Danish Pharmacovigilance Update #2

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Contents

News from the EU

News from the DHMA

Short news

News from the EU

Further restrictions on the use of osteoporosis medicine strontium ranelate (Protelos®)

In April 2013, the use of Protelos®, which contains strontium ranelate, was restricted to treatment of patients with severe osteoporosis at high risk of fracture due to cardiovascular effects.

A new analysis of the benefit-risk profile of strontium ranelate has now been completed by the European Medicines Agency (EMA). The analysis concluded that strontium ranelate should remain available in Europe, but should be restricted to patients who cannot be treated with other osteoporosis medicines. In addition, these patients should be evaluated regularly, and treatment should be stopped if they develop symptoms of cardiovascular disease.

Educational material will be prepared and sent out to relevant prescribers to ensure that strontium ranelate is used in compliance with the new recommendations.

Doctors should be aware of the following:

- Strontium ranelate should only be used to treat severe osteoporosis in postmenopausal women and men at high risk of fracture, for whom treatment with other medicinal products approved for the treatment of osteoporosis is not possible due to, for example, contraindications or intolerance.
- Strontium ranelate must not be used in patients with established, current or past history of cardiovascular disease (such as coronary infarction or apoplexy), or patients with uncontrolled hypertension. Treatment with strontium ranelate must be stopped if the patient develops cardiovascular disease or if hypertension cannot be controlled.
- The decision to treat a patient with strontium ranelate should continue to be based on the risk profile of that patient. Patients at risk of developing cardiovascular disease should be evaluated before treatment is started and on a regular basis thereafter, generally every 6 to 12 months.
- Doctors should reassess patients who are already treated with strontium ranelate.

Analysis results

The final recommendation by the EMA is based on an analysis of pooled data from randomised studies of some 7,500 postmenopausal women with osteoporosis. The results showed an increased risk of myocardial infarction with strontium ranelate compared with placebo (1.7% versus 1.1%), with a relative risk of 1.6 (95% CI, 1.07 to 2.38), and an increased risk of venous thrombotic and embolic events – 1.9% versus 1.3 % with a relative risk of 1.5 (95% CI, 1.04 to 2.19).

There were no signs of increased cardiovascular risk in patients without established, current or past history of cardiovascular disease, or in those with controlled hypertension. Strontium ranelate has showed an effect in the prevention of fractures – also in patients at high risk of fracture.

Danish reports on strontium ranelate

Since the marketing of Protelos® in 2004, the DHMA has received a total of 33 reports of suspected adverse reactions to strontium ranelate. Eight of them were assessed to be serious, including two cases of venous thrombosis, one case of atrial fibrillation, three cases of pulmonary embolism and one case of retinal venous occlusion.

In 2013, 1136 persons in Denmark were treated with Protelos®[1].

For further information, please see EMA's press release here: *European Medicines Agency recommends that Protelos/Osseor remain available but with further restrictions*

1) Source: Statens Serum Institut, National Institute for Health Data and Disease Control (SSI)

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

Anticoagulant therapy to be stopped before initiating treatment with the new oral anticoagulants (NOACs)

The DHMA has been informed of an incident with a patient treated for pulmonary embolism who experienced severe bleeding. Bleeding occurred in connection with the switch from anticoagulant therapy with low-molecular-weight heparin to Xarelto® (rivaroxaban) whereby the patient was prescribed both products concomitantly for several days.

In this connection, the DHMA emphasises that any other anticoagulant therapy should be stopped before a patient is started on one of the new oral anticoagulants (NOACs): Xarelto® (rivaroxaban), Pradaxa® (dabigatran etexilat), Eliquis® (apixaban) as indicated in their summaries of product characteristics.

Doctors should be aware of the following:

- When switching from low-molecular-weight heparin to NOAC, low-molecular-weight heparin must be stopped. Treatment with NOAC is then initiated at the time when the next dose of low-molecular-weight heparin was to be given. Xarelto® and Pradaxa® may, however, be initiated up to two hours before this time.

- When switching from a vitamin K antagonist, the vitamin K antagonist must be stopped. NOAC treatment should first be initiated once INR levels have dropped sufficiently. Please see each medicine's summary of product characteristics for further details.

- When switching between two NOACs, the renal function should be measured. If the renal function is normal, the NOAC can be substituted for another NOAC, with the exception of Xarelto®, where, for example, doses are given once every 24 hours. 24 hours must elapse before switching to one of the other NOACs.

Background

The three NOACs, Xarelto®, Pradaxa® and Eliquis® are characterised by being quick-acting. Therefore, no overlapping treatment is to be given when switching from other anticoagulant therapy to an NOAC.

In case of traditional oral anticoagulant therapy with vitamin K antagonists (e.g warfarin), the effect is slower. Therefore, when a switch is made from other anticoagulant treatment to a vitamin K antagonist, concomitant treatment is necessary for a few days, until INR levels are satisfactory.

Please also see the recommendations in the summaries of product characteristics for Xarelto®, Pradaxa® and Eliquis® about bridging different types of anticoagulant treatment. Also note that INR levels cannot be used to measure the anticoagulant effect of NOACs.

The DHMA still watches the consumption of contraceptive pills

The latest report on the consumption of contraceptive pills shows that doctors and patients are still following the DHMA's recommendation to use second generation pills as their first choice.

Statistics from SSI (figure 1) show that the consumption of 2nd generation contraceptive pills has increased significantly since early 2011 and is matched by a corresponding drop in consumption of the newer 3rd and 4th generation pills, which pose a slightly higher risk of blood clots.

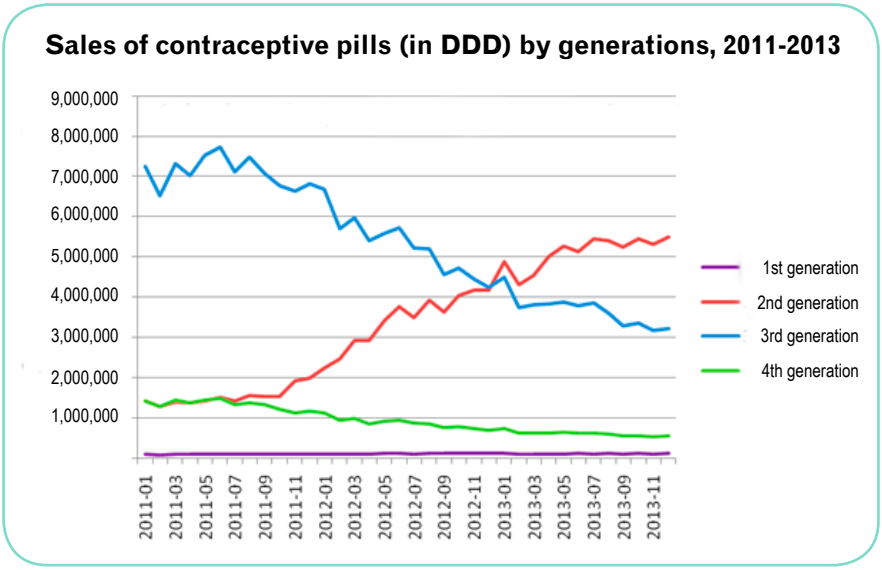

Figure 1. Consumption of contraceptive pills in Denmark from January 2011 to November 2013

Doctors should be aware of the following:

- 2nd generation contraceptive pills should still be prescribed as first choice in general.
- The benefits and risks should be weighed for women who have used 3rd and 4th generation pills for a long period without having problems – while observing the precautions for use always.
- Before prescribing contraceptive pills, a medical history should be taken and evaluated, and the woman should be informed of the risk of blood clots – including their early warning signs.
- Contraceptive treatment should be monitored regularly – especially in the beginning when the risk is highest. The fact that the woman's risks may change should also be considered.

Clozapine (Leponex etc.) and myocarditis

In December 2013, the DHMA received an adverse reaction report concerning a younger woman who developed myocarditis while she was treated with clozapine.

After one month of clozapine treatment, she was diagnosed with myocarditis. The medicine was subsequently stopped, and the woman has regained her health today.

Reports of myocarditis in connection with clozapine treatment

The DHMA has received a total of eight reports of myocarditis associated with clozapine treatment.

In 2013, 3252 people were treated with clozapine in Denmark[1].

Doctors should be aware of the following:

- Clozapine is associated with an increased risk of myocarditis which has, in rare cases, been fatal. The increased risk of myocarditis is greatest in the first two months of treatment.
- Before clozapine therapy is initiated, a medical history should be taken and a physical examination should be performed. Patients with a heart disease or abnormal cardiac findings on physical examination should be referred to a specialist for other examinations that might include an ECG, and the patient should only be treated if the expected benefits clearly outweigh the risks.
- Myocarditis or cardiomyopathy should be suspected in patients who experience persistent tachycardia at rest, especially in the first two months of treatment, and/or palpitations, arrhythmias, chest pain and other signs and symptoms of heart failure (e.g. fatigue, dyspnoea, tachypnoea) or symptoms that mimic myocardial infarction.
- If myocarditis or cardiomyopathy is suspected, clozapine treatment should be promptly stopped and the patient should immediately be referred to a cardiologist.

Indication for clozapine

The medicine is indicated in treatment-resistant schizophrenic patients and in schizophrenia patients who have severe, untreatable neurological adverse reactions to other antipsychotic agents, including atypical antipsychotics.

Treatment resistance is defined as a lack of satisfactory clinical improvement despite the use of adequate doses of at least two different antipsychotic agents, including an atypical antipsychotic agent, prescribed for adequate duration.

Leponex is also indicated in patients with psychotic disturbances occurring during the course of Parkinson's disease when other standard treatment has failed.

1) Source: Statens Serum Institut, National Institute for Health Data and Disease Control (SSI)

All cases referred to in this article originate from the Danish Health and Medicines Authority'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 Danish Health and Medicines Authority.

Remember to enter gadolinium-containing contrast agents in medical records

In 2010, a major investigation into gadolinium-containing MRI contrast agents and the risk of nephrogenic systemic fibrosis (NSF) was concluded in the EU. It brought several changes to the terms of marketing authorisation to minimise the risk of NSF.

One such term was a requirement imposed to ensure traceability through correct and harmonised entries in medical records when contrast agents are used. In recent years, the use of electronic medical records has progressed throughout the EU, and the recommendations are therefore now being updated to reflect that corresponding entries should be made in electronic medical records, cf. the Danish executive order on medical-record keeping.

Updated requirements for doctors:

To ensure the traceability of gadolinium-containing contrast agents, the product name, dose applied and batch number should always be entered in the patient's medical record:

- **When electronic medical records are used,** this information should be recorded therein.
- **When paper medical records are used,** any removable labels on vials, syringes and bottles should be placed in the medical record with an indication of the dose applied.

The product information for gadolinium-containing contrast agents will be revised to include the information on record-keeping when electronic medical records are used.

In 2013, the DHMA updated the guidelines for using gadolinium-containing contrast agents in examination of patients of with renal disease. Further information is also available in the DHMA's note on radiology of 11 December 2011: *Note on radiology (in Danish only)*.

Follow this link to read more about the EU investigation on our website: *Gadolinium-containing MRI contrast agents and risk of nephrogenic systemic fibrosis (NSF)*.

In Denmark, the following gadolinium-containing contrast agents for MRI are authorised:

Gadodiamid (Omniscan®)
Gadobenic acid (MultiHance®)
Gadobutrol (Gadovist®)
Gadoteridol (ProHance®)
Gadoteric acid (Dotarem®)
Gadoversetamide (Optimark®)
Gadopentetic acid (Magnevist®).

See the updated Danish *guidelines for examination of patients with renal disease using gadolinium-containing contrast agents for MRI*.

Development in the number of melatonin users younger than 25 years from 2007-2013

In December 2013, the DHMA published a report with an analysis of users of melatonin (magistrally manufactured and Circadin®) from 2007 to 2012 among people younger than 25 years of age.[1] *Users younger than 25 of melatonin-containing drugs (in Danish only)*.

A report for 2013 on the number of users of magistral melatonin and Circadin® is now available, and we can now look at how the number of users younger than 25 years has developed over the past two years.

In our analysis from December 2013, we concluded that it was impossible to provide the exact number of users in 2011 since magistrally manufactured melatonin was not assigned its own product number until March 2011, and it took a few months before registration of the new product number was fully implemented. Thus, it was not possible to compare the development in the number of users of magistrally manufactured melatonin from 2011 to 2012.

You can read more about the report from 2013 in Danish in the appendix to the previous report: *Development in the number of melatonin users under 25 years from 2007-2013 (in Danish only)*.

1 The analysis related to drug consumption has been prepared in collaboration with Data Delivery and Medicinal Product Statistics at Statens Serum Institut, National Institute for Health Data and Disease Control (SSI)

Short news

New study on linkage between paracetamol use during pregnancy and ADHD development in children

A new Danish study[1] suggests a possible link between the mother's use of paracetamol painkillers during pregnancy and the risk of development disorders such as ADHD (Attention Deficit Hyperactivity Disorder) in children.

DHMA maintains its recommendations so far

Based on the data from the study, the DHMA assesses that presently, there are no reasons to change the recommendations for use of pain-relieving medicines during pregnancy.

Recommended use of paracetamol during pregnancy:

- It is generally recommended that women take as little medicine as possible during pregnancy.
- Women who experience mild and/or short-term pain during pregnancy should as far as possible opt for non-medical treatment.
- In the case of pregnant women, paracetamol painkillers are still first choice for treatment of pain and fever.
- Pain-relieving medicines of the NSAID type should, due to the risk of malformations, be used cautiously in the 1st and 2nd trimesters of pregnancy and must not be used in the 3rd trimester of pregnancy due the risk of bleeding and circulatory disturbances in the child.

Further analyses are needed

The DHMA together with the European drug regulatory authorities are presently assessing the safety of paracetamol during pregnancy, and the results from the new Danish study will be included in the analysis together with other knowledge in the area.

The results of the new study

The study is a cohort study enrolling 64,000 women from the Danish birth cohort in the period 1996-2002. The results showed that children whose mothers had used paracetamol during pregnancy were at a slightly higher risk of being diagnosed with a hyperkinetic disorder like ADHD, of being treated with ADHD medicine and of having ADHD-like behaviour at the age of 7. This risk appeared to be higher, the longer the mother had used paracetamol during pregnancy.

The Danish study is a major and well-desinged study, but since there are a number of limitations in this type of study, it is not possible to conclude whether in fact there is a linkage to paracetamol use during pregnancy or whether other factors in the women have affected the results.

1 Zeyan Liew, Beate Ritz, Cristina Rebordosa, Pei-Chen Lee, Jørn Olsen. *Acetaminophen Use During Pregnancy, Behavioral Problems, and Hyperkinetic Disorders*. JAMA Pediatr. Published online February 24, 2014.

Short news

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

- **Antiemetic medicine metoclopramide (Primperan, etc.):** Indications and dose are changed to minimise the risk of in particular neurological reactions.

  Please also see the article in *Danish Pharmacovigilance Update, 19 December 2013*.

- **Cancer medicine paclitaxel formulated as albumin bound nanoparticles (Abraxane®):** Visible strands in the intravenous infusion bag.

- **Cancer medicine vismodegib (Erivedge):** Important information concerning the label on the Erivedge container as a precaution for safe use of the medicine.

- **Hormonal contraceptive pills:** Information from the DHMA about a European review of the risk of thromboembolism and use of contraceptive pills.

  Please also see the article in *Danish Pharmacovigilance Update, 31 October 2013*.

- **Sodium valproate (Deprakine and Delepsine) for epilepsy and bipolar disorder:** Notification on future short supply of Deprakine 300 mg and 500 mg gastro-resistant tablets, and Delepsine 300 mg and 500 mg gastro-resistant tablets.

The DHPCs are available in Danish at the DHMA website: *Direct Healthcare Professional Communication (DHPC) sent to healthcare professionals*.

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