



Ondansetron (Zofran) – Risk of QTc prolongation and new intravenous dose restriction

Ondansetron is a selective 5HT₃ receptor antagonist indicated for the management of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy and also for the prevention and treatment of post-operative nausea and vomiting. The new maximum single intravenous dose of ondansetron for the management of chemotherapy-induced nausea and vomiting (CINV) in adults is now 16 mg (infused over at least 15 minutes). This restriction follows a review of new study data, which showed that there is a greater risk of prolongation of the electrocardiographic-corrected QT interval (QTc), a known side effect of ondansetron, when it is used at the higher doses previously authorised for CINV.

In a study in healthy adults, ondansetron 32 mg given intravenously (IV) over 15 minutes caused a maximum mean QTc prolongation of 19.57 (upper 90% confidence interval 21.49) milliseconds (ms). This dose may therefore result in a clinically significant degree of QT prolongation in certain individuals. Ondansetron 8 mg IV over 15 minutes caused a QTc prolongation of 5.84 (upper 90% CI 7.76) ms – this level of prolongation is not usually associated with increased risk of cardiac arrhythmias. Extrapolating from the observations from this study, it is possible to predict that an IV dose of 16 mg over 15 minutes would cause a QTc prolongation of 9.1 (95% confidence interval 11.2) ms. For the oral and rectal formulations, the various dosages are predicted to have less than 10 ms effect on QTc prolongation.

Prolongation of the QTc can lead to Torsade de Pointes (TdP), a potentially life-threatening cardiac arrhythmia. Although no cases of TdP were observed in the study, TdP has been reported in association with the use of ondansetron in clinical practice.

This **information** was recently communicated to healthcare professionals by the Innovator marketing authorization holder in conjunction with the IMB and is available on www.imb.ie. There are no changes to the recommendations currently included in the **product information** for:

- Oral and rectal dosing for CINV in adult patients.
- IV or oral dosing for the prevention and treatment of post-operative nausea and vomiting in adult patients.
- IV or oral dosing for any indication in the paediatric population.

Advice for Healthcare Professionals

- A single dose of intravenous ondansetron given for the prevention of chemotherapy-induced nausea and vomiting in adults, must not exceed 16 mg (infused over at least 15 minutes).
- Ondansetron should be avoided in patients with congenital long QT syndrome.
- Caution must be observed if administering ondansetron to patients with risk factors for QT interval prolongation or cardiac arrhythmias. These include electrolyte abnormalities, congestive heart failure, bradyarrhythmias or use of other medicines that prolong the QT interval (including cytotoxic drugs) or may lead to electrolyte abnormalities or which lower the heart rate.
- Hypokalemia and hypomagnesaemia should be corrected prior to ondansetron administration.
- Any suspected adverse reactions associated with the use of ondansetron should be reported to the IMB in the usual way.

Key Message

The new maximum single intravenous dose of ondansetron for the management of chemotherapy-induced nausea and vomiting in adults is now 16 mg (infused over at least 15 minutes). This restriction follows a review of new study data, which showed that there is a greater risk of prolongation of the electrocardiographic-corrected QT interval (QTc), a known side effect of ondansetron, when it is used at the higher doses previously authorised for chemotherapy induced nausea and vomiting in adults.

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Levodopa, dopamine agonists and COMT inhibitors – Risk of impulse control disorders

Levodopa and dopamine agonists have been available since the 1970s as forms of dopamine replacement therapy in Parkinson's disease. Some of these medicines are also authorised for indications other than Parkinson's disease. Levodopa may be used alone or in combination with various metabolic inhibitors, including catechol-O-methyltransferase (COMT) inhibitors. COMT is an enzyme which degrades dopamine in the body.

Accumulating data on the risk of impulse control disorders (ICDs) in association with medicinal products containing levodopa and/or a dopamine agonist have become available and were recently reviewed by the Pharmacovigilance Working Party (PhWVP) of the European Medicines Agency. Data from spontaneous reports, published case reports and studies relating to this risk were assessed.¹⁻⁴¹

The review concluded that a range of behavioural symptoms of ICDs may occur in patients taking levodopa and/or dopamine agonists, at normal doses, irrespective of the indication and patients should be encouraged to inform their doctor should they develop any relevant symptoms.⁴² The product information for these medicines will be updated to include the reported symptoms.

Advice for Healthcare Professionals

- Patients taking dopamine agonists and/or other dopaminergic treatments should be regularly monitored for the development of impulse control disorders. Review of treatment is recommended if such symptoms develop.
- Patients and carers should be made aware that behavioural symptoms of impulse control disorders including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge/compulsive eating can occur and advised to inform their doctor should they experience these symptoms.

Key message

Behavioural symptoms of impulse control disorders may occur in patients taking levodopa and/or dopamine agonists at normal doses, irrespective of the indication. Patients should be made aware of the behavioral symptoms of impulse control disorders and be advised to inform their doctor should they experience such symptoms. Treatment should be reviewed if such symptoms develop.

The active substances included in the review were levodopa, the dopamine agonists apomorphine, bromocriptine, cabergoline, lisuride, pergolide, priribedil, pramipexole, quinagolide, ropinirole and rotigotine and the COMT inhibitors benserazide, carbidopa, entacapone and tolcapone.

References available on request from the IMB.

Miacalcic (calcitonin, salmon) nasal spray – Association with malignancies with long term use

Calcitonin is a calcitropic hormone which inhibits bone resorption by a direct action on osteoclasts. It is indicated in the treatment of some bone disorders including osteoporosis. Following a recent review of the benefits and risks of calcitonin by the European Medicines Agency's (EMA) Committee for Medicinal Products for human use (CHMP), it was concluded that calcitonin should no longer be used in the treatment of established post-menopausal osteoporosis due to an increased risk of malignancies with long term use. As the nasal spray formulation is only authorised in osteoporosis, the CHMP recommended that this formulation be withdrawn.

The review considered information on the risk of all types of malignancies from randomised controlled trials in patients with osteoporosis or osteoarthritis receiving calcitonin nasal spray or an unlicensed oral calcitonin formulation. Patients treated with calcitonin in these trials had a higher incidence of malignancies. The increased rate of malignancies varied between 0.7% in the oral calcitonin trials and 2.4% for the calcitonin nasal spray trials. Taking into account the limited efficacy of calcitonin when used to treat post-menopausal osteoporosis to reduce the risk of vertebral fractures, the CHMP concluded that the benefits of calcitonin-containing medicines did not outweigh their risks in this indication.

Advice for healthcare professionals:

- Calcitonin should no longer be used in the treatment of established post-menopausal osteoporosis, since the risks associated with calcitonin outweigh the benefits in this indication.
- Patients being treated for osteoporosis with Miacalcic 200IU Nasal Spray should be switched to alternative treatment during the next scheduled (or routine) appointment.
- For all other approved indications the CHMP considered that the benefit-risk balance remains positive, but recommended that calcitonin treatment should be given for the shortest possible time and using the minimum effective dose (see the product information on www.imb.ie for further information).
- Any suspected adverse reactions associated with the use of calcitonin should be reported to the IMB in the usual way.

Key Message

A review of the benefits and risks of calcitonin has concluded that there is an increased risk of malignancies with long term use. As a result of these findings, calcitonin nasal spray (Miacalcic 200IU nasal spray), which is authorised only for treatment of post-menopausal osteoporosis, will be withdrawn from the market.



Adverse Reaction Reporting Experience during 2011

The IMB places great emphasis on encouraging and promoting reports from a range of stakeholders in relation to suspected adverse reactions to medicines. These reports are important to signal potential safety issues from medicines in use and ultimately assist the IMB in monitoring the safety of medicines on the Irish market.

During 2011, the IMB received a total of 2,784 suspected adverse reaction reports occurring in Ireland from healthcare professionals, patients/consumers and pharmaceutical companies. While this represents a decrease of some 14% in reporting rates compared with 2009/2010, it reflects a return to expected levels, following the enhanced rates of reporting particularly stimulated by the H1N1 immunisation programme and shows a small increase over reporting rates for 2008.

Breakdown of Reports by Source

Marketing Authorisation Holder	1898
Community Care Doctor	260
General Practitioner	172
Hospital Doctor	160
Community Nurse	135
Pharmacist Hospital	134
Pharmacist Community	105
Hospital Nurse	80
Member of Public	45
Healthcare Professional - other	15
Dentist	2
Haemovigilance Officer	2

* Some cases are reported by more than one reporter

The **on-line reporting system**, available to healthcare professionals and patients/consumers continued to be used during 2011, with a small increase in the number of reports (345) submitted by year end via this method. The online report form can be accessed on the IMB homepage at www.imb.ie.

The IMB greatly appreciates the contribution of busy healthcare professionals in reporting suspected adverse reactions, facilitating the continued surveillance of the safety of medicines. While the time-consuming nature of form-filling and the provision of follow-up information to the IMB is recognised, the collection and evaluation of comprehensive reports is essential to ensure that appropriately detailed case information is available for the continuous surveillance of the safety of medicines.

Donepezil – Risk of neuroleptic malignant syndrome

Donepezil* is a specific and reversible inhibitor of acetylcholinesterase authorised for use in the treatment of Alzheimer's disease.

Data related to concerns about the risk of serotonin syndrome (SS) associated with donepezil were recently reviewed by the PhVWP of the EMA.¹ The review was expanded to also consider neuroleptic malignant syndrome (NMS), since the diagnosis of NMS may include symptoms of SS, in addition to other symptoms such as muscle stiffness and very high temperature.

Data from pre-clinical, clinical trial and spontaneous reports were assessed in addition to information from the medical literature.²⁻⁵ The evidence to support an association between donepezil and SS was not considered strong, with no case reports of SS identified from clinical trials data and very few, spontaneous case reports identified, all of which involved concomitant use of other medicines known to cause SS (i.e. paroxetine, sertraline or trazodone).

The review suggested however that there was reasonably good evidence of a causal relationship between the occurrence of NMS with donepezil, both when used alone and together with other medication, usually anti-psychotics. Factors that suggested causality included positive dechallenge in the majority of cases, with positive rechallenge also reported in one case. In addition there were several cases where the clinical event occurred in a plausible time relationship to administration of donepezil and also where NMS developed after a dose increase.

It was also considered that there are plausible biological mechanisms for the occurrence of this reaction. The neuropathophysiology of NMS is thought to relate to dysregulation of cortical-subcortical circuits between motor cortex and basal ganglia. Blockage of the striatal D2-receptors relative to regulatory cholinergic pathways was considered to be the most likely neurochemical cause. Thus an NMS-like syndrome may be precipitated by increasing cholinergic functioning in the presence of a compromised dopaminergic system.

Advice for Healthcare Professionals

- NMS is a potentially life-threatening condition and is characterised by hyperthermia, muscle rigidity, autonomic instability, altered consciousness and elevated serum creatine phosphokinase levels; additional signs may include myoglobinuria (rhabdomyolysis) and acute renal failure.
- If a patient develops signs and symptoms indicative of NMS, or presents with unexplained high fever without additional clinical manifestations of NMS, treatment should be discontinued.

Key message

Neuroleptic malignant syndrome has been reported in patients treated with donepezil with or without concomitant antipsychotic medication.

Based on the currently available information, there is insufficient evidence to suggest a causal relationship between donepezil and serotonin syndrome.

* Brands include Aricept, Donesyn, Dozept, Donecept, Arizime, Aripil and Aripez. See www.imb.ie for further details.

References available on request from the Irish Medicines Board.



Dabigatran (Pradaxa) – Further information on contraindications and management of bleeding

Dabigatran is a reversible inhibitor of free thrombin, fibrin-bound thrombin, and thrombin-induced platelet aggregation. It is licensed through a European centralised procedure for primary prevention of venous thromboembolic events in adults who have had elective total hip replacement surgery or total knee replacement surgery (at 220 mg/day), and for prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation and one or more cardiovascular risk factors (at 300 mg/day).

Haemorrhage is a well-known adverse reaction of all anticoagulant medicines including dabigatran, and this risk has been closely monitored. A review of world-wide data on the risk of bleeding with dabigatran, including results from clinical trials (such as the phase III RELY study)¹ and post-marketing surveillance, has resulted in further information and clearer advice on use of dabigatran and how best to minimise the risk of bleeding.

Updated advice for Healthcare Professionals

Contraindications:

- Dabigatran is contraindicated in clinical conditions associated with a significant risk of bleeding, such as:
 - Current or recent gastrointestinal ulceration
 - Presence of malignant neoplasms at high risk of bleeding
 - Recent brain or spinal injury
 - Recent brain, spinal or ophthalmic surgery
 - Recent intracranial haemorrhage
 - Known or suspected oesophageal varices
 - Arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities
- Dabigatran is contraindicated with dronedarone, and with other anticoagulants, except when switching

treatment to and from dabigatran, or with the use of unfractionated heparin for maintenance of venous or arterial catheter patency. For detailed advice on switching treatment to and from dabigatran see the revised [product information](#) for details on www.ema.europa.eu.

Management of bleeding

- There is no specific antidote to dabigatran and excessive anticoagulation may require interruption of treatment.
- In the event of haemorrhagic complications, dabigatran must be discontinued and the source of the bleeding investigated. Adequate diuresis must be maintained and appropriate supportive treatment, such as surgical haemostasis and blood volume replacement, should be undertaken at the prescribers discretion.
- Activated prothrombin complex concentrates (e.g. FEIBA) or recombinant Factor VIIa or concentrates of coagulation factors II, IX and X, may be considered. Coagulation tests may become unreliable following administration of reversing agents, caution must be exercised when interpreting these results. Prescribers should follow all the necessary precautions with regard to the risk of bleeding with dabigatran, including the assessment of kidney function before treatment in all patients and during treatment if deterioration is suspected, as well as dose reductions in certain patients (see [IMB Drug Safety Newsletter 45](#) on www.imb.ie).
- Patients should be aware that they are at an increased risk of bleeding. If they fall or injure themselves during treatment, especially if they hit their head, they should seek urgent medical attention.

Key Message

The product information has been updated to provide further guidance relating to contraindications and the management of bleeds.

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

Product	Safety Issue
Miacalcic 200IU nasal spray (calcitonin)	Withdrawal from the market, increased risk of malignancies with long term use
Peyona (caffeine citrate)	Information on safe use
Ti-Tre 20mcg (liothyronine)	Information on potential quality issue and supply
Vectibix (panitumumab)	Association with life-threatening and fatal infectious complications of severe skin reactions including necrotising fasciitis
Volibris (ambrisentan)	New contraindication in Idiopathic pulmonary fibrosis
Zofran (ondansetron)	Dose-dependent QT interval prolongation and new dose restriction for intravenous use