Danish Pharmacovigilance Update #3

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Strengthened recommendations for use of zolpidem (Stilnoct® etc.)

A new review of the benefits and risks of zolpidem-containing medicines has just been concluded in the EU. The conclusion is that the benefit-risk balance of these medicines is still positive. However, the warnings related to the risks of drowsiness and slower reactions the morning after taking the medicine should be strengthened in the product information.

The recommendations for zolpidem are now:

- The recommended daily dose for adults remains at 10 mg, and this dose should not be exceeded.
- The medicine should be taken as a single dose just before bedtime, and users should not take more zolpidem during the same night.
- The recommended dose for elderly patients and patients with reduced liver function is 5 mg.
- It is recommended not to drive or perform activities that require mental alertness until 8 hours after taking zolpidem.
- The risks of next-morning drowsiness and slower reactions are higher with concurrent use of alcohol and other medicines that affect the central nervous system.

The review in detail

The EU review was initiated after reports of impaired driving and road accidents involving patients who took zolpidem. It is well known that zolpidem can cause drowsiness and slower reactions the day after taking zolpidem, which could increase the risk of accidents during activities that require alertness.

Additional to the changed recommendations, it was also concluded that a convincing effect has only been established at a dose of 10 mg zolpidem. However, some studies have shown some effect of a lower dose of 5 mg. Zolpidem should be used at the lowest possible dose, and in some patients a dose of 5 mg could have sufficient effect.

Indication for Stilnoct®
Short-term treatment of insomnia in situations where the insomnia is debilitating or is causing severe distress for the patient.

Follow this link to read more about the review of zolpidem: *PRAC recommends product information of zolpidem be updated with new advice to minimise the risk of next-morning impaired driving ability and mental alertness*.

News from the EU

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

The most important recommendations on safety signals from the PRAC meeting in February 2014 concern the following products:

- Amiodarone – carcinogenicity
- Basiliximab – cardiovascular instability resulting in fatal outcome following off-label use in heart transplantation
- Interferon beta 1$^{a/b}$ – thrombotic microangiopathy (TMA)
- Mefloquine – possibly permanent neurologic (vestibular) adverse reactions
- Paracetamol – drug-induced Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalised exanthematous pustulosis (AGEP)
- Ustekinumab – dermatitis exfoliative

See the list on EMA's website. *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.

Fampridine (Fampyra®) and seizures

In January, the DHMA received an adverse reaction report about a patient who had experienced seizures after two months' treatment with Fampyra®. The patient had no history of seizures in the past. The medicine was discontinued, and the patient has not suffered seizures since.

Doctors should be aware of the following:

- Fampyra® is contraindicated in patients with a prior history of seizures.
- Treatment with Fampyra® increases seizure risk.
- Fampyra® should be administered with caution in the presence of any factors which may lower seizure threshold.
- Treatment with Fampyra® should be discontinued in patients who experience a seizure while on treatment.

Number of Fampyra® users and reported adverse reactions

Year	2011	2012	2013
Reported adverse reactions	–	4	7
Number of users*	8	320	398

**Number of users having redeemed at least one prescription for Fampyra®.[1] Fampyra® was marketed in 2011.*

The DHMA has received a total of 12 adverse reaction reports on Fampyra®. The first 11 reports were received in 2012 and 2013, and the latest report was received in January 2014. Five of the reports concern suspected serious[2] adverse reactions, three of which describe the development of spasms or epileptic seizures in patients treated with Fampyra®.

Indication for Fampyra®
Fampyra® is indicated for the improvement of walking in adult patients with multiple sclerosis with walking disability.

1 The analysis related to drug consumption has been prepared in collaboration with Data Delivery and Medicinal Product Statistics at Statens Serum Institut, National Institute for Health Data and Disease Control (SSI).

2 A serious adverse reaction caused by a medicine for human use is a reaction that results in death, is life-threatening, requires hospitalisation or prolongation of hospitalisation, or which results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect, cf. section 3(4) of the Danish executive order no. 826 of 1 August 2012 on the reporting of adverse reactions from medicines etc. (in Danish only).

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, pharmaceutical companies should not report these cases to the Danish Health and Medicines Authority.

Childhood vaccines and suspected adverse reactions in second half of 2013

Possible adverse reactions of vaccines is one of the DHMA's focus areas. Every three months, a vaccination panel meets to assess reports of suspected adverse reactions to vaccines included in the Danish immunisation programme.

The May issue of Danish Pharmacovigilance Update will review the reports of suspected adverse reactions to the HPV vaccine separately. Reports of suspected adverse reactions to the HPV vaccine are therefore not included in this article.

Reports in second half of 2013

In the second half of 2013, we received altogether 91 reports describing a total of 334 suspected adverse reactions. 37 of the reports are classified as serious.

Table 1a shows the distribution between serious and non-serious reports. If a report contains both serious and non-serious adverse reactions, it is classified as serious.

One report may cover several suspected adverse reactions. Table 1b shows the number of suspected adverse reactions reported for each vaccine. >

Vaccine	Serious	Non-serious	Total
DTaP-IPV	0	1	1
DTaP-IPV booster	1	5	6
DTaP booster/Gardasil	1	7	8
DTaP-IPV/Act-Hib and Prevenar13	5	6	11
Prevenar 13	2	2	4
DTaP-IPV/Act-Hib	16	12	28
DTaP-IPV/Act-Hib and Prevenar	0	2	2
DTaP-IPV booster and Prevenar	1	2	3
Priorix/MMR	7	9	16
Priorix and Gardasil	2	0	2
Pneumovax	1	0	1
MMR vaxpro	1	8	9
Total	**37**	**54**	**91**

Table 1a. Reports broken down by serious and non-serious suspected adverse reactions

Vaccine	Number of adverse reactions
DT booster	30
DTaP-IPV booster	18
DTaP-IPV/Act-Hib	145
DTaP-IPV	2
Prevenar13	47
Prevenar	7
Priorix®/MMR	50
Pneumovax	14
MMR vaxpro	21
Total	**334**

Table 1b. Number of suspected adverse reactions reported for individual vaccines in the second half of 2013. The table does not consider the fact that several vaccines may have been given at the same time – and hence that the adverse reactions could possibly have been caused by another vaccine.

Unexpected and non-serious adverse reactions

During the period, the DHMA also received reports of unexpected[2] adverse reactions, including thirst, insomnia, nail changes and cold urticaria – adverse reactions that are classified as non-serious.

In the category of known, non-serious adverse reactions, the DHMA received 54 reports. These reports concerned various types of adverse reactions described in the authorised summaries of product characteristics. The most frequently reported known, non-serious adverse reactions are local reactions at the injection site, general malaise, fever and pain.

Review of the reports classified as serious

As shown in table 1a, the DHMA has received 37 reports of suspected serious adverse reactions.

DTaP-IPV/Act-Hib and Prevenar13

- A 3-month-old boy develops an episode of apnoea on the day of vaccination.
  Causality is considered likely.
- A now 3-year-old boy with granuloma and verified aluminium allergy (the Danish Patient Insurance Association).
  Causality is considered likely.
- A 3-month-old girl is admitted to hospital with fever cramps, tachycardia, vomiting, neurological reactions and severe crying on the day of vaccination. She was subsequently discharged and in good health.
  Causality is considered likely.
- A 1-year-old girl develops aluminium granuloma on both thighs (injection sites). Aluminium allergy test is positive.
  Causality is considered likely.
- A 3-month-old girl develops granuloma on both thighs. Positive test for aluminium allergy.
  Causality is considered likely.

DTaP-IPV Booster and Prevenar

- A 6-year-old boy develops granuloma on right thigh after DTaP-IPV Booster vaccination. Is tested positive for aluminium allergy.
  Causality is considered likely.

DT Booster and Gardasil

- A 22-year-old woman is vaccinated with DT Booster and Gardasil. She subsequently develops stomach ache, back pain, dizziness, joint pain, headache, muscle weakness, orthostatic intolerance and several other symptoms. The symptoms started after the Gardasil vaccination, but got worse after the DT Booster. The criteria for POTS are not met. Examined using the tilt table test and blood tests. Since no diagnosis is available, it is not possible to assess whether there is a possible causal link to the vaccines.

Prevenar13

- A 5-month-old boy diagnosed with pneumococcal pneumonia. Serotype 3 established.
  Hence a case of "vaccine failure" (lack of efficacy).
- In connection with the 1-year vaccination, a girl develops an itching lump (granuloma) at the injection site approx. 14 days after vaccination with Prevenar13. No aluminium allergy test performed.
  Causality is considered likely.

DTaP-IPV Booster

- Shortly after vaccination, a 5-year-old boy had an indisposition – interpreted as anaphylaxis.
  Causality is considered likely.

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2 An unexpected adverse reaction caused by a drug means an adverse reaction, the nature, severity or outcome of which is not consistent with the summary of product characteristics, cf. section 3(6) of the Danish Executive Order no. 826 of 1 August 2012 on the reporting of adverse reactions from medicines etc. (in Danish only).

Priorix®/MMR

- Morbilliform rash on day 5. IgM and IgG positive, PCR positive for measles virus in urine, examined to check for wild-type measles. The case is mild.
  A causal relationship with the vaccine is considered less likely due to the time factor.

- Morbilliform rash (mild). IgM and IgG positive, PCR negative.
  Assessed to be a vaccine reaction and not vaccine failure.

- A 1-year-old girl who develops fever of 39.5C three days after vaccination. Day 12, exanthema, fever and general malaise. Is admitted to hospital. Morbilli serology not performed.
  Causality is considered likely.

- A 12-year-old boy develops Guillain-Barré syndrome a good month after vaccination. Had Guillain-Barré syndrome two years earlier.
  Causality is considered likely.

- 1-year-old girl who immediately after vaccination develops paresis of the arm lasting for four hours. A relapse occurs 11 days after with fever – this time for three hours.
  Based on the available information, it is not possible to assess whether a causal relationship exists.

- A 12-year-old boy develops headache the day after vaccination (has suffered this before, but to a minor degree). Cells in the spinal fluid are later detected. MRI scan normal. Treated with immunoglobulin on slight suspicion of encephalitis/meningitis. Mycoplasma titer is positive, and the picture is unclear. Due to possible other intercurrent causes of the symptoms, a causal relationship with the vaccine is considered less likely.

- Uncomplicated case of fever cramps in a 1-year-old boy five days after vaccination.
  Causality is considered likely.

Priorix and Gardasil

- A 12-year-old girl is vaccinated with Priorix and Gardasil. On the same day, the girl has a seizure.
  A causal relationship with the vaccine is considered possible.
  The report states that the girl has epilepsy, but this diagnosis is unclear.

- A 13-year-old girl develops peripheral facial palsy approx. 6 months after vaccination with Priorix and one month after the last dose of Gardasil. Blood tests are normal. No lumbar puncture. The girl is recovering.
  It is not possible to assess whether a causal relationship exists since no tests for agents have been done.

MMR vaxpro

- A 2-year-old boy is admitted to hospital seven days after vaccination in an epileptic state (lasting for two hours) and fever. Has a history of fever cramps. Is treated with Fosfenytoin with resulting dizziness, balance disturbance and asynergia. Nine days after vaccination, a morbiliform rash develops as well as thrombopenia and leukopenia. The boy has subsequently recovered. Fever with cramps as well as thrombopenia and leukopenia after vaccination are possible adverse reactions of the vaccine.

Pneumovax

- A 31-year-old woman with known diabetes is treated with pneumovax. Case from the Danish Patient Insurance Association. Develops profound local swelling and redness of left upper extremity and left axillary lymphadenitis. Examined by MRI scan – apparently normal.
  Causality is considered likely.

DTaP-IPV/Act-Hib

- 1-year-old girl develops Haemophilus Influenza type b meningitis despite three vaccinations.
  A case of "vaccine failure".

- A now 9-year-old girl who has developed autism at an unknown time after vaccination. There is left hemisphere venous anomaly.
  Causality is considered less likely.

- A 2-year-old girl develops granuloma at the injection site. Is tested positive for aluminium allergy.
  Causality is considered likely.

- A 1-year-old girl develops granuloma at the injection site. Is tested positive for aluminium allergy.
  Causality is considered likely.

- A 3-year-old boy develops granuloma at the injection site. Is tested positive for aluminium allergy. Causality is considered likely.

- A 2-year-old boy develops granuloma at the injection site. Is tested positive for aluminium allergy.
  Causality is considered likely.

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- A 1-year-old boy develops granuloma at the injection site. Is tested positive for aluminium allergy.
  Causality is considered likely.

- A 1-year-old girl develops pertussis after three vaccinations with DTaP-IPV/Act-Hib. The diagnosis is verified by laboratory tests.
  This is a case of vaccine failure, which is possible since protection is not 100 % even after three vaccinations.

- A 21-month-old boy develops pertussis. Diagnosis is verified by antigen. Has received three vaccinations with DTaP-IPV/Act-Hib.
  This is a case of vaccine failure, which is possible since protection is not 100 % even after three vaccinations.

- An approx. 1-year-old boy develops granuloma on both thighs (six months after vaccination). There is no indication of whether the boy has been tested for aluminium allergy. The Danish Patient Insurance Association has granted compensation.
  Causality is considered likely.

- A 1-year-old boy develops pertussis (verified by PCR) despite three vaccinations with DTaP-IPV/Act-Hib.
  This is a case of vaccine failure, which is possible since protection is not 100 % even after three vaccinations.

- A 1-year-old boy develops vaccination granuloma approx. five months after vaccination. Test for aluminium allergy positive.
  Causality is considered likely.

- A 6-month-old boy develops itching vaccination granuloma on both thighs. Tested positive for aluminium allergy.
  Causality is considered likely.

- A 1-year-old girl develops granuloma after vaccination. Tested positive for aluminium allergy. Has been granted compensation.
  Causality is considered likely.

- A 2-year-old girl develops pertussis despite three vaccinations. The diagnosis is verified by tests (by culture).
  This is a case of vaccine failure, which is possible since protection is not 100 % even after three vaccinations.

- An 11-month-old boy develops granuloma after vaccination. Not tested for allergies.
  Causality is considered likely.

Conclusion

In the last six months of 2013, we received a total of 91 reports on vaccines in the childhood immunisation programme, of which 37 were classified as serious. Reports concerning the HPV vaccine will be assessed separately in the May issue.

The number of reports is steady, mainly reflecting known adverse reactions that appear from the summaries of product characteristics.
Among the serious reports, there are quite many cases of granuloma and aluminium allergy. Among the non-serious reports, cases of granuloma are also found. Most of the serious cases were reported through the Danish Patient Insurance Association. The rise in reports was already seen in the first half of 2013. Most likely, it is caused by increased focus on the condition, and not because there are more incidents of granuloma than before[1]. We can see this because several of the reports date back to previous years.

The remaining reports of suspected non-serious adverse reactions are largely well-known; first and foremost covering local reactions at the injection site, general malaise, fever and pain.

The Danish Health and Medicines Authority assesses that the benefits of the vaccines still outweigh the possible risks.

1 The latest issue of the Danish Medical Journal at *Ugeskriftet.dk* features an article in Danish on the topic of *Aluminium allergy and granuloma caused by vaccination in children (in Danish only)*.

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