Sundhedsstyrelsen
Danish Health and Medicines Authority

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DANISH PHARMACOVIGILANCE UPDATE

Contents

News from the EU

News from the DHMA

Short news

EMA warns against using certain types of hepatitis C medicines and amiodarone together

The European Medicines Agency (EMA) has confirmed that severe bradycardia or heart block may occur in patients taking amiodarone and the hepatitis C virus (HCV) medicine Harvoni (sofosbuvir + ledipasvir) or Sovaldi (sofosbuvir) in combination with Daklinza (daclatasvir).

Advice for prescribers

EMA recommends the following:

- Patients treated with Harvoni or Sovaldi plus Daklinza should only be treated with amiodarone if other antiarrhythmics are contra-indicated or not tolerated.
- If concomitant use with amiodarone is unavoidable, patients should be closely monitored. Due to amiodarone's long half-life, patients who have discontinued amiodarone within the past few months should also be monitored when starting treatment with the hepatitis medicines.
- All patients receiving Harvoni or Sovaldi plus Daklinza in combination with amiodarone should, regardless of whether or not they take other medicines that lower heart rate, be warned of the symptoms of bradycardia and heart block and should be advised to seek urgent medical advice if they have these symptoms.

Background leading to warning

The warning follows a review of cases of bradycardia or heart block in patients who received amiodarone and started HCV treatment – one case resulted in fatal cardiac arrest and two required pacemaker intervention. It was considered that there was a likely relationship between these events and the medicines, and this potential relationship is now being investigated further.

The product information for these medicines will be updated accordingly, and doctors have been informed through circulated DHPCs.

Indications:

Harvoni can be used alone or, like Daklinza, in combination with other antiviral medicines for treatment of chronic HCV genotypes 1, 3 or 4 in adults.

Sovaldi is indicated in combination with other medicines for the treatment of chronic HCV genotypes 1-6 in adults.

EU's list of recommendations on safety signals

As part of routine surveillance of medicines in the EU, the Pharmacovigilance Risk Assessment Committee (PRAC) assesses signals of possible adverse reactions every month to determine whether further measures are needed to improve medicines safety[1].

The list of signals leading the PRAC to recommend further measures is published on the website of the European Medicines Agency (EMA) every month.

The most important safety signals discussed on the PRAC meeting in April 2015 concern the following products:

- Daclatasvir; sofosbuvir; sofosbuvir/ledipasvir – arrhythmia
- Interferon alfa and beta – pulmonary arterial hypertension
- Trabectedin – capillary leak syndrome

See EU's list of recommendations on safety signals: *PRAC recommendations on signals*.

[1] The fact that a signal has been assessed does not mean that there is a causal link to the medicine.

Pregabalin and abuse potential

The DHMA has received a total of 13 ADR reports about abuse or potential abuse of pregabalin (Lyrica®, etc.) since the product was marketed in 2004. The reports describe addiction to the medicine and/or withdrawal symptoms.

In parallel, the number of pregabalin users has risen sharply in Denmark since marketing (figure 1).

The DHMA is therefore alert to the problem and is discussing the issue with the Danish Poison Control Hotline which has reviewed all calls about abuse and suicide attempts. In collaboration with Aalborg University Hospital, the DHMA will prepare a thorough literature review of pregabalin to further assess the substance's abuse potential and analyse the consumption of pregabalin in Denmark. The focus will be to identify characteristics in patients who consume larger quantities than recommended in the SPC.

These investigations are intended to form the basis for regulatory measures as needed and are to raise awareness among doctors about any risk population.

In Denmark, pregabalin is authorised for the treatment of neuropathic pain, epilepsy and generalised anxiety.

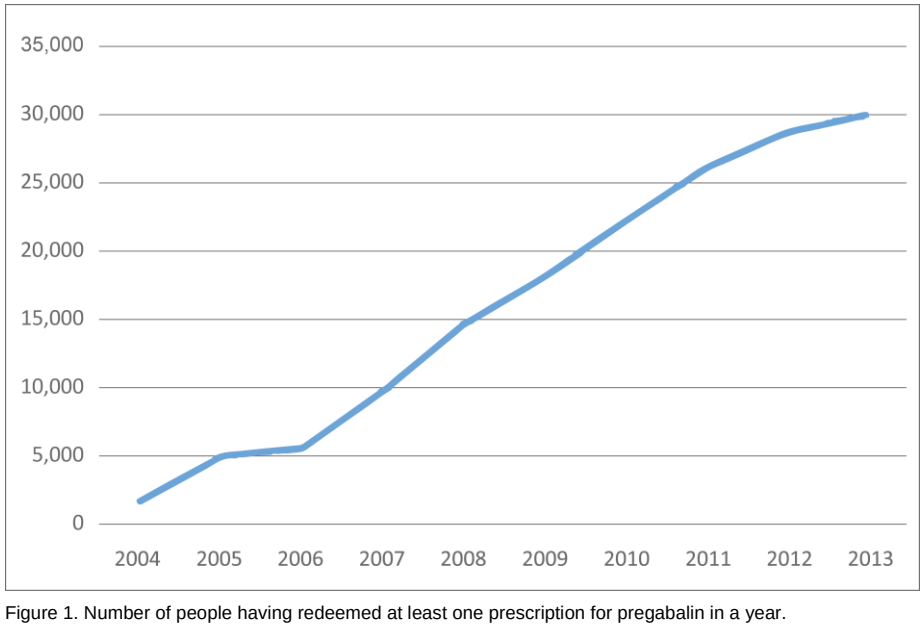

Figure 1. Number of people having redeemed at least one prescription for pregabalin in a year.

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.

DHMA advises doctors to pay attention to warnings and precautions for use described in the summary of product characteristics for pregabalin

Misuse, abuse potential and dependence are described in the medicine's SPC based on ADR reports on tolerance, dose escalation and drug-seeking behaviour. Caution is therefore advised when treating patients who have a history of substance abuse, and patients should be monitored for symptoms of misuse, abuse or dependence.

See the summary of product characteristics for *Lyrica®*.

Review of ADR reports submitted to the DHMA describing abuse and abuse potential of pregabalin

In six of the 13 ADR reports, medicine dependence is described. One of the reports describes a patient who escalates the dose and experiences mood swings and feels euphoric. Another report describes a patient who experiences that pregabalin has the same effect as benzodiazepines. In a third report, a patient cannot describe any effect, not even when sniffing pregabalin – the patient has a history of drug and alcohol abuse and has misused various medicines.

Three ADR reports describe scenarios where patients have been prescribed extra pregabalin by another doctor or through other channels illegitimately. In one of the ADR reports, the reporting doctor assesses that overall, the patient's daily consumption corresponds to 8.5 g Lyrica® – the maximum daily dose is 600 mg.

Four reports describe patients who have abused e.g. alcohol, cocaine and various other medicines including Ritalin® and Seroquel®.

Six ADR reports describe withdrawal symptoms after dose reduction or when weaning off the medicine. Symptoms have been described as internal restlessness and incipient anxiety attacks coming on a couple of hours before the medicine is to be taken – symptoms which disappear when the medicine is taken. In another report, the withdrawal symptoms are described as mental discomfort and aggravation of pain when attempting to wean off the medicine.

Blood clots in the brain as suspected adverse reaction to contraceptive pills in women with high BMI

In February, the DHMA received two ADR reports of blood clots in the brain suspected to be adverse reactions to the contraceptive pills (Cilest® and Yasmin®). Both of the two women described in the reports had high BMIs (34 and 35).

One of the women had been taking contraceptive pills for several years, the other only for six months.

The reports describe no other risk factors for blood clots.

At the time of reporting, both women had suffered injuries from the blood clots; one had sustained short-term memory loss, attention impairment and balance disturbances among other things; the other had spastic paralysis in the extremities among other things.

Doctors should be aware of the following:

- The risk of thromboembolic complications in women using combined hormone contraceptives increases substantially with rises in the Body Mass Index[2].
- This is particularly important to consider if other risk factors are present (age above 35 years, smoking, hypertension, etc.).

Before prescribing these products, we recommend using the DHMA's *checklist* and remind prescribers to inform the users of contraceptive pills about the known risk factors. For convenience, prescribers can hand out a *patient card* to users of contraceptive pills, which provides information about the products and the symptoms of blood clots.

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Olanzapine and ADR reports of deaths

As part of our pharmacovigilance activities, we have focus on antipsychotic drugs among other products. We have received 50 ADR reports that describe deaths suspected as adverse reactions to olanzapine – 20 of them were received over the last five years. The most recent ADR report is from July 2014. In this issue of Danish Pharmacovigilance Update, we provide a brief overview of the ADR reports of deaths of patients in olanzapine treatment.

Review of the 50 reported deaths related to olanzapine treatment

Age and gender distribution

Gender

- Women (18)
- Men (30)
- Gender unknown (2)

[2] *www.produktresume.dk* (Danish website)

Age
- Age unknown (14)
- Age 19-40 (17)
- Age 41-60 (10)
- Age over 61 (9)

Reported causes of death in the 50 patients

Cause of death	Number
Sudden death (cause of death not determined)	14
Drug intoxication (sudden death)	11
Pulmonary embolism	10
Unknown cause of death	5
Acute cardiac arrest	3
Eosinophilic myocarditis	2
Pulmonary hypertension	1
Death from drug overdose (prescribed overdose)	1
Cerebellar bleeding and sepsis (prescribed overdose)	1
Unintended overdose due to memory loss	1

Indications reported for olanzapine use in the 50 patients:

- Schizophrenia (17)
- Anxiety (1)
- Bipolar disorder (1)
- Hallucinations (2)
- Depression with suicidal ideation (1)
- Manias (3)
- Psychotic disorders (3)
- Not provided (22)

Co-medication/polypharmacy/treatment with several antipsychotics

27 of the 50 patients who died were treated with several different medicinal products. 25 of the 27 patients were treated concomitantly with two or more antipsychotics, and 16 of the 27 patients were treated concomitantly with a benzodiazepine. 13 of the 50 patients were treated concomitantly with another type of medicine, whereas the last 10 ADR reports did not describe use of other medicines.

Number of olanzapine users and volume sold

The number of people treated with olanzapine in the primary sector has since 2005 remained relatively stable at around 17,000-18,000 (18,703 individuals in 2005 and 17,905 in 2013), see figure 1 below.

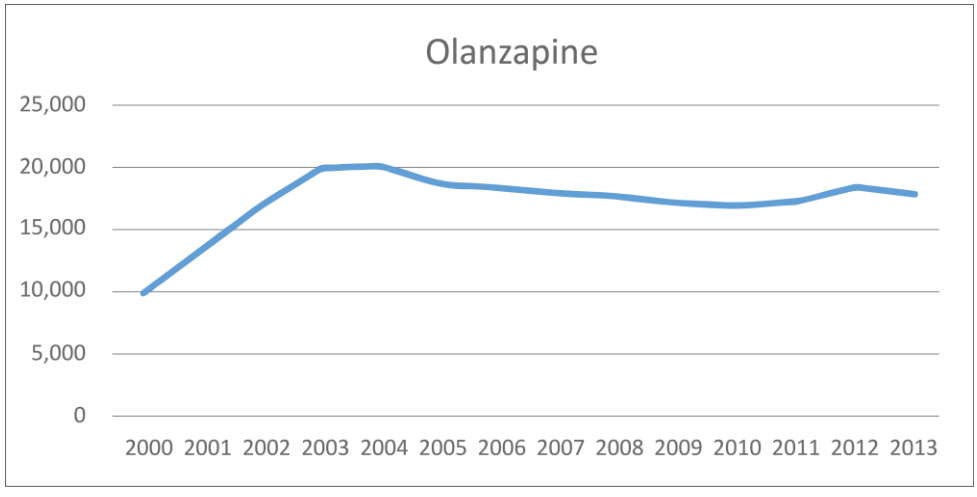
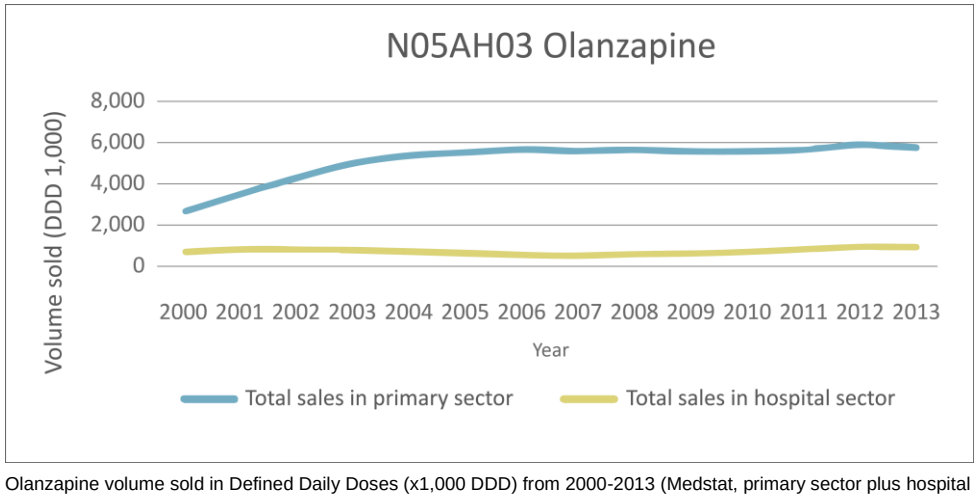


Figure 1. Number of persons treated with olanzapine from 2000-2013 (Medstat).

A small proportion of the patients are treated with olanzapine in the hospital sector. Figure 2 shows the volume sold of olanzapine in Defined Daily Doses (x1,000 DDD) in both the primary and hospital sectors.



Olanzapine volume sold in Defined Daily Doses (x1,000 DDD) from 2000-2013 (Medstat, primary sector plus hospital sector).

Conclusion

Half of the patients who died in connection with olanzapine treatment were treated concomitantly with one or several other antipsychotic medicines. Some patients were also being treated with benzodiazepines at the same time. This does not comply with the current guideline on antipsychotic treatment. Nonetheless, the problem is known and was addressed in the DHMA's report about medical treatment of adults diagnosed with

schizophrenia (in Danish only): *Medicinsk behandling af voksne diagnosticeret med skizofreni, DHMA. 8 October 2014*. The report was prepared based on a comprehensive investigation, which showed that many of the patients were treated with more than one antipsychotic medicine. The scientific evidence on antipsychotic polypharmacy is limited, and for most combinations, polypharmacy does not provide improved effects compared to monopharmacy. Antipsychotic polypharmacy may be associated with an increased risk of adverse reactions.

In October last year, the mental health centres in the regions were informed about the conclusions of the report.

Treatment guideline

It is well-known that treatment with antipsychotics can cause numerous adverse reactions, including arrhythmia. Mortality increases when antipsychotics are taken together with sleeping pills and/or tranquillisers, and polypharmacy generally increases the risk of adverse reactions.

Danish and international data indicate that the risk of death is higher when several antipsychotics are taken together. The DHMA's previous Guideline no. 9763 of 28 June 2007 on treatment with antipsychotics in people over 18 years already highlighted the importance to carefully monitor treatment efficiency and development of possible adverse reactions and avoid the concomitant use of several antipsychotics. Likewise, the DHMA has advised against concomitant treatment with sleeping pills and tranquillisers.

In compliance with the DHMA's present guideline *"Behandling med antipsykotiske lægemidler til personer over 18 år med psykotiske lidelser* no. 9276 of 6 May 2014" (in Danish only), doctors should, among other things, be aware of the following:

- Avoid concomitant treatment with antipsychotics and benzodiazepines after the acute phase (1-2 weeks) as combination treatment increases the risk of serious adverse reactions.
- There is no evidence that concomitant treatment with several antipsychotics increases efficacy. On the contrary, polypharmacy causes more adverse reactions.

The patient should be monitored at the start of treatment and after 2, 4, 8, and 12 weeks; In long-term treatment, at least once a year.

Prescribers should ensure the following are performed:

- Height and weight measurement
- BMI calculation
- Waist measurement
- Blood pressure measurement
- Hba1c and lipid measurements
- ECG monitoring

After each monitoring, the doctor treating the patient must decide on the continued medical treatment based on the guideline's criteria.

The Danish Society of Cardiology and the Danish Psychiatric Society have developed an algorithm that is to reduce the risk of cardiac arrhythmia and sudden death induced by psychoactive drugs (in Danish only): *Arytmi-risiko ved anvendelse af psykofarmaka*.

Indications for olanzapine

Olanzapine – oral – adults

- Treatment of schizophrenia.
- Treatment of moderate to severe manic episode.
- Prevention of recurrence of manic or depressive episodes in patients with bipolar disorders whose manic episode has previously responded to olanzapine treatment.

Olanzapine – prolonged release suspension for injection (Zypadhera)
Maintenance treatment of adult patients with schizophrenia sufficiently stabilised during acute treatment with oral olanzapine.

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ADR reports of substitution problems and lack of efficacy of Methylphenidate "Sandoz"

Methylphenidate "Sandoz" is authorised for the treatment of ADHD (attention deficit hyperactivity disorder) in children over six years of age when other remedial measures alone prove insufficient. Since this generic product was marketed in Denmark in April 2013, the DHMA has received 22 ADR reports of which 21 describe substitution problems when switching from the original brand product Concerta® to the generic product Methylphenidate "Sandoz". 15 of the ADR reports describe lack of efficacy of Methylphenidate "Sandoz".

It is primarily doctors who have submitted the ADR reports to the DHMA. In parallel, the DHMA has continually been contacted by doctors, patients and other European drug regulatory authorities who describe lack of efficacy of Methylphenidate "Sandoz".

DHMA has performed laboratory analyses of Methylphenidate "Sandoz"

In response to the many reports and approaches, the DHMA laboratory has subjected Methylphenidate "Sandoz" to a number of tests to measure and compare its active substance against the active substance of the original product. The results showed that the products are very similar and that there were no deviations from the specifications. Based on the laboratory results, the DHMA cannot conclude that there is a difference between Methylphenidate "Sandoz" and the original product.

Problem has been reported to the EU

The DHMA considers the ADR reports be an ADR signal[1]. The signal will be forwarded to the British drug regulatory authority, which is responsible for monitoring all methylphenidate-contaning products in the EU.

Generic substitution

On the website of the DHMA, you can find *questions and answers about generic substitution*.

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[1] An ADR signal reflects a new possible causal relationship between an adverse reaction and a certain type of medicine or a new angle on an already known causality.

Most recent Direct Healthcare Professional Communications (DHPCs)

Below is a list of the most recent DHPCs that have been (or soon will be) sent out to relevant doctors and healthcare professionals with safety information and updated recommendations about medicines:

- **Gilenya (fingolimod):** First reported case of progressive multifocal leukoencephalopathy in a multiple sclerosis patient. Sent out on 5 May 2015.
- **Sovaldi (sofosbuvir), Harvoni (ledipasvir and sofosbuvir) or Daklinza (daclatasvir) in combination with amiodarone**: risk of clinically significant arrhythmias in combination with amiodarone. Sent out on 7 May 2015.

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

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