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DANISH MEDICINES AGENCY

Danish Pharmacovigilance Update

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Danish Pharmacovigilance Update

Danish Pharmacovigilance Update is an electronic newsletter for doctors intended to ensure easy access to current, updated knowledge about medicines and adverse reactions. It provides quick updates on current medicine safety issues with a practical focus for doctors.

By putting focus on special problems and applicable recommendations, we seek to support medical subscription to reduce the risk of adverse reactions.

The newsletter (in Danish) is sent out to email subscribers on the last Thursday of every month (excluding July) and is available from the website of the DKMA: *Danish Pharmacovigilance Update*

In this issue

Ciprofloxacin and risk of polyneuropathy and tendon disease/disorder

The Danish Medicines Agency (DKMA) has in March and April 2017 received two independent reports from younger men about suspected adverse reactions in connection with the use of the broad-spectrum antibiotic ciprofloxacin. The two reports concern:

- Polyneuropathy in the form of pain and a burning/tingling sensation in the extremities.
- Pain and soreness in the Achilles tendon.

Doctors should be aware of the following
Ciprofloxacin is normally well tolerated in patients, but it is important to be aware that the medicine may cause serious adverse reactions. Both polyneuropathy and tendon disease/disorder such as tendinitis and tendon rupture (especially of the Achilles

tendon) are known, although rare adverse reactions, in the use of ciprofloxacin and other fluoroquinolones. If there are signs of the development of either polyneuropathy or tendon disease/disorder related to ciprofloxacin, treatment should be discontinued. The following appears from the summary of product characteristics for ciprofloxacin:

Polyneuropathy

- Cases of polyneuropathy have been reported in patients receiving ciprofloxacin. Ciprofloxacin should be discontinued in patients experiencing symptoms of neuropathy, including pain, burning, tingling, prickling, numbness, and/or muscle weakness in order to prevent the development of an irreversible condition.

Tendon disease/disorder

- Tendinitis and tendon rupture (especially of the Achilles tendon), sometimes bilateral, may occur with ciprofloxacin, even within the first 48 hours of treatment. Inflammation and ruptures of tendon may occur even up to several months after discontinuation of ciprofloxacin treatment. The risk of tendinopathy may be increased in elderly patients, but is also seen in younger patients. The risk of developing tendinopathy is increased in patients treated concomitantly with corticosteroids (such as dexamethasone or prednisolone).
- At any sign of tendinitis (e.g. painful swelling or inflammation), ciprofloxacin treatment should be discontinued, and the affected limb should be kept at rest.
- Ciprofloxacin should generally not be used in patients with a history of tendon disease/disorder related to quinolone/fluoroquinolone treatment. Nevertheless, in very rare instances, after microbiological documentation of the causative organism and evaluation of the risk/benefit balance, ciprofloxacin may be prescribed for the treatment of certain severe infections, particularly in the event of failure of the standard therapy or bacterial resistance, where the microbiological data may justify the use of ciprofloxacin.
- Ciprofloxacin should be used with caution in patients with myasthenia gravis.

The Danish Health Authority's recommendations for use of ciprofloxacin and other fluoroquinolones

The use of ciprofloxacin and other fluoroquinolones may be necessary to treat certain infections, but the Danish Health Authority recommends restrictive use of the products. The Danish Health Authority gives the following recommendations:

Fluoroquinolones may be prescribed in the primary sector, but should only be used in connection with microbiological tests showing that other products cannot be used. Treatment with fluoroquinolones before test results are available may only be used in:

1. Patients allergic to penicillin who have acute exacerbation of chronic obstructive pulmonary disease (COPD), are clinically affected and fulfil the following criteria: increased dyspnoea, increased expectoration and increasing purulent expectorate;
2. Patients allergic to penicillin who have pyelonephritis;
3. Patients with severe gastroenteritis who have a higher risk of complications (age > 60 years, arteriosclerosis or immunosuppression) and in whom Salmonella infection is suspected;
4. Men > 35 years with epididymitis.

See additional recommendations on the use of antibiotics in the *Danish Health Authority's Guidelines on prescribing antibiotics*.

Disclaimer
All cases referred to in this article originate from the DKMA's database of adverse drug reactions. The cases have been forwarded to all relevant pharmaceutical companies and to the EudraVigilance database. Therefore, the pharmaceutical companies are not to report these cases to the DKMA.

Rosuvastatin and risk of renal effects and rhabdomyolysis

The Danish Medicines Agency, DKMA, has received a report about an elderly woman with heart disease and elevated cholesterol levels who developed fatal rhabdomyolysis and acute renal failure while receiving treatment with rosuvastatin 40 mg. The woman was known to have chronic nephropathy, which is a contraindication for the use of high-dose rosuvastatin.

The DKMA has previously received ADR reports describing 10 cases of serious rhabdomyolysis or renal effects as suspected adverse reactions to rosuvastatin treatment – none of which were fatal. In two of the cases, it is described that the patient had a history of renal impairment.

Like the other statins, rosuvastatin may in rare cases cause serious myopathy and rhabdomyolysis.

Doctors should pay special attention to the current contraindications and precautions for use in rosuvastatin's product information
The recommended start dose is 5 mg in elderly patients and patients with moderate renal impairment.

Rhabdomyolysis and other serious effects on skeletal muscle have in particular been seen with doses higher than 20 mg. Renal impairment has been observed as a suspected adverse reaction in particular with the highest dose of 40 mg. Specialist supervision is recommended when the 40 mg dose is initiated.

The 40 mg dose is contraindicated in patients with predisposing factors for myopathy/rhabdomyolysis. Predisposing factors include:

- Moderate renal impairment (creatinine clearance < 60 ml/min)
- Hypothyroidism
- Personal or family history of hereditary muscular disorders
- Previous history of muscular toxicity with fibrate or statin treatment
- Alcohol abuse
- Asian patients as pharmacokinetic studies have shown an increase in exposure in Asian subjects compared with Caucasians.
- Concomitant use of fibrates.

Like other statins, Rosuvastatin should, regardless of dose, be used cautiously in patients predisposed to myopathy/rhabdomyolysis.

Before initiating treatment, Creatine Kinase (CK) should be measured in patients with a predisposition. If CK levels are significantly elevated (>5 x upper limit of normal, ULN), treatment should not be initiated.

At the start of treatment, patients should be advised to report inexplicable muscle pain, muscle weakness or cramps immediately, particularly if associated with malaise or fever. CK levels should be measured in these patients, and the treatment should be discontinued if CK levels are markedly elevated (>5 x ULN) or if muscular symptoms are severe and cause daily discomfort.

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The DKMA's annual pharmacovigilance report 2016

The DKMA's annual pharmacovigilance report for 2016 has just been published on our website. In the annual report, you can read about the development in the number of ADR reports, gain an insight into our focus areas and the European collaboration in the pharmacovigilance area as well as see a selection of the ADR signals we processed in 2016, and much more.

Read the *DKMA's annual pharmacovigilance report 2016*.

Report on the use of and ADR reports on selected biological medicinal products now available

In September 2015, an action plan for better monitoring of biological medicinal products was initiated[1]. As part of the action plan, the DKMA has had increased focus on the reporting of suspected adverse reactions from the use of biological medicinal products – including suspected adverse reactions arising from switches between biological medicines and biosimilar products.

We have provided quarterly updates on ADR reports and consumption data here in the newsletter. During evaluation of the action plan, the DKMA has also prepared a report, which reviews the relevant scientific literature for the selected reference medicinal products and their corresponding biosimilar versions to assess if there are differences between their respective profiles of adverse drug reactions. We have also included ADR reports about selected biological medicinal products, and we have analysed the period's consumption data of infliximab- and etanercept-containing medicines.

The Danish report is downloadable here: *ADR reports on and the use of selected biological medicinal products (Danish title: Bivirkningsindberetninger om og forbrug af udvalgte biologiske lægemidler)*.

[1] Report is available in Danish only at *http://laegemiddelstyrelsen.dk/da/nyheder/2015/handlingsplan-om-biologiske-laegemidler,-biosimilaere-laegemidler-og-vacciner-2015-2016/~/media/97CF12E8D9A944DE9B536FF9899699EC.ashx*

EU's list of recommendations on safety signals

As part of routine surveillance of medicines in the EU, the Pharmacovigilance Risk Assessment Committee (PRAC) assesses signals of possible adverse reactions every month to determine whether further measures are needed to improve medicines safety.

The list of signals leading the PRAC to recommend further measures is published on the website of the European Medicines Agency (EMA) every month.

The most important safety signals discussed at the PRAC meeting from 6-9 March 2017 concern the following products:

- **Loperamide** – serious cardiac events with high doses of loperamide from abuse and misuse
- **Nivolumab**; pembrolizumab – transplant rejection.

See EU's list of recommendations on safety signals: *PRAC recommendations on signals adopted 6-9 March 2017 as well as the Danish translations of the product information.*

ADR signals
An ADR signal is a new observation that raises suspicion of a potential association between a medicine and an adverse reaction or a new aspect of a known adverse reaction, e.g. that the adverse reaction is more common than described previously.

ADR signals can come from a multitude of sources, including ADR reports, clinical studies or scientific literature.

The DKMA uses Danish ADR reports to detect possible new ADR signals. Signals about new possible adverse reactions are forwarded in the EU system to the European Pharmacovigilance Risk Assessment Committee (PRAC). The PRAC assesses if there is sufficient documentation to establish causality and, for example, if changes to the medicine's product information are warranted.

Most recent Direct Healthcare Professional Communications (DHPCs)

Below is a list of the most recent DHPCs that have been sent out to relevant doctors and healthcare professionals with safety information and updated recommendations about medicines:

- **Herceptin (trastuzumab):** Reminder about the importance of monitoring cardiac function during and after treatment with trastuzumab to reduce the frequency and severity of left ventricular dysfunction and congestive heart failure. Sent out: 22 March 2017.
- **Cotellic (cobimetinib):** Important additional warnings about haemorrhage and rhabdomyolysis in treatment with Cotellic® (cobimetinib) as well as new recommendations about dose adjustments. Sent out: 21 April 2017.

The DHPCs are available at the DKMA website – most of them in Danish only: *Direct Healthcare Professional Communication (DHPC) sent to healthcare professionals*.

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