Danish Pharmacovigilance Update

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News in brief

Vimpat® 15mg/ml syrup (lacosamide) for treatment of epilepsy recalled due to a quality defect

The defect consists in precipitates which cause an uneven distribution of active substance in the syrup.

Doctors should contact their patients in order to switch them to other formulations of Vimpat®.

For further information, please read *here*.

Nplate® (romiplostim) may increase the risk of disease progression in patients with myelodysplastic syndrome (MDS)

Romiplostim is approved for treatment of thrombocytopenia in connection with chronic immune (idiopathic) thrombocytopenic purpura (ITP). New data from a randomised clinical study of patients with thrombocytopenia associated with MDS shows an increased risk of disease progression to acute myelogenous leukaemia (AML) in patients treated with romiplostim (Nplate®) compared to placebo. Treating physicians have therefore received a letter recommending them only to use this medicine for the approved indication.

For further information, please read *here*.

Sprycel® (dasatinib) for treatment of certain types of leukaemia and risk of precapillary pulmonary arterial hypertension (PAH)

Treating physicians have received a letter recommending them to evaluate patients for signs and symptoms of underlying cardiopulmonary disease prior to initiating dasatinib therapy.

They are also advised to discontinue the dasatinib treatment permanently in patients undergoing treatment who are diagnosed with PAH.

For further information, please read *here*.

MabThera® (rituximab) and risk of fatal infusion-related reactions in patients with rheumatoid arthritis

Treating physicians have received a letter alerting them of rare fatal cases of infusion reactions. If a serious hypersensitivity/infusion reaction occurs, the administration of rituximab must stop immediately and appropriate medical treatment be initiated.

For further information, please read *here*.

Antipsychotic treatment during pregnancy and risk of withdrawal symptoms and extrapyramidal effects in newborns

The European Pharmacovigilance Working Party (PhVWP) has reviewed data from worldwide adverse reaction reports and information from the U.S. Food and Drug Administration (FDA) concerning adverse reactions in newborns following the mother's antipsychotic treatment during pregnancy.

The conclusion is that:
Antipsychotic treatment during the third trimester of pregnancy entails a risk of withdrawal symptoms and extrapyramidal effects in newborns. This group of infants should therefore be watched carefully. Symptoms may include tremor, sleepiness, agitation and difficulty in feeding and breathing.

All summaries of product characteristics for antipsychotics to be updated
Although limited data was available for some antipsychotics, the PhVWP agreed that it is most likely a class effect, and the product information for all antipsychotics must therefore be updated with consistent warnings on these adverse reactions.

For further information, please read the PhVWP monthly report *here*.

Hydrochlorothiazide is not recommended during breast-feeding – but no evidence suggests a contraindication

The European Pharmacovigilance Working Party (PhVWP) has reviewed data regarding use of hydrochlorothiazide during breast-feeding in order to draw up harmonised recommendations for all products containing this substance.

The PhVWP concluded that the available evidence does not justify adding breast-feeding as a contraindication, as the available data shows that the quantity of hydrochlorothiazide excreted into the breast milk is insignificant.

Also, no adverse reactions have been reported concerning hydroclorothiazide and children being breast-fed.

Hydrochlorothiazide is not recommended during breast-feeding
Hydrochlorothiazide during breast-feeding is not recommended. The product information should reflect that hydrochlorothiazide is excreted into the breast milk in small quantities and that high doses of thiazides can generally inhibit milk production by causing intense diuresis. The doses should therefore be kept as low as possible.

For further information, please read the PhVWP monthly report *here*.

In Denmark, hydrochlorothiazide is contained in combination products with e.g. ACE inhibitors (Triatec Comp® and other products) and angiotensin II receptor antagonists (Cozaar Comp® and other products), or it is given in combination with other diuretics (Sparkal® and other products).

Multaq® (dronedarone) study stopped due to cardiovascular adverse reactions

At the request of the European Medicines Agency (EMA) and the national competent authorities, the pharmaceutical company Sanofi-Aventis sent out a "dear doctor letter" at the end of July to report that the clinical study PALLAS was stopped prematurely because of several serious cardiovascular incidents – cardiovascular death, apoplexy and cardiovascular hospitalisation – in patients given dronedarone compared to the control group. The study set out to examine high risk patients with permanent atrial fibrillation (AF).

Until the findings of the PALLAS study have been reviewed more closely, doctors should pay attention to:

- The current indication of Multaq®: Adult clinically stable patients with current or previous non-permanent AF to prevent recurrence of AF or to lower the ventricular rate.
- Regular monitoring of patients to ensure that they remain within the authorised indication and do not develop permanent atrial fibrillation or symptoms that Multaq® are contraindicated for.
- Contraindications and warnings in the summary of product characteristics. With regard to cardiovascular risks, the following is particularly relevant:
  - Multaq® is contraindicated in patients with bradycardia < 50 beats per minute and in patients in unstable hemodynamic conditions, including patients with symptoms of heart failure at rest or with minimal exertion (corresponding with NYHA class IV and unstable class III patients).
  - Multaq® is not recommended for stable patients with NYHA class III or LVEF < 35 %.
  - If heart failure develops or worsens, consider suspending or discontinuing Multaq®.
  - INR should be monitored closely after initiation of Multaq® in patients taking a vitamin K antagonist (the summary of product characteristics is being updated with this recommendation).

It is also being assessed whether the PALLAS study findings influence the use of Multaq in its approved indication and whether the product information should be updated with further warnings.

Guidelines on the use of dronedarone will be issued in September.

> Multaq® has been on the Danish market since January 2010.

Please find the summary of product characteristics for Multaq® at the EMA website: *Multaq: EPAR – Product Information*

Concomitant treatment with fusidic acid and statins cause increased risk of rhabdomyolysis

The European Pharmacovigilance Working Party (PhVWP) identified several incidents of rhabdomyolysis while reviewing adverse reaction reports and medical literature on the concomitant use of fusidic acid and statins.

Warning against concomitant use of fusidic acid and statins

Due to the increased risk of rhabdomyolysis, a warning is issued against concomitant treatment with fusidic acid and statins.

In patients where treatment with systemic fusidic acid is required, the statin treatment should be discontinued during treatment with fusidic acid. The statin treatment may be resumed seven days after discontinuation of the fusidic acid treatment.

Contraindication in the summary of product characteristics of medicines containing fusidic acid

In Danish summaries of product characteristics of medicines containing fusidic acid, concomitant use of statin is contraindicated. If concomitant treatment is deemed necessary despite the contraindication, the patient must be monitored closely for symptoms of muscle weakness, pain or soreness.

The warning against concomitant use of fusidic acid and statins can also be found in *the Danish Drug Interaction Database*.

Read more in the PhVWP monthly report, July 2011, Annex 2, *here*.

The European Medicines Agency recommends limited use of anti-diabetic medicine with pioglitazone (Actos®)

The European Medicines Agency (EMA) reacts to data suggesting that diabetics treated with medicine containing pioglitazone have a slightly increased risk of bladder cancer. Therefore, EMA recommends restricting the use of this medicine.

The risk of developing bladder cancer seems to be greatest in patients who have used the medicine in large doses or for a long period of time. But it cannot be excluded that even a minor use may lead to a slightly increased risk of bladder cancer.

However, medicine with pioglitazone may still be the right option for some patients. At the same time, the Committee for Medicinal Products for Human Use (CHMP) underlines that these patients should be monitored closely:

Treating doctors should be aware of the following:

- Whether the patient has or a has had bladder cancer. If so, the patient should not be given pioglitazone.
- Patients with gross hematuria, to which a cause has not been determined, should be examined for possible bladder cancer before treatment with pioglitazone is initiated.
- Patients who are started on pioglitazone should be examined after three to six months to ensure that the patient has a beneficial effect of the treatment.

These warnings will be added to the summary of product characteristics for products containing pioglitazone.

For further information, please read EMA's press release *here*.

Actos® is the only product with pioglitazone on the Danish market. Actos® is used by approximately 350 patients in Denmark.

Limited availability of Thyrogen® (thyrotropin alfa) expected to continue in 2011 and 2012

In March 2011, the Danish Medicines Agency together with the manufacturer of Thyrogen® announced that Thyrogen® would be in limited supply until July 2011.

However, it is now estimated that the limited supply of Thyrogen® will persist throughout 2011 and in 2012 due to unexpected delays in the release of three lots destined for global markets.

Specialists who treat thyroid cancer with Thyrogen® should therefore pay attention to the following:

- No new patients should be prescribed Thyrogen®.
- In countries where Thyrogen® is still available, Thyrogen® should first and foremost be used for patients who are already treated with the product and who will not tolerate thyroid hormone withdrawal or patients for whom thyroid hormone withdrawal will not be effective.

The Danish Medicines Agency will provide regular updates on the supply of Thyrogen®.

Read more in the CHMP's monthly report from July, page 6, *here*.

The European Medicines Agency still concludes that the benefits of the smoking cessation product Champix® (varenicline) outweigh the risks.

The Committee for Medicinal Products for Human Use (CHMP) under the European Medicines Agency (EMA) has assessed a new study suggesting that the smoking cessation product Champix® (varenicline) may be associated with a risk of cardiovascular events.

The study is a so-called meta-analysis, which combines the results of 14 clinical trials involving a total of 8216 participants. The meta-analysis showed that 1.06 % of the participants on varenicline experienced serious cardiac problems compared to 0.82 % of those on placebo.

The study does not change the recommendations

The CHMP highlighted a number of methodological limitations of the meta-analysis, which meant that no firm conclusions could be drawn from the analysis.

Furthermore, the CHMP concluded that the benefits of the smoking cessation product Champix® still outweigh the risks. The CHMP has requested the marketing authorisation holder of varenicline to elaborate on the risk of cardiovascular events in the product information.

For further information, please read EMA's press release *here*.

Beta-blockers for ophthalmic use – harmonisation of product information with regard to the risk of systemic adverse reactions

The Pharmacovigilance Working Party (PhVWP) recommends harmonisation across the EU of product information for ophthalmic beta-blockers. This happens after the PhVWP has identified major product information differences regarding possible systemic effects.
After reviewing all available data, the PhVWP has published the recommended guidelines for the summaries of product characteristics concerned.

For further information, please read the PhVWP monthly report from June, Annex 1, *here*.

Update on Pandemrix® and narcolepsy

After the European Medicines Agency's latest assessment on the connection between Pandemrix® and narcolepsy, the recommendation is as follows:

- Pandemrix® should not be used in persons under the age of 20 if a seasonal flu vaccine protects against influenza H1N1. In Denmark, the seasonal flu vaccine does protect against influenza H1N1.

Since the summer 2010, the Pandemrix® vaccine has been evaluated regularly in the EU due to reports of narcolepsy in children and adolescents, especially in Finland and Sweden, but also in a number of other countries. No instances of narcolepsy have been reported in Denmark after use of Pandemrix®.

The benefit-risk balance of reboxetine (Edronax®) remains positive

The European Pharmacovigilance Working Party (PhVWP) has reviewed the safety and efficacy of the antidepressant reboxetine. The reassessment was initiated based on a meta-analysis published in November 2010[1], which concluded that reboxetine was "an ineffective and potentially harmful antidepressant".

The PhVWP has therefore reviewed the 13 trials included in the meta-analysis and reviewed the original documentation from the company and the company's responses to a detailed list of questions on the safety and efficacy of reboxetine.

The review concludes that no new and unexpected risks associated with reboxetine are identified and that the benefit-risk balance of reboxetine remains positive when it is used in accordance with the approved indication.

For further information, please read the PhVWP monthly report *here*.

Use of reboxetine in Denmark

Edronax® is the only product containing reboxetine on the Danish market. Reboxetine is authorised for acute treatment of depressive illness/severe depression and for maintaining clinical improvement in patients initially responding to the treatment.

In 2010, 1100 persons in Denmark were treated with reboxetine. According to the Register of Medicinal Product Statistics at the Danish Medicines Agency, the consumption of reboxetine has been falling over the past ten years.

From 1998 to 2010, the Danish Medicines Agency received a total of 17 reports of suspected adverse reactions concerning reboxetine. Most of the reactions reported are already known, such as rash, sexual dysfunction, dizziness, dry mouth, sweating and a sensation of incomplete bladder emptying.

[1] *Eyding D, Lelgemann M, Grouven U, Härter M, Kromp M, Kaiser T, Kerekes MF, Gerken M, Wieseler B. Reboxetine for acute treatment of major depression: systematic review and meta-analysis of published and unpublished placebo and SSRI controlled trials. Br Med J. 2010; 341: c4737.*

Magistrally manufactured testosterone 10 % for topical use – risk of virilisation in children after exposure

Children may develop virilisation after skin contact with a person using testosterone gel at concentrations higher than the authorised 1-2 %.

In Belgium, there are five reported cases of virilisation in children, where the father has used a magistral preparation of 10 % testosterone gel.

At this high concentration, only some of the testosterone is absorbed after application of the gel, and the rest remains on the skin. The testosterone remaining on the skin may be transferred to other persons through skin-to-skin contact.

The product information of the authorised concentrations of testosterone gel already includes information on the risk of transfer of the medicine through skin contact.

Doctors should instruct patients in taking the necessary precautions:

- Thoroughly wash the hands with water and soap after application of the gel.
- Once the gel has dried, the application area should be covered by clothes.
- Take a shower before any situations where close contact is expected.

Testosterone gel is used as substitution treatment for male hypogonadism.

The gel is typically applied either to both shoulders, both inner thighs, both arms or to the stomach.

Long-term use of bisphosphonates and a risk of atypical fractures

Treatment with bisphosphonates may cause atypical fractures of the femur – especially in patients who have received long-term treatment for osteoporosis. The European Medicines Agency (EMA) has reached this conclusion on the basis of a review it completed in April 2011.

The European Commission granted its final approval of this latest conclusion in July 2011, and it was decided that the product information for all medicines containing bisphosphonates must be updated, and that all marketing authorisation holders must submit/update their risk management programmes to ensure that they include atypical femoral fractures as a potential risk.

However, the benefits of bisphosphonate-containing medicines continue to outweigh their potential risks when used according to the approved indication.

Signs of atypical fractures

The fractures can occur after minor or no trauma. Many patients feel pain in the thigh or groin weeks or months before a complete fracture occurs. In that period, X-rays will often show signs of stress fracture. In some cases, the fractures may take a long time to heal.

Doctors should be aware of the following:

- The fractures often occur in both legs. Therefore, the opposite leg should also be examined in patients who have been treated with bisphosphonates and who have a femoral neck fracture.

- Risks and benefits must be assessed individually in patients with a suspected atypical femoral fracture before the treatment is stopped.

- Patients treated with bisphosphonates should be advised to contact their doctor if they experience pain in the thigh, hip or groin.

- The optimal duration of bisphosphonate treatment of osteoporosis has not been determined. Therefore, doctors should regularly review the need for continued treatment on the basis of an individual assessment of benefits and risks for each patient – especially after five or more years of use.

Doctors are encouraged to continue reporting cases of atypical fractures linked to bisphosphonate treatment to the Danish Medicines Agency at *Report a side effect*.

For further information, please read EMA's press release from April 2011 *here*.

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