Danish Pharmacovigilance Update

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Risk of administration errors for memantine oral solution (Ebixa, etc.)

Memantine for treatment of patients with Alzheimer's disease has been on the market since 2002 and is available as tablets and oral solutions.

After a pump device for oral solutions was released on the market in March 2010, several cases of overdosage have been reported. Overdosage occurred because the dose of memantine oral solution for administration via dropper applicator was mixed up with the dose for the new pump device.

Doctors should therefore advise patients and their relatives/nursing staff that

- a new pump device for memantine has been introduced, as well as instruct them on how to use the pump and the new dosing schedule.
- they must carefully read the package leaflet for the new pump device with memantine oral solution before use.

Doctors and pharmacists in Denmark will be informed about the problem by letter. The medicine's summary of product characteristics and package leaflet will be updated with a wording about the risk of overdosage and with thorough instructions about the dosage/dosing schedule.

For more information, please read page 4 of the EMA's Monthly Report: *http://www.ema.europa.eu/docs/en_GB/document_library/Committee_meeting_report/2010/10/WC500097446.pdf*

Lamotrigine (Lamictal, etc.) and risk of aseptic meningitis

Recently, the U.S. Food and Drug Administration announced that lamotrigine (used for e.g. epilepsy) could cause aseptic meningitis. Since 2008, this extremely rare adverse reaction has been included in the product information for Lamictal in the EU.

The FDA announcement caused the European Medicines Agency (EMA) to investigate whether there was cause to update the current EU product information with regard to aseptic meningitis. Based on the available data, the EMA concluded that the current product information is adequate.

In Denmark, aseptic meningitis is also included in the product information for some generic versions of lamotrigine. We expect the product information for the remaining generics to be updated soon.

The frequency of the adverse reaction is listed as unknown because it has hardly ever been seen in controlled clinical trials. In Denmark, we have registered no cases of aseptic meningitis associated with the use of lamotrigine. In 2009, about 27,000 patients were treated with lamotrigine in Denmark.

For more information, please read page 6 of the EMA's Monthly Report: *http://www.ema.europa.eu/docs/en_GB/document_library/Report/2010/10/WC500097444.pdf*

Tamoxifen and risk of reduced therapeutic response

Studies have shown that there is a risk of reduced effect of tamoxifen in breast cancer patients who are treated concomitantly with tamoxifen and medicines which inhibit the CYP2D6 enzyme, which is the case for paroxetine-containing drugs. Concurrently, a number of studies have shown that genetic variations in CYP2D6 might impact the therapeutic response in patients treated with tamoxifen. Consequently, the European Pharmacovigilance Working Party has decided to investigate the causality between treatment with tamoxifen and the inhibition of the CYP2D6 enzyme.

Tamoxifen is a selective oestrogen-receptor modulator used for the treatment of oestrogen-receptor positive breast cancer. Inhibition of CYP2D6 prevents the metabolism of tamoxifen to the active metabolite endoxifen, thus reducing the therapeutic effect.

Doctors should therefore:

- to the extent possible, avoid using medicines that inhibit CYP2D6 in patients treated with tamoxifen.
- be aware of the risk of poor responsiveness to tamoxifen in patients known to be unable to metabolise CYP2D6 properly.

Summaries of product characteristics and package leaflets for tamoxifen-containing medicines will be updated according to the above information.

For more information, please read page 2 in the EMA's Monthly Report: *http://www.ema.europa.eu/docs/en_GB/document_library/Report/2010/10/WC500097444.pdf*

Please also visit the Danish Drug Interaction Database at *www.interaktionsdatabasen.dk* for drug interactions worded in Danish

Medicines containing rosiglitazone (Avandia, Avandamet and Avaglim) have been suspended

In late September, the Committee for Medicinal Products for Human Use (CHMP) under the European Medicines Agency (EMA) recommended to suspend the marketing authorisation for rosiglitazone-containing medicine for the treatment of diabetes.

The suspension followed a review by the CHMP, which concluded that the benefits of rosiglitazone no longer outweigh its risks.

Rosiglitazone (Avandia) was authorised in the EU in July 2000 for the treatment of type 2 diabetes. Rosiglitazone was subsequently approved in combination with metformin (Avandamet) and with glimepiride (Avaglim). Since then, the use of these medicines has been further restricted several times by new warnings and contraindications on their use in patients with heart problems.

Avandia, Avandamet and Avaglim will still be available in pharmacies within the next few months. After that it will no longer be possible to redeem prescriptions for these medicines.

Doctors should:

- stop prescribing Avandia, Avandamet and Avaglim.
- review the individual patient to establish future treatment.

Patients are advised not to stop taking Avandia, Avandamet or Avaglim without speaking to their doctor first. Patients should consult the doctor/hospital in charge of their diabetes treatment to discuss future treatment options.

Read the EMA's press release here: *European Medicines Agency recommends suspension of Avandia, Avandamet and Avaglim*

Danish Pharmacovigilance Update

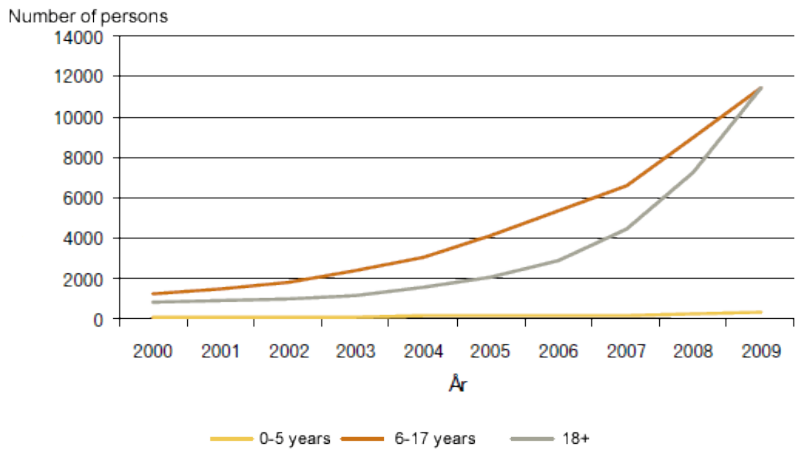
New report from the Danish Medicines Agency on the safety of methylphenidate (Ritalin, etc.) in ADHD treatment

In early 2010, we decided to look closer at the safety, the side effects and the consumption pattern for methylphenidate-containing drugs for treatment of ADHD. The review was initiated because of the recent years' explosive increase in methylphenidate consumption. See chart to the right. Our findings have just been published in a Danish report.

Our review of the data on methylphenidate consumption and adverse reactions did not give rise to immediate concern. The increase in consumption is matched by an increase in the number of adverse reaction reports for methylphenidate over the last decade. The majority of the reported adverse reactions are well-known, and we have not received any new information that would cause us to change the current safety information with regard to the use of methylphenidate for the treatment of children and adolescents with ADHD. When a particular medicine is considered for treatment, its benefits are always balanced against its side effects; and when it comes to treating children and adolescents with methylphenidate, we assess that the benefits still outweigh the risks.

But the report does point to the growing use of methylphenidate in adults with ADHD, which must be given special attention because there is no adequate documentation available for the medicine's safety in relation to this patient group.

Medicines containing methylphenidate are authorised for treatment of ADHD in children and adolescents (aged 6-18 years), and for the treatment of the rare disorder narcolepsy. Even so, in Denmark more than 11,000 adults were prescribed methylphenidate in 2009.



Number of users by age groups: Children younger than 6, children and adolescents aged 6-18 and adults > 18 years who have redeemed at least one prescription for methylphenidate-containing drug in the period 2000-2009.

Clinical experience with methylphenidate for the treatment of adults with ADHD is positive. But the report puts focus on the fact that the risk profile of methylphenidate may be different for adults with ADHD. Four risk areas have been identified, which the Danish Medicines Agency concludes are important to focus on in methylphenidate treatment of adults.

The areas are:

- Risk of cardiovascular disease,
- Lack of knowledge about treatment during pregnancy,
- Risk of abuse of methylphenidate,
- Monitoring of patients regarding serious mental disorders.

We expect the risk profile for adults treated with methylphenidate to be at least identical with the risk profile for children, but it is more difficult to minimise the risks for adults because there are no instructions in the medicine's summary of product characteristics and no detailed guide for treatment of adults – which there is for children. Increasing patient safety relies heavily on the formation of consensus on treatment of adult ADHD – which is even more important today, given the continuously growing number of adults treated with methylphenidate.

By bring attention to the treatment of adults with ADHD and potential risk factors, we will also make doctors, patients and relatives more aware of the importance of reporting possible side effects from methylphenidate. This will help improve the treatment practice and patient safety of ADHD patients.

The Danish report is downloadable here: *link*

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