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DANISH MEDICINES AGENCY

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DANISH PHARMACOVIGILANCE UPDATE

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Short news

The European Pharmacovigilance Risk Assessment Committee (PRAC) has started a review of the risk of amputations in connection with canagliflozin treatment

The PRAC has initiated a review of the safety of the diabetes medicine canagliflozin. It comes after the observation of an almost twofold increase in amputations (mostly affecting toes) in the canagliflozin group compared to the placebo group in a canagliflozin clinical trial (CANVAS, an ongoing clinical trial of cardiovascular outcomes).

Background to the PRAC review

The clinical trial reported cases of amputations in both the canagliflozin and placebo groups. However, it is not possible at present to determine if the increase in amputations in the canagliflozin group was caused by canagliflozin treatment. The PRAC has therefore requested further information from the companies that market canagliflozin-containing medicines.

Possible class effect

Canagliflozin belongs to the class of SGLT2 inhibitors, which also comprises dapagliflozin and empagliflozin. The PRAC has also requested information about these medicines to broaden the scope of the review if relevant.

Further information about the risk

DHPCs will be distributed to doctors and other healthcare professionals with detailed information, including the following:

- The importance of routine foot care to avoid cuts or sores of the feet and to treat them promptly should they occur to prevent infection and ulceration.
- Patients at increased risk of amputation (patients with previous amputations) should be carefully monitored. As a precautionary measure, doctors may consider stopping treatment with canagliflozin in patients who develop significant foot complications.

Read the press release from the EMA: *EMA reviews diabetes medicine canagliflozin.*

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 at the PRAC meeting in March 2016 concern the following products:

- **Axitinib** – nephrotic syndrome
- **Mercaptopurine and azathioprine** – lymphoproliferative disorders
- **Tigecycline** – hypofibrinogenaemia

See EU's list of recommendations on safety signals: *PRAC recommendations on signals March 2016* as well as the *Danish translations of the product information*.

Reports of cardiac arrest after treatment with methylphenidate

In the beginning of April, the DKMA received an ADR report about a child treated with methylphenidate who went into cardiac arrest. The child's ADHD was adequately managed by Medikinet, and there had been no adverse reactions prior to the event. No signs of trauma were found when the child was hospitalised. The child suffered several episodes of ventricular fibrillation. Long QT syndrome was found, and the child had a pacemaker implanted and was treated with beta blockers.

Doctors should be aware of the following:

- **Contraindications for methylphenidate**
  Pre-existing cardiovascular disorders including severe hypertension, heart failure, arterial occlusive disease, angina, haemodynamically significant congenital heart disease, cardiomyopathies, myocardial infarction, potentially life-threatening arrhythmias and channelopathies (disorders caused by the dysfunction of ion channels).

- **Pre-treatment screening**
  Prior to prescribing ADHD medication, it is necessary to evaluate the patient's cardiovascular status, including blood pressure and heart rate. An appropriate medical history must be taken, covering (concomitant) medications, past and present medical and psychiatric disorders or symptoms, family history of sudden cardiac or unexplained death.

- **Ongoing monitoring of the patient's cardiovascular status**
  - Blood pressure and pulse should be recorded at each adjustment of dose and then at least every 6 months.
  - Patients should be informed of symptoms such as palpitations, exertional chest pain, unexplained syncope, dyspnoea or other symptoms suggestive of cardiac disease during medical treatment of ADHD. A patient experiencing any of these symptoms should seek medical advice immediately for evaluation by a cardiologist.

The DKMA is presently obtaining follow-up information to the ADR report for further assessment.

Influenza vaccines and reports of suspected adverse reactions

The DKMA has reviewed ADR reports of suspected adverse reactions to the influenza vaccines from the 2015/2016 influenza season.

Two vaccines (Fluarix and Vaxigrip) from two different manufacturers have been used this season. Both vaccines contain components of inactivated influenza vaccine and are considered equal for protection against influenza.

In Danish Pharmacovigilance Update, December 2015, we reviewed ADR reports for the period of 1 August to 30 November 2015. In this present review, we are examining the ADR reports received in the DKMA from 1 December 2015 to 31 March 2016.

ADR reports from 1 December 2015 to 31 March 2016
We received a total of 8 ADR reports. One was classified as serious[1].

Review and assessment of the serious ADR reports
When we assess the serious ADR reports, we consider if it is likely that there is a causal link to the vaccine.

The classification of our causality assessment is based on four categories:

- Possible
- Insufficient documentation[2]
- Less likely
- Unclassifiable (not possible to assess because of inadequate information)

[1] An ADR report is serious when one or more of the adverse reactions are serious. 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.

[2] This category contains the reports for which it was not possible to determine whether or not there is a possible connection between the reaction and the vaccine because of insufficient documentation. Reports in this category concern symptoms occurring in temporal association with the vaccination, where the vaccinee has no other immediate factors that may explain the symptoms (other disease, other medicine, etc.), but where there is no evidence in the literature or other available data that can confirm a causal relationship.

Vaccine	ADR description	Assessment and causality
Fluarix	Two days after a citizen was vaccinated, he developed right-sided abducens palsy and mild pain in the right eye. A neurological examination was performed, which raised suspicion of Tolosa-Hunt syndrome (THS).	There is a consistent temporal association between palsy and influenza vaccination, but abducens palsy is not a known adverse reaction to the vaccine. The exact cause of THS is often unknown, but it is assumed to be related to inflammation of the area behind the eye. In the literature, there are no descriptions of an association between influenza vaccine (or other vaccines) and abducens nerve palsy, which is why causality is classified in the category of **insufficient documentation**.

Table 1: Description of the adverse reactions in the serious ADR reports and subsequent causality assessment.

Review of the non-serious ADR reports
The non-serious reports most frequently describe known adverse reactions such as reactions at the injection site and influenza-like symptoms.

Conclusion
In the period 1 December 2015 to 31 March 2016, the DKMA received a total of 8 reports of suspected adverse reactions to the influenza vaccines. One was classified as serious.

The number of ADR reports in the year-earlier period was 16.

The serious ADR report concerned a citizen who developed abducens palsy in temporal association with vaccination. Abducens palsy has not previously been described as an adverse reaction to the vaccine. Causality is therefore classified in the category of "Insufficient documentation".

The non-serious reports mainly describe known adverse reactions to the vaccines.

None of the new ADR reports shift the benefit-risk balance of the influenza vaccines.

All cases referred to in this article originate from the DKMA'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 the to DKMA.

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:

- **Pomalidomide (Imnovid) for treatment of multiple myeloma**: New important advice – hepatitis B virus status to be established before initiating treatment with pomalidomide.

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

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Information material for healthcare professionals and patients about biological medicines and biosimilars

As part of the *Action plan on biological medicines, biosimilars and vaccines for 2015-2016 (in Danish only)*, the DKMA has prepared information material for healthcare professionals and patients about biosimilar medicines.

A flyer has been distributed to healthcare professionals with information about the new rules on the recording and reporting of adverse reactions of certain biological medicines – including biosimilars.

For patients who are to take a biosimilar medicine, the DKMA and the patient organisations have together prepared a folder which answers a number of questions that patients may have about biosimilar medicines.

See the flyer for healthcare professionals: *Flyer for healthcare professionals about biosimilar medicines (PDF in Danish only)*
See the folder for patients: *Folder for patients about biosimilar medicines (PDF in Danish only)*

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