Danish Pharmacovigilance Update
Year 4 #1
17 January 2013

The Pharmacovigilance Risk Assessment Committee, PRAC, finds that the risks outweigh the benefits from the use of Tredaptive®

In December, a review of benefits and risks was initiated for the drug Tredaptive® triggered by the release of results from a large, long-term study with more than 25,000 patients. The review showed that the risks from the use of this drug outweigh the beneficial effects. Therefore, the PRAC recommends withdrawal of Tredaptive® from the European market. However, the final decision will not be made until the 14-17 January 2013 meeting of the EMA's Committee for Medicinal Products for Human Use, CHMP.

Until the CHMP has made its final decision, doctors are recommended not to start new patients on Tredaptive®. Patients currently using the drug may continue their treatment or discuss their future treatment with the initiating doctor.

Higher frequency of serious adverse reactions from the use of Tredaptive® as an add-on therapy

The assessment is based on the results from a large, long-term study with more than 25,000 patients comparing the effects of adding Tredaptive® to statins. The results indicate that adding Tredaptive® does not reduce the risk of serious vascular events compared with statins alone. Furthermore, a higher frequency of various serious, but non-fatal adverse reactions was seen in patients taking Tredaptive® in addition to statins. The adverse reactions included bleedings, muscle weakness, infections and diabetes, among others.

Letters have been sent to all relevant doctors and professional organisations to inform them about the initiation of the review. If a final decision is made to withdraw Tredaptive®, another letter will be sent in week 3.

The CHMP's decision will be published on *the Danish Health and Medicines Authority's website* (in Danish only).

You can read EMA's press release here: *European Medicines Agency starts review of Tredaptive, Pelzont and Trevaclyn.*

Indication for Tredaptive®

Tredaptive® is approved for the treatment of adults with dyslipidaemia, particularly primary hypercholesterolaemia and combined dyslipidaemia. Persons suffering from combined dyslipidaemia have elevated levels of LDL cholesterol and triglycerides and low levels of HDL cholesterol. Tredaptive® is a combination of nicotinic acid and laropiprant. Tredaptive® is also approved under the names Pelzont® and Trevaclyn® in Europe.

All cases referred to in the articles in the Danish Pharmacovigilance Update originate from the Danish Health and Medicines Authority's adverse reaction database. 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.

Sundhedsstyrelsen
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Information to doctors concerning the correct use of the approved dosing regimen for bivalirudin (Angiox®) in percutaneous coronary intervention

The EMA's Committee for Medicinal Products for Human Use, CHMP, has decided that a letter must be sent to doctors and other healthcare professionals to inform them about the need to follow the approved dosing for Angiox®. The decision is based on reports of inappropriate use of Angiox® in percutaneous coronary intervention (PCI). The reports described that some patients have only received an intravenous bolus dose of Angiox®, without the required subsequent intravenous infusion. Such underdosing will lead to inadequate ischaemic protection within a few minutes due to the short half-life of bivalirudin (25 minutes).

As a doctor you should be aware of the following:

- Patients who are to undergo PCI should be given an intravenous bolus injection of 0.75 mg/kg body weight followed immediately by an intravenous infusion of 1.75 mg/kg/hour during the entire PCI procedure, as a minimum. This dosing regimen is required to achieve and maintain the plasma concentration needed to ensure effective ischaemic protection during PCI.
- Failure to initiate intravenous infusion immediately after the intravenous bolus injection will result in a sub-therapeutic plasma concentration of bivalirudin.
- Following primary PCI, patients must be monitored closely for signs and symptoms consistent with myocardial ischaemia.
- Renal impairment: Since approx. 20% of the bivalirudin is excreted via the kidneys, patients with moderate renal impairment should receive a reduced dose. The intravenous infusion dose should be reduced to 1.4 mg/kg/hour in patients with moderate renal impairment (GFR 30-59 ml/min), and the activated coagulation time should be monitored. The intravenous bolus dose remains 0.75 mg/kg for all patients.
- Bivalirudin is contraindicated in patients with severe renal impairment and in dialysis-dependent patients.

Indication for Angiox®

Angiox® is indicated as an anticoagulant in adult patients who are to undergo percutaneous coronary intervention (PCI), including patients with ST-elevation myocardial infarction (STEMI) who are to undergo primary PCI.

Angiox® is also indicated in adults with unstable angina/non-ST-elevation myocardial infarction (UA/NSTEMI) in case of urgent or early intervention.

New recommendations for the use of the tissue adhesives Tisseel®, Tissucol®, Artiss® and Beriplast®

The EMA's Committee for Medicinal Products for Human Use, CHMP, has reviewed the benefits and risks of the tissue adhesives Tisseel®, Tissucol®, Artiss® and Beriplast P®. The review was initiated following concerns over the risk of air embolisms when these products are administered using a pressurised air regulator. Even though the risk of air embolisms from the use of these products is very low, it cannot be ruled out. Therefore, the CHMP has recommended a number of new instructions with the aim of optimising the safety of these products, when they are given by spray application during surgical procedures. These recommendations are in line with the CHPM's recommendations for Evicel®, which were presented in *Danish Pharmacovigilance Update in December 2012*.

For the tissue adhesive Beriplast P®, the CHMP concluded that no risk is associated with this product as it is applied without the use of a pressurised air regulator.

*Please note that only Artiss® and Tisseel Duo Quick® are marketed in Denmark. In August, Tisseel Duo Quick® will be replaced by Tisseel®.

As a doctor you should be aware of the following:

Tisseel®*, Tisseel Duo Quick® and Artiss®:

- During open surgery: when applying tissue adhesives using a pressurised air regulator, the pressure must not exceed 2.0 bar (28.5 psi). The product must be sprayed at least 10 cm from the tissue surface.
- Prior to applying a tissue adhesive, the wound area must be wiped using standard techniques only (e.g., repeated use of compresses, gauze, and use of a suction device).
- Blood pressure, pulse, oxygen saturation and end-tidal CO_2 should be closely monitored when spraying tissue adhesive using a pressurised air regulator, because of the possibility of air or gas embolism.

Tisseel®*, Tisseel Duo Quick®:

- During laparoscopic procedures: when applying the product using a pressurised air regulator, the pressure must not exceed 1.5 bar (22 psi). The product must be sprayed at least 2 cm (recommended distance 2 to 5 cm) from the tissue surface.

Artiss®:

- Artiss® is intended for subcutaneous use only. Artiss® is not indicated for laparoscopic use.

A letter will be sent to doctors treating with Tisseel Duo Quick® and Artiss® to inform them about the new recommendations. The summaries of product characteristics for Tisseel Duo Quick® and Artiss® will also be updated with the new information.

Indication for Tisseel Duo Quick® and Artiss®

Artiss® is used to adhere subcutaneous tissue and to stop local bleedings on subcutaneous surfaces.

Tisseel Duo Quick® is used to adhere tissue and to stop local bleedings.

Monovalent and multivalent vaccines against measles, mumps, German measles (rubella) (MMR) and/or chickenpox (varicella) (MMRV) should continue to be avoided during pregnancy and in patients with a weakened immune system

On 13 December 2012, the European Medicines Agency, EMA, completed a review of the safety of monovalent and multivalent vaccines against measles, mumps, German measles (rubella) and/or chickenpox (varicella) (MMR/MMRV) during pregnancy and in patients with immune deficiencies.

The EMA's Committee for Medicinal Products for Human Use, CHMP, concluded that these vaccines should continue to be avoided during pregnancy, but that vaccination of pregnant women with vaccines containing measles, mumps and/or rubella should not be a reason for termination of pregnancy. In addition, MMR/MMRV should continue to be avoided in patients with a severely weakened immune system, but their use could be considered in patients with less severe immune deficiencies.

The Committee also recommended that some changes be made to the product information to clarify the risks and precautions to be taken.

As a doctor you should be aware of the following:

- Vaccination with MMR/MMRV remains contraindicated during pregnancy and in patients with severe humoral or cellular immunodeficiency (such as severe combined immunodeficiency, agammaglobulinaemia or AIDS).
- Women should be advised to avoid becoming pregnant for one month after MMR/MMRV vaccination. Vaccination with rubella-containing vaccines during pregnancy is not a reason for termination of pregnancy.
- In children with HIV infection, vaccination is contraindicated in those with age-specific CD4+ percentages of less than 25% aged below 12 months, less than 20% in those aged between 12 and 35 months, or less than 15% in those aged between 36 and 59 months.
- Vaccination may be considered in patients with certain immune deficiencies where the benefits outweigh the risks of vaccination (e.g., asymptomatic HIV-infected patients, patients with selective IgG subclass deficiencies, congenital neutropenia, chronic granulomatous disease and complement deficiencies).
- Immunocompromised patients who are vaccinated cannot develop adequate immunity and should be monitored for subsequent development of measles, mumps, rubella or varicella following contact with these diseases.

The European Commission's decision on this opinion will be issued later.

For further information, please visit the EMA's website: *Questions and answers on the review of monovalent and multivalent measles, mumps, rubella and/or varicella vaccines*

Reports of adverse reactions comprising hearing loss and memory problems in association with the use of tadalafil (Cialis®)

In November 2012, the Danish Health and Medicines Authority (DHMA) received two adverse reaction reports concerning men using Cialis® for the treatment of erectile dysfunction. One of these men often experienced varying hearing intensity 4-8 hours after taking the product. The other report describes that the user experienced memory loss for 2-4 hours after taking the product. He was admitted to a neurological department.

The DHMA has received a total of eight adverse reaction reports of hearing problems (hearing loss, tinnitus) and four reports of temporary memory loss in association with the use of PDE-5 inhibitors. Some of the reports describe that the hearing loss was temporary.

Hearing loss as well as temporary memory loss are described in the summaries of product characteristics.

Indication for tadalafil
Used for the treatment of erectile dysfunction in adult men.

The Danish Health and Medicines Authority has prepared a new status report for Pradaxa® (dabigatran etexilate) and Xarelto® (rivaroxaban)

In a new report, the DHMA briefly describes the status of the consumption and adverse reactions reported for the products Pradaxa® and Xarelto®, which have been marketed for the new indication of atrial fibrillation within the past year.

This status shows that adverse reactions in the form of serious bleeding are still seen. Also, six cases of deaths associated with these bleeding episodes have been reported to the DHMA.

As a doctor you should be aware of the following:

- Prescribers of anticoagulant therapy should draw particular attention to the patient's age and overall bleeding risk. Elderly patients are at an increased risk of bleeding, per se.
- It is important to monitor the renal function closely, since the renal elimination pathway is important for these products to different degrees. Therefore, the dose recommendations depend on the renal function. Pradaxa® is contraindicated in patients with severe renal impairment (creatinine clearance (CrCL) < 30 ml/min), and Xarelto® should not be used in patients with a creatinine clearance (CrCL) < 15 ml/min).
- Several medical conditions and concomitant use of other medicines may increase the risk of bleeding associated with anticoagulant therapy. This is described in the summaries of product characteristics for the individual drugs.

Read the entire report on the DHMA's website. *News on Pradaxa®(dabigatran etexilate) and Xarelto® (rivaroxaban).*

The most frequent drugs in adverse reaction reports concerning children/foetuses are nervous system drugs (ATC group N)

The Danish Health and Medicines Authority has performed an analysis to gain an overview of all mother-child cases in the Danish adverse drug reaction database. A mother-child case is a report of a suspected adverse reaction in a child/foetus resulting from a parent's, typically the mother's, medicine use.

The analysis concluded that:

- When comparing the number of reports to the increasing consumption of drugs among women of child-bearing potential, the reporting frequency for SSRIs is significantly higher than for other groups of drugs, which may be partly ascribed to the stimulated reporting resulting from the heavy media coverage at the end of 2010 and during 2011.
- The most frequently reported drugs concerning children/foetuses are nervous system drugs (ATC group N).
- Based on a review of the summaries of product characteristics for the various drugs, it remains very important to monitor the safety of drugs in pregnant and lactating women. Therefore, doctors are encouraged to report suspected adverse reactions to the DHMA.

Analysis

Since the thalidomide case in the 1960s, the manufacturers of new drugs have been very cautious about studying their effect on pregnant women. Also, a review has shown that the majority of the summaries of product characteristics for the various drugs state that the data concerning use in pregnant women are insufficient, for which reason treatment should be avoided unless absolutely necessary and, if so, only after careful consideration of the benefit/risk ratio (SPCs, in Danish only: *www.produktresume.dk*). However, pregnant women may become ill, and women with chronic diseases may become pregnant. Different studies have shown that around two-thirds of all pregnant women take at least one drug during their pregnancy and that 60% of the drugs taken are prescription medicines (Adam et al., 2011).

As part of monitoring the drug safety, the Danish Health and Medicines Authority receives reports of suspected adverse drug reactions. Adverse reaction reports are recorded, even if a correlation between the medicine and an injury is only suspected. Thus, a report of a suspected adverse reaction does not imply that a correlation between the injury occurring and the medicine used has been demonstrated.

Mother-child reports

A report of a suspected adverse reaction (injury) in a child/foetus resulting from a parent's medicine use is typically called a mother-child report, since, most often, the mother's medicine use is suspected to be the cause of the adverse reaction in the child/foetus. Typically, the mother received the suspected drug during her pregnancy, so that the foetus was exposed via the placenta. The mother may also have used the drug during lactation, so that the child was exposed via the breast milk. There are very few father-child reports in the database. These reports concern transfer of the suspected drug via sperm to the mother, who passed it on to the foetus.

The purpose of this analysis was to gain an overview of all mother-child cases in the Danish adverse drug reaction database, including finding the most frequent drugs in adverse reaction reports and assessing whether the results would trigger further and more thorough analysis.

Method

Early spontaneous abortion (up to 12 weeks) and missed abortion were excluded from the analysis, as the background incidence is already high. Reports concerning hormonal contraceptives were also excluded, as they mainly refer to pregnancy in spite of treatment and agents for induction of labour.

Furthermore, the analysis focused only on the drugs suspected to be the cause of a given adverse reaction and not on other concomitant drugs administered to the patients. Since a mother-child report may also comprise information on adverse reactions in the mother, the analysis does not comprise a review of the type of adverse reaction in the child/foetus. That would require more thorough review of the reports, which is beyond the scope of this analysis. That type of analyses are typically performed for specific drugs/groups of drugs in the event of particular concern regarding the safety during pregnancy and lactation (e.g., SSRIs, methylphenidate and paracetamol – see ref. in the annual report 2010).

Finally, the analysis focused on adverse reaction reports received within the past ten years, since older reports often comprise only a little additional information on the onset and consequences of the adverse reaction, among other things due to receipt of more and better electronic reports in recent years.

Results

The final dataset consists of 338 mother-child reports.

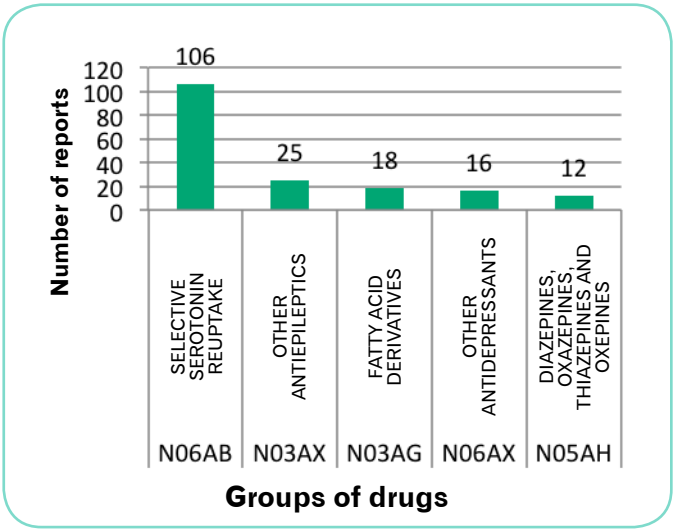

Figure 1: The five most frequently reported groups of drugs in mother-child cases

Figure 1 shows that more than half (52%) of all the mother-child reports concern the following five groups of drugs only: *Selective serotonin reuptake inhibitors (SSRIs), Other antiepileptics, Antiepileptics-fatty acid derivatives, Other antidepressants* and *Antipsychotics* (diazepines, oxazepines, thiazepines and oxepines). The number of reports concerning SSRIs is significantly higher than for all other groups of drugs and accounts for almost a third (31%) of the total number of mother-child reports. This significantly higher reporting frequency may also be explained by the stimulated level of reporting since 2011, when the media focused heavily on the use of SSRIs during pregnancy. The high number of reports has lead to increased focus upon and strengthened monitoring of the use of SSRIs in pregnant women, and the Danish Health and Medicines Authority has followed up with descriptive analyses *(www.sst.dk/english)* as well as registry studies.

Table 1 shows the distribution of the reports by active substance within the five most frequent groups of drugs. In the groups *Other antiepileptics* and *Fatty acid derivatives*, the reports mainly concern a single active substance (lamotrigine and valproic acid, respectively), whereas the distribution is more even in the groups *Antidepressants* and *Antipsychotics*. All other mother-child reports are distributed on a total of 111 different groups of drugs with only a few reports per group. For the majority of the groups, there are less than five reports per group.

Figure 2 shows that the number of users within the five most frequent groups of drugs has increased steadily among women of child-bearing potential (the 20-39 year age group). However, this does not apply to the group *Fatty acid derivatives* (valproic acid and others), for which the consumption has decreased slightly. Also, there has been a decrease in the consumption of SSRIs since 2010. According to the Danish Register of Medicinal Product Statistics at the Statens Serum Institut, National Institute for Health Data and Disease Control, this decreasing tendency continued into 2012 as part of the general downward trend in the sale of SSRIs. The decrease in the use of *Fatty acid derivatives* could indicate that doctors follow the recommendations in the summaries of product characteristics in terms of avoiding prescription of valproic acid to women of child-bearing potential, where possible.

Conclusion

A comparison of the number of reports to the increasing consumption of drugs among women of child-bearing potential shows that the reporting frequency for SSRIs is significantly higher than for other groups of drugs, which may be partly ascribed to the stimulated reporting resulting from the heavy media coverage at the end of 2010 and during 2011.

ATC group	Group of drugs	Active substance	Number of reports
N06AB	SELECTIVE SEROTONIN REUPTAKE INHIBITORS	CITALOPRAM	33
		ESCITALOPRAM	6
		FLUOXETINE	30
		PAROXETINE	7
		SERTRALINE	30
	Total		**106**
N03AX	OTHER ANTIEPILEPTICS	GABAPENTIN	1
		LAMOTRIGINE	16
		LEVETIRACETAM	3
		TOPIRAMATE	4
		ZONISAMIDE	1
	Total		**25**
N03AG	FATTY ACID DERIVATIVES	VALPROIC ACID	17
		VIGABATRIN	1
	Total		**18**
N06AX	OTHER ANTIDEPRESSANTS	BUPROPION	1
		DULOXETINE	5
		MIRTAZAPINE	3
		VENLAFAXINE	7
	Total		**16**
N05AH	DIAZEPINES, OXAZEPINES THIAZEPINES AND OXEPINES	CLOZAPINE	1
		OLANZAPINE	7
		QUETIAPINE	4
	Total		**12**

Table 1. Distribution of the reports received by active substance within the five most frequent groups of drugs.

The analysis confirms the Danish Health and Medicines Authority's assumption that the most frequent drugs in adverse reaction reports concerning children/foetuses are nervous system drugs (ATC group N). Even if the high number of reports concerning SSRIs is disregarded, other nervous system drugs are frequently represented. A review of the summaries of product characteristics for the five groups of drugs reveals that they already specify a number of adverse reactions that may occur in newborns. The summaries of product characteristics for antipsychotics and antidepressants specify, e.g., that persistent pulmonary hypertension and discontinuation symptoms may occur, while the summaries of product characteristics for antiepileptics specify, e.g., that the risk of congenital malformations is increased with a factor of 2 to 3 in children of mothers treated with antiepileptics as compared to the expected incidence of approx. 3% in the general population. Based on the above, the DHMA concludes that it remains very important to monitor the safety of drugs in pregnant and

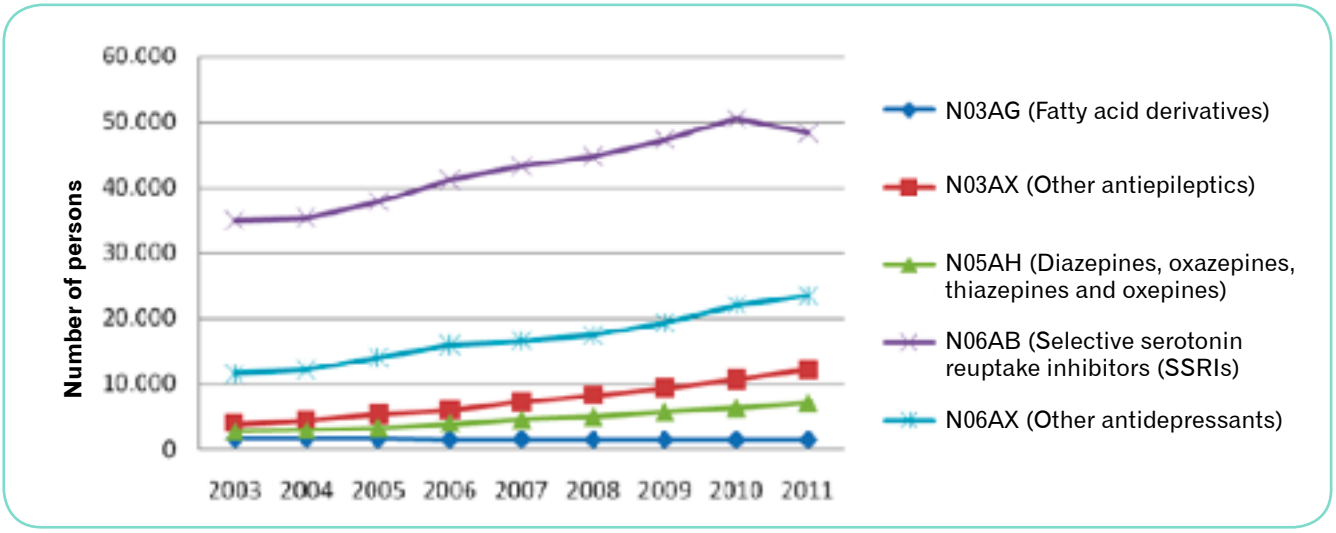

Figure 2: Development in the sales of prescription-only drugs in the five groups of drugs during the period 2003-2011 for women aged 20-39 years (in the primary care sector) (data from http://www.medstat.dk/en).

lactating women. However, the results do not give rise to any further analyses. The DHMA analyses adverse reaction data on an ongoing basis. As a follow-on to the mother-child analysis, it could be considered to perform an analysis of father-child reports to shed light on the more infrequent correlation between the father's drug use and adverse reactions in the child/foetus as well as a more general analysis of reports concerning children. The DHMA needs more knowledge of potential adverse reactions in children/foetuses resulting from treating the mother with drugs during pregnancy, since such knowledge may lead to the implementation of necessary precautions. The adverse reaction database is an important source of information on the effects of drugs in children/foetuses. Therefore, doctors are encouraged to be aware of suspected adverse reactions and report them to the Danish Health and Medicines Authority. The reports will help increase the safety of drugs in pregnant women and will provide a better data basis for analyses with the aim of issuing the necessary recommendations on the use of drugs during pregnancy.

You can report suspected adverse reactions at *http://laegemiddelstyrelsen.dk/en/topics/side-effects-and-trials/side-effects/report-a-side-effect-or-incident/humans*

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Danish Pharmacovigilance Update is published by:
Danish Health and Medicines Authority
www.laegemiddelstyrelsen.dk
Editor-in-Chief:
Henrik G. Jensen (HGJ)
Editor:
Louise Benner (LOBE)
ISSN 1904-2086