Danish Pharmacovigilance Update

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Risk of severe liver injury with Multaq®

At the request of the European Medicines Agency (EMA) and national competent authorities, the pharmaceutical company Sanofi-Aventis has in mid-January issued a 'Dear Healthcare Professional' letter communicating that the summary of product characteristics for Multaq® (dronedarone) will be revised to include the following recommendations for use:

Section 4.4 "Special warnings and precautions for use":

- Liver function tests should be performed prior to initiation of treatment with dronedarone and then repeated monthly for six months, at months 9 and 12, and periodically thereafter.
- If ALT levels are elevated to ≥3 ×upper limit of normal (ULN), ALT levels should be re-measured within 48 to 72 hours. If ALT levels are confirmed to be ≥3 × ULN, treatment with dronedarone should be withdrawn. Appropriate investigation and close observation of patients should continue until normalization of ALT.
- Patients should be advised to immediately report to their physician any symptoms of potential liver injury (such as sustained or new-onset abdominal pain, anorexia, nausea, vomiting, fever, malaise, fatigue, jaundice, dark urine or itching).

Section 4.8 "Undesirable effects" in the summary of product characteristics will include hepatic adverse drug reactions (i.e., liver function test abnormal (frequency common ≥1/100 to <1/10) and hepatocellular liver injury, including life-threatening acute liver failure (frequency rare ≥1/10,000 to <1/1,000).

The reason behind the updated information is that since Multaq® was licensed in 2009, there have been reports of abnormal liver function tests and hepatocellular liver injury in patients treated with dronedarone, including two case reports of acute liver failure requiring transplantation. The two cases of liver transplantation occurred 4.5 and 6 months after initiation of treatment in patients with normal liver function at the start of treatment. Both patients were taking concomitant medicines, but a causal relationship with dronedarone could not be excluded.

In cases where the doctor, perhaps in consultation with a specialist in cardiology, estimates that the benefits of continued treatment with Multaq® outweigh the risks, the doctor should pay notice to the following points in the summary of product characteristics for Multaq®.

Doctors should be aware of the following:

- For patients taking dronedarone, liver function tests should be performed within the next month, and thereafter according to the recommendations in the summary of product characteristics.
- Dronedarone is contraindicated in patients with severe hepatic impairment.

Dronedarone is indicated in adult clinically stable patients with current or previous non-permanent atrial fibrillation (AF) to prevent recurrence of AF or to lower ventricular rate.

In Denmark, we have not received any reports of liver-related adverse drug reactions associated with treatment with Multaq®. Since January 2010, when Multaq® was marketed in Denmark, 810 persons have received the medicine.

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

Please find more information on Multaq® at the EMA website: *Benefit-risk review of Multaq started*

Risk of eosinophilic pneumonia with daptomycin (Cubicin®)

There have been rare but potentially serious reports of eosinophilic pneumonia associated with daptomycin (Cubicin®). The exact incidence of eosinophilic pneumonia associated with daptomycin is unknown, but to date, the reporting rate is very low (<1/10,000).

Although a large proportion of the reports relate to patients who were receiving daptomycin for non-approved indications, use of daptomycin for approved indications has also been associated with this risk.

In Denmark, we have not received any reports of eosinophilic pneumonia associated with use of daptomycin.

Healthcare professionals should be aware of the following:

- The most common symptoms of eosinophilic pneumonia include cough, fever and dyspnoea. The majority of cases have occurred after two weeks of treatment*. In severe cases, hypoxic respiratory insufficiency requiring mechanical ventilation may occur.
- Healthcare professionals should react promptly to signs of eosinophilic pneumonia in patients treated with daptomycin. Daptomycin should be discontinued immediately and the patient treated with corticosteroids if the diagnosis of eosinophilic pneumonia is confirmed.
- Do not re-administer daptomycin to patients with suspected or confirmed eosinophilic pneumonia.
- Please report any suspected adverse reactions associated with the use of daptomycin to the Danish Medicines Agency at *www.meldenbivirkning.dk*.

The summary of product characteristics will be updated shortly, and a 'Dear Healthcare Professional' letter from Novartis Healthcare A/S containing this safety information will be sent to infection pathologists and microbiologists.

Daptomycin (Cubicin®) is indicated for the treatment of complicated skin and soft-tissue infections; right-sided infective endocarditis due to Staphylococcus aureus; and Staphylococcus aureus bacteraemia when associated with complicated skin and soft-tissue infections, or right-sided infective endocarditis.

** Diagnostic findings include increased eosinophilic leukocytes in the lung tissue or bronchoalveolar lavage fluid, along with diffuse infiltrates on chest radiographs. Although clinical suspicion should be raised if there is an elevated peripheral number of eosinophilic leukocytes in the setting of pulmonary infiltrates, there have been cases of eosinophilic pneumonia where the peripheral count is normal. Therefore, the absence of peripheral eosinophilic leukocytes does not exclude the diagnosis.*

New study from Finland raises suspicion of increased risk of narcolepsy from the influenza vaccine Pandemrix®

Since the first cases of narcolepsy as a possible adverse reaction to the Pandemrix® vaccine were reported in i.a. Finland and Sweden, the European authorities have tried to investigate the possible link between narcolepsy and the influenza vaccine.

A registry study from Finland now shows that the sleep disorder, narcolepsy, could be linked to the influenza vaccine Pandemrix®. In the period 2009-2010, approx. 70 percent of Finnish children and adolescents aged 4-19 years received the Pandemrix® vaccine. Interim analyses show a nine-fold increased rate of new narcolepsy incidents among vaccinated children aged 4-19 years in Finland compared to the group of non-vaccinated children.

An increased number of reports of narcolepsy from use of Pandemrix® have also been observed in Sweden and Iceland, but not elsewhere in Europe. However, Iceland and Sweden have also experienced an increase in the number of new cases of narcolepsy in the non-vaccinated population.

In Denmark, we have not received any reports of narcolepsy, but we will of course stay updated with the development since we have used the same vaccine.

In total, at least 30.8 million people in Europe have received the Pandemrix® vaccine. As at 15 February 2011, 339 cases of narcolepsy possibly associated with Pandemrix® have been reported in the EU and EEA.

Narcolepsy is a rare sleep disorder involving sudden sleep attacks. The incidence is approx. ten in a million each year. The cause of illness has still not been established, but it is suspected to be caused by genetic and environmental factors, including infections.

Problems with peritoneal dialysis solutions from Baxter A/S persist

In December 2010, the Danish Medicines Agency announced that some batches of the peritoneal dialysis solutions Extraneal Viaflex®, Nutrineal Viaflex® and Dianeal® from Baxter A/S could be contaminated with endotoxins which may increase the risk of inflammation of the peritoneum (aseptic peritonitis). Contamination occurred during the manufacturing of the dialysis solutions.

The contamination problem has proven more difficult to solve than expected, and it is therefore not possible, at present, to guarantee endotoxin-free products on the market.

The European authorities are presently investigating what caused the contamination and are working on securing the availability of dialysis solutions through import from countries outside the EU. It will be some weeks before the replacement products will be available in adequate quantities. Until then, the current dialysis solutions are to be used despite the risk that they may be contaminated with endotoxins.

Doctors should still be alert to symptoms suggestive of inflammation of the peritoneum, e.g. cloudy effluent seen in drain bag at the end of dialysis, abdominal pain, nausea, vomiting and possibly fever.

Doctors are reminded of the importance of reporting incidents of inflammation of the peritoneum electronically to the Danish Medicines Agency on *www.meldenbivirkning.dk*

The risk of contamination with endotoxins recently came out, and, since then, the Danish Medicines Agency has received one single report of inflammation of the peritoneum for a patient who had used Extraneal in December 2010.

Read the Danish Medicines Agency's previous announcements regarding peritoneal dialysis solutions on our website:
Recommendation for doctors and dialysis patients in connection with peritoneal dialysis solutions from Baxter A/S

Insulin products and the risk of heart failure from concomitant use of pioglitazone (Actos®)

In October 2010, the European Pharmacovigilance Working Party adopted the inclusion of a warning in the summary of product characteristics for insulin products regarding concomitant use of pioglitazone.

The decision follows clinical studies that have shown a risk of heart failure, oedema and weight gain in patients with type 2 diabetes who were treated concomitantly with insulin and pioglitazone. The warning affects all insulin products.

The summary of product characteristics for Actos® already contains a description of this risk, which has made it natural also to revise the summaries of product characteristics for the remaining insulin products.

In order to gain an overview of the various insulin products, the Danish Medicines Agency sent out an inquiry in November 2010 to the EU Member States, which showed that none of the summaries of product characteristics of the more than 200 authorised insulin products contained information about the above-mentioned risk.

The work of harmonising all these summaries of product characteristics is expected to start soon.

Despite the indicated risk, combination treatment with insulin and thiazolidinediones (of which pioglitazone is the only one marketed in the EU) is still considered an option for diabetics, provided that a medical benefit-risk evaluation is done in each individual case.

For further information, please read *the CHMP monthly report*.

Danish Pharmacovigilance Update

New e-forms for reporting adverse drug reactions (ADRs) in Denmark

The Danish Medicines Agency has recently implemented a new database of adverse drug reactions called Sentinel. In this connection, we will be launching a revised version of our electronic e-forms (in Danish) for side effect reporting at end-February.

The forms have been improved and simplified, and the design has changed slightly.

Mandatory information in a Danish ADR report

An ADR report, as defined by Danish law, must fulfil four criteria. This means that the Danish Medicines Agency must be given information about each of the following:

- The adverse drug reaction
- The medicine suspected of causing the adverse reaction
- The patient's civil registration number (CPR) and /or initials
- The reporter's name and workplace.

These fields are mandatory and therefore marked with * in the form. In addition, it is also important to know if the adverse drug reaction fell under one of the five seriousness criteria; hospitalisation, disability, life-threatening condition, congenital malformation or death.

Naturally, it helps our further evaluation significantly when we are provided with as many details as possible about the course of events, which is why the form contains several questions. Some of them are conditionally mandatory, e.g. if it has been indicated that the adverse drug reaction caused the patient to die, it is mandatory to answer whether an autopsy has been performed.

New features

MedDRA terms – international medical dictionary

One of the new features is the possibility for healthcare professionals to retrieve a specific term from an international medical dictionary to describe the adverse drug reaction, cause of death, indication and other diseases/conditions in the patient.

The dictionary is called MedDRA (Medical Dictionary for Regulatory Activities) and has some 60,000 English terms to choose from, allowing healthcare professionals to select a term that best describes the concerned adverse drug reaction, symptom or diagnosis.

A drop-down list of terms to choose from appears when you enter three letters in a field, and as you type more letters, the selection of terms becomes fewer. If you prefer to write in Danish, you can disable the feature as you please.

Dictionary of medicines

When you are to enter the name of the medicine you suspect has caused the adverse reaction, you can use a dictionary which contains all the names of medicines marketed in Denmark. Like MedDRA, the dictionary of medicines uses a drop-down list.

Another new feature is that the choices of pharmaceutical form and strength now match the medicine or active substance that you choose in the dictionary of medicines. You can disable this feature, and enter the names of medicines that are not listed in the dictionary of medicines.

Look-up based on address

As before, general practitioners in Denmark have the possibility of retrieving workplace details via their provider IDs, but it is new that hospital staff can retrieve details about workplace, department, telephone number, etc. via the department's SKS code (Danish Healthcare Sector's Classification System).

Summary of your ADR report

Before clicking submit, a summary of entries is provided to make it possible to check that the entered information is correct.

Receipt

In future, a receipt will be sent by email to the provided email address. It gives us the opportunity to provide better feedback. Also, our new IT system makes it possible to target our feedback more efficiently. We are looking forward to launching it in 2011.

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