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DANISH MEDICINES AGENCY

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DANISH PHARMACOVIGILANCE UPDATE

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Short news

Available data do not suggest an association between HPV vaccination and the syndromes POTS and CRPS according to new EMA review

The European Medicines Agency (EMA) has just completed a review of the risk profile of the HPV vaccines with particular focus on the two syndromes POTS[1] and CRPS[2]. The review was initiated at the request of Danish authorities because the DKMA has received increasing numbers of ADR reports of suspected adverse reactions describing POTS and POTS-like symptoms in particular.

Background leading to the EMA's conclusion

The conclusion by the EMA is based on a thorough review of published research articles, clinical trial data from the companies and reports of suspected adverse reactions submitted by patients and doctors as well as further data delivered by the Member States, Denmark included. The PRAC also consulted a group of leading experts in the field of vaccines, POTS and CRPS and took into account detailed information received from a number of patient groups.

Overall, the EMA concluded that the available evidence does not support that CRPS and POTS are caused by HPV vaccines. Therefore there is no reason to change the way the vaccines are used or amend the current product information.

Read the conclusions from the EMA on the EMA website: *HPV vaccines: EMA confirms evidence does not support that they cause CRPS or POTS*

Monitoring of HPV vaccine safety will continue

The safety of the vaccines will continue to be monitored by both the EMA and the DKMA. Every quarter the DKMA publishes a list covering all reports received on suspected adverse reactions to vaccines in the childhood immunisation programme, including the HPV vaccine. The next quarterly review is due in the December issue of Danish Pharmacovigilance Update.

[1] POTS (Postural Orthostatic Tachycardia Syndrome) is a clinical syndrome whereby the heart rate increases on sitting or standing up (by more than 30bpm after more than 30 seconds) without coexisting orthostatic hypotension. There are coexisting clinical symptoms when standing up, e.g. dizziness, palpitations, tremor, weakness and fatigue. (All diagnostic criteria are available in e.g. Harden (2010)).

[2] CRPS (Complex Regional Pain Syndrome) is a chronic pain condition affecting a limb with symptoms such as hyperaesthesia, vasomotor changes or motor impairment (such as tremor or weakness). (All diagnostic criteria are available in e.g. Sheldon (2015).

Serious risk of teratogenicity from the use of mycophenolate mofetil – new important contraception guidelines for men and women

Following a routine re-assessment of the benefits and risks of medicines containing mycophenolate mofetil, the European Medicines Agency (EMA) has established that mycophenolate mofetil is a teratogen associated with an increased rate of spontaneous abortions and birth defects in pregnant women exposed to the medicine. The EMA has therefore issued a warning not to use mycophenolate mofetil during pregnancy. Concurrently, the summary of product characteristics for mycophenolate mofetil has been updated, adding information about effective contraception for patients who are to be treated with the medicine.

Mycophenolate mofetil is used for the prevention of acute transplant rejection in patients receiving allogeneic renal, cardiac or hepatic transplants.

Data confirms mycophenolate is a teratogen

Spontaneous abortion has been reported in 45 to 49% of pregnancies in women exposed to mycophenolate mofetil, compared with reported frequencies of 12 to 33% in organ transplant female patients treated with other immunosuppressants. Furthermore, the literature shows malformation in 23 to 27% of live-born children of mothers who were exposed to mycophenolate mofetil during pregnancy. By comparison, the occurrence of malformations in live-born children in the general population is 2 to 3% and around 4 to 5% in organ transplant patients treated with immunosuppressants other than mycophenolate mofetil.

The most common malformations reported in mothers exposed to mycophenolate mofetil include abnormalities of the ear, congenital heart diseases, malformations of the face, eye and fingers, tracheo-oesophageal malformations, effects on the nervous system as well as renal abnormalities.

At the DKMA, we have received no ADR reports on mycophenolate mofetil and teratogenic affects.

The summary of product characteristics is updated with the following contraindications:

- Mycophenolate should not be used during pregnancy unless there is no suitable alternative to prevent transplant rejection.
- Mycophenolate should not be used in women of childbearing potential not using highly effective contraception.

- Mycophenolate treatment should not be initiated in women of childbearing potential without the presence of a negative pregnancy test to avoid unintended use during pregnancy.

Advice for doctors:

- Always inform women and men taking mycophenolate about the risks of injury to children, the necessity of using effective contraception and instruct them to contact their doctor immediately on suspicion of pregnancy.
- Advise sexually active men taking mycophenolate to use condoms for sex during treatment and for 90 days thereafter. Partners of childbearing potential are also recommended to use highly effective contraception for the same period.
- Patients should not donate blood during or for 6 weeks after stopping treatment. In addition, men treated with mycophenolate should be advised not to donate sperm during therapy or for 90 days after stopping mycophenolate treatment.

Risk minimisation measures
Educational material will be made for health professionals describing the risk of teratogenicity in mycophenolate treatment as well as guidance on contraception before during and after treatment and about the need for pregnancy tests.

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 signal discussed at the PRAC meeting in October 2015 concerns the following product:

- **Anakinra –** thrombocytopenia

See EU's list of recommendations on safety signals: *PRAC recommendations on signals, September* as well as the *Danish translations for the product information*.

Second analysis of reported suspected adverse reactions and reported adverse events associated with using labour-stimulating medicines for induction of labour

In 2013, at the request of the Danish Ministry of Health, the DKMA (formerly the Danish Health and Medicines Authority) prepared a *Plan for the monitoring and supervision of the Danish regions' use of labour-inducing medicines*.

The main purpose of the plan is to increase the quality, safety and security of medically-induced labour. The plan provides for the implementation in 2014-2016 of cross-cutting analyses of reported suspected adverse reactions and reported adverse events related to medically-induced labour.

The first analysis was published in Danish Pharmacovigilance Update in December 2014, and described reported suspected adverse reactions and adverse events associated with dinoprostone, misoprostol and oxytocin received in 2013. The second analysis has been prepared jointly by the Danish Patient Safety Authority and the DKMA and follows up on the first analysis by investigating reported suspected adverse reactions and reported adverse events received in 2014.

Results of second analysis

In 2014, 28 birth processes describing suspected adverse reactions were reported to the DKMA, which is on level with the 30 birth processes reported in 2013.

In 2013, 20% of the ADR reports in the analysis were submitted by midwives, in the second report the proportion was 60%. Most likely, the difference reflects the fact that midwives from April 2014 were bound by the same executive order to report adverse reactions on a par with doctors.

The majority of the ADR reports received by the DKMA in 2014 involved known adverse reactions to the medicines such as hyperstimulation, hypertonic uterus/tetanic labour and fast delivery. Around one fourth of the ADR reports described complications affecting the mother or the child.

The number of reports of adverse events received in 2014 was 60, increasing from 37 in 2013. The increase does not necessarily imply that more errors occur; It could just as well be a sign of an improved patient safety culture and increased awareness in this area.

The most common reported adverse event involved induction of labour in women who had previously delivered by caesarean section, induction of labour in twin deliveries using misoprostol instead of dinoprostone as well as events related to the dose/administration of oxytocin. The vast majority of events had no complications for the mother or the child. One of the reported events had serious consequences, as the woman after labour was induced developed frequent contractions affecting the foetus and ending in a caesarean section.

Overall conclusion on the analysis

The DKMA and the Danish Patient Safety Authority maintain that the benefits of using medicines for induction of labour outweigh the possible risks.

The DKMA and the Danish Patient Safety Authority will maintain focus on any problems associated with using medicines for induction of labour and will, as necessary, provide information thereon in Danish Pharmacovigilance Update and on the website of the Danish Patient Safety Authority.

Read the analysis here (in Danish only): *Use of labour-stimulating medicines for induction of labour (Danish title: Anvendelse af vestimulerende lægemidler til igangsættelse af fødsler)*

Clarithromycin and cardiovascular risk

A potential association between clarithromycin and increased mortality rates in persons with cardiovascular diseases has repeatedly been discussed in Denmark and abroad. Even so, it has not been possible to reach any firm conclusion because of divergent results from research in the area. A new analysis from 2015 is now reopening discussions.

The CLARICOR study showed increased mortality

In 2005, a Danish research group (the CLARICOR group) published a randomised, placebo-controlled clinical trial, which showed that mortality 2.6 years after a two weeks treatment with clarithromycin was significantly higher (hazard ratio: 1.27, 95% confidence interval: 1.03 to 1.54; P = 0.03) compared to the placebo arm, in persons with cardiovascular disease.

Clarithromycin is contraindicated in patients treated with statins

Further analyses of the CLARICOR study have subsequently shown that the mortality was significantly higher only among patients who were not treated with statins. Treatment with clarithromycin in patients treated with statins has since been contraindicated due to an increased risk of myopathy, including rhabdomyolysis. The DKMA maintains its recommendation not to use this combination of medicines.

New analysis of cardiovascular risk in clarithromycin use

In 2015, a comprehensive European analysis of cardiovascular risk in clarithromycin use was completed. The analysis covered an evaluation of the published studies in the area (including several articles from the CLARICOR group) as well as an analysis of the company's clinical data. On the basis of the analysis, it was assessed that presently there are no grounds to introduce further restrictions for clarithromycin use in patients with cardiovascular disease.

It is well-known and described in the product information that clarithromycin may cause QT prolongation that can result in serious cardiac arrhythmias, however, this adverse reaction is short-termed. In regard to long-term adverse reactions, it is still not possible to reach a final conclusion, one of the reasons being lack of evidence of a biologial mechanism explaining the long-term adverse reactions of clarithromycin.

The risk of cardiovascular adverse reactions of clarithromycin will continue to be monitored.

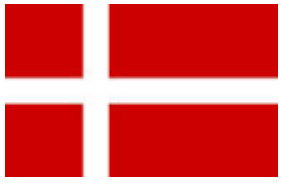
Indication for clarithromycin
Clarithromycin is a microlide antibiotic used for infections caused by clarithromycin-susceptible microorganisms e.g. of the respiratory tract and soft tissues. In addition, it is used for eradication treatment of Helicobacter pylory in combination with antacid treatment.

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:

- Bactroban nasal – Supply problems – alternative medications until Bactroban supplies become available are given in the letter. Sent out 16 October 2015.
- Morfin DAK – Supply problems. Sent out 20 October 2015.
- Cellcept (mycophenolate mofetil) – Serious risk of teratogenicity – important new pregnancy prevention advice for women and men. Sent out 10 November 2015.
- Thalidomide (Thalidomide Celgene) – Initial dose for thalidomide in combination with melphalan should be reduced in patients older than 75 years. Sent out 10 November 2015.

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



Danish Pharmacovigilance Update celebrates 6-year anniversary

This year, we are pleased to celebrate the sixth anniversary of Danish Pharmacovigilance Update, which now has more than 4000 subscribers to the Danish and the English versions.

We appreciate the great interest in our newsletter and especially the interest in the pharmacovigilance area, which we continually strive to improve even further through the launch of various initiatives.

We hope Danish Pharmacovigilance Update will reach even more subscribers in future.

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