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Danish Pharmacovigilance Update

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Danish Pharmacovigilance Update

Danish Pharmacovigilance Update is an electronic newsletter for doctors intended to ensure easy access to current, updated knowledge about medicines and adverse reactions. It provides quick updates on current medicine safety issues with a practical focus for doctors.

By putting focus on special problems and applicable recommendations, we seek to support medical subscription to reduce the risk of adverse reactions.

The newsletter (in Danish) is sent out to email subscribers on the last Thursday of every month (excluding July) and is available from the website of the DKMA: *Danish Pharmacovigilance Update.*

In this issue

New knowledge about interaction between warfarin and antimycotics

The Danish Medicines Agency has updated the *Drug Interaction Database* based on two recently published studies about the interaction between antimycotics and warfarin. A cohort study has shown significantly increased INR in warfarin users treated concurrently with miconazole oral gel, but not in warfarin users exposed to nystatin oral solution (1). A systematic review of the evidence of interaction between nystatin and miconazole concluded that the interaction is unlikely (2).

The Drug Interaction Database has been updated with the following recommendations:

Warfarin and nystatin
The recommendation for concurrent use of warfarin and the antimycotic nystatin has been changed from ”yellow interaction” to ”green”, i.e. the combination can be used.

Warfarin and miconazole
The recommendation for concurrent treatment with warfarin and miconazole has been tightened, but it is still assessed that the combination can be used when special precautions are taken (”yellow interaction”).

Reports about interaction between warfarin and antimycotics

In October 2015, the DKMA drew attention to the interaction between warfarin and the antimycotic miconazole oral gel (Brentan) for treatment of fungal infection of the oral cavity. In June 2016, the Danish Patient Safety Authority also recommended to exercise caution when the two medicines are used in combination in the monthly newsletter issued by the Institute for Rational Pharmacotherapy. Both authorities had experienced an increase in reported cases of bleeding in regular users of warfarin co-administered with miconazole for the treatment of fungal infections of the oral cavity.

The DKMA has since received new ADR reports about interactions between miconazole and warfarin, but also a number of new ADR reports about interactions between warfarin and systemic fluconazole.

Doctors should be aware of the following:

- Nystatin can be used with warfarin.
- Interaction between warfarin and the antimycotics fluconazole, miconazole and voriconazole may cause serious bleeding.
- The risk of interaction also applies to miconazole oral gel as a large share is absorbed systemically.
- If concurrent treatment with warfarin and either of the three antimycotics fluconazole, miconazole and voriconazole is necessary, the anticoagulant effect should be monitored closely, and the dose should be adjusted as needed.

References

[1]: Hellfritzsch M;Pottegard A;Pedersen AJ;Burghle A;Mouaanaki F;Hallas J;Grove EL;Damkier P, Basic Clin Pharmacol Toxicol, 2016; Topical Antimycotics for Oral Candidiasis in Warfarin Users.

[2]: Pemberton MN, Oral Dis, 2016, 22:761-765; Nystatin and miconazole: pharmacological and clinical evidence regarding interactions with warfarin.

Diabetes medicine canagliflozin may contribute to risk of toe amputation

The European Pharmacovigilance Risk Assessment Committee, PRAC, has concluded that canagliflozin may increase the risk of toe amputation following a review of the risk of amputations in patients with type 2 diabetes who are treated with sodiumglucose co-transporter-2 (SGLT2) inhibitors.

Background leading to PRAC's conclusion

Two clinical studies (CANVAS and CANVAS-R) had observed an increased risk of amputations (mostly affecting the toes) in patients treated with canagliflozin compared to the placebo group.

Based on the data reviewed, PRAC recommends that lower limb amputations (mostly of the toes) be added to the product information for canagliflozin as an uncommon adverse reaction (occurring in between 1 and 10 patients in 1,000).

Diabetes patients, especially those with poorly controlled diabetes and pre-existing cardiovascular disease, are at increased risk of infection and ulcers (sores) which can lead to amputations. The mechanism behind the potentially increased risk in patients treated with canagliflozin is still unclear.

A similar increased risk has not been seen in studies of the other SGLT2 inhibitors dapagliflozin and empagliflozin, but since only limited data are available, the risk cannot be ruled out for these medicines.

Doctors should be aware of the following:

- Routine preventive foot care is important, and early treatment of foot complications is necessary to prevent infection and ulcers.
- Patients at increased risk of amputation, e.g. patients with a history of amputations or patients with existing peripheral vascular disease or neuropathy, should be monitored closely.
- As a precautionary measure, doctors may consider stopping treatment with canagliflozin in patients who develop significant foot complications.
- Patients should be advised about the importance of sufficient fluid intake and monitored for signs and symptoms of loss of fluids and sodium. Use of diuretics could worsen dehydration.

Links:
Read the press release from the PRAC: *PRAC concludes that diabetes medicine canagliflozin may contribute to risk of toe amputation*

DHPC sent out in April 2016: *Canagliflozin-containing medicines (Ivokana and Vokanamet): Risk of lower limb amputation (in Danish only).*

The Danish Health Authority's clinical guideline from 2013: *National clinical guideline for assessment and treatment of diabetic foot ulcers (in Danish only)*.

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 from 9-12 January 2017 concern the following products:

- **Azacitidine** – pericarditis and pericardial effusion
- **Propofol; valproate** – pharmacokinetic drug interaction leading to an increased propofol exposure

See EU's list of recommendations on safety signals: *PRAC recommendations on signals adopted 9-12 January 2017* as well as the *Danish translations of the product information*.

ADR signals
An ADR signal is a new observation that raises suspicion of a potential association between a medicine and an adverse reaction or a new aspect of a known adverse reaction, e.g. that the adverse reaction is more common than described previously.

ADR signals can come from a multitude of sources, including ADR reports, clinical studies or scientific literature.

The DKMA uses Danish ADR reports to detect possible new ADR signals. Signals about new possible adverse reactions are forwarded in the EU system to the European Pharmacovigilance Risk Assessment Committee (PRAC). The PRAC assesses if there is sufficient documentation to establish causality and, for example, if changes to the medicine's product information are warranted.

Most recent Direct Healthcare Professional Communications (DHPCs)

Below is a list of the most recent DHPCs that have been sent out to relevant doctors and healthcare professionals with safety information and updated recommendations about medicines:

- **DepoCyte (cytarabine):** Notice of expected supply failure. Sent out 30 January 2017.
- **Orgalutran (ganirelix):** Possible supply difficulties for Orgalutran® 0.25 mg/0.5 ml solution for injection. Sent out 30 January 2017.

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

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