Danish Pharmacovigilance Update

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Contents

News from the EU

News from the Danish Health and Medicines Authority

Short news

News from the EU

Restrictions on the use of metoclopramide (Primperan® etc.) for the treatment of nausea and vomiting

Following a European review of the benefits and risks of medicines containing metoclopramide, restrictions in the dosage and treatment duration are now recommended to reduce the risk of serious neurological adverse reactions.

Metoclopramide is known to sometimes cause neurological adverse reactions such as acute extrapyramidal symptoms and tics. The risk of these adverse reactions is higher in children and adolescents, and at high doses. Other neurological adverse reactions may occur following long-term treatment, especially in elderly people. Very rare, but serious cardiovascular adverse reactions have also been reported.

Doctors should be particularly aware of the following:

Indications and use in adults and children:

- Metoclopramide should only be prescribed for short-term use (up to 5 days).
- Metoclopramide should not be used in chronic conditions such as gastroparesis, dyspepsia and gastro-oesophageal reflux disease, nor as an adjunctive treatment in surgical and radiological procedures.
- In adults, metoclopramide remains indicated for short-term use to prevent and treat postoperative nausea and vomiting (PONV), nausea and vomiting associated with radiotherapy, delayed (but not acute) nausea and vomiting following chemotherapy and for symptomatic treatment of nausea and vomiting associated with migraine attacks.
- In children and adolescents aged 1-18 years, metoclopramide should only be used as a second-line option for the prevention of delayed chemotherapy-induced nausea and vomiting and for the treatment of established PONV.
- Metoclopramide is contraindicated in children under 1 year of age.

Dosage:

- The maximum dose in 24 hours is 0.5 mg per kg body weight.
- For adults, the recommended single dose is 10 mg, administered up to three times daily.
- For children above 1 year of age, the recommended dose is 0.1 to 0.15 mg per kg body weight, administered up to three times daily.

Administration:

- Intravenous doses should be administered as a slow bolus (over at least 3 minutes) to reduce the risk of adverse effects.
- Overdose in children has mainly been reported in association with the use of oral liquids. Therefore, oral solutions for the treatment of children should be administered using a graduated oral syringe to ensure accuracy.
- Very rare cases of serious cardiovascular adverse reactions have been reported, especially in association with intravenous administration of metoclopramide. Therefore, doctors should pay particular attention to monitoring when treating risk groups such as elderly patients, patients with cardiac conduction disturbances, electrolyte disturbances, bradycardia, and patients in concomitant treatment with other drugs known to prolong the QT interval.

Currently, the following products containing metoclopramide are marketed in Denmark:

Emperal®, 10 mg tablets

Gastro-Timelets®, 30 mg prolonged-release hard capsules

Primperan®, 5 mg/ml solution for injection

Primperan®, 20 mg suppositories

Due to the new restrictions, Primperan suppositories most likely will be withdrawn from the market.

Read more in the EMA's press release: *European Medicines Agency recommends changes to the use of metoclopramide.*

News from the EU

Letters of safety information sent to doctors

The below DHPCs (Direct Healthcare Professional Communications) have recently been sent out to relevant doctors and other healthcare professionals in Denmark, or will be sent out to them asap, to communicate safety information and provide updated recommendations for medicines:

- **The antithrombotic prasugrel (Efient):** Increased risk of serious bleeding in patients with unstable angina (UA)/NSTEMI when administering Efient prior to diagnostic coronary angiography
- **The cancer medicine ofatumumab (Arzerra):** All patients should be screened for hepatitis B virus before starting treatment with ofatumumab
- **The cancer medicine capecitabine (Xeloda):** Serious skin reactions associated with the use of capecitabine
- **The cancer medicine temozolomide (Temodal):** Severe hepatic toxicity associated with the use of temozolomide
- **The cancer medicine cetuximab (Erbitux):** The importance of establishing wild-type RAS status (exons 2, 3 and 4 of KRAS and NRAS) before starting treatment with cetuximab
- **The sclerosis medicine fingolimod (Gilenya):** Cases of haemophagocytic syndrome have been reported in patients treated with fingolimod.

The DHPCs issued are available on the Danish Health and Medicines Authority's website: *List of issued DHPCs (in Danish only)*

Patients with mechanical heart valves should not be treated with the new oral anticoagulants Pradaxa®, Xarelto® and Eliquis®

The Danish Health and Medicines Authority (DHMA) points out to doctors that patients with mechanical heart valves who require anticoagulant treatment may not be treated with the new oral anticoagulants Pradaxa® (dabigatran etexilate), Xarelto® (rivaroxaban) and Eliquis® (apixaban).

Contraindicated in patients with mechanical heart valves

In December 2012, the European Medicines Agency, EMA, decided that a contraindication for use of Pradaxa® in patients with mechanical heart valves was to be added. Therefore, upon request from the EMA, the marketing authorisation holder for Pradaxa® issued a letter to doctors on 4 January 2013 to inform them about the new contraindication.

The DHMA has previously drawn attention to the contraindication on the following website (in Danish only): *News on Pradaxa® (dabigatran etexilate) and Xarelto® (rivaroxaban)*. The contraindication is also specified at Promedicin.dk (in Danish only).

The contraindication applies to Pradaxa®, Xarelto® and Eliquis®

According to the summary of product characteristics for Xarelto®, this treatment is not recommended in patients with mechanical heart valves (section 4.4 of the spc), since no studies have demonstrated efficacy and safety in this group of patients. Promedicin.dk also recommends not to use Eliquis® in patients with mechanical heart valves.

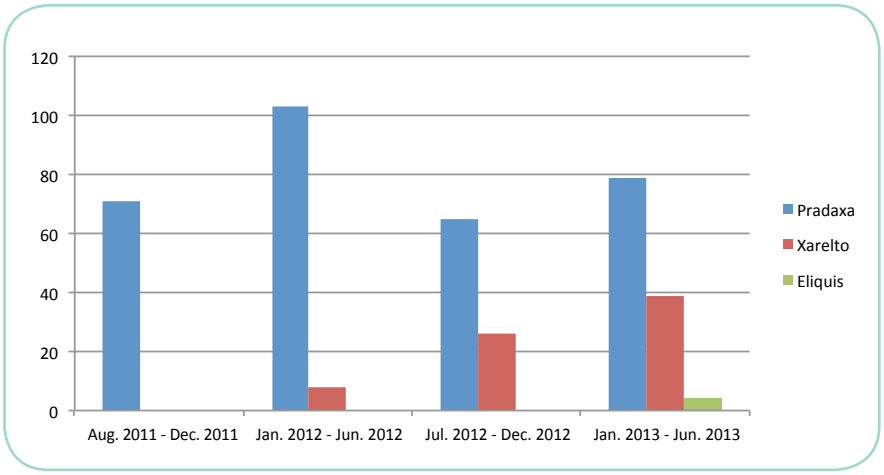

Figure 1. Patients with mechanical heart valves who redeemed their first prescription for Pradaxa®, Xarelto® and Eliquis®, respectively, during the periods stated.

Patients with mechanical heart valves should be treated with warfarin

Patients with mechanical heart valves should be treated with the vitamin K antagonist warfarin or, alternatively, phenprocoumon (see reference 2). The alternative should be selected in case of intolerance to one of the substances. In case of lack of efficacy during treatment of a patient with one of these drugs, the therapeutic level should be increased according to an individual assessment.

Increased focus on the new anticoagulants

The DHMA collaborates with the Thrombosis Centre in Aalborg University Hospital on a monitoring project with a particular focus on the consumption and safety of the new anticoagulants. Among other things, the monitoring includes drawing upon data from the Danish national health registers.

Consumption and adverse effects following the marketing of Pradaxa®, Xarelto® and Eliquis®

Following the marketing of the three oral anticoagulants, a total of 401 patients with a mechanical heart valve have redeemed their first prescription. Approx. 120 of these have redeemed a prescription for one of the new anticoagulants after the addition of the contraindication to the product information, see Figure 1.

The DHMA has received a total of 6 adverse reaction reports concerning patients with mechanical heart valves who had been treated with Pradaxa®. Of the 6 adverse reaction reports, 3

1. Eikelboom JW, Connolly SJ, Brueckmann M, et al. Dabigatran versus warfarin in patients with mechanical heart valves. N. Engl. J. Med. 2013;369:1206-14.
2. Whitlock RP, Sun JC, Fremes SE, Rubens FD, Teoh KH. Antithrombotic and thrombolytic therapy for valvular disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141:e576S-600S.

have been received after the addition of the contraindication. A single report concerns a death where Pradaxa® is suspected to be a contributing factor. The report of the death was received prior to introducing the contraindication.

The background for adding the contraindication

The revision of the summary of product characteristics for Pradaxa® was motivated by data from a clinical study in which Pradaxa® was compared to warfarin in a total of 252 patients (see reference 1). The study comprised both patients with a recently implanted mechanical heart valve and patients whose heart valve had been replaced more than three months prior to their inclusion in the study. The study was prematurely terminated following the observation of several cases of blood clots (mainly strokes and blood clots in the vicinity of the heart valve) and bleeding events during treatment with Pradaxa® as compared to warfarin.

Stricter reporting requirements for suspected adverse reactions following vaccination with Infanrix hexa®

As of the middle of January 2014, children starting vaccination according to the Danish childhood immunisation programme will receive a hexavalent vaccine (Infanrix hexa®) which in addition to protecting against diphtheria and tetanus protects against hepatitis B. Stricter reporting requirements apply for adverse reactions from this vaccine. All suspected adverse reactions must be reported to the Danish Health and Medicines Authority (DHMA) at *Report side effects in humans*.

Potential adverse reactions from Infanrix hexa® described in the summary of product characteristics:

Very common (≥ 1/10) adverse reactions:
- Loss of appetite
- Abnormal crying
- Irritability
- Restlessness
- Fatigue
- Fever ≥ 38°C
- Local swelling at the injection site ≤ 50 mm
- Pain and redness.

Common (≥ 1/100 to < 1/10) adverse reactions:
- Nervousness
- Diarrhoea
- Vomiting
- Fever > 39°C
- Injection site reactions including induration and local swelling > 50 mm.

Information about more rare adverse reactions, contraindications and special warnings and precautions for use can be found in the summary of product characteristics for *Infanrix hexa®*.

Infanrix Hexa® will be subject to stricter reporting requirements

The DHMA has decided that Infanrix Hexa® will be subject to stricter reporting requirements, since the vaccine has not been part of the Danish childhood immunisation programme in the past. Therefore, the DHMA has increased focus on monitoring adverse reactions from the vaccine.

This means that doctors have an obligation to report all suspected adverse reactions associated with the use of the vaccine Infanrix Hexa®.

Serious adverse reactions must be reported to the DHMA within 15 days from a doctor's suspicion of them.

All suspected adverse reactions must be reported to the DHMA at *Report side effects in humans*.

You can find the DHMA's updated list of medicines subject to stricter reporting requirements here: *stricter reporting requirements for doctors, dentists and veterinarians*.

We will review and assess the suspected adverse reactions reported in association with the use of Infanrix hexa® in Danish Pharmacovigilance Update on an ongoing basis.

The reason for the introduction of Infanrix hexa® in the Danish childhood immunisation programme

The introduction is due to technical manufacturing problems at the SSI in association with the manufacture of the polio vaccine included in two of the vaccines in the standard childhood immunisation programme in Denmark. The vaccines are the DTaP-IPV/Act-Hib vaccine for primary immunisation, which is given to children at 3, 5 and 12 months of age, and the DTaP-IPV booster, which is given to children at 5 years of age. Other suppliers have been located to prevent a temporary short supply situation in 2014.

Read more about Infanrix hexa® and the temporary change in the Danish childhood immunisation programme in the newsletter EPI-NEWS from the Statens Serum Institut, National Institute for Health Data and Disease Control (SSI) (in Danish only): *Midlertidigt skift af børnevaccine til Infanrix Hexa® og 5-års booster til DiTeKi (dTap) booster og separat poliovaccine (IPV)* (Temporary replacement of childhood vaccine with Infanrix Hexa® and 5-year booster with DTaP booster and separate polio vaccine (IPV)).

Childhood vaccinations and reported suspected adverse reactions during the first half of 2013

In September 2013, the Danish Health and Medicines Authority (DHMA) published a separate listing of adverse reaction reports associated with the use of the HPV vaccine *Danish Pharmacovigilance Update, 26 September 2013*. **Therefore, the listing in this article only concerns reports of adverse reactions associated with the use of the other vaccines in the Danish childhood immunisation programme.**

The DHMA will publish an updated listing of adverse reactions associated with the HPV vaccine in January 2014.

Adverse reaction reports associated with the Danish childhood immunisation programme during the first half of 2013

During the first half of 2013, the DHMA received a total of 86 reports comprising a total of 341 suspected adverse reactions – including 41 reports classified as serious[1].

The majority of the suspected adverse reactions reported are well-known, such as local reactions at the injection site and general malaise, and are all described in the product information for the vaccines. General symptoms such as fatigue, fever, pain, local irritation, rash and temporary changes of the skin accounted for approx. 50% of the suspected adverse reactions reported.

The vaccines were given to persons aged 0-70 years, and 6 of the serious reports concerned persons over the age of 18.

Table 1a lists the reports by seriousness, and Table 1b lists the number of suspected adverse reactions.

Vaccine	Serious	Non-serious	Total
Td booster	2	2	4
DTaP-IPV booster and Prevenar	1	8	9
DTaP-IPV/Act-Hib and Prevenar13	11	13	24
DTaP-IPV/Act-Hib and Prevenar	3	2	5
DTaP-IPV/Act-Hib	14	11	25
DTaP-IPV	1	1	2
Priorix/MMR	5	7	12
Gardasil and Priorix	1	0	1
Pneumovax	2	0	2
Tetanus	1	1	2
Total	**41**	**45**	**86**

Table 1a. Distribution of the reports according to seriousness

Vaccine	Number of suspected adverse reactions
DTaP-IPV booster	22
DTaP-IPV/Act-Hib	138
Prevenar13	68
Prevenar	16
Tetanus	9
Td booster	22
DTaP-IPV	7
Priorix/MMR	52
Pneumovax	7
Total	**341**

Table 1b. The number of suspected adverse reactions reported for each individual vaccine

Non-serious adverse reactions

One unexpected (non-serious) adverse reaction concerning a case of metal allergy was reported. Other non-serious adverse reactions reported are local reactions at the injection site, general malaise, fever and pain.

1 A serious adverse reaction is defined as an adverse reaction which is fatal, life-threatening, causes or prolongs hospitalisation, or causes permanent or significant disability or inability to work, or which is a congenital anomaly or birth defect.
This means that any person who has, e.g., been briefly hospitalised (e.g., in a paediatric admission ward) with an adverse reaction will have been classified as a patient with a serious adverse reaction.

Review of adverse reactions reported and classified as serious

DTaP-IPV/Act-Hib and Prevenar13:

- A 2-month-old girl developed fever and stiffness and trembling accompanied by cyanosis. Fully recovered. A correlation is deemed possible.
- A 3-month-old boy briefly developed stiffness/eye turning . Later the same day, he developed a high fever. A correlation is deemed possible.
- A 5-month-old girl developed infantile spasms two days after the second vaccination. A correlation with the vaccine is deemed less likely.
- A 5-month-old girl was brought dead to an emergency room on the day of her second vaccination. The autopsy revealed a large ruptured malignant liver tumour. A correlation with the vaccine is less likely.
- A 2-year-old boy developed granulomas and was under observation for aluminium allergy following vaccination. He also developed pseudocroup after the vaccinations. A correlation with the vaccine is deemed possible for the first-mentioned and less likely for the latter.
- A 5-month-old girl became pale and started gasping for her breath on the day of the vaccination. This was followed by a whooping breathing every day for a period of time. A correlation with the vaccines is deemed possible for the event on the day of the vaccination, whereas a correlation is deemed less likely for the whooping.
- Aluminium allergy and granuloma – a correlation is deemed possible
- A 2-month-old boy developed dyspnoea, became distant and had twitching arms and legs and a fever of 38.1°C. A correlation is deemed possible.
- A 3-month-old boy developed fever and twitching legs interpreted as febrile convulsions. A correlation is deemed possible.
- A 1-year-old boy with aluminium allergy and a granuloma. A correlation is deemed possible.
- Hepatic impact in a 3-month-old baby was identified when diagnosing the baby due to a bleeding tendency during vaccination. Therefore, the impact was likely present before the vaccination. A correlation is deemed less likely.

DTaP-IPV booster and Prevenar:

- A 6-year-old boy developed a granuloma in his right thigh following booster vaccination. Was tested positive for aluminium allergy. A correlation is deemed possible.

DTaP-IPV/Act-Hib:

- A 5-month-old girl developed eczema at the injection site; approx. two years later generalised vesicles appeared. Possibly impetigo? Local eczema is a potential adverse reaction, impetigo is less likely to be an adverse reaction.
- A 2-year-old girl with a granuloma and aluminium allergy. A correlation is deemed possible.
- A girl developed continuous screaming and poor well-being after the 5-month vaccination – later reportedly diagnosed with 'leaky gut syndrome' in the USA. The results of the examinations are not available. Therefore, it is not possible to assess the report. The report was received when the girl was 11 years old.
- A 7-month-old girl developed a granuloma and aluminium allergy. The Danish Patient Insurance Association has awarded a compensation. A correlation is deemed possible.
- A 4-year-old boy diagnosed with granulomas, which appeared following vaccinations done three years earlier, was tested positive for aluminium allergy. A correlation is deemed possible.
- A 3-year-old girl with granulomas, which appeared following vaccinations done three years earlier, was tested positive for aluminium allergy. A correlation is deemed possible.
- A total of 7 children developed pertussis in spite of vaccination (a 1-year-old girl (2 vaccines), a 1-year-old boy (2 vaccines), a 1-year-old girl (at least one vaccine?), a 1-year-old girl (3 vaccines), a 1-year-old girl (3 vaccines), a 1-year-old girl (3 vaccines), a 1-year-old boy (3 vaccines?)). All are considered 'vaccine failures'.
- The Danish Patient Insurance Association has awarded a compensation corresponding to a degree of permanent injury of 5% for granuloma and aluminium allergy. A correlation is deemed possible.
- A 1-year-old boy developed a granuloma and aluminium allergy following vaccination. A correlation is deemed possible.
- A 2-month-old girl developed symptoms compatible with a hypotonic-hyporesponsive episode 5-7 hours after vaccination. A correlation is deemed possible.
- A 6-month-old boy developed a granuloma after the second vaccination. A correlation is deemed possible.

DTaP-IPV:

- A 17-year-old boy, who is undergoing evaluation by a psychologist due to personality problems, reportedly developed these problems after the third DTaP-IPV vaccination which was followed by fever and distance. A correlation with personality change is deemed to be less likely.

Td booster:

- A 40-year-old woman developed a marked granuloma following vaccination with Td booster and Havrix. A correlation is deemed possible.

- A 20-year-old woman developed itching throat, malaise, hyperventilation, fainting and convulsions immediately after vaccination. A correlation is deemed possible.

Tetanus vaccine:

- A 40-year-old woman developed pain at the injection site five weeks after the vaccination (also Havrix). Was observed for an abscess and hospitalised to receive intravenous antibiotics. Was treated with antibiotics. A correlation is possible.

Priorix® (MMR):

A 1-year-old girl developed long-lasting febrile convulsions on the day of the vaccination. The summary of product characteristics lists febrile convulsions as a rare adverse reaction from the vaccine. Therefore, a correlation is deemed possible.

- A 21-year-old man was vaccinated with Havrix and Priorix and subsequently started to feel bad. Diagnosed with IDDM a year later. Based on the literature, a correlation is deemed less likely.

- A 2-year-old boy had been vaccinated with Priorix at 5 months of age and subsequently with a booster vaccine at 15 months of age. An invasive pneumococcal infection (positive blood culture) was identified 14 days after the vaccination. The boy was subsequently diagnosed with hearing loss. Based on the medical history, the hearing loss is most likely related to a pneumococcal infection. Therefore, a correlation with the vaccine is deemed less likely.

- Concomitant Gardasil vaccination – previously causality assessed when looking at that vaccine, since adverse

Estimated coverage in Denmark of each individual childhood vaccine[2]:

DTaP-IPV booster vaccination	85.1-86.3%
DTaP-IPV/Hib1	94.1%
DTaP-IPV/Hib2	90.6%
DTaP-IPV/Hib3	90.7%
MMR1	90.7%

The participation in the PCV (pneumococcal vaccination), HPV (human papilloma virus) vaccination, DTaP-IPV/Hib vaccination and MMR vaccination, respectively[3]:

a. During the period 2007-2010, the participation was 92% for the first PCV, 81-92% for the second PCV and 79-90% for the third PCV.

b. For HPV, the participation for girls born in 1996, 1997 and 1998 was 88-90%, 83-86% and 76-82% for the first, second and third vaccinations, respectively.

c. For DTaP-IPV/Hib, the coverage for the years of birth 2002-2010 has been calculated to be 89-94%, 88-93% and 87-91% for the first, second and third vaccinations, respectively.

d. For the first MMR vaccination, the participation for the years of birth 2007-2009 is 88%, whereas the participation for the second MMR vaccination is lower. However, since the immunisation programme has been changed to offer the second MMR vaccination at the age of 12 instead of the age of four, the participation per year of birth varies from 69-88%. This is below the target of 95%.

At present, there are no data on the number of persons receiving vaccines from the immunisation programme later in life.

2 The Statens Serum Institut, National Institute for Health Data and Disease Control, EPI-NEWS, No. 20, 2012. The figures are based on a questionnaire survey showing that vaccinations are under-reported to the Danish Childhood Vaccination Database.

3 The Statens Serum Institut, National Institute for Health Data and Disease Control, EPI-NEWS, No. 21, 22, 23a and 23b, 2012.

reactions are primarily attributable to Gardasil.

- A 15-month-old boy developed a parotitis-like image approx. 14 days after the vaccination. A correlation is deemed possible.

- A 15-month-old girl developed measles exanthema approx. 12 days after the vaccination. The reporter considers this serious, due to vaccine failure? A correlation is deemed possible, but is considered to be an adverse reaction from the vaccine and not vaccine failure.

Pneumovax:

- A 28-year-old woman was followed due to observed immunodeficiency; pneumovax and haemophilus influenza vaccine were given to test her B cell response. Developed marked swelling and redness of the left upper extremity locally, axillary adenitis and fever. Hospitalised in spite of administration of prednisolone. A correlation is deemed possible.

- A 66-year-old man known to suffer from paroxystic atrial fibrillation developed a long-lasting attack three hours after vaccination. Disappeared spontaneously. It cannot be ruled out that the vaccine or fever due to administration of the vaccine may trigger the condition in a predisposed individual. A correlation is deemed possible.

Conclusion for the first half of 2013

One report concerns a death, where a 5-month-old girl died on the day of her vaccination with DTaP-IPV/Act-Hib and Prevenar. However, an autopsy revealed that death was caused by a malignant ruptured liver tumour. Therefore, a correlation with the vaccines is less likely.

The serious reports comprise 11 cases of granulomas and aluminium allergy and an additional case of a granuloma where aluminium allergy is not mentioned. The non-serious reports comprise an additional 11 cases of granulomas and 1 case of metal allergy. For many of the serious cases, the report was submitted via the Danish Patient Insurance Association. The increased number of reports concerning metal allergy may be due to the heightened focus at present and not necessarily an increase in the occurrence of granulomas.

Pertussis (whooping cough) infection occurred in 7 cases after vaccination. This is an expected number, since the vaccine does not offer 100% protection.

There was 1 case of infantile spasms which had their onset 2 days after vaccinating with DTaP-IPV/Act-Hib and Prevenar in a 5-month-old child. Based on the literature, a causality between the vaccines and the disease is deemed less likely.

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

Desmopressin and hyponatraemia

In October 2013, the Danish Health and Medicines Authority (DHMA) received an adverse reaction report concerning an elderly patient who developed hyponatraemia during treatment with desmopressin and subsequently a mania.

The adverse reaction occurred two months after initiating desmopressin against nocturia. The start-up dose was 120 mg, and the serum sodium level had been stable in the lower end of the normal range prior to start-up. Following six weeks of treatment, the patient's dose was doubled, since the treatment did not have the desired effect. There is no information on serum sodium levels prior to the dose increase. Shortly after the dose increase, the patient seemed manic and was subsequently admitted to a psychiatric hospital.

During the hospitalisation, sodium levels measured ranged from 120 to 138 mmol/l. This is compatible with a non-continuous intake of the product. The product was discontinued during the hospitalisation, and the patient was treated with olanzapine. The patient was discharged at a later date and is mentally healthy today.

Reports of hyponatraemia in association with the use of desmopressin

The DHMA has received a total of 19 reports concerning patients who developed hyponatraemia in association with the use of desmopressin. Some of the reports describe that the patients became confused, and 1 report furthermore describe that the patient hallucinated.

Doctors should pay attention to the following:

- The most serious adverse reaction in association with desmopressin is hyponatraemia with symptoms such as headache, abdominal pain, nausea, vomiting, weight gain, dizziness, confusion, malaise, forgetfulness, vertigo, falling and, in serious cases, convulsions and coma. The cause of the potential hyponatraemia is the well-known antidiuretic effect. Hyponatraemia is reversible.
- Among adults treated for nocturia, the majority of the patients who experienced low serum sodium developed hyponatraemia during the first days of the treatment or in association with a dose increase.
- The treatment of elderly patients should be monitored closely due to the increased risk of hyponatraemia. Serum sodium levels should be measured prior to initiating the treatment, three days after start-up or in association with a dose increase and regularly during long-term treatment.
- Elderly patients and patients with serum sodium levels in the lower end of the normal range may have an increased risk of hyponatraemia.

Indication for desmopressin
- Diabetes insipidus
- Enuresis nocturna
- Treatment of nocturia in adults.

The Danish Health and Medicines Authority's analysis of melatonin users under the age of 25

The Danish Health and Medicines Authority (DHMA) has analysed the development in the number of melatonin users in Denmark during the years 2007-2012. The analysis included users of magistrally manufactured melatonin and users of Circadin®.

Additionally, the DHMA looked into whether children and adolescents under the age of 25 who were given melatonin in 2012 had a diagnosis for which prescription of melatonin was relevant.

Read the report (in Danish only) on the DHMA's website: *Brugere under 25 år af lægemidler med melatonin* (Users under the age of 25 of drugs with melatonin).

Alle sager, der refereres til i artiklen, stammer fra Sundhedsstyrelsens egen bivirkningsdatabase. Sagerne er udsendt til alle relevante lægemiddelvirksomheder og til Eudravigilancedatabasen. Lægemiddelvirksomheder skal derfor ikke indberette disse sager til Sundhedsstyrelsen.

Short news

New opportunity to report adverse reactions from dietary supplements to the Danish Veterinary and Food Administration

By the Danish Veterinary and Food Administration:

Doctors and other healthcare professionals are now offered the possibility to report adverse reactions related to patients' intake of dietary supplements.

Many Danish consumers have a daily intake of various dietary supplements. Dietary supplements may have desired effects as well as adverse reactions (undesired effects). To strengthen the consumer safety, the Danish Veterinary and Food Administration (DVFA) has established a system for reporting of adverse reactions related to dietary supplements.

Therefore, doctors and other healthcare professionals are now offered the possibility to report adverse reactions which, in their opinion, may be related to the patient's intake of dietary supplements. On the DVFA's website, you can find a reporting form (in Danish only), in which information concerning cases of adverse reactions can be entered and submitted to the DVFA. See *Bivirkninger relateret til indtag af kosttilskud – Indberetningsskema* (Adverse reactions related to the intake of dietary supplements – Reporting form).

When to report:
Doctors and other healthcare professionals are free to choose whether to report adverse reactions from dietary supplements.

The DVFA is interested in reports, regardless whether the products are legal or not and whether they are sold in Danish shops or via the Internet. All information about adverse reactions that may have been caused by dietary supplements or may be related to products comparable to dietary supplements is very valuable, as it may contribute to increase the knowledge of potentially harmful products, ingredients or substances.

How will the reports be processed by the DVFA?
Upon receipt of a report, the DVFA will assess the case, including determining whether a correlation between the dietary supplement consumed according to the patient and the adverse reaction reported can be established.

Generally, the DVFA will obtain an assessment from DTU Food (the National Food Institute at the Technical University of Denmark). The DVFA may also find it relevant to contact the reporters of the adverse reaction or the patient to obtain more information. Additionally, the DVFA will inform the company responsible for the first marketing of the product in Denmark. Sensitive personal data are always treated as confidential.

What are dietary supplements?
Dietary supplements comprise a wide range of products from the most common vitamin and mineral tablet to fish oils or products containing plants or plant extracts.

Dietary supplements are subject to Danish food legislation, and – contrary to drugs – intake of dietary supplements may not result in adverse reactions (undesired effects). All dietary supplements marketed in Denmark must be registered at the DVFA at the time of the first marketing at the latest. Especially at the Internet, you can find marketed dietary supplements which are unregistered and therefore not covered by the DVFA's control programmes.

Read more about dietary supplements, and see the DVFA's register of all dietary supplements registered for sale in Denmark, at *www.altomkost.dk* (in Danish only).

For further information please contact:
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Short news

Clarification to the article 'Bisphosphonates/denosumab and the risk of osteonecrosis of the jaw' in Danish Pharmacovigilance Update, 28 November 2013

Based on an inquiry, the Danish Health and Medicines Authority (DHMA) wishes to clarify the recommendations in the presentation 'Bisphosphonates/ denosumab and the risk of osteonecrosis of the jaw', *Danish Pharmacovigilance Update, 28 November 2013*.

The presentation contained a number of recommendations for the prescribing doctors. These recommendations included the following: 'The patient should, whenever possible, complete major dental treatments prior to initiating treatment with bisphosphonates or denosumab, and the patient should direct the dentist's attention to the ongoing treatment with these medicines, in case major dental treatments become necessary during such ongoing treatment.' The DHMA wishes to clarify the recommendation by replacing 'major dental treatments' with 'invasive dental treatments'.

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