Danish Pharmacovigilance Update

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Reports of serious side effects in Japan from the childhood vaccines Prevenar (PCV7)® and Act-Hib®

After four reports of deaths among children, the Japanese authorities have temporarily suspended the marketing authorisations for the vaccines Prevenar (PCV7)® and Act-Hib®.

The deaths occurred within a few weeks.

None of the lots/batches of the vaccines (Prevenar (PCV7)® or Act-Hib®) used in Japan have been used in Denmark. Therefore, the Danish Medicines Agency assesses that no actions are required in Denmark. The situation in Japan is watched closely.

The number of deaths in Japan is not higher than expected compared to the number of born and vaccinated children – neither in Japan nor in other western countries. An expert panel in the Japanese Ministry of Health has subsequently assessed that there is no clear connection between the vaccinations and the deaths. The authorities are, however, awaiting further information before they are prepared to give permission to resume vaccination with the vaccines involved.

The deaths occurred in two children who had severe malformations, and in one healthy child who, after an autopsy, was found to have severe pneumonia. One other child died, under the diagnosis crib death, three days after vaccination.

Read more on the Agency's website: *Reports of serious side effects in Japan from the childhood vaccines Prevenar (PCV7)® and Act-Hib®*.

Reports in Denmark

In Denmark, Prevenar (PCV7)® is not used routinely anymore. Prevenar13® is included in today's childhood immunisation programme.

In Denmark, a total of two reports of deaths after vaccination with Prevenar (PCV7)® have been reported. A case from 2008 concerned a 15-month-old child who died from a respiratory infection 10 days after vaccination with Prevenar (PCV7)®, and a case from 2009 concerned a 6½-month-old child with a progressive neurological disorder who died from respiratory and heart failure.

Two further deaths have been reported after vaccination with Act-Hib®. Both reports describe cases of crib death, which occurred in 1997 and 2002. This is not more frequent than expected compared to the number of children born and number of vaccinated children. We assess the risk that the deaths were caused by the vaccination to be very small.

Reports of serious side effects in France from the childhood vaccine Prevenar13®

The French drug regulatory authorities recently sent out an announcement about three cases of crib death after vaccination with Prevenar13®.

Two of the three cases in France concern reports of crib death from 2011, where respectively a 3-month-old and a 9-month-old child died after vaccination with Prevenar13®. In a third similar case from 2010, a 2½-month-old child died the day after vaccination with Prevenar13®. The authorities assess that the first and the third cases were not caused by the vaccination. The second case is still being investigated.

Read more on the Agency's website: *Reports of serious side effects in France from the childhood vaccine Prevenar13®*

In Denmark, Prevenar13® has been included in the childhood immunisation programme since 2010.

There are no reports of deaths in Denmark that can be related to Prevenar13®. The Danish Medicines Agency assesses that no further actions are required in Denmark, but it will be watching the situation in France closely.

Indication for Zerit® (stavudine) restricted due to potentially serious side effects

The European Committee for Medicinal Products for Human Use (CHMP) has recommended restricting the use of Zerit®.

Zerit is used in combination with other antiviral medicines to treat HIV-infected patients. Studies have now shown that compared to other HIV treatments, the use of Zerit® may put patients at an increased risk of potentially severe toxicity such as lactic acidosis, lipoatrophy and peripheral neuropathy.

It is therefore recommended that Zerit® should be used for as short a time as possible and only when there are no appropriate alternatives.

The product information for Zerit® will be updated, and letters will be sent to infectious disease specialists and hospital pharmacists.

For further information, please read the CHMP monthly report (p. 3): *here*.

Rotarix and RotaTeq® and risk of intussusception

The European Committee for Medicinal Products for Human Use (CHMP) has recommended that information about intussusception (invagination) be included in the summaries of product characteristics for Rotarix and RotaTeq® (rotavirus vaccines).

The recommendation follows post-marketing data, which have indicated that there could be a small increased risk of intussusception in the 31-day period, and mostly within the first 7 days, after the first dose has been given. However, clinical studies of Rotarix and RotaTeq observed no increased risk of intussusception compared with placebo.

Due to the above-mentioned post-marketing data, healthcare professionals should stay alert to any symptoms indicative of intussusception: severe abdominal pain, persistent vomiting, bloody stools, abdominal bloating and/or high fever.

Likewise, parents should be advised to promptly report any such symptoms to their doctor.

For further information, please read the CHMP monthly report (p. 4): *here*.

The rotavirus vaccines are indicated for the active immunisation of infants from 6 weeks of age for prevention of gastro-enteritis due to rotavirus infection.

In Denmark, the vaccines are only used to a limited degree, and we have received no reports of intussusception related to vaccination with Rotarix and RotaTeq®.

Tygacil® (tigecycline) and increased mortality in clinical studies

The European Committee for Medicinal Products for Human Use (CHMP) has reviewed the benefit-risk balance for Tygacil® as part of the product's marketing authorisation renewal. Data from clinical studies and post-marketing data have been reviewed. The review also included studies on the treatment of infections for which the product is not approved.

The CHMP found Tygacil® to be associated with more deaths than the comparator product, but, nonetheless, recommended to continue using the product, but only for its approved indications, and only when other medicines are not suitable.

The product information for Tygacil® will be updated, and a letter will be sent to healthcare professionals to make them aware of the increased mortality. The letter will go out to intensive care units, hospital pharmacists and various internists and surgeons.

For further information, please read the CHMP monthly report (p. 3): *here*.

Tygacil® is indicated for the treatment of complicated skin and soft tissue infections (excluding diabetic foot infections) and complicated intra-abdominal infections.

Tygacil is only used to a limited extent in Denmark.

Thalidomide Celgene (thalidomide) and risk of myocardial infarction and thromboembolic events

The European Committee for Medicinal Products for Human Use (CHMP) reports that post-marketing data have shown that patients treated with Thalidomide Celgene have an increased risk of arterial thromboembolism such as myocardial infarction and cerebrovascular events as well as an increased risk of deep vein thrombosis and pulmonary embolism.

This makes it important to try to minimize all modifiable risks factors such as smoking, hypertension and hyperlipidaemia.

The summary of product characteristics will be updated with the new knowledge, and a letter will be sent to hospital pharmacists and relevant doctors.

For further information, please read the CHMP monthly report (p. 4): *here*.

In Denmark, there is one authorised thalidomide-containing product, Thalidomid Celgene.

Thalidomide Celgene is authorised in combination with melphalan and prednisone as first-line treatment in patients with untreated multiple myeloma aged >65 years, or patients ineligible for high dose chemotherapy.

New recommendations for use of Brinavess®

In early March 2011, a letter was sent to healthcare professionals with new safety information for Brinavess® (vernakalant). The new safety information was sent out in response to a reported case of severe hypotension and subsequent cardiogenic shock in a patient who received vernakalant intravenously in an ongoing clinical trial in the USA.

The new safety information regarding use of Brinavess® (vernakalant) provides the following recommendations:

- Patients receiving vernakalant should be frequently monitored, in particular the blood pressure should be monitored, during administration of the medicine and for at least 15 minutes after the end of infusion.
- The heart rhythm should be frequently monitored during administration of vernakalant and up to two hours after the start of infusion until clinical and ECG parameters have stabilised.
- The patient must not be given any i.v. antiarrhythmic medicines (class I or class III) within 4 hours prior to and up to 4 hours after vernakalant administration.

If a patient during infusion of Brinavess® develops bradycardia, becomes hypotensive or develops ECG changes, the administration of Brinavess® should be discontinued and the patient must be stabilised.

The letter sent to healthcare professionals informs of the changes that will be added to sections 4.2, 4.3, 4.4 and 4.8 of the summary of product characteristics. Please note that section 4.8 will include the term “cardiogenic shock” (frequency = uncommon (≥1/1,000 to <1/100).

For further information, please read the CHMP monthly report (p. 3): *here*.

Brinavess® (vernakalant) is indicated for rapid conversion of recent onset atrial fibrillation to sinus rhythm in:

- non-surgery adult patients: atrial fibrillation ≤ 7 days duration
- post-cardiac surgery adult patients: atrial fibrillation ≤ 3 days duration.

Brinavess® was authorised in September 2010. As at 31 January 2011, the Danish hospital sector had used 71.5 DDD (Defined Daily Doses), corresponding to 40 sold packages.

The Danish Medicines Agency has received a report of a death in connection with treatment with Concerta® (methylphenidate) for the treatment of ADHD

In January 2011, the Danish Medicines Agency received an adverse reaction report concerning a 34-year-old man who was treated with Concerta® (methylphenidate) for ADHD and who died suddenly. In the six months prior to his death, he had been treated with Concerta® for approx. six weeks. It cannot be ruled out that Concerta® contributed to his death.

The Agency is presently awaiting the autopsy report, which will help clarify whether or not there is a causal relationship between the death and treatment with Concerta®.

Within the past six months, this is the second time that a death concerning an adult treated for ADHD with a methylphenidate-containing product is reported to the Agency.

The Danish Medicines Agency wants to highlight that methylphenidate is not authorised for ADHD in adults.

According to the summary of product characteristics, cardiovascular disease is a possible side effect that doctors must stay particularly alert to when they treat children and adolescents. This is not of lesser importance when adults are treated, since it is well-established that the risk of cardiovascular disease increases with age and that certain adult lifestyle factors, such as smoking and alcohol consumption, also increase the risk of cardiovascular disease.

The Danish Medicines Agency advises prescribers to follow the recommendations in the summary of product characteristics for methylphenidate-containing medicines:

- Prior to prescribing methylphenidate, it is necessary to take a detailed history – including assessment for a family history of sudden cardiac or unexplained death or malignant arrthymia – and to conduct a baseline evaluation of the patient's cardiovascular status.

- Blood pressure and pulse should be measured in connection with dose adjustment or every six months, and patients with symptoms such as palpitations, chest pain triggered by physical exertion, inexplicable fainting, dyspnoea or other symptoms indicating a heart disease during treatment with methylphenidate must immediately have their heart examined by a specialist.

- Stimulants such as methylphenidate are not recommended for children or adolescents with a history of structural cardiac deformities, cardiomyopathy, severe cardiac arrhythmia or other serious heart problems which can lead to increased vulnerability to sympathomimetic effects of a stimulant drug.

Also see *Danish Pharmacovigilance Update, 16 December 2010*.

Antidepressants (SSRIs) and deaths or serious side effects in newborns

At the end of February, several Danish media addressed the side effects from the antidepressant fluoxetine including death in newborns to mothers who had been treated with fluoxetine. The Danish Medicines Agency followed up with information on our website on 1 and 11 March.

As at 7 March 2011, the Danish Medicines Agency's database of adverse reactions had received 51 reports describing suspected serious adverse reactions in newborns caused by the mother's use of an antidepressant of the SSRI type during pregnancy. 22 of these reports describe congenital diseases or malformations, four describe deaths.

Even though the risk is small, serious adverse reactions may occur in the foetus and the newborn child if pregnant women are treated with an antidepressant of the SSRI type. The risk should, however, be weighed against the beneficial effect of SSRIs for pregnant women who suffer from a serious disorder requiring treatment.

A more detailed description of the reports of deaths and serious side effects in newborns and mothers' use of antidepressants (SSRIs) is given at the Agency's website: *Data on deaths or serious side effects in newborns from use of antidepressants (SSRIs)*
Also see *Danish Pharmacovigilance Update, 15 April 2010*

Consumption and side effects from the weight-loss product Regenon®

In a new report in Danish, the Danish Medicines Agency has reviewed the consumption trends of weight-loss products in Denmark. The report generally concludes that the sale as well as the number of persons taking weight-loss products are declining.

The OTC product Alli was the most-sold weight-loss product in 2010, but like the other weight-loss products, the sale of Alli has declined since its market entry in May 2009.

Regenon®, which contains amfepramone, is the oldest weight-loss product on the Danish market*, and there are a number of precautions for its use in the summary of product characteristics.

Duration of treatment with Regenon® – generally longer than recommended

Regenon® is only authorised for short-term treatment, four to six weeks, and the duration of treatment should, according to the recommendations, not last longer than three months. The Agency's analysis, however, shows that more than 75 percent of Regenon-users have been treated for periods longer than the recommended three months, and there are also indications that individual Regenon-users have received treatment since 1994 at least, (data only goes back to 1994 when the Danish Medicines Agency's Register of Medicinal Product Statistics was established).

Nearly half of Regenon-users are also treated with an antipsychotic or have had an abuse despite the contraindication

Because of Regenon®'s profile of adverse drug reactions, it should not be prescribed to patients who suffer from a psychiatric disorder or patients susceptible to abuse. However, according to our analysis, 42 percent of Regenon-users have either been treated with an antidepressant/ antipsychotic or have had an alcohol or opioid abuse or have used benzodiazepines for a long time.

Psychiatric reactions such as psychoses and depression are common side effects of Regenon®, which doctors should watch out for. The Danish Medicines Agency's analysis shows that from the group of Regenon-users who have not previously been treated for a psychiatric disorder, only a small share (0.74 percent) were started on antidepressants or antipsychotics while they were treated with Regenon®, which may suggest an occurrence of serious psychiatric adverse effects in these patients.

A further analysis of data showed that 84 percent are still treated with Regenon® 90 days after start-up with an antidepressant or antipsychotic, and 78 percent after one year.

Based on the conclusions of the report, the Danish Medicines Agency draws attention to the following recommendations for use of Regenon®:

- Regenon® should only be used in obese patients (BMI>30) who have not responded adequately to a weight-reducing programme. The duration of treatment is 4-6 weeks and maximum three months.
- Regenon® should not be used in patients with past or present psychiatric disorders which cover anorexia nervosa and depression, or to patients susceptible to drug abuse or a history of alcoholism. Nor should Regenon® be prescribed to patients with past or present cardiovascular, cerebrovascular disorders or hypertension.**
- Generally, the severity of the possible side effects should always be assessed relative to the medicine's potential effect. Consequently, Regenon® should not be used for purely cosmetic weight loss.

Follow this link to read an English summary of the report or the full report in Danish: *Decreasing sales of weight-loss medicines in 2010*.

In the Danish Medicines Agency's database of adverse reactions, at total of 16 reports related to Regenon® were recorded from December 1984 to January 2011. Four of these concern psychiatric side effects.

In 2010, 7,600 persons in Denmark bought Regenon® (amfepramone).

* Regenon® was authorised on 18 May 1960, whereas Regenon Retard® was authorised on 26 October 1982.

** The full list of contraindications for Regenon® can be found in the summary of product characteristics (only in Danish): *here*.

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