Danish Pharmacovigilance Update

Volume 2 #11
17 November 2011

In this issue of Danish Pharmacovigilance Update:

Domperidone (Motilium® etc.) and potential risk of cardiac disorders

Use of domperidone may be associated with an increased risk of severe ventricular arrhythmia or sudden cardiac death, especially in patients over the age of 60 or patients taking daily doses of more than 30 mg.

For these reasons, domperidone should be used at the lowest effective dose in adults and children.

Given this new information from a published study[1], the European Pharmacovigilance Working Party (PhVWP) reviewed the risk of cardiac disorders associated with domperidone and concluded that the summaries of product characteristics and package leaflets of medicines containing domperidone should be updated with the new information.

Moreover, the PhVWP has recommended the marketing authorisation holder to conduct an additional epidemiological study to clarify the association between domperidone and heart disease – with particular focus on dose relationship.

For further information, please read the *PhVWP monthly report from October 2011*.

Domperidone is approved for the following indications:
Adults: Relief of nausea and vomiting, epigastric sense of fullness, upper abdominal discomfort, regurgitation of stomach contents.
Children: Relief of nausea and vomiting.

In 2010, 3692 patients were treated with domperidone in the primary sector in Denmark. Around half of these patients were 60 years or older.

1 van Noord C, Dieleman JP, van Herpen G, Verhamme K, Sturkenboom MC. Domperidone and ventricular arrhythmia or sudden cardiac death: a population-based case-control study in the Netherlands. Drug Saf. 2010; 33: 1003-1014.

The European Medicines Agency, EMA, recommends a lower dose of the antidepressant citalopram

In October 2011, the European Pharmacovigilance Working Party concluded to reduce the maximum dose of the antidepressant medicine citalopram. The recommendation follows from a drug trial and adverse reactions showing that citalopram may affect the heart rhythm, especially when given in high doses.

The new recommendations

The new recommended maximum daily dose is 40 mg in adults and 20 mg in the elderly and patients with impaired liver function. Citalopram should not be used in children and adolescents under the age of 18.
The Danish Medicines Agency is represented in the Pharmacovigilance Working Party and endorses the dose adjustment. It will be a few months before the package leaflets are updated with information on the lower dose.

Information for prescribers of citalopram

Citalopram has been linked with a dose-dependent QT interval prolongation.

- From now on, the recommended dose of citalopram is 40 mg/day in adults.
- In the elderly and in patients with hepatic impairment, the maximum dose is reduced to 20 mg/day.
- Citalopram is contraindicated in patients with a known QT interval prolongation, including congenital long QT syndrome.
- Citalopram is contraindicated for use with other medicines known to prolong the QT interval.
- Citalopram should be used cautiously in patients at increased risk of developing torsade de pointes. This includes, for example, patients with heart failure, recent myocardial infarction, bradyarrhythmia or patients predisposed to hypokalaemia or hypomagnesaemia as a result of other disease, or if they take other medicine concurrently.

For further information, please read the *PhVWP monthly report from October 2011*.

Indication for citalopram
Citalopram is an antidepressant drug of the SSRI type (selective serotonin reuptake inhibitor), which is used, among other things, for the treatment of moderate to severe depression and panic disorder.

Pradaxa® – new recommendations for assessment of renal function

A set of new recommendations have been drawn up for the assessment of renal function in patients treated with Pradaxa® (dabigatran etexilate) or patients intended to be treated with Pradaxa®.

The new recommendations are based on a review of adverse reaction reports on haemorrhaging with a fatal outcome after use of dabigatran in Japan.
Many of these adverse reactions occurred in patients with severe renal impairment.

The new recommendations:

- The renal function must be examined in all patients before start-up of treatment with Pradaxa®.
- Pradaxa® is contraindicated in patients with severe renal impairment (creatinine clearance < 30 ml/min.).
- During treatment with Pradaxa®, the renal function should be examined in certain clinical situations, where a decline in renal function is suspected (e.g. hypovolaemia, dehydration, interactions with other medicine).
- In elderly patients (> 75 years) or patients with renal impairment, the renal function should be examined at least once a year.

The summary of product characteristics and the prescribing guidelines will soon be updated with the new recommendations.
For further information, please visit the *EMA website*.

Indication for Pradaxa®
Pradaxa® is used for preventing venous thromboembolism in adult patients after knee and hip prosthesis surgery and for preventing apoplexy and systemic embolism in adult patients with atrial fibrillation.

The Danish Medicines Agency participates in a research project on Pradaxa®
The Danish Medicines Agency cooperates with the Trombosecenter Aalborg (the Thrombosis Research Unit) under Aalborg Hospital on monitoring and analysing the use of new anticoagulants. Pradaxa® is one of the new anticoagulants, and several medicines await the same approval. The new anticoagulants are expected to replace the current anticoagulant treatment to an increasing extent, and therefore the project follows the development of the use of anticoagulants in Denmark. The cooperation consists in ongoing monitoring of consumption and adverse reactions, as well as research and scientific advice.

Antiepileptics and the risk of bone disorders

Osteomalacia is a known adverse reaction from certain types of antiepileptics – carbamazepine (Tegretol® etc.), phenytoin (Fenytoin®), phenobarbital (Fenemal® etc.) and primidone.

The European Pharmacovigilance Working Party, PhVWP, has completed a review of all antiepileptics in order to examine the potential risk of bone disorders. The review shows that long-term use of carbamazepine, phenytoin, phenobarbital, primidone, oxcarbazepine (Trileptal®, Lancyl®, etc.), lamotrigine (Lamictal®) and sodium valproate (Deprakine® etc.) is associated with a risk of decreased bone mineral density that may lead to osteopenia, osteoporosis and bone fractures.

The risk of bone disorders is especially relevant to elderly patients, who are already at risk of osteoporosis. In addition, these patients often use antiepileptics – also for other indications than epilepsy.

The summaries of product characteristics and package leaflets will soon be updated with the new knowledge.

For further information, please read the *PhVWP monthly report from October 2011*.

No evidence of causal relationship between treatment with angiotensin II antagonists and increased risk of developing cancer

The Committee for Medicinal Products for Human Use (CHMP) has completed a review of the possible link between the occurrence of new cancers and use of angiotensin II antagonists. The Committee concluded that the available evidence does not support any increased risk of cancer in patients using angiotensin II antagonists. This means that the benefit-risk balance of treatment with angiotensin II antagonists remains positive.

The review was initiated following publication of a meta-analysis[1] published in June 2011 in The Lancet which showed a small increased risk of new cancers (particularly lung cancer) in patients treated with angiotensin II antagonists compared with placebo or active controls (beta blockers or ACE inhibitors) in the order 7.2% versus 6%. The meta-analysis included data from nine randomised controlled trials and involved 95,000 patients.

The CHMP found several methodological limitations in the meta-analysis: Patients in the trials were not followed up for long enough to clearly establish a link between use of angiotensin II antagonists and development of cancer. Information on the risk of cancer before start of treatment with angiotensin II antagonists was lacking. Also, there was a possible publication bias, whereby studies that showed a link with cancer were more likely to have been included in the analysis.

The CHMP reviewed all available published data, i.e. the findings from the meta-analysis together with other clinical data on the risk of cancer and treatment with angiotensin II antagonists – including data from clinical trials and epidemiological studies – and other non-clinical data on angiotensin II antagonists.

For further information, please visit the *EMA website*.

Indication for angiotensin II antagonists
Angiotensin II antagonists are indicated for treatment of hypertension. They are used for treatment of heart failure and renal disease in type 2-diabetes patients as well as for prevention of stroke and heart disease.

These angiotensin II antagonists are approved in Denmark:

- Candesartan
- Eprosartan
- Irbesartan
- Losartan
- Olmesartan
- Telmisartan
- Valsartan

1 Angiotensin-receptor blockade and risk of cancer: meta-analysis of randomised controlled trials. Lancet Oncol. 2010 Jun 11 Sipahi I, Debanne SM, Rowland DY, Simon DI, Fang JC.

Xigris® for treatment of adults with severe sepsis and multiple organ failure to be withdrawn

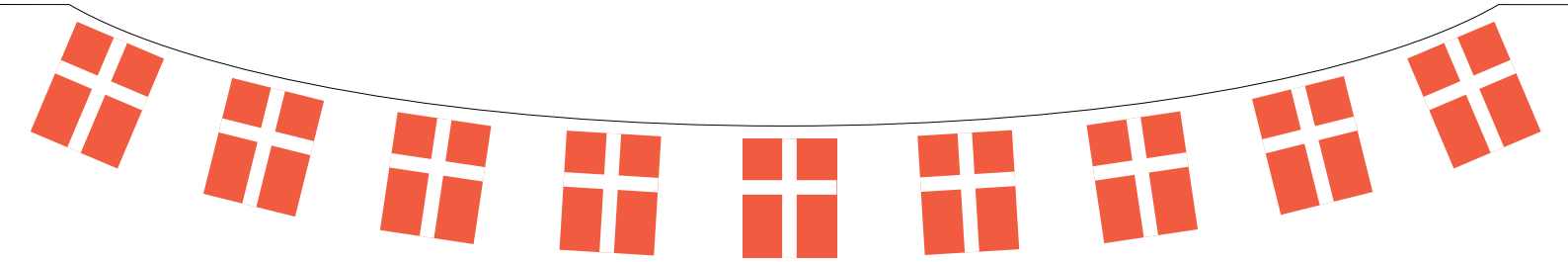
The pharmaceutical company Eli Lilly has decided to withdraw Xigris® (drotrecogin alfa) from the market, effective immediately. This happens after a study of patients with septic shock, the PROWESS-SHOCK study, has shown that the survival rate of patients treated with Xigris® is no better than for placebo.

The overall 28-day mortality of patients treated with Xigris® was 26.4 % compared to 24.2 % for placebo. Apart from failing to improve the survival rate in patients treated with Xigris®, no other observations were made concerning the safety profile of Xigris®.

For further information, please visit the *EMA website*.

Indication for Xigris®
Xigris® was approved in Europe in 2002 for treatment of severe sepsis in adult patients with multiple organ failure as an addition to best standard care based on the findings of the PROWESS study, where Xigris® showed significantly improved 28-day mortality. The cause of the new unexpected findings is still unknown.

Danish Pharmacovigilance Update celebrates 2-year anniversary



The first issue of Danish Pharmacovigilance Update was published in November 2009. This means that we can now celebrate this newsletter's 2nd anniversary with 1800 Danish subscribers and 170 international subscribers.

The past two years have included a variety of articles ranging from updates of summaries of product characteristics and new initiated studies to articles on withdrawals and the occurrence of new serious adverse drug reactions.

A new feature this year is the theme-based articles written by external clinical experts. One such article dealt with medicine and dry mouth in *Danish Pharmacovigilance Update, June 2011* and another such article dealt with analgesics (NSAIDs) and the risk of ulcer in arthritis patients in *Danish Pharmacovigilance Update, April 2011*. We will continue to publish more of these articles in the future issues, where we have also changed the format in order to make it even easier to access the articles.

We are very pleased with the great interest in and the positive feedback we get on this newsletter, and we hope that the interest will continue to spread.

Subscribe to *Danish Pharmacovigilance Update*.

Danish Pharmacovigilance Update
is published by
Danish Medicines Agency
www.dkma.dk
Editor-in-Chief:
Henrik G. Jensen (HGJ)
Editor:
Nina Vucina Pedersen (NVP)
ISSN 1904-2086