Danish Pharmacovigilance Update

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Atomoxetine (Strattera®) and the risk of increased blood pressure and heart rate

A recent analysis of the overall data from controlled and non-controlled clinical trials of atomoxetine showed blood pressure and heart rate increases exceeding those expected. In November 2011, the European pharmacovigilance working party, PhVWP, decided to issue information about this new knowledge.

A number of the patients, approx. 6-12% of children and adults, experienced increased heart rate (20 bpm or more) or blood pressure (15-20 mmHg or more). Around 15-32% of these patients had persistent or progressive increases.

The SPCs will be updated with the new information as soon as possible.

For further information, please read the *PhVWP monthly report from November 2011*.

Indication for atomoxetine
Atomoxetine is licensed for the treatment of ADHD.

Increased suspicion of risk of congenital malformations with the antiepileptic topiramate (Topimax® and others)

It is well-known that the use of antiepileptics during pregnancy can cause congenital malformations. A recent review of data from two birth registries confirmed this suspicion as regards the antiepileptic topiramate[1].

Among other things, the review showed that the use of topiramate during the first trimester of pregnancy can cause increased risk of cleft lip/palate, hypospadias and deformities of other parts of the body.

This new knowledge will be added to the summary of product characteristics and the package leaflet for drugs containing topiramate as soon as possible.

For further information, please read the *PhVWP monthly report from November 2011*.

Indication for topiramate
Topiramate is licensed for the treatment of epilepsy and as a prophylactic against migraine, but topiramate may not be used during pregnancy for the latter.

Reported cases of congenital malformations with topiramate
The Danish Medicines Agency has received a total of four reports on congenital malformations in children whose mothers underwent treatment with topiramate during their pregnancy.

In 2010, 825,000 defined daily doses were sold, corresponding to 2,260 adults under continuous treatment.

1 The birth registries are 'North American Antiepileptic Pregnancy Registry (NAAED)' and the 'UK Epilepsy and Pregnancy Register'.

Pradaxa® capsules are NOT to be opened

The Danish Medicines Agency has received an enquiry regarding the anticoagulant Pradaxa® (dabigatran etexilate), asking whether Pradaxa® capsules may be opened.

The Agency would like to stress that Pradaxa® capsules are **not** to be opened. If the contents are taken without the capsule casing, the oral bioavailability of dabigatran etexilate may be increased by 75% compared to ingestion of an unopened capsule, which increases the risk of bleeding.

Advice for doctors
Doctors should therefore inform their patients not to open the capsules in order to only ingest the contents (e.g. spreading them over food or pouring them into drinks).

This information is also listed in the approved summary of product characteristics and in the package leaflet for Pradaxa®.

Pradaxa® is centrally authorised in Europe, which is why the Danish Medicines Agency has raised the issue with the European medicines agencies to discuss the possibility of further initiatives regarding the package leaflet and risk management plan for this drug.

See *summary of product characteristics for Pradaxa®*

New recommendations for the antidepressant escitalopram

In October 2011, the European pharmacovigilance working party, PhVWP, decided that the summaries of product characteristics and package leaflets for drugs containing the antidepressant citalopram will be updated with information about a lower maximum dose.

The European Medicines Agency, EMA, has since reviewed the antidepressant escitalopram and has issued new recommendations following clinical trials showing a dose-dependent prolongation of the QT interval as well as adverse reaction reports of cases involving heart rate impact.

New recommendations
For elderly patients, the maximum dose is reduced to 10 mg per day, and for patients with reduced liver function, the maximum dose remains 10 mg per day. The previous maximum adult dose is retained at 20 mg per day.

The Danish Medicines Agency supports the new dosage change.

It will be a few months, however, before the package leaflets have been updated with the new information regarding the lower dose.

Please note the following items in the summary of product characteristics for escitalopram:

- Escitalopram is contraindicated in patients with known prolongation of the QT interval, including congenital long QT syndrome.
- Use of escitalopram with other drugs known to prolong the QT interval is contraindicated.
- Caution must be exercised when used for patients with an increased risk of developing torsade de pointes, e.g. patients with heart failure, recent myocardial infarction, bradyarrhytmias or patients susceptible to hypokalaemia or hypomagnesaemia due to other illness or concomitant use of other drugs.

For further information, please read the *PhVWP monthly report from November 2011*.

Indication for escitalopram
Like citalopram, escitalopram is an antidepressant of the SSRI type (selective serotonin reuptake inhibitor), used e.g. for the treatment of moderate to severe depression and panic disorder.

Tibolone and a potential risk of thromboembolisms, myocardial infarction, breast cancer and ovarian cancer

The European pharmacovigilance working party, PhVWP, has reviewed new data from various epidemiological studies on the relationship between the use of tibolone (Livial® and Tibolon Orifarm) and the risk of thromboembolisms, myocardial infarction, breast cancer and ovarian cancer.

On the basis of the new data it was concluded that:

The risk of venous thromboembolisms (VTEs) is lower than for users of other hormone replacement therapy (HRT) drugs. The studies only included a small number of users, and it cannot be ruled out that there is a slightly elevated risk of VTE compared to the control group.

There is no evidence to suggest that tibolone reduces the risk of myocardial infarction in postmenopausal women.

The risk ratio for breast cancer in women using tibolone is 1.3, for HRT drugs only containing oestrogen it is 1.2, and for HRT drugs containing oestrogen and progestagen, it is 1.7.

The relative risk of ovarian cancer is comparable to the risk observed for users of other types of HRT drugs.

The SPCs will be updated with the new information as soon as possible.

For further information, please read the *PhVWP monthly report from November 2011*.

Indication for tibolone
Tibolone is licensed for the treatment of menopausal oestrogen deficiency symptoms and for the prevention of osteoporosis.

Reports on thromboembolisms, myocardial infarction, breast cancer and ovarian cancer
Up until 31 October 2011, the Danish Medicines Agency had received a total of two adverse reaction reports involving women who developed breast cancer, and six cases involving thromboembolic events in connection with the use of tibolone.

The Agency deems it to be likely that there is a relationship between these adverse reactions and the use of tibolone.

The Agency has not received reports on cancer or myocardial infarction in connection with the use of tibolone.

In 2010, 2,913 persons received treatment with tibolone.

Rosuvastatin and the risk of gynaecomastia

The European pharmacovigilance working party, PhVWP, recommends updating the product information for rosuvastatin with information about the risk of the very rare adverse reaction gynaecomastia.

This recommendation is made on the basis of adverse reaction reports involving cases of gynaecomastia following the use of rosuvastatin.

Therefore, a relationship between rosuvastatin and gynaecomastia cannot be ruled out. However, non-clinical data have not demonstrated an effect of rosuvastatin on the mammary glands.

For further information, please read the *PhVWP monthly report from November 2011*.

Indication for rosuvastatin
Rosuvastatin is licensed for the treatment of hypercholesterolemia and for the prevention of cardiovascular events.

In October, the Danish Medicines Agency received two reports involving cases of lactic acidosis in patients undergoing treatment with metformin for the treatment of type 2 diabetes

The first report involved an elderly patient with diabetes 2 and chronic renal impairment, undergoing treatment with metformin. The patient was hospitalised acutely with digestive tract bleeding.

The second report also involved an elderly patient undergoing treatment with metformin. However, this patient was also undergoing treatment with the HIV drug Viread®. The patient was hospitalised with lactic acidosis and renal impairment and with suspected reduced intestinal blood supply. Viread® can affect the kidneys and lead to renal failure, nephritis.

Up until November 2011, the Danish Medicines Agency had received a total of 11 serious reports involving patients who developed lactic acidosis in connection with the use of metformin. Two of these reports involved a combination product.

The 11 reports all involve patients aged 49 or more with type 2 diabetes. Some of the reports described that patients had been diagnosed with renal impairment, but the metformin dose had not been correspondingly reduced.

Advice for doctors
Metformin is secreted through the kidneys, which is why the serum creatinine level should be determined before treatment start and then regularly at least once a year in patients with normal renal function and at least 2-4 times annually in patients with serum creatinine levels at the upper normal range limit as well as for elderly patients.

The lactic acidosis incidence rate can and should be reduced by also evaluating other related risk factors, such as poorly controlled diabetes, ketosis, long-term regular, excessive alcohol use, renal impairment and any condition related to hypoxia.

Reported cases of lactic acidosis
Lactic acidosis is a rare, but serious metabolic complication (high mortality in the absence of quick treatment) which can occur due to metformin build-up. Reports on cases of lactic acidosis in patients undergoing treatment with metformin have primarily involved diabetic patients with significant renal impairment.

Consumption analysis of Daxas® for COPD patients with known depression

The Danish Medicines Agency has carried out a consumption analysis of Daxas®, which is licensed for the treatment of severe chronic obstructive pulmonary disease (COPD) in order to determine compliance with the drug warning against potential mental disorders. We have investigated how many patients were prescribed Daxas® in the period from 1 September 2010, when Daxas® was approved, until 30 June 2011, and who (before or after prescription) underwent treatment with an antidepressant.

A total of 563 patients were prescribed Daxas® during this period. Of these, 29% had redeemed a prescription of at least one antidepressant within six months of the first prescription redemption for Daxas®. The vast majority of these continued treatment with antidepressants after start-up of treatment with Daxas®.

In addition, 24 patients were prescribed antidepressants after prescription of Daxas®. The analysis does not indicate whether this was due to adverse reactions from Daxas®, and it was not investigated whether the patients underwent treatment with other drugs that may have a psychiatric adverse reaction profile.

A total of 26% redeemed a prescription for antidepressants following start-up of treatment with Daxas®.

Indication for the antidepressants used concomitantly with Daxas®
Antidepressants have been selected as a broad marker for the depression diagnosis. Antidepressants can be used for indications other than depression, e.g. for the treatment of neuropathic pain. A review of the indications on the prescriptions showed that the vast majority had the indication depression.

Indication for Daxas®
Since 1 September 2010, Daxas® has been licensed for the treatment of severe chronic obstructive pulmonary disease (COPD) with previous repeated exacerbations. Daxas® is only licensed for maintenance treatment together with bronchodilators.

Daxas® is subject to a so-called risk management plan, describing a number of additional activities to the usual monitoring of the medicine's safety to be implemented to ensure the highest possible safety and effect when using the drug. The reason for the risk management plan requirement is that clinical studies have shown very serious adverse reactions that require additional monitoring.

The same doctor prescribing Daxas® and antidepressants to the same patient
For more than 7 out of 10 patients undergoing treatment with Daxas®, who had either previously or concomitantly undergone treatment with an antidepressant, the same doctor prescribed Daxas® as well as the antidepressant, indicating that the doctor had knowledge of both diagnoses. Daxas® was typically prescribed by the patient's general practitioner.

However, the analysis cannot indicate whether the doctor knew about the increased risk of psychiatric adverse reactions in these patients. On the other hand, the analysis does offer a clear signal that a large part of the patients definitely suffered from psychiatric disorders.

Analysis delimitation
The antidepressants analysis is only based on a single marker, which was the prescription of one or more antidepressants before or during treatment with Daxas®. The analysis says nothing about the risk profile in the patients undergoing treatment with antidepressants.

Advice for doctors
Doctors should carefully consider the advantages and disadvantages of start-up of treatment with Daxas® for patients with current or previous mental disorders, or if concomitant treatment is planned with other drugs with a known psychiatric adverse reaction profile.

Daxas® and increased risk of mental adverse reaction
Daxas® is associated with increased risk of severe mental adverse reactions such as insomnia, anxiety, nervousness and depression. Rare cases of suicidal ideation – involving suicidal thoughts and behaviour (including suicide) – have been seen in clinical studies. Since the approval of the product, the Danish Medicines Agency has received one adverse reaction report involving a suicide and one involving a suicide attempt. The Agency cannot rule out a relationship between these events and Daxas®.

Childhood vaccinations and adverse reactions in the third quarter of 2011

One of the Danish Medicines Agency's focus areas is potential adverse reactions from vaccinations.

The Vaccinationspanelet (Danish medical scientific vaccination panel), represented by the Danish Medicines Agency, the Danish National Board of Health and the Danish State Serum Institute, convenes once a quarter to assess the suspected adverse reactions reported from vaccines – primarily suspected adverse reactions from vaccines involved in the childhood immunisation programme.

Vaccine	Total no. of reports for third quarter by vaccine
Diphtheria-tetanus (DTa) booster	4
DTa-pertussis-polio (DTaP-IPV) booster	7
DTaP-IPV/Act-Hib	3
Gardasil®	9
Prevenar®	2
Priorix®	11
Tetanus®	1
Total	**37**

Our October issue featured an article on adverse reactions in connection with the childhood immunisation programme for the first half of 2011, and we have now reviewed the third quarter of 2011.

No changes in the routine programme
The third quarter of 2011 saw no new changes in the Danish childhood immunisation routine programme. It is estimated that the figure of 80-90 per cent of children being vaccinated, depending on the vaccine, is unchanged.

Adverse reaction reports for the third quarter
In the third quarter, the Danish Medicines Agency received a total of 35 reports involving the childhood immunisation programme. If reports on the HPV vaccine Gardasil® are subtracted, 15 reports (58%) involved suspected adverse reactions in girls/women.

The vast majority of the adverse reactions reported were well-known, such as local reactions at the injection site and general malaise, i.e. general symptoms such as fatigue, fever, pain, local irritation (43%), rash and temporary changes of the skin (22%), nausea and vomiting (2%).

A total of nine reports were classified as serious.

The vaccines were given to patients aged 0-55 years. The third quarter saw several adverse reaction reports involving adults who had been vaccinated with diphtheria-tetanus booster, Priorix® and Gardasil®.

The table shows the distribution of the number of reports for the various vaccines in the third quarter of 2011.

For Gardasil®, there were no occurrences of eczema following vaccination, as opposed to 2009, when there was focus on this suspected adverse reaction and consequently many reports.

Unknown adverse reactions classified as non-serious and applicable to all vaccines were: increased perspiration, increased hair growth and one case of exanthema subitum.

Adverse reactions classified as serious:

1. 10 days after vaccination with DTa booster and Havrix: One case of unilateral loss of hearing ('sudden deafness') in a 33-year-old woman. Hearing has not yet returned. This is not a known adverse reaction from any of the vaccines and has only be described in case reports with relation to other vaccines, and a relationship is therefore deemed to be less likely.

2. Development of pain, swelling and redness at injection site in 5-year-old boy on the same day as vaccination with DTaP-IPV booster. Immediately treated with antihistamine and on day 2 with oral prednisone.

3. 1-year-old boy vaccinated with Priorix® developed left-foot limp 4 days after vaccination and fever approx. 14 days after vaccination. The symptoms disappeared spontaneously. Insufficient information available.

4. 12-year-old girl vaccinated with Priorix® and Gardasil® fainted the

next day. Developed morbilliform rash 3 days after vaccination, glands were swollen. Developed fatigue and fever for 4 days, 13 days after vaccination. The girl is now fine.

5. 3-year-old girl fainted immediately after vaccination with Priorix® vaccine, hospitalised for observation. Unclear if this was actual anaphylaxis or fainting. The patient is now fine.

6. 1-year-old boy vaccinated with Priorix® developed fever and swollen lymph nodes after 7 days. Confused and unsure gait on day 9. Checked for ADEM (acute disseminated encephalomyelitis) using lumbar puncture; diagnosis ruled out. The patient is now fine.

7. 43-year-old woman vaccinated with Gardasil® developed voice problems and vocal cord dysfunction the next day. Symptoms at follow-up time still present. A relationship to the vaccine is deemed to be less likely.

8. A 4-year-old boy developed afebrile seizures 3 weeks after vaccination with Priorix®. Additional seizures occurred later and he was diagnosed with epilepsy. Based on literature, afebrile seizures are no more frequent after measles, mumps and rubella vaccination than corresponding to the background rate. It is therefore deemed to be less likely that a relationship exists.

9. 12-year-old girl vaccinated with Gardasil® developed tonic-clonic seizures 73 and 83 days after vaccination. EEG is compatible with idiopathic generalised epilepsy. There is a family predisposition for epilepsy. It is deemed to be less likely that a relationship to the vaccine exists.

Overall conclusion for the third quarter of 2011

The Danish Medicines Agency received a total of 168 reports throughout 2010. The number of reports thus appears to be stable in the third quarter of 2011 in comparison.

Among the serious adverse reactions, two patients were diagnosed with epilepsy and one adult patient developed loss of hearing following DTa booster. In all three cases, a relationship between vaccination and the disorders is deemed to be less likely.

The third quarter saw an increase in the number of adult patients receiving vaccines included in the childhood immunisation programme with subsequent reports of suspected adverse reactions.

There were five reports of serious adverse reactions after vaccination with Priorix® in the third quarter, which is a proportionately higher percentage than in previous quarters, but the figures continue to be quite low.
The adverse reactions described for Priorix® have no special pattern. Only two of the reports involve the same batch number.

The other adverse reactions reported were largely well-known, primarily with local reactions at the injection site and general malaise, fever and pain.

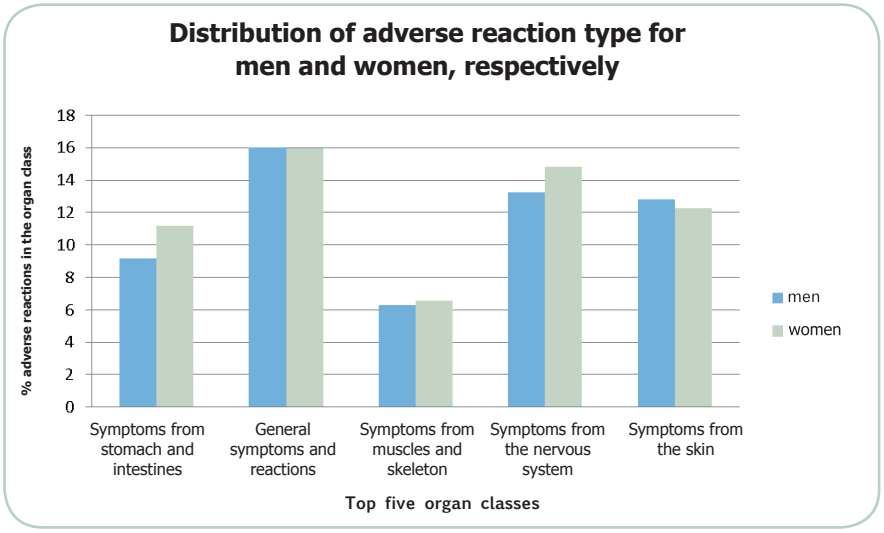
The Danish immunisation programme continues to appear safe, based on the adverse reaction reports received by the Danish Medicines Agency in the third quarter of 2011.

Gender differences in adverse reaction reports

According to the Danish Consolidation Act on Gender Equality (*Ligestillingsloven*), gender equality must be incorporated in all public administration and task handling.

The Danish Medicines Agency has investigated whether gender differences exist concerning the number and type of adverse reaction reports in the Agency's adverse reaction database.

The study included adverse reaction reports received by the Agency in the period 2005-2010.



Percentage distribution of adverse reactions between the five most frequently reported organ classes. The Y axis indicates the percentage represented by the organ class out of all adverse reactions reported for men and women, respectively.

More adverse reaction reports involving women
During the period, the Agency received a total of 17,642 adverse reactions reports, but the patient's gender is only known for 17,372 reports. A review of the reports reveals that 11,494 (66%) pertained to women, whereas 5,878 (34%) pertained to men. A significant predominance of the reports thus involved adverse reactions in women compared to men.

Men and women often report the same types of adverse reactions
An adverse reaction report may include several suspected adverse reactions. An overall assessment of the adverse reactions reported at organ class level [a] shows that the types of adverse reactions are distributed equally between the genders. For both genders, the most frequently reported adverse reactions by organ classes are: symptoms from the skin, general symptoms and reactions and symptoms from the nervous system, which can also be seen in the figure above.

Larger proportion of serious reports involving men
Of the total number of reports during the period mentioned, 7,417 (43%) were classified as serious [b].

Among the women, 4,592 (40%) of the adverse reactions reported were classified as serious, whereas that figure is 2,825 (48%) for the reports involving men. There is thus a higher proportion of serious adverse reaction reports among men.

Who submits reports?
In Denmark, patients and relatives have had the possibility of reporting since the summer of 2003. When it comes to serious adverse reaction reports, there are no gender differences. 80-90% of reports are submitted by a doctor, whereas the remainder is reported by patients themselves or by relatives.

For non-serious adverse reactions, the trend seems to be that women submit reports slightly more frequently than men – 35% of the non-serious adverse reaction reports involving women were submitted by the woman herself or her relatives. For men, the corresponding self-reporting figure is approx. 23%.

a The adverse reactions in the adverse reaction database are classified on the basis of the Medical Dictionary for Regulatory Activities (MedDRA), an international and clinically validated medical terminology used by all medicines agencies and industries for coding adverse reactions, diseases and other events. It is divided into five levels. The top layer, System Organ Class, is the widest definition based on where in/on the body the event occurs.

b A serious adverse reaction is defined as an adverse reaction which is fatal, life-threatening, causes or prolongs hospitalisation, or causes permanent or significant disability, or which is a congenital anomaly or birth defect. An adverse reaction report is classified as serious if it contains one or more serious adverse reactions.

Conclusion

The Danish Medicines Agency's review of the adverse reaction reports received during the period 2005-2010 has shown that the majority involves women, but that the proportion of adverse reaction reports classified as serious is larger among men, which is consistent with literature[1].

There may be different reasons for the gender differences in connection with adverse reaction reports. On the one hand, there may be gender-specific physiological differences in pharmacokinetics and pharmacodynamics, but it may also be the case that men and women use the health sector in different ways, e.g. in relation to when or how often the doctor is consulted. A higher medicine consumption among women may also have influenced the study results[1,2,3].

Contrary to literature, we found no significant gender differences in this review when we look at the most frequently reported adverse reactions at System Organ Class level[4]. However, the three organ classes most frequently involved in reports generally correspond well to a previous study[5].

This study only reviewed the overall trends for adverse reaction types reported for all medicines at organ class level. It would require further in-depth investigations and statistical analyses to conclude whether gender distribution differences exist in relation to specific symptoms or in connection with treatment involving specific types of medicine.

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When is it important for doctors to report adverse reactions to the Danish Medicines Agency?

In accordance with the Danish Executive Order on reporting of adverse reactions to medicines, etc., doctors are obliged to report all adverse reactions occurring during the first 2 years from marketing of a specific type of medicine is initiated, after which the obligation to report includes all serious and/or unexpected adverse reactions for all medicines.

An adverse reaction is **serious** if it:

- Is fatal
- Is life-threatening
- Causes or prolongs hospitalisation
- Causes permanent or significant disability
- Causes congenital anomaly or birth defect.

An adverse reaction is **unexpected** if it is not listed in the summary of product characteristics for the medicine. Please see *www.produktresume.dk*

You can report adverse reactions at *report a side effect or incident*

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