Danish Pharmacovigilance Update
Year 3 #7
16 August 2012

Maximum single dose of intravenous ondansetron (Zofran® and others) now restricted to 16 mg

Results from a recently completed study show that ondansetron induces a dose-dependent prolongation of the frequency corrected QT interval (QTc) which may lead to torsade de pointes, a potentially life-threatening cardiac arrhythmia.

Because of the potential safety risk, there are new dosing restrictions for intravenous use of ondansetron:

- A single dose of intravenous ondansetron given for the prevention of chemotherapy-induced nausea and vomiting (CINV) in adults **must not exceed 16 mg** (infused over 15 minutes).
- Ondansetron should be avoided in patients with congenital long QT syndrome.
- Caution should be exercised when administering ondansetron to patients with risk factors for QT-interval prolongation or cardiac arrhythmias. These include
  – electrolyte disturbances
  – congestive heart failure
  – bradyarrhythmias
  – use of other medicines that may lead to QT prolongation or electrolyte disturbances.

  Hypokalaemia and hypomagnesaemia must be corrected prior to ondansetron administration.
- Caution must be exercised with concomitant use of ondansetron and drugs that prolong the QT interval, including some cytotoxic agents.

There are no changes to the recommendations for the oral or rectal dosing for CINV in adult patients.

There are no changes for paediatric treatment or changes to the IV dosing for other indications as these doses are all lower than for IV CINV treatment in adults.

Letter to doctors on the update of the summary of product characteristics with the new dosing restrictions

Within the next 14 days, letters will be sent to relevant doctors informing them about the new dosing restrictions.

The risk of prolongation of the QTc interval and cardiac arrhythmia, including torsade de pointes, in association with the use of ondansetron, is already included in the summary of product characteristics for Zofran®. The summary of product characteristics will be updated as soon as possible with the new dosing restrictions and information on data from the new study.

Indication for ondansetron

Ondansetron is an antiemetic approved for the treatment of nausea and vomiting associated with chemotherapy, radiotherapy or surgery.

Correlation between calcitonin and malignant disease – new restrictions on the use and withdrawal of nasal spray from the market

The European Medicines Agency recently completed a review of the benefits and risks associated with calcitonin and concluded that randomised, controlled clinical studies showed signs of an increased risk of malignant disease in long-term calcitonin users as compared to patients treated with placebo.

Due to the higher incidence of malignant disease, the following was concluded:

- Calcitonin should no longer be used in the treatment of verified postmenopausal osteoporosis as the benefits of calcitonin do not outweigh the risk for this indication.

Based on these conclusions, calcitonin nasal spray, which is approved for use in postmenopausal osteoporosis only, will be withdrawn from the market. Thereafter, calcitonin will be available as a solution for injection and infusion only.

Patients being treated for osteoporosis with calcitonin should be switched to an alternative treatment at the next planned (or routine) appointment.

The benefits of calcitonin are still deemed to outweigh the risks of short-term treatment for:

- Paget's disease for patients not responding to alternative treatments or for patients for whom such treatments are not appropriate, e.g. patients suffering from severe renal impairment. In most cases, treatment for this indication should be limited to three months.
- Prevention of acute bone loss due to sudden immobilisation such as in patients with recent osteoporotic fractures undergoing a treatment limited to two to four weeks.
- Hypercalcaemia caused by malignant disease

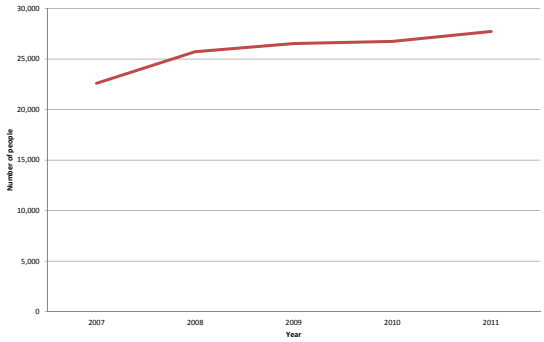
Letters with the new information will be sent to doctors, and the product information for calcitonin will be updated with information on the risk of malignant disease and the new provisos.

In Denmark, only very few patients are being treated with calcitonin nasal spray.

Risk of impulse control disorders in patients undergoing treatment with dopamine-increasing drugs

It has been known for a long time that compulsive gambling and hypersexuality are potential adverse reactions from the use of dopamine agonists such as ropinirole and pramipexole when used for Parkinson's disease. In recent years, it has become evident that these symptoms are merely part elements in a broader symptom complex referred to as "impulse control disorders". Also, among other things, this complex includes hypersexuality, obsessive spending or buying enthusiasm, overeating and obsessive eating. The symptoms have also emerged during use for indications other than Parkinson's disease and with levodopa-containing drugs such as Sinemet®, Madopar® and Stalevo®.

Figure 1. Number of people who redeemed a prescription for dopamine-increasing drugs in 2007-2011



Summaries of product characteristics and package leaflets for levodopa-containing drugs as well as dopamine agonists will be updated as soon as possible with information on adverse reactions and recommendations to monitor patients for the development of impulse control disorders.

Advice for doctors

Doctors should inform patients and nursing staff that these symptoms may emerge. Moreover, it is recommended to monitor the patients regularly for the development of impulse control disorders. The treatment should be reconsidered in case of such symptoms in a patient.

Serious skin reactions correlated to the use of carbamazepine, oxcarbazepine or allopurinol and association with certain genetic alleles

Based on a review of new pharmacogenetic studies, the European Pharmacovigilance Working Party, PhVWP, has updated the recommendations for allopurinol, carbamazepine and oxcarbazepine. The studies concern skin reactions associated with these substances - from mild skin reactions to toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS).

Carbamazepine and oxcarbazepine
In European Caucasians and Japanese patients serious skin reactions correlated to the use of carbamazepine and oxcarbazepine can be associated with a genetic marker, the HLA-A*3101 allele. However, there are no data to support testing for HLA-A*3101 in this population prior to initiation of treatment.

Serious skin reactions are also associated with the HLA-B*1502 allele. For this association, data show that clinical utility of testing in patients of Han Chinese or Thai origin has been proven. Almost 100% of these cases could be avoided by genetic testing prior to initiation of treatment.

At present, the PhVWP recommendations are as follows:

- Individuals of Han Chinese or Thai origin should, whenever possible, be tested for the HLA-B*1502 allele prior to initiation of treatment
- Testing for the HLA-B*1502 allele in other Asian populations at genetic risk may be considered
- Routine testing for the HLA-A*3101 allele is not recommended. If European Caucasians or patients of Japanese origin are known to be positive for HLA-A*3101, the use of carbamazepine or oxcarbazepine may be considered if the benefits outweigh the risks.

Product information and package leaflets for carbamazepine and oxcarbazepine will be updated with the new information within a few months' time.

Allopurinol
The serious skin reactions (TEN, SJS) correlated to the use of allopurinol can be associated with the allele HLA-B*5801. However, the clinical utility of testing for this allele has not been proven in any population.

At present, the PhVWP recommendations are as follows:

- The applicability of genotyping as a screening tool to make assessments prior to treatment with allopurinol has not been established
- Routine testing for HLA-B*5801 is not recommended. If patients are known carriers of HLA-B*5801, the use of allopurinol should be considered
- Doctors should inform patients of the need to stop treatment immediately at the first signs of hypersensitivity syndrome or TEN/SJS.

Indication for carbamazepine
Used for the treatment of epilepsy; simple or complex partial seizures (with or without loss of consciousness) with or without secondary generalisation, generalised tonic-clonic seizures. Mixed type seizures. Also indicated for the treatment of trigeminal neuralgia and alcohol withdrawal symptoms.

Indication for oxcarbazepine (analogue of carbamazepine)
Used for the treatment of epilepsy; partial seizures with or without secondary generalisation.

For further information, please read the *PhVWP monthly report* from July 2012.

Indication for allopurinol

Adults: Used for all forms of hyperuricaemia that cannot be controlled with dietary measures, including secondary hyperuricaemia of various origin, and in managing clinical complications from hyperuricaemia conditions, especially for manifest arthritis, urate nephropathy and in dissolving and preventing uric acid stones. Also used for the treatment of recurrent mixed calcium oxalate stones in the presence of hyperuricaemia, when fluid, dietary and similar measures have failed.

Children and young people: Used for the treatment of secondary hyperuricaemia of various origin, uric acid nephropathy during leukaemia treatment, hereditary enzyme deficiencies, Lesch-Nyhan syndrome (partial or total hypoxanthine-guanine-phosphoribosyltransferase deficiency) or adenine-phosphoribosyltransferase deficiency.

Reports of suicide correlated to initiation of antidepressants

The Danish Health and Medicines Authority has received a few reports of patients committing suicide shortly after initiation of an antidepressant.

Patients should be monitored closely when initiating antidepressants

The product information for antidepressants contain extensive information on the risk of suicide. Depression is associated with an increased risk of suicidal thoughts, self harm, suicide attempts and suicide. This risk persists until significant remission of the disease occurs. As improvement of the depression may not occur until several weeks after initiating the treatment, the patient should be monitored closely until the condition has improved. General clinical experience shows that the suicidal risk may increase in the early treatment stages.

Other psychiatric disorders for which antidepressants are prescribed can also be associated with an increased risk of suicidal events. In addition, these conditions may be co-morbid with major depression. Therefore, the same precautions observed when treating patients with major depression should be observed when treating patients with other psychiatric disorders.

Patients in high risk group should be monitored particularly closely

Patients with past suicidal events or patients with suicidal thoughts or a history of suicide attempt prior to treatment are at greater risk of suicidal thoughts or suicide attempts. Therefore, they should be monitored closely during the treatment. A meta-analysis has shown an increased risk of suicidal behaviour in patients under the age of 25 treated with antidepressants compared with the placebo group.

Close monitoring, in particular of patients in the high risk group, should accompany the drug treatment, especially when initiating treatment and changing the dose. Patients (and nursing staff) should be alerted about the need to monitor for any clinical worsening, suicidal behaviour or thoughts and unusual changes in behaviour. The patient must see a doctor immediately if such symptoms present.

You can find summaries of product characteristics for antidepressants at *www.produktresume.dk*.

Medication errors and incorrect use of Exelon® transdermal patch for treatment of Alzheimer's dementia

In *Danish Pharmacovigilance Update from June 2010* we pointed out problems concerning medication errors and inappropriate use of Exelon® transdermal patches. Since the problem continues to be relatively extensive, we urge to use the patches correctly.

Among other things, the errors and incorrect use have lead to overdose of the substance rivastigmine with symptoms such as nausea, vomiting, diarrhoea, hypertension, and hallucinations. The most frequent overdose causes are lack of patch removal and application of more than one patch at a time.

As a doctor you should ensure that patients, healthcare professionals and caregivers are using the transdermal patch correctly as follows:

- Only one patch should be applied per day. The patch must be applied to healthy skin on the upper or lower back, upper arm, or chest.
- After 24 hours, the patch should be replaced by a new one, and the previous day's patch must be removed prior to applying the new patch to a different skin area.
- The patient should avoid application to the same skin area within 14 days to minimise the risk of skin irritation.
- The transdermal patch must not be cut into pieces.
- Remove the patch immediately in case of overdose.

Indication for Exelon® transdermal patch
Exelon® transdermal patch has been approved in Denmark for the symptomatic treatment of mild to moderately severe Alzheimer's dementia and for the symptomatic treatment of mild to moderately severe dementia in patients with idiopathic Parkinson's disease. Exelon® transdermal patch is available in two strengths: 4.6 mg/24 hours and 9.5 mg/ 24 hours.

Short news

Risk of oesophageal irritation with bisphosphonates for oral use, but no evidence of a correlation with oesophageal cancer

Four new epidemiological studies support the outcome of the European Pharmacovigilance Working Party, PhVWP, review from October 2010. Hence, there is no evidence of a correlation between bisphosphonates for oral use and development of oesophageal cancer.

For further information, please read the *PhVWP monthly report* from July 2012.

Risk of neuroleptic malignant syndrome in association with donepezil (Aricept® and others), but no evidence of a correlation with serotonin syndrome

The PhVWP has reviewed data on serotonin syndrome and neuroleptic syndrome in association with the use of donepezil. Based on the review, The PhVWP concluded that summaries of product characteristics and package leaflets for products containing donepezil are to be updated to include the risk of neuroleptic syndrome.

For further information, please read the *PhVWP monthly report* from July 2012.

Correlation between pantoprazole (Pantoloc® and others) and other proton pump inhibitors and increased risk of pneumonia cannot be confirmed

Based on a data review, The PhVWP concluded that the use of pantoprazole and other proton pump inhibitors is not associated with an increased risk of developing pneumonia. The PhVWP undertook the review because several observational studies and meta-analyses suggested a possible correlation.

For further information, please read the *PhVWP monthly report* from July 2012.

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> **Concerns over off-label use of pimecrolimus (Elidel®)**
Due to a potential, but yet unconfirmed increased risk of malignant disease, pimecrolimus should not be used for conditions other than corticosteroid-resistant dermatitis and should not be used in patients under the age of 2.

For further information, please read the *PhVWP monthly report* from July 2012.

Update of the product information for tramadol (Nobligan® and others)
PhVWP has reviewed safety data for tramadol and recommends an update of the product information to minimise the risk of central nervous system-related adverse reactions and to provide further information on dosing in elderly patients and patients with renal or hepatic impairment.

For further information, please read the *PhVWP monthly report* from July 2012.

Medicintjek (Medicine check): Mobile app with information about medicines

A free app (in Danish only) is available from the Danish Health and Medicines Authority for iPhones running iOS version 4.0 or later and Androids running Android version 4.0 or later.

Medicintjek is an app enabling product search or scanning of barcodes on medicine packages to access various information in Danish about medicines. Medicintjek also provides one single entry point to information in Danish from the websites *medicinpriser.dk, medicinkombination.dk, indlaegsseddel.dk* and *laegemiddelstyrelsen.dk* at the same time.

You can read more about the options offered by Medicintjek and see how to download the app on our website: *Medicintjek: Mobile app with information about medicines*.

Danish Pharmacovigilance Update is published by:
Danish Health and Medicines Authority
www.laegemiddelstyrelsen.dk
Editor-in-Chief:
Henrik G. Jensen (HGJ)
Editor:
Louise Benner (LOBE)
ISSN 1904-2086

Sundhedsstyrelsen
Danish Health and Medicines Authority