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DANISH PHARMACOVIGILANCE UPDATE

Contents

News from the EU

News from the DHMA

Short news

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.

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 June and July 2015 concern the following products:

- **Dexlansoprazole, esomeprazole, lansoprazole, omeprazole, pantoprazole, rabeprazole** – subacute cutaneous lupus erythematosus
- **Donepezil** – rhabdomyolysis

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

The DHMA has requested the EMA to further clarify the safety profile of HPV vaccines

The European Medicines Agency's Pharmacovigilance Risk Assessment Committee, PRAC, will be conducting an additional review of the HPV vaccines and their safety profile at the request of the Danish Health and Medicines Authority. The review is to supplement the documentation that is already available for the vaccines. More specifically the review will be investigating if there is a possible connection between the symptoms being reported and HPV vaccination.

Review data basis

The EMA has announced that the review will focus on reported data for two conditions: CRPS (Complex Regional Pain Syndrome), a chronic pain condition affecting the limbs, and POTS (Postural Orthostatic Tachycardia Syndrome), a condition whereby the heart rate increases abnormally after sitting or standing up, causing symptoms such as dizziness and fainting, as well as headache, chest pain and weakness.

ADR reports of these conditions in young women who have received a HPV vaccine have been considered previously during routine safety monitoring by the PRAC. At the time, a causal link between the conditions and the vaccines could, however, not be established. Both conditions can occur in non-vaccinated individuals, which is why it is important to investigate further if the number of cases reported with HPV vaccine is greater than would be expected.

In its review, the PRAC will consider the latest scientific knowledge, which is hoped to help clarify if there is a causal link between the vaccines and CRPS and POTS, respectively. Based on the review, the PRAC will decide whether to recommend any changes to the product information to better inform patients and healthcare professionals. Presently, there is no change in recommendations for the use of the vaccines.

The PRAC review is expected to be completed in May 2016.

Read more about the safety of the HPV vaccine on the website of the Danish Health and Medicines Authority: *HPV vaccination and adverse reactions.*

Read EMA's press release: *EMA to further clarify safety profile of human papillomavirus (HPV) vaccines.*

Dialogue conference on HPV vaccine and adverse reactions

On 19 August, the Danish Pharmacovigilance Council hosted a conference at the DHMA under the heading: Greater knowledge about the HPV vaccine. The purpose was to elucidate the vaccine's adverse reactions and the advice that the authorities provide to children and families.

The conference was joined by a number of professionals representing different specialties from all five regions in Denmark. Also represented were the Organization of General Practitioners, the Danish Cancer Society, the DHMA, the relatives' group known as HPV Update, and others.

The conference featured presentations from three panels each bringing forward the problems they are working with every day. Each panel presentation was followed by group discussions and elaborate questions posed to the presenters in the plenum.

Panel 1: Status on HPV vaccine programme results and possible adverse reactions
MD Ole Mogensen from Odense University Hospital opened with a presentation of how infection with the human papillomavirus (HPV) occurs, including how HPV vaccination can prevent the virus infection which is a precondition for later development of cell changes and cervical cancer. Next, he went through the evidence for adverse reactions from the controlled studies based on which the vaccine was authorised as well as subsequent studies conducted by different research groups. This led to the conclusion that the HPV vaccine is highly beneficial and that so far, no accumulation of serious adverse reactions has been recorded in neither studies nor monitoring surveys.

Physician, PhD and Senior Scientist Christian Munk from the Danish Cancer Society, picked up after Ole Mogensen's presentation and gave an account of what we know at present about the immunisation programme's effect in Denmark. Christian Munk concluded that the vaccine has already proven beneficial as figures show a drop in the occurrence of genital warts as well as a decrease in the occurrence of various early stages of cervical cancer in the period after the vaccine’s launch in Denmark – in particular, the incident rates were lower in vaccinees compared to non-vaccinees.

Line Michan, Special Adviser in the DHMA's Pharmacovigilance & Medical Devices Division closed the first panel's contributions by going through the monitoring of adverse reactions since the vaccine was introduced in the childhood immunisation programme in 2009. Line Michan provided an overview of the number and type of reported symptoms and went on to describe the possible signals and unifying features of the symptoms particularly in focus. Among the serious adverse reactions, one group is characterised by headache, fatigue, neurological symptoms (e.g. sensory disturbances), pain and circulatory symptoms (e.g. dizziness) of a long-term nature. In closing, the audience was informed that the DHMA has now asked the European Medicines Agency to conduct an additional review of the safety profile of HPV vaccines and that it considers further research within the area of importance.

Panel 2: The possible adverse reactions
During the panel 2 presentation, the audience was presented with various perspectives on the current adverse reactions problem. The first presenter was Trine Wichmann, who represents HPV Update under the Danish Association of the Physically Disabled. Also, the mother of a girl with suspected adverse reactions to the HPV vaccine, Trine Wichmann told the audience about the relatives' group HPV Update and gave examples of the varying symptoms and often serious daily consequences for those suffering from the symptoms. She explained how important it is for these girls to be diagnosed and receive treatment and called for research to be initiated in parallel to identify connections and groups at risk.

Michael Dupont, Vice-President of the Danish Medical Association and General Practitioner in the city of Birkerød continued by explaining the dilemmas that he faces when parents and girls seek pre-vaccination advice, or when they experience illness after the first HPV vaccine dose and want to know whether or not to proceed with the next two doses. Michael Dupont called for more knowledge and clarification so that doctors can give the best possible advice to girls and their parents.

The third presenter was Doctor Louise Brinth from the Syncope Centre at Frederiksberg Hospital. She has examined girls presenting with suspected adverse reactions to the vaccine. Louise told the audience about the patterns she sees and the POTS diagnosis, which she has given quite many of the girls. In general, the girls who come to the Syncope Centre at Frederiksberg Hospital are former athletes who after vaccination have developed the same series of symptoms with headache, fatigue, pain and signs of functional imbalances in the autonomic nervous system – often with massive impact on their daily activities, the result being that they have been incapable of attending school or work for a long time. She emphasised that there is still no evidence of causality – presently, there is only circumstantial evidence. The majority of them have no diagnosis, or different diagnoses have been made despite similar symptoms, and Louise Brinth pointed out that it is crucial to find a "common reality" to clarify causes and find treatment for these girls.

Last up was Professor, MD, Per Fink who heads the Research Clinic for Functional Disorders and Psychosomatics at Aarhus University Hospital. He explained the definition of functional disorders as conditions whereby the affected person experiences physical symptoms impairing functional ability and life-quality when no other somatic or psychiatric disorder is the cause. The conditions are based on the patient's subjective experience and cannot be verified objectively with biomarkers or other tests. Per Fink assessed that a number of the patients who experience having adverse reactions after HPV vaccination satisfy the criteria for functional disorders and could benefit from the treatment methods used in the area. Therefore, Per Fink stressed the importance of diagnosing any functional disorders in these patients.

Panel 3: Advice to citizens – the process so far and next steps
In the last panel discussion, Søren Brostrøm, Head of the DHMA's Hospital Services & Emergency Management Division, started with information about the assessments which decided that the vaccine should be introduced in the Danish childhood immunisation programme. He described how concerns about the severity of the disease, efficacy and safety of the vaccine as well as health economic and ethical justifications are important when vaccinating healthy children. He also told the audience about the informative material

available to health professionals and parents of girls about to be vaccinated. Søren Brostrøm also expressed that the DHMA is concerned about seeing that the participation rate for HPV vaccination is falling and said that the DHMA is presently examining the new 9-valent vaccine and the possibilities of implementing it in the childhood immunisation programme.

Speaking lastly was Chief Physician Iben Holten from the Danish Cancer Society. She told the audience about the Society's informative efforts, including social media activities where also adverse reactions debaters are very active. Iben Holten expressed that it is pivotal to balance the communication with respect to the target group. She encouraged the health authorities to be more proactive in their information campaigns, focusing more on knowledge about the disease than on factual figures and graphs and talked about the dilemma of assessing how open we should be about various suspicions when we provide information.

The conference was closed by Ib Valsborg, Chairman of the Danish Pharmacovigilance Council. He outlined the next perspectives and thanked everyone for good and constructive discussions which had shifted the focus from 'either or' to 'all of the above'. The Danish Pharmacovigilance Council will incorporate all input from the conference in its further work.

All presentations from the dialogue conference (in Danish only):

Panel 1:
Effekt og bivirkninger af HPV-vaccination (Efficacy and adverse reactions of HPV vaccination)
Effekten af vaccinationsprogrammet i Danmark (Effect of the immunisation programme in Denmark)
Status for indberettede bivirkninger til HPV-vaccination (Status on reported adverse reactions to HPV vaccination)
Panel 2:
Paneldebat: De mulige bivirkninger (Panel discussion: The possible adverse reactions)
Bivirkninger ved HPV-vaccinen (Adverse reactions to the HPV vaccine)
Bivirkning eller noceboeffekt (Adverse reaction or nocebo effect)

Panel 3:
Børnevaccinationsprogrammet (Childhood immunisation programme)
Hvordan afvejer vi perspektiverne (How to balance the perspectives)

Clozapine (Leponex etc.) and myocarditis

Clozapine is associated with an increased risk of myocarditis which, in rare cases, can be fatal. The risk is highest during the first two months of treatment, but can also develop later.

A new study has shown that apparently myocarditis is a commonly occurring (>1%) adverse reaction in Australian patients treated with clozapine. It is unclear if the findings

are merely a result of better monitoring procedures, implying that more incidents are identified, or if a genetic variant is the cause[1].

In the current summary of product characteristics for Leponex, myocarditis is indicated to be a rare adverse reaction whose frequency is ≥1/10,000 to <1/1000. Based on the Australian study, the DHMA has requested the EMA's Pharmacovigilance Risk Assessment Committee, PRAC, to initiate a review of all literature concerning clozapine-induced myocarditis.

Doctors should be aware of the following:

- Clozapine should be prescribed under strict medical supervision in accordance with official recommendations. See *the summary of product characteristics for clozapine (Leponex® m.fl.) (in Danish only).*
- Myocarditis or cardiomyopathy should be suspected in patients who experience persistent tachycardia at rest, especially in the first two months of treatment, and/or palpitations, arrhythmias, chest pain and other signs and symptoms of heart failure (e.g. unexplained fatigue, dyspnoea, tachypnoea) or symptoms presenting in myocardial infarction.
- Other symptoms that may be present in development of myocarditis, other than those listed above, include influenza-like symptoms such as fever, fatigue, sore throat, etc.
- If myocarditis or cardiomyopathy is suspected, clozapine treatment should be promptly stopped and the patient should immediately be referred to a cardiologist.
- Patients with clozapine-induced myocarditis or cardiomyopathy should not be re-exposed to clozapine.

Indication for clozapine
Treatment-resistant schizophrenia:
Leponex is indicated in treatment-resistant schizophrenic patients and in schizophrenia patients who have severe, untreatable neurological adverse reactions to other antipsychotic agents, including atypical antipsychotics. Treatment resistance is defined as a lack of satisfactory clinical improvement despite the use of adequate doses of at least two different antipsychotic agents, including an atypical antipsychotic agent, prescribed for adequate duration.

Psychosis during the course of Parkinson's disease
Leponex is also indicated in patients with psychotic disturbances occurring during the course of Parkinson's disease when other standard treatment has failed.

[1] Ronaldson KJ, Fitzgerald PB, McNeil JJ. (2015). Clozapine-induced myocarditis, a widely overlooked adverse reaction. Acta Psychiatrica Scandinavia: 1-10.).

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.

Sertindole, ziprasidone, asenapine and paliperidone and reports of deaths

As part of our pharmacovigilance activities, we have focus on antipsychotic drugs among other products. In the last four issues of Danish Pharmacovigilance Update, we have reviewed and described all received reports of deaths suspected to be adverse reactions of 2nd generation antipsychotic medicines – including quetiapine, clozapine, olanzapine and risperidone/aripiprazole/amisulpride. This month's review is the last one in the series and concerns reports of deaths in connection with the use of sertindole, ziprasidone, asenapine and paliperidone, respectively.

We have received 21 ADR reports that describe deaths suspected as adverse reactions to sertindole (12 deaths), ziprasidone (4 deaths), asenapine (2 deaths) and paliperidone (3 deaths). We have received ten of the 21 ADR reports in the last five years – the most recent one is from July 2015.

Review of the 21 reported deaths related to treatment with sertindole, ziprasidone, asenapine and paliperidone:

Gender

- Women (12)
- Men (9)

Age

- Age 19-40 (7)
- Age 41-60 (5)
- Age over 61 (4)
- Unknown (5)

Reported causes of death in the 21 patients

Cause of death	Ziprasidone	Sertindole	Asenapine	Paliperidone
Sudden unexpected death	1	10		1
Suicide	1			1
Myocarditis		1		
Organ failure	1			
Cardiac arrest after ileus and renal failure			1	

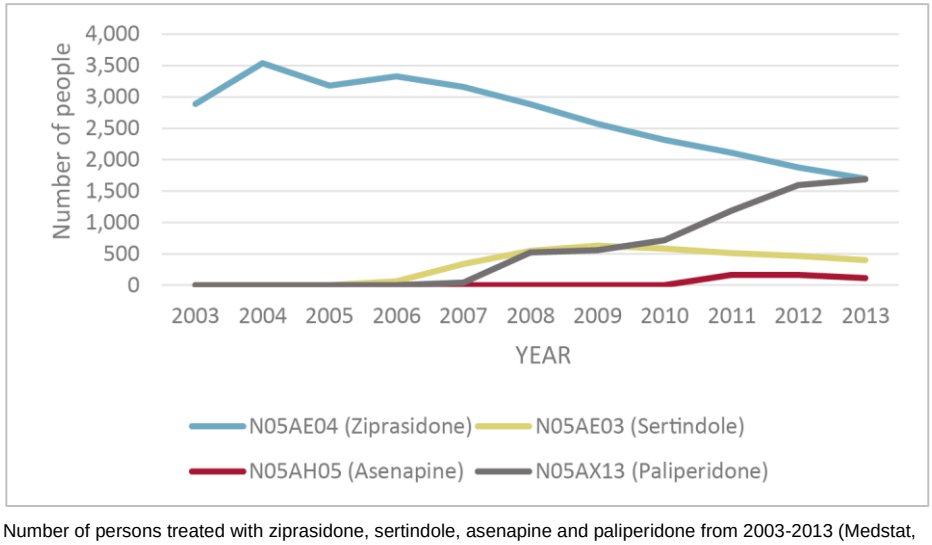
Sepsis, ileus and liver failure				1
Volvulus			1	
Unknown	1	1	1	

Indications reported for sertindole, ziprasidone, asenapine and paliperidone use in the 21 patients:

- Schizophrenia (14)
- Psychotic disorder (1)
- Not provided (6)

Co-medication/polypharmacy/treatment with several antipsychotics
11 of the 21 patients who died were treated with several medicines concomitantly – including two or more antipsychotics at the same time. Ten of the 21 patients were treated concomitantly with a benzodiazepine.

Number of users
The number of people on ziprasidone medication in the primary sector has fallen from approx. 3,500 in 2004 to 1,697 in 2013. The number of people treated with sertindole has remained around 500 since 2008. The number of people treated with asenapine is modest – in 2013 there were 112 people on this medication. The number of people on paliperidone medication has risen from 39 persons in 2007 to 1,686 in 2013.



Number of persons treated with ziprasidone, sertindole, asenapine and paliperidone from 2003-2013 (Medstat, primary sector).

Conclusion
A little more than one third of the patients who died in connection with ziprasidone, sertindole, asenapine or paliperidone treatment were treated concomitantly with one or

several other antipsychotic medicines. Some patients were also being treated with benzodiazepines at the same time. This is inconsistent with the current guideline on antipsychotic treatment – a known problem which 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, Sundhedsstyrelsen, 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 is associated with an increased risk of adverse reactions.

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 with respect to the tests below 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 .*

Indication for ziprasidone
Ziprasidone is indicated for the treatment of schizophrenia in adults.
Ziprasidone is indicated for the treatment of manic or mixed episodes of moderate severity in bipolar disorder in adults and children and adolescents aged 10-17 years.

Indication for paliperidone
Indicated for the treatment of schizophrenia in adults and in adolescents aged 15 years and older.
Indicated for the treatment of schizoaffective disorder in adults.

Indication for sertindole
Sertindole is indicated for the treatment of schizophrenia.

Due to cardiovascular safety concerns, sertindole should only be used for patients intolerant to at least one other antisychotic agent.

Sertindole should not be used in emergency situations for urgent relief of symptoms in acutely disturbed patients.

Indication for asenapine
Asenapine is authorised for the treatment of moderate to severe manic episodes associated with bipolar affective disorder (Bipolar I disorder) in adults.

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Analysis of users and reported adverse reactions for desmopressin-containing medicines

The DHMA has analysed users of desmopressin-containing medicines and ADR reports of suspected adverse reactions to these medicines, the focus being on users older than 65 years and hyponatraemia.

In the investigated period, the older users accounted for 19% of all users, and 75% of them started treatment after the age of 65.

The most commonly reported adverse reaction is hyponatraemia, and it has particularly been reported for older users. Older patients and patients with blood sodium below the normal range may be at increased risk of developing hyponatraemia.

It is not recommended to start older patients on oral formulations of desmopressin[2] (tablets, including freeze-dried/lyophilisates).

Read the analysis here (in Danish only): *Analysis of users and reported adverse reactions for desmopressin-containing medicines*

[2] Summary of product characteristics for Minirin® (in Danish only)

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:

- **SGLT2 inhibitors** – (Invokana (canagliflozin), Vokanamet (canagliflozin / metformin), Forxiga (dapagliflozin), XIGDUO (dapagliflozin / metformin), Jardiance (empagliflozin), Synjardy (empagliflozin / metformin) and risk of diabetic ketoacidosis

- **Ketoconazole HRA** – authorised for the treatment of endogenous Cushing's syndrome – information to doctors about contraindications in patients with acute or chronic liver disease + monitoring of liver function tests to minimise the risk of severe liver injury

- **Integrilin (eptifibatide)** – indicated for the prevention of myocardial infarction – supply difficulties for 10 ml vials (2mg/ml)

- **Enbrel (etanercept**) – batch no. L75213 packed with the wrong package leaflet

- **Epirubicin** (powder for solution and solution for injection) – risk of dosage error in the form of overdose as several SPCs only state epirubicin and not epirubicin hydrochloride, which means that hospital pharmacists cannot tell if it is to be dispensed based on salt or base.

- **InductOs** – shortage of supply due to import restrictions

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

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