the use of Olumiant in the short-term treatment of COVID-19, which is under assessment by EMA.

Reference

1. *Ytterberg, Steven R., et al. "Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis." New England Journal of Medicine 386. 4 (2022): 316-326.*
2. *European Medicines Agency's (EMA's)Public Health Communication confirming measures to minimise risk of serious side effects with Janus Kinase inhibitors for chronic inflammatory disorders. Available on the EMA website.*

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Key Message

The European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) has finalised a review of the Janus Kinase inhibitors (JAKi) Cibinqo (abrocitinib), Jyseleca (filgotinib), Olumiant (baricitinib), Rinvoq (upadacitinib) and Xeljanz (tofacitinib).

An increased incidence of major cardiovascular events (MACE), venous thromboembolism (VTE), malignancy, serious infections and mortality has been observed in patients with rheumatoid arthritis (RA) and certain risk factors using JAKi treatment compared to TNF-alpha inhibitors.

These risks are considered class effects and relevant across all approved indications of JAKi in inflammatory and dermatological diseases.

These JAKi should only be used if no suitable treatment alternatives are available in patients:

- 65 years of age and older,
- with history of atherosclerotic cardiovascular disease or other cardiovascular risk factors,
- who are current or past long-time smokers,
- with malignancy risk factors (e.g. current malignancy or history of malignancy).

JAKi should be used with caution in patients with VTE risk factors other than those listed above.

A lower dose of JAKi may be recommended for patients with risk factors for serious adverse reactions, depending on the medicine, the indication and individual patient characteristics.

Periodic skin examination is recommended for all patients.

Healthcare professionals should discuss these risks with their patients.

* *Further information on JAKi are available on www.hpra.ie and www.ema.europa.eu.*

** *The approved product information is comprised of the Summary of Product Characteristics (SmPC) and Package Leaflet (PL) and is available from www.hpra.ie and www.ema.europa.eu.*

Gabapentin – expanded warnings around abuse potential, dependence, and withdrawal

Gabapentin-containing medicines* are authorised in Ireland and across the EU for the treatment of neuropathic pain in adults, and as monotherapy or as adjunctive therapy for specific forms of epilepsy. Product information** for gabapentin already describes the risk of abuse, dependence, and withdrawal. Following a review of available data, the European Medicines Agency's (EMA's) Pharmacovigilance Risk Assessment Committee (PRAC) has recommended expanded warnings in the product information with respect to these risks.

Warnings in the product information will be expanded to indicate that drug dependence can occur at therapeutic doses. Patients with a history of substance abuse may be at higher risk of gabapentin misuse, abuse and dependence, and gabapentin should be used with caution in such patients. Healthcare professionals should carefully evaluate an individual patient's risk of misuse, abuse and dependence before prescribing gabapentin. Patients treated with gabapentin should be monitored for symptoms of misuse, abuse, or dependence, such as development of tolerance, dose escalation and drug-seeking behaviour.

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The product information for gabapentin-containing medicines will also be updated to include a warning regarding the occurrence of withdrawal symptoms following discontinuation of gabapentin and will note that after discontinuation of short-term and long-term treatment with gabapentin, withdrawal symptoms have been observed. Withdrawal symptoms may occur shortly after discontinuation, usually within 48 hours. Most frequently reported symptoms include;

- anxiety
- insomnia
- sweating
- tremor
- headache
- depression
- nausea
- pains
- feeling abnormal
- dizziness
- malaise

The occurrence of withdrawal symptoms following discontinuation of gabapentin may indicate drug dependence. Patients prescribed gabapentin should be informed of this risk. If gabapentin use is to be discontinued, it is recommended this should be done gradually over a minimum of one week independent of the indication.

The PRAC have also recommended updates to the product information to note that neonatal withdrawal syndrome has been reported in newborns exposed in utero to gabapentin. Co-exposure to gabapentin and opioids during pregnancy may increase the risk of neonatal withdrawal syndrome. Newborns should be monitored carefully.

Key Message

Drug dependence with gabapentin can occur at therapeutic doses.

Patients with a history of substance abuse may be at a higher risk.

Healthcare professionals should carefully evaluate an individual patient's risk of misuse, abuse and dependence before prescribing gabapentin.

Patients treated with gabapentin should be monitored for symptoms of misuse, abuse or dependence such as development of tolerance, dose escalation and drug-seeking behaviour.

Withdrawal symptoms have been observed after discontinuation of short-term and long-term treatment with gabapentin and may occur shortly after discontinuation, usually within 48 hours. Withdrawal symptoms may indicate dependence.

Patients should be alerted to these risks when treatment is commenced and advised to monitor for signs of dependence.

If gabapentin is to be discontinued, the dose should be reduced gradually over a minimum of one week.

Neonatal withdrawal syndrome has been reported in newborns exposed in utero to gabapentin. Co-exposure to gabapentin and opioids during pregnancy may increase the risk of neonatal withdrawal syndrome.

* *Further details on gabapentin-containing medicines including Neurontin and generics are available at www.hpra.ie and www.ema.europa.eu.*

** *The approved product information is made up of the Summary of Product Characteristics (SmPC) and Package Leaflet (PL)*

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Amoxicillin – Drug-induced enterocolitis syndrome (DIES)

Amoxicillin* is a semi-synthetic broad spectrum penicillin antibiotic licensed for the treatment of bacterial infections caused by amoxicillin-sensitive gam-positive and gram-negative pathogens.

Following a recent review by the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) of the available safety data a causal relationship between amoxicillin and drug-induced enterocolitis syndrome (DIES) is considered at least a reasonable possibility.

DIES is an allergic reaction with the leading symptom of protracted vomiting (1-4 hours after drug administration) in the absence of allergic, skin or respiratory symptoms. Further symptoms could comprise of abdominal pain, diarrhoea, hypotension or leucocytosis with neutrophilia. There have been severe cases including progression to shock. DIES has been reported mainly in children receiving amoxicillin.

Product information** will be amended accordingly. These updates apply both to single ingredient amoxicillin medicinal products, and also the amoxicillin-clavulanic acid combination of co-amoxiclav.

* *Amoxicillin-containing medicinal products, including co-amoxiclav medicinal products, licensed in Ireland include Amoclav, Amoxicillin/clavulanic acid, Amoxicillin, Augmentin, Clavamel Forte, Co-amoxiclav, Germentin, Ormaox, and Pinamox. Further details on amoxicillin-containing medicines are available at www.hpra.ie.*

** *The approved product information is comprised of the Summary of Product Characteristics (SmPC) and Package Leaflet (PL).*

Product information updates recommended by the EMA's Pharmacovigilance Risk assessment Committee (PRAC)

The HPRA is highlighting a selection of recommendations, made by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC), to update product information for medicines in clinical use. The PRAC, in which the HPRA participate, are responsible for assessing and monitoring the safety of medicines. Healthcare professionals (HCPs) are reminded to regularly check the HPRA or EMA websites for current product information* concerning medicines they prescribe or dispense.

Cabergoline: serious adverse events in postpartum women treated for inhibition of lactation

Cabergoline is indicated for the treatment of dysfunctions associated with hyperprolactinaemia in female patients, including amenorrhoea, oligomenorrhoea, anovulation and galactorrhoea. It may also be used to suppress lactation when considered essential. Cabergoline is also indicated in the management of Parkinson's disease as monotherapy, or as an adjunct to levodopa therapy to reduce `end-of-dose' or `on-off' fluctuations in response.

- Product information has been updated to reflect that serious adverse events including hypertension, myocardial infarction, seizures, stroke or psychiatric disorders have been reported in postpartum women treated with cabergoline for inhibition of lactation. In some patients the development of seizures or stroke was preceded by severe headache and/or transient visual disturbances. Blood pressure should be carefully monitored after treatment.
- Cabergoline should be discontinued and the patient should be evaluated promptly in case of hypertension, suggestive chest pain, severe, progressive, or unremitting headache (with or without visual disturbances), or evidence of any central nervous system toxicity. A similar warning already exists in the product information for another ergot derivative, bromocriptine.

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Buproprion: unmasking of Brugada syndrome, which may lead to cardiac arrest or sudden death

Bupropion hydrochloride is licensed for use in various forms and indications, including for the treatment of major depressive disorder (MDD), the treatment of nicotine dependence as an aid to smoking cessation, and for weight management in specific patients.

- Product information for bupropion containing medicines is to be updated to advise that use may unmask Brugada syndrome. Brugada syndrome is a rare hereditary disease of the cardiac sodium channel with characteristic ECG changes (right bundle branch block and ST segment elevation in right precordial leads).
- Treatment with bupropion, in patients with Brugada syndrome may lead to cardiac arrest or sudden death and caution is advised in these patients or in patients with a family history of cardiac arrest or sudden death.
- Patients are advised to talk to their doctor before taking bupropion if they have pre-existing Brugada syndrome or if there is a family history of cardiac arrest or sudden death.

Clobetasol: risks associated with prolonged use due to potency

Clobetasol propionate is a very potent topical corticosteroid licensed in various formulations (cream, ointment, scalp application, shampoo) for the relief of inflammatory and pruritic manifestations of steroid-responsive dermatoses that are resistant to less potent corticosteroids.

- Product information for clobetasol containing medicines has been updated to include a boxed warning in section 4.2 of the Summary of Product Characteristics (SmPC) on the risk of serious undesirable effects with prolonged use due to potency of clobetasol.
- The boxed text outlines, that clobetasol propionate belongs to the most potent class of topical corticosteroids (class IV) and prolonged use may result in serious undesirable effects.
- These effects could include osteonecrosis serious infections (including necrotizing fasciitis), and systemic immunosuppression (sometimes resulting in reversible Kaposi's sarcoma lesions). In some cases, patients were using other potent oral/topical corticosteroids or immunosuppressors (e.g. methotrexate, mycophenolate mofetil) at the same time.
- If treatment with a local corticosteroid is clinically justified beyond 4 weeks a less potent corticosteroid preparation should be considered. Repeated but short courses of clobetasol propionate may be used to control exacerbations.

Gabapentin: risk of Toxic Epidermal Necrolysis (TEN)

Gabapentin is licensed for the treatment of neuropathic pain in adults, and as monotherapy or as adjunctive therapy for specific forms of epilepsy.

- Steven-Johnson-Syndrome (SJS) and Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) are already listed as known adverse reactions in the product information for gabapentin-containing medicines. Following a review of available data, PRAC has recommended that warnings in the product information are expanded to include the risk of toxic epidermal necrolysis (TEN) under the heading of severe cutaneous adverse reactions (SCARs).
- The product information for gabapentin-containing medicines will be updated in relation to these reactions stating that SJS, TEN and DRESS, which can be life-threatening or fatal, have been reported in association with gabapentin treatment.
- When starting treatment with gabapentin, patients should be advised of the signs and symptoms and monitored closely for skin reactions. If signs and symptoms suggestive of these reactions appear, gabapentin should be withdrawn immediately, and an alternative treatment considered, as appropriate. If a patient has developed a serious reaction such as SJS, TEN or DRESS with the use of gabapentin, treatment with gabapentin must not be restarted in this patient at any time.

* *The approved product information is made up of the Summary of Product Characteristics (SmPC) and Package Leaflet (PL) and is available at www.hpra.ie and www.ema.europa.eu*

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

PRODUCT	SAFETY ISSUE
Pholcodine-containing medicines	European Medicines Agency (EMA) safety committee recommends pholcodine-containing medicines are no longer marketed
Chlormadinone acetate and nomegestrol acetate	Measures to minimise the risk of meningoma
Spikevax	Correct dosing of Spikevax bivalent original/Omicron booster vaccines

Reporting suspected adverse reactions

Healthcare professionals are encouraged to report suspected adverse reactions to the HPRA via the available options at www.hpra.ie/report, which include an online report form.

All reports submitted to the HPRA are reviewed and stored on the HPRA's national adverse reaction database. They are subsequently submitted to the EMA's EudraVigilance database where they are available for analysis and to support early detection and monitoring of possible safety signals.

Reporting suspected adverse reactions, even those known to occur in association with a medicine, adds to knowledge about the frequency and severity of these reactions and can help to identify patients who are most at risk.

A privacy notice relating the to the processing of personal data collected by the HPRA in relation to adverse reaction reports is available on the HPRA website

Correspondence/comments should be sent **by email only** to the Pharmacovigilance Section, Health Products Regulatory Authority, medsafety@hpra.ie.

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