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Risk of overdose with methotrexate in the treatment of rheumatoid arthritis and psoriasis

Fatal overdose
From January 2009 to August 2011, several cases of overdose with methotrexate were reported in the EU due to daily instead of weekly intake. In several cases, the overdose was fatal.

The reports describe prescribing and administration errors as well as errors in self-administration by the patients.

Methotrexate for oral use for the treatment of rheumatoid arthritis and psoriasis must be taken once a week only.

The European Pharmacovigilance Working Party (PhVWP) has assessed how to minimise the risk of overdose
Following an evaluation of the submitted reports supported by the conclusions of scientific publications, the PhVWP agreed to include harmonised information in the product information for methotrexate-containing medicines for oral use, stating that the medicine must be taken once a week on the same day of the week as well as a warning on the risk of overdose, when methotrexate is used in the treatment of rheumatoid arthritis and psoriasis.

In addition, the package should be labelled with information that the medicine is to be taken once a week when used to treat rheumatoid arthritis and psoriasis.

Methotrexate – indications
Methotrexate tablets are authorised for the treatment of rheumatoid arthritis and psoriasis in adults and for the treatment of different types of cancers.

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

Gilenya (fingolimod) – intensified monitoring of heart rate and blood pressure after first dose

It is well known and described in the product information that Gilenya could cause temporary bradycardia and atrioventricular block (AV block) after the first dose.

The European Medicines Agency (EMA) now recommends to intensify monitoring of heart rate and blood pressure for the first six hours after the first dose in patients who are started on Gilenya and to continue monitoring if necessary.

The new recommendations follow the receipt of several adverse reaction reports describing cardiovascular effects, including the death of a 59-year-old woman, which occurred 24 hours after the first dose of Gilenya. The woman was treated with metoprolol and amlodipine for hypertension. The exact cause of death has not yet been established.

Monitoring for the first six hours after the first dose of Gilenya should include the following:

- A 12-lead ECG when treatment is started and for six hours after the first dose
- Continuous ECG monitoring for six hours
- Measurement of blood pressure and heart rate every hour.

Patients who experience clinically important heart-related effects during the first hours should continue to be monitored until the symptoms stop.

At the request of EMA, Novartis is reviewing all cardiovascular effects seen in clinical trials and experience from post-marketing.

For further information, please see *EMA's press release*.

Gilenya – indications
Gilenya has been authorised since 2011 for the treatment of patients with multiple sclerosis who have a high disease activity despite treatment with a beta-interferon, and in patients with rapidly evolving severe relapsing remitting multiple sclerosis.

Newest data on the safety of methylphenidate (Ritalin etc.) in ADHD therapy

In 2010, the Danish Medicines Agency published a report in Danish on the safety of methylphenidate-containing medicines, which are used in the treatment of ADHD (Attention Deficit Hyperactivity Disorder).

The Agency has since received more than 100 reports of suspected adverse reactions from the use of methylphenidate, which brings the total number of reports contained in the Agency's adverse reaction database to 302 for this medicine.

The majority of the new reports concern children, as was the case in the Agency's previous report. Overall, the nature of the reported adverse reactions matches what has been described earlier. The most frequently reported adverse reactions are psychiatric symptoms and symptoms from the nervous system. The majority of them are adverse reactions that are already described in the summary of product characteristics.

Below, we describe some of the reported adverse reactions that have received considerable focus.

New adverse reaction reports that concern adults

Two reported deaths
When the report from 2010 was written, no deaths had been reported in connection methylphenidate treatment. But we have since received two reports of two deaths that might be associated with methylphenidate. Both cases concern adult males who had been treated for ADHD.

Both cases have been evaluated by the Danish Medicines Agency and were described in *Danish Pharmacovigilance Update, December 2010* and *Danish Pharmacovigilance Update, March 2011*.

The Danish Medicines Agency has emphasised that methylphenidate is not authorised for ADHD treatment in adults and has drawn attention to the precautionary measures to be taken. In particular, doctors should evaluate the risk of cardiovascular adverse reactions before possibly deciding to prescribe the medicine.

Reports of abuse
When data was extracted for the above-mentioned report, the database contained seven reports of methylphenidate abuse in total.

But an additional six reports of possible methylphenidate abuse have been reported since. These new reports primarily concern abuse by the patients themselves. In two of the cases, the patients had opened prolonged-release capsules to sniff the content, and in one case a patient had a deliberate excessive use of tablets and capsules.

Another report described a case where methylphenidate tablets had been abused to improve concentration and to stay awake longer.

In the remaining two cases, one concerned a report where the doctor had not described whether the patient was suspected of having taken an overdose deliberately. In the other case, the patient felt dependent and unwell from the medicine shortly after having started treatment at normal doses.

Because methylphenidate is a stimulant of the central nervous system, the risk of abuse is well-known, and the Danish Medicines Agency has already tightened the import and dispensing provisions for this medicine.

Reported adverse reactions in connection with pregnancy
According to the summary of product characteristics, methylphenidate is generally not recommended for use during pregnancy, because there is limited data about the use of methylphenidate in pregnant women.

Since the report was published in 2010, the Danish Medicines Agency has received two reports on the use of methylphenidate during pregnancy. The one report describes a spontaneous abortion in the first trimester of pregnancy in a woman who received treatment with methylphenidate and valproate. The other report describes a woman who developed pre-eclampsia and reported a suspected correlation to the father's use of methylphenidate at the time of conception.

Consumption and adverse reactions reported for small children

Methylphenidate is authorised for children from the age of six. The previous report had particular focus on off-label use of methylphenidate

> in adults because they had a large consumption.

However, consumption data show that in some cases methylphenidate is also used to treat children below the age of six. Data from the Danish Medicines Agency's Register of Medicinal Product Statistics show that nearly 300 children younger than six years of age were treated with methylphenidate in 2010. The majority were 5-year-olds.

The Danish Medicines Agency's adverse reaction database contains six reports that describe adverse reactions in children younger than six years of age: five 5-year-olds and one 3-year-old. Three of the children had experienced psychiatric symptoms in the form of tics, compulsive actions, hallucinations and confusion. In the other three children, the medicine did not work, and one of them had also experienced involuntary eye movements.

Methylphenidate is well-known to cause psychiatric reactions, which is described in the summary of product characteristics together with information that doctors should monitor patients to see if they develop new or if pre-existing psychiatric disorders worsen so that treatment can be stopped if necessary. However, the summary of product characteristics only includes the safety profile of the authorised age group, and it cannot be ruled out that the effects and side effects of the medicine are different when it comes to the smallest of children.

The new data do not alter the Agency's previous conclusions

In the past few years, the Danish Medicines Agency has received a large number of reports of suspected adverse reactions from the use of methylphenidate, which is probably a result of the large increase in consumption as well as awareness on this type of medicine – including coverage in the press.

However, the new adverse reaction reports do not alter the conclusions of the previous report, and, in the opinion of the Danish Medicines Agency, should not lead to changes to the summary of product characteristics.

The Danish Medicines Agency will maintain focus on the safety of methylphenidate, including especially long-term use and special risks associated with the treatment of patient groups outside of the approved indication.

Follow this link to read the report from 2010 (in Danish only). *Report on the assessment of safety of methylphenidate in ADHD treatment (in Danish only)*.

Risk of thromboembolism or death after discontinuation of anticoagulant therapy in patients with atrial fibrillation

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Patients in anticoagulant therapy in Denmark

According to the Danish Medicines Agency's Register of Medicinal Product Statistics at least 100,000 people in Denmark are in anticoagulant therapy with warfarin (Marevan®) or phenprocoumon (Marcoumar®), the so-called vitamin K antagonists, and a least three times as many are treated with platelet function inhibitors such as low-dose aspirin and clopidogrel.

About half of them are senior citizens with atrial fibrillation, and their number increases because of the age composition of the Danish population. Warfarin and phenprocoumon have been used for more than a half-century, and they are among the medicines that receive the most attention because of their risks of severe adverse reactions, first of all severe haemorrhage.

Risk evaluation and treatment with anticoagulant medicines

Anticoagulant therapy range among the most risky medical treatments known to us, and it is therefore imperative that the indications for use are weighted carefully against any possible contraindications and risk factors. Included in this risk assessment should be the risk of haemorrhage as well as the risk of blood clots and death.

The prevalence of atrial fibrillation is increasing, and it is estimated that about 2 % of the Danish population have atrial fibrillation. By 2020, this proportion will have increased to 8 % due to the population's increasing average age. Atrial fibrilation is associated with a considerable risk of mortality and morbidity in the form of apoplexy and thrombosis. In this patient group, the known risk factors for strokes are advanced age, heart insufficiency, hypertension, diabetes, other heart diseases and pre-existing strokes[1].

In 2010, two risk scoring schemas were compared in the Euro Heart Survey, called $CHADS_2$ and CHA_2DS_2VASc[2], respectively, which can be used to group patients at high or at low risk of death and thrombosis (table 1). These two schemas are recommended by both Europe and Denmark as a basis for grouping patients with atrial fibrillation based on their needs for antithrombotic treatment.

Risk of thromboembolism or death after discontinuation of anticoagulant therapy

There may be several reasons for stopping anticoagulant therapy. A major Canadian study called AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) found that the reasons for discontinuing anticoagulant therapy was restored sinus rhythm after cardioversion (45 %), bleeding complications (21 %), surgical treatment (13 %), medical evaluation combined with the patient's own wish to discontinue treatment (12 %), non-acceptance by the patient (8 %), and patients deemed unfit for anticoagulant therapy due to tendency to fall, etc. (7 %)[3]. This illustrates that decisions to stop anticoagulant therapy could be medically reasoned (surgery and after DC conversion), or could be based on patient-related factors (bleeding, compliance, reluctance).

The knowledge we have about the risk of thromboembolic complications when anticoagulant therapy is discontinued derives primarily from clinical randomised studies. Obviously, the problem with these observations is that they are very few, the patients are monitored constantly by experienced doctors and nurses, and the follow-up period is often rather short.

A new Danish cohort study has studied the risk of thromboembolic complications or death after discontinuation of anticoagulant therapy with warfarin in patients with atrial fibrillation. The study is based on prescription data from the Danish Medicines Agency's Registry of Medicinal Product Statistics and information about hospital admissions from the National Patient Registry[4].

Nearly 50,000 patients in anticoagulant therapy with warfarin were monitored in the period 1997 to 2008, with an average observation time of 3 1/2 years. 35 % of these patients had experienced a period where anticoagulant therapy had been paused for a shorter period (less than 90 days) or a longer period (up to 360 days). The group for whom treatment had been paused were sub-divided into four groups (in addition to the above in periods of 91-180 and 181-270 days, respectively). During the observation period, the combined endpoint thromboembolism was observed (apoplexy, TCI, pulmonary embolism or arterial embolism) and death.

The study showed that the number of blood clots or deaths increased >

Table 1. $CHADS_2$ & CHA_2DS_2VASC risk scores

$CHADS_2$ acronym	Score	CHA_2DS_2-VASc acronym	Score
Heart insufficiency	1	Heart insufficiency	1
Hypertension	1	Hypertension	1
Age ≥75 years	1	Age ≥75 years	2
Diabetes mellitus	1	Diabetes mellitus	1
Apoplexy/TIA/TE	2	Apoplexy/TIA/TE	2
Maximum score	6	Vascular disorder	
		(preexist. AMI, PAD, or aorta plaque)	1
		Age 65-74 years	1
		Female	1
		Maximum score	9

threefold in the first 90 days after anticoagulant therapy was paused, following which the numbers declined and stabled around the same level after 180 days. The study also showed that in patients in anticoagulant therapy, about three blood clots per 100 patient years are seen. This corresponds to the risk in patients without atrial fibrillation, which shows that the treatment is rather effective. However, in the group of patients who paused treatment, the risk increases threefold in the first 90 days, i.e. nine cases per 100 patient years, after which it declines. It was, however, rather surprising that this risk was independent of the patients' co-morbidity and current risk score.

The most recent American and European guidelines recommend that anticoagulant therapy may be paused or discontinued four weeks after successful DC conversion and for up to one week, when the patient is to undergo surgical procedures[5,6]. Conversely, the before-mentioned Danish study shows that caution should be taken with this strategy because it must be presumed that the distribution of patients pausing treatment due to DC conversion can be compared to what we have seen in the AFFIRM study. It should be noted that the Danish study did not have access to information about why treatment was paused. Likewise, it was not possible to see the effect of any shorter pauses in connection with planned surgical procedures.

The overall conclusion is that doctors should be cautious not to pause or discontinue treatment uncritically in patients with atrial fibrillation, but should carefully consider and weigh the risk of bleeding and thromboembolic complications, respectively, in the individual patient. Anyone who monitors patients in anticoagulant therapy, or who, for example, performs operations on patients in anticoagulant therapy should be familiar with the risk of thromboembolism or death after discontinuation of anticoagulant treatment in patients with atrial fibrillation, just as they should be familiar with how to ensure the best safety for patients, e.g. by using so-called briding therapy with heparin or low-molecular heparin when anticoagulant therapy is paused. In this connection, we refer to the guidelines from the Danish Society of Cardiology and the Danish Society on Thrombosis and Haemostasis.

Patients with mechanical heart valves must always be started on bridging therapy if their treatment is paused because of surgery as well as if they fall outside the therapeutic interval[7].

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Risk of venous thromboembolism from the use of 4th generation contraceptive pills (Yasmin® etc.)

The European Pharmacovigilance Working Party has evaluated two new studies[1,2] on the risk of venous thromboembolism (VTE) from the use of 4th generation contraceptive pills containing drospirenone.

The conclusions from the new studies comply with the previous assessment from May 2011 and do not call for further tightening of the medicine's summary of product characteristics.

The conclusion therefore remains:
The risk of venous thromboembolism (VTE) for drospirenone-containing combined oral contraceptives (COCs) is higher than for levonorgestrel-containing COCs (so-called 2nd generation COCs) and may be similar to the risk for COCs containing desogestrel or gestodene (so-called 3rd generation COCs).
For further information, please read the *PhVWP monthly report from January 2012*.

1 Gronich N, Lavi I, Rennert G. Higher risk of venous thrombosis associated with drospirenone-containing oral contraceptives: a population-based cohort study. Can Med Assoc J. 2011; 183: E1319-1325.

2 Ouellet-Hellstrom R, Graham DJ, Staffa JA. Combined hormonal contraceptives (CHCs) and the risk of cardiovascular disease endpoints. Available under: http://www.fda.gov/downloads/Drugs/DrugSafety/UCM277384.pdf; accessed 15 December 2011.

New report from the Danish Medicines Agency about the use of contraceptive pills and risk of thrombosis

In a new report, the Danish Medicines Agency has reviewed the most important literature on contraceptive pills and the risk of blood clots as well as the most recent data on consumption and reported adverse reactions in Denmark.

The conclusion is that the existing summaries of product characteristics and package leaflets already contain the newest knowledge about the medicine's safety.

The review confirms that the overall risk of having blood clots when using oral contraceptive pills is low. It further concludes that contraceptive pills of the older type – the so-called 1st and 2nd generation pills – are associated with the lowest risk.

However, consumption shows that Danish women predominantly use 3rd generation pills and that particularly 3rd generation pills are what doctors most frequently prescribe to first-time users.

Types of contraceptive pills (on the market as at January 2012):

1st Generation: Contains the progesterones norethisterone or dienogest – brand names: Trinovum®, Qlaira®.
2nd Generation: Contains the progesterones norgestrel, levonorgestrel and norgestimate – brand names: Cilest®, Femicept, Malonetta, Microgyn®, Triminetta®, Trinordiol® "Paranova", Triquilar®.
3rd Generation: Contains the progesterones desogestrel and gestodene – brand names: Daisynelle®, Desorelle®, Femelle, Femigen, Gestinyl®, Gestodilat®, Gestonette®, Harmonet®, Lindynette®, Marvelon®, Mercilon®, Milna, Minero, Minulet®, Modina, Novynette®, Gracial®, Milligest, Milvane®.
4th Generation: Contains the progesterone drospirenone – brand names: Yasmin 28®, Yasmin®, Yasminelle 28®, Yasminelle®, Yaz®.

The review cause us to make the following recommendations to doctors:

- 2nd generation contraceptive pills should as far as possible be prescribed as first choice.

Before prescribing contraceptive pills to first-time users, doctors should:

- take a complete personal and family medical history to identify risk factors for blood clots, etc.,
- measure the blood pressure and perform a physical examination.
- inform patients who take contraceptive pills about the risk of blood clots and their early warning >

> signs, including the differences in risks between the different generations of contraceptive pills.
- Finally, doctors should follow-up on the treatment, especially at the beginning when the risk is highest, but also if the patient switches to a new type of contraceptive pill, and should generally follow the medical guidelines in the area.
- In cases where contraceptive pills are used for indications other than birth-control, any switch to another product should be assessed individually to ensure a continued optimal treatment of the underlying disease.

Read more on the Agency's website: *Older contraceptive pills still pose the lowest risk of blood clots*.

Gilenya and macular oedema

In January 2012, the Danish Medicines Agency received an adverse reaction report describing a patient with multiple sclerosis who had taken the medicine Gilenya and had developed a macular oedema in the left eye and a beginning macular oedema in the right eye.

The patient had been given 0.5 mg daily for about two months when blurred vision in the left eye occurred. 14 days later, the patient was diagnosed with beginning macular oedema in the right eye, following which the treatment was stopped.

This is the only report describing macular oedema in connection with the administration of the product received by the Danish Medicines Agency, but there are reports of macular oedema with or without visual symptoms in 0.4 % of patients treated with 0.5 mg fingolimod, mainly reported in the first 3-4 months of treatment.

Advice for prescribers

Doctors are therefore advised to make an ophthalmic examination 3-4 months after commencement of treatment. If a patient develops visual disturbance at any time during treatment, the fundus, including macular, should be evaluated.

Continued treatment with Gilenya in patients with macular oedema has not be examined. It is recommended to stop treatment if the patient develops macular oedema. When a decision is to be made whether or not to resume treatment with Gilenya after macular oedema has disappeared, any potential advantages and risks should be considered for the individual patient

A risk management plan is linked to the marketing authorisation, which provides, among other things, that the patients should be given a patient information card. The card should contain information about the necessity that the patient must inform the doctor immediately if there are signs of impaired vision during and up to two months after treatment with Gilenya has stopped.

Haemorrhagic disease in a newborn whose mother was treated with valproate during pregnancy

In December 2011, the Danish Medicines Agency received an adverse reaction report about a newborn baby, whose mother had used valproate for epilepsy throughout her pregnancy.

At birth, the baby's Apgar score was 8/10 points after 1 minute and 10/10 points after 5 minutes. When the baby was one and a half days old, the baby got cramps. A lumbar puncture and an MRI scan were made. The conclusion was that the cramps were probably caused by bleeding in the cerebellum.

It can neither be ruled out nor confirmed that valproate caused this incident.

The Danish Medicines Agency has not received any similar reports.

According to the summary of product characteristics of valproate-containing medicines, doctors should be alert that:

When a woman plans pregnancy, the need for antiepileptics should be carefully considered. There is an increased risk of congenital malformations in children born by mothers treated with antiepileptics, and in rare cases haemorrhagic disease has been reported in children whose mothers have used valproate during pregnancy. This syndrome is related to hypofibrinogenemia.

Cases of afibrinogenemia have also been reported, which might be fatal. This may be related to a drop in clotting factors.

Thus, the blood platelet count, the fibrinogen plasma level, coagulation tests and clotting factors should be examined in newborns of mothers who have used valproate.

Study of the linkage between urine-derived fertility products and Creutzfeldt-Jakob

Foreign reports have described detection of prion protein in urine-derived fertility hormones, and there have been speculations about a possible association with Creutzfeldt-Jakob Disease. A linkage of Danish registers has provided no basis for such a conclusion.

Registry data does not suggest any links

In cooperation with the Danish National Board of Health, the Danish Medicines Agency has linked several national health registers. The objective was to see if women who had died from Creutzfeld-Jakob Disease (CJD) in Denmark had previously received artificial insemination or redeemed a prescription for a so-called urine-derived fertility hormone to treat involuntary childlessness, e.g. Menopur® and Pregnyl®.

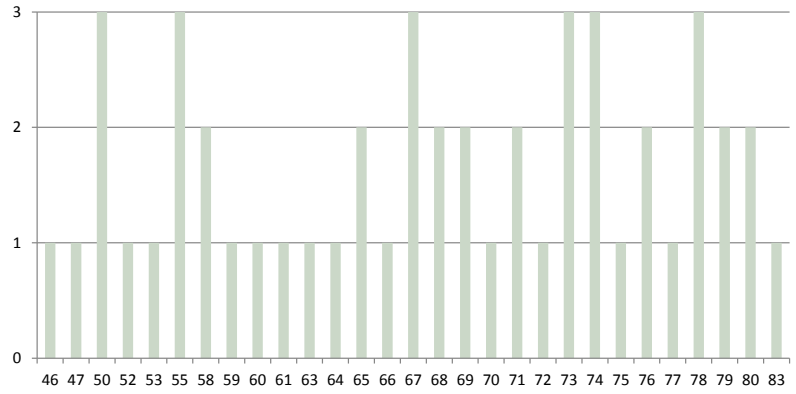
The findings have not given us any cause to take further action, as we have not seen any data suggestive of a possible link, and currently the data available is too unsubstantial to even be able to hint at a link.

No linkage found

In Denmark, CJD is the cause of death for approximately six persons a year. However, it was only possible to check for a connection for women who had died from CJD in the period 1994-2009, as the Danish registers only began to register fertility treatment and medicine consumption in 1994[1].

In this period, 49 women in Denmark died from CJD. In 1994, 44 of these 49 women were older than 45 years, i.e. they were above the age limit for artificial insemination introduced in 1997[2]. This means that for 90 % of the women, we are unable to find information about any previous fertility treatment in the Danish registers.

Figure 1. Age distribution of women who died from Creutzfeldt-Jakob Disease in the period 1994-2009



The remaining five women, who died from CJD in the period 1994-2009, were not registered as having received fertility treatment, including treatment with urine-derived fertility hormones.

As we have no available data prior to 1994, we cannot conclude that the women who died from CJD in the period 1994-2009 had not received fertility treatment.

Linkage of four registers

We came to the result by extracting the civil registration numbers of women who have died from CJD from The Causes of Death Registry.

We tried to find these civil registration numbers in the IVF registry (In Vitro Fertilisation), in the Register of Medicinal Product Statistics under redemption of prescriptions for urine-derived fertility hormones as well as in The National Patient Registry under codes for all types of fertility treatment.

However, based on the study, we can positively say that we have not detected any signals that give us cause to investigate this matter any further.

The women's age distribution is shown in figure 1. The women's median age was 68 years.

The Danish Medicines Agency will continue to follow the development.

[1] The IVF registry, which contains data on artificial insemination in both public and private clinics, was started in 1994 at the same time as the Register of Medicinal Product Statistics. The National Patient Registry began to register data on all types of fertility treatment in the public sector from 1999 and inseminations at private clinics in 2006.

[2] From 1997, it was enacted that women older than 45 years were not to receive artificial insemination (neither IVF or insemination) by Danish act no. 460 of 10 June 1997 on artificial insemination in connection with medical treatment, diagnostics and research, etc. ("Lov nr. 460 af 10. juni 1997 om kunstig befrugtning i forbindelse med lægelig behandling, diagnostisk og forskning m.v.").

The Danish Medicines Agency has drawn up a new report on pregnancy and adverse reactions from antidepressants

The new report covers the period from October to December 2011.

Read more on the Danish Medicines Agency's website:

Adverse reaction reports on antidepressants and pregnancy - October to December 2011.

New mobile app for checking medicines

Danish patients have just been given easy access to information about the medicines they use. Through one single entry point, the Danish Medicines Agency's new app Medicintjek (which literally means "medicine check") gives patients access to information in Danish from the websites medicinpriser.dk (on medicine prices), medicinkombination.dk (on combining medicines), indlaegsseddel.dk (on package leaflets) and dkma.dk.

Medicintjek is available for download on iPhone and Android mobiles.

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