Danish Pharmacovigilance Update

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Patients treated with statins at risk of developing diabetes

The European Pharmacovigilance Working Party (PhVWP) has concluded a review concerning the possible risk of developing diabetes in patients treated with HMG-CoA reductase inhibitors (statins).

The review concluded that there is evidence of a causal relationship between the use of HMG-CoA reductase inhibitors (statins) and development of diabetes in patients at high risk of developing diabetes. However, it was further concluded that overall the risk-benefit balance remains clearly positive, also in patients at high risk of developing future diabetes, and in patients who already have diabetes at the start of treatment.

The product information for all authorised statins in the EU will be updated with the following:

- A warning that HMG-CoA reductase inhibitors could raise blood glucose levels in patients at high risk of developing diabetes.
- Patients treated with statins who are at high risk of developing diabetes (i.e. those with fasting glucose 5.6-6.9 mmol/L, body mass index > 30, raised triglycerides or hypertension, should be monitored closely both clinically and biochemically.

In addition, diabetes mellitus will be included as a common adverse reaction, i.e. occurring in 1 or more patients out of 100 patients and less than 1 out of 10 patients).

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For further information, please read the *PhVWP's monthly report from December 2011*.

PhVWP review - background

The PhVWP's review was initiated on the basis of a meta-analysis published in the Lancet in February 2010, which showed that treatment with HMG-CoA reductase inhibitors is associated with a moderate risk of developing diabetes.

The review covered all available data, including clinical and non-clinical studies of the following HMG-CoA reductase inhibitors: atorvastatin, fluvastatin, pitavastatin, pravastatin, rosuvastatin and simvastatin.

Proton-pump inhibitors (PPI) and risk of hypomagnesaemia with long-term use

Proton-pump inhibitors (PPIs) may cause serious hypomagnesaemia after three months' use or longer. Therefore, magnesium levels should be monitored before treatment and periodically during treatment.

The European Pharmacovigilance Working Party, PhVWP, has performed a risk analysis on the basis of adverse reaction reports describing cases of serious hypomagnesaemia associated with PPI treatment. The PhVWP concluded that the product information of all PPI-containing medicines authorised in the EU should be updated with information about the risk of hypomagnesaemia associated with long-term treatment with PPI.

The product information of PPI-containing medicines will be updated as soon as possible.

For further information, please read the *PhVWP's monthly report from December 2011*.

New large Nordic study confirms a causal relationship between treatment with antidepressants of the SSRI type and increased risk of persistent pulmonary hypertension of the newborn (PPHN)

Previous studies have shown an increased risk of persistent pulmonary hypertension of the newborn (PPHN) in cases where the mother had been treated with a serotonergic antidepressant. As a result, the summaries of product characteristics for all antidepressants with a serotonergic effect were updated in 2010.

A new Nordic study covering a population of 11,000 children now confirms this risk for antidepressants of the SSRI type (selective serotonin reuptake inhibitors). The new study is based on a cohort of 1.6 million newborns in Denmark, Finland, Norway and Sweden, and it has followed the approx. 11,000 children whose mothers were treated with an SSRI in late pregnancy.

The study shows that the risk of PPHN in newborns who had been exposed to an SSRI is 3 out of 1000 children. In comparison, the occurrence of this disorder in non-exposed children is 1 in 1000 newborns.

The new data does not give rise to implementing further changes to the medicines' summaries of product characteristics.

Doctors should still follow the Danish Medicines Agency's previous recommendations:

- Doctors - midwives, obstetricians, etc. - should pay attention to decreases in oxygen saturation caused by PPHN in newborns of mothers who have taken a serotonergic antidepressant during pregnancy.
- Doctors should inform pregnant patients who are treated with a serotonergic antidepressant to contact the hospital immediately if their newborn child shows symptoms of PPHN - e.g. if the baby starts to breathe faster and turns bluish.

The present recommendations apply to antidepressants of the SSRI type as well as to other antidepressants with a similar serotonergic effect (duloxetine, mirtazapine and venlafaxine).

Please also see an earlier update in *Danish Pharmacovigilance Update, from April 2010.*

Please also read about the *Nordic study in BMJ* .

PPHN is a condition in which high blood pressure in the lungs prevents the newborn's blood vessels from dilating naturally, causing a sudden decrease in oxygen saturation at birth.

Symptoms of PPHN usually begin within 24 hours after birth.

Study of Rasilez® and Rasilez® HCT (aliskiren) was stopped early and has now triggered a review of efficacy and safety

At the beginning of January, a Dear Doctor Letter was distributed, which informed doctors that the ALTITUDE clinical study had been halted prematurely because the study showed no benefit of treatment and an increased occurrence of apoplexy, renal complications, hyperkalemia among patients that received aliskiren. The objective of the ALTITUDE study was to assess aliskiren's potentially beneficial effect in reducing the risk of cardiovascular and renal complications in type 2 diabetics with a relatively well-controlled blood pressure, but who were at high risk of fatal and non-fatal cardiovascular and renal complications. The patients were also treated with an ACE inhibitor or an angiotensin II antagonist at the same time.

Within the last year, approx. 3000 people have redeemed at least one prescription for aliskiren in Denmark. It is estimated that at least one third of them have type 2 diabetes because they also bought antidiabetic medication during the same period. The majority of them also redeemed at least one prescription for an ACE inhibitor and/or an angiotensin II antagonist (combination products included) during the same period. Against this background, it is estimated that potentially 1000 patients need to have their treatment evaluated according to the recommendations.

Until further analyses of the ALTITUDE study are available, doctors should pay attention the following:

- Routine check-ups (non-urgent) are recommended for patients treated with aliskiren-containing medicines (Rasilez® and Rasilez HCT®).
- Aliskiren should not be prescribed to diabetics who are treated with either an ACE inhibitor or an angiotensin II antagonist.
- Treatment with an aliskiren-containing medicine should be stopped in patients with diabetes who receive an ACE inhibitor or an angiotensin II antagonist at the same time. Alternate antihypertensive treatment should be considered if needed.
- Patients must not stop treatment with aliskiren without consulting a doctor first.

Further analyses of the ALTITUDE study could imply that these recommendations will be updated. Based on interim data from the ALTITUDE study, the European Medicines Agency, EMA, has initiated a review of the efficacy and safety data of aliskiren, to assess whether or not the benefits still outweigh the risks relative to the approved indications. Furthermore, it will be assessed if the therapeutic indications should be narrowed.

For further information, please read EMA's press release here *European Medicines Agency starts review of aliskiren-containing medicines following termination of ALTITUDE study*

Please read the article in *BMJ.*

Indication for Rasilez® and the combination product Rasilez® HCT
Rasilez® and Rasilez® HCT were authorised in 2007 and 2009, respectively, and are authorised for treatment of essential hypertension.

Rasilez® HCT is also indicated in patients whose blood pressure is not adequately controlled on aliskiren or hydrochlorothiazide used alone. It is also indicated as substitution therapy in patients adequately controlled with aliskiren and hydrochlorothiazide, given concurrently, at the same dose level as in the combination.

Risk of depression from gonatropin-releasing hormone (GnRH) agonists

Following reports of severe depression and suicide among women with endometriosis who were treated with GnRH agonists, the European Pharmacovigilance Working Party, PhVWP, has conducted a review of the evidence for a possible risk of depression linked with GnRH agonists. The reports received were evaluated taking into account that depressive symptoms are already common in patients who require treatment with GnRH agonists.

The review found an increased risk of depression in patients with endometriosis and prostate cancer as well as an increased risk of suicidal behaviour in patients with prostate cancer.

Indication for GnRH agonists
GnRH agonists are used to treat various gynaecological conditions for gonadal suppression to lower the levels of endogenous sex hormones.

Updating of product information

The PhVWP therefore recommends that the product information be updated with information on the risk of depression and mood changes for all products that contain GnRH agonists (buserelin, goserelin, histrelin, leuprorelin, nafarelin and triptorelin).

The product information should include a warning about the increased risk of depression - possibly severe in patients being treated with GnRH agonists. In addition, the package leaflets (PLs) should warn the patient about this risk and advise the patient to contact a doctor to discuss the treatment of possible symptoms. Also, mood changes and depression should be included in the section on undesirable effects with the frequency category “common” in long term use and “uncommon” in short term use.

For further information, please read the *PhVWP’s monthly report from December 2011*.

No evidence for increased risk of mortality in children treated with the growth hormone somatropin

The European Medicines Agency, EMA, decided to review all data on somatropin-containing medicines after a not yet published French epidemiological study had raised suspicion about an increased risk of mortality in children treated with somatropin, compared with healthy untreated children.

EMA’s review of the study along with all other available data have, however, not confirmed any causality.

EMA thus concluded that the benefits of the medicine continue to outweigh the risks.

Advice for prescribers

EMA reminds prescribers to strictly follow the approved indications and doses and to carefully consider the warnings and precautions for somatropin-containing medicines.

EMA has harmonised the product information for somatropin-containing medicines throughout the EU in connection with the review of data.

For further information, please see EMA’s press release here: *European Medicines Agency confirms positive benefit-risk balance of somatropin-containing medicines.*

Progressive multifocal leukoencephalopathy (PML) in connection with Tysabri® (natalizumab)

In November 2011, the Danish Medicines Agency received an adverse reaction report concerning a patient receiving Tysabri® for the treatment of multiple sclerosis.

The patient had received approx. 50 doses of the product over a period of four years. In autumn 2011, the patient developed progressive confusion and speech impairment. An MRI scan was done, and the result was consistent with PML. JC virus (polyomavirus) was subsequently detected in the patient's cerebrospinal fluid.

The Danish Medicines Agency has received a total of two reports about patients who developed PML in connection with Tysabri®. It cannot be excluded that Tysabri® is the cause of PML in these two cases.

Doctors should pay attention to the following:

- An MRI scan must be obtained before the patient is started on Tysabri®. MRI scans must be repeated once a year to update this reference.
- If PML is suspected, treatment with Tysabri® should be stopped until PML has been ruled out. The doctor should evaluate the patient to determine whether the symptoms are suggestive of neurological dysfunction and whether these symptoms are typical for multiple sclerosis or PML.

Each of the following independent risk factors are associated with an increased risk of PML:

- The duration of treatment, especially if exceeding more than two years. There is limited experience with patients treated longer than four years. The risk of PML in these patients can therefore not be estimated at present.
- The use of immunosuppressive therapy prior to treatment with Tysabri®.
- The presence of anti-JC virus antibodies.

Patients with all three risk factors are at the highest risk of developing PML - approx. nine out of 1000 patients.

Tysabri® is linked to a risk management plan, which describes special conditions to be followed, to ensure a safe and effective use of the medicine.

Please read the *risk management plan for Tysabri®* (in Danish only).

Assessment of Articain® – an anaesthetic in dental treatment

The Danish Medicines Agency has for a number of years monitored the safety of the local anaesthetic Articain® from the company Septodont. The product's safety was also the topic of discussion in the Danish media in autumn 2011.
We have requested the company to perform an extraordinary safety update report. We have received the report and are assessing it at present. The material will also be assessed by two foreign experts. We expect the overall assessment to be concluded in March 2012.

Please also see the Danish Medicines Agency's latest announcement about Articain® on our website: *Number of suspected adverse reactions reported to the Danish Medicines Agency for articaine*

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