Danish Pharmacovigilance Update

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Vfend® and the risk of liver adverse reactions

There are several examples of patients treated with Vfend® whose liver function is altered. Moreover, it has caused adverse reactions as hepatitis, cholestasis and hepatic failure – but the latter reactions are rare.

Prescribers should therefore:

- perform liver function tests (AST/ ALT, serum alkaline phosphatases, bilirubin, albumin, INR) in all patients (including children) at the start of treatment.
- monitor the liver function in children and adults undergoing treatment.
- seriously consider discontinuation of the Vfend® treatment if the patient develops clinical indications and symptoms of voriconazole-induced liver damage.
- consider other possible causes for altered liver function, including other simultaneous medication and other conditions that may occur in patients treated with Vfend® (e.g. graft versus host disease (GVHD) in transplanted patients).

As soon as possible, the Danish Medicines Agency will send a letter to relevant practitioners with additional information about Vfend® and the risk of liver adverse reactions.

Vfend® contains the active substance voriconazole and is part of the group of triazoles used for treatment of invasive aspergillosis and a number of other invasive fungal infections.

Antidepressant treatment and risk of broken bones

Epidemiological studies have shown a slightly increased risk of bone fractures in patients treated with antidepressants of the types Selective Serotonin Reuptake Inhibitors (SSRIs) or Tricyclic Antidepressants (TCAs).

The majority of the study subjects were 50 years and older. The available data does not allow for any conclusions about a potential connection between dosage or duration of treatment. The underlying mechanism is still unknown.

Physicians should therefore consider this slightly increased risk of fractures when prescribing antidepressant medicines.

Read more at: *http://www.ema.europa.eu/pdfs/human/phvwp/17301110en.pdf*
Link to MHRA with additional info: *http://www.mhra.gov.uk/Publications/Safetyguidance/DrugSafetyUpdate/CON081863)*

Medication errors and incorrect use of Exelon® transdermal patch for treatment of Alzheimer's dementia

After the marketing of the transdermal patch Exelon®, several European medical authorities have received reports of medication errors and incorrect use.

This has led to overdosage of the active substance rivastigmine with symptoms as nausea, vomiting, diarrhoea, hypertension and hallucinations. The most frequently reported causes of overdose are failure to remove the patch before applying a new patch and application of more than one patch at the same time.

Prescribers should therefore focus on whether patients and caregivers use transdermal patches correctly and according to the following recommendations:

- Only one patch should be used a day. The patch should be affixed on healthy skin on the upper or lower part of the back, on the upper arm or on the chest.
- After 24 hours, the patch should be replaced, and the old patch should be removed before the new patch is attached to another area of the skin.
- To minimise the risk of skin irritation, the patient should avoid placing the patch on the same area of the skin within 14 days.
- The transdermal patch must not be cut up into smaller pieces.
- In case of overdosage, the patch must be removed immediately.

In Denmark, the Exelon® transdermal patch is licensed for symptomatic treatment of mild to moderate Alzheimer's dementia and for symptomatic treatment of mild to moderate dementia in patients with idiopathic Parkinson's disease. The Exelon® transdermal patch is available in two strengths: 4.6 mg/24 hours and 9.5 mg/24 hours.

Status on the Danish pharmacovigilance action plan

In January 2009, the Danish Minister for Health launched a national action plan for the side effect area. The plan aims to improve patient safety in connection with medicine use. To reach this target, a number of different initiatives have been launched which involve many different parties in the Danish health sector.

The implementation of the action plan has progressed rapidly since its launch. The Danish Medicines Agency has learned that relevant stakeholders are very interested in contributing to strengthening the pharmacovigilance area to benefit patients.

In a national perspective, this action plan is the most comprehensive change process seen in the pharmacovigilance area in Denmark in modern times. In an international perspective, the Danish action plan matches many international trends currently characterising the development in the pharmacovigilance area, such as openness, network cooperation, risk-based approaches and user involvement. In several areas, Denmark is a pioneer. For example in connection with user involvement, where Denmark – as the first country in the EU – has given consumers access to report side effects themselves.

The action plan covers seven focus areas:

1. Improved utilisation of existing side effect data from various sources.
2. Adjustment of reporting requirements.
3. Increase the number of reported side effects – it must be easy.
4. Strengthen the motivation to report – it must make sense.
5. Strengthen the competences for reporting side effects.
6. Strengthen the assessment and utilisation of side effect data.
7. Strengthen research into side effect data.

1. Improved utilisation of existing side effect data from various sources

Spontaneously submitted adverse reaction reports from doctors and patients are an important source of information about medical safety, but there are also other sources. The Danish Medicines Agency has investigated the prevalence of hospital clinical databases that also include side effect data.

So far, the Danish Medicines Agency has initiated cooperation with the owners of the databases DANBIO (registers data on biological medicines), DERMBIO (registers data on medicines for skin disorders) and DANHEP (registers data on treatment of liver diseases). We are currently working on technical solutions for an uncomplicated transfer of side effect data to the Danish Medicines Agency.

2. Adjustment of reporting requirements

Problems with gadolinium-containing contrast agents and the serious adverse reaction nephrogenic systemic fibrosis in kidney patients – the Omniscan case – demonstrated the need for improved legislation concerning doctors' reporting requirements.

On this background, we have introduced a 15-day deadline within which doctors must report serious side effects, even if it is only a suspected serious side effect. Previously, there was no deadline. The 15-day deadline for doctors is in line with the 15-day deadline that applies to both the Danish Medicines Agency and marketing authorisation holders. The Danish Medicines Agency must send information about serious adverse reactions to the marketing authorisation holder within 15 days after receipt and vice versa.

In addition, the reporting requirement for generics is amended, so these products no longer carry a reporting requirement during the first two years after a product is marketed.

3. Increase the number of reported side effects – it must be easy

It must be easy to report adverse reactions. Therefore, the Danish Medicines Agency – in cooperation with both primary and secondary healthcare sector – is working on eliminating technical barriers for reporting. The target is that electronic reporting of side effects must be an integral part of IT systems both at general practices and in the hospital sector – and we have achieved this target in most general practices.

Another initiative in this focus area aims to strengthen the competencies among other healthcare professionals (than doctors) and consumers. We have therefore initiated a cooperation with medical societies and patient organisations. And at the end of May, the Danish Medicines Agency

launched an information campaign at Danish pharmacies.

In the coming period, a campaign in hospitals will also focus on reporting of side effects, and after a pilot phase, this campaign will run at all Danish hospitals.

4. Strengthen the motivation to report – it must make sense

It must make sense to report adverse reactions. This makes it important to clarify how the Danish Medicines Agency and other authorities use the reported side effect data. This is one of the things the campaigns are intended to show.

For example, it is emphasised that side effects reported in Denmark are passed on to the European adverse reaction database EudraVigilance and to the WHO's database. This means that Danish observations are made available to authorities internationally, and similarly Denmark can see what is reported in other countries. This provides a good overview and contributes to informed decision-making.

Since November 2009, the Danish Medicines Agency has published monthly newsletters and in March this year we published our annual pharmacovigilance report. Moreover, the Danish Medicines Agency has presented side effect data for Pandemrix® and Gardasil® several times during 2009 and 2010.

5. Strengthen the competences for reporting side effects

The Danish Medical Association is the central player in this focus area, which strives to strengthen physicians' education in adverse drug reactions and to strengthen the knowledge of the pharmacovigilance monitoring system. It is intended to take place through a combination of both pre- and postgraduate education.

Furthermore, we are working on integrating the pharmacovigilance aspect in the Danish Healthcare Quality Programme. More specifically, we are working on establishing a cooperation with local medical committees and on establishing a network of physicians, who can aid the Danish Medicines Agency in the medical assessment of adverse reaction data.

6. Strengthen the assessment and utilisation of side effect data

The latter initiative – foundation of a network of physicians – is linked with the 6th focus area, which aims toward a more (pro)active use of side effect data. Apart from the network of physicians, the Danish Medicines Agency will soon get a new version of the pharmacovigilance database and improved search tools. With the network of physicians and the new technology, the way is paved for systematic use of the large mass of gathered data. The focus areas will be discussed with the Council for Adverse Drug Reactions and (other) external stakeholders on an ongoing basis.

7. Strengthen research into side effect data

This last focus area is closely linked with focus areas 1 and 6. On the one hand, adverse reaction reports constitute an important source of information. On the other hand, adverse reaction reports are only (potential) signals that can form the basis for hypotheses, which can then be tested in different types of scientific studies.

Side effects from Pandemrix®
– international experience

Until recently, the Danish Medicines Agency published a number of status updates on adverse reaction reports concerning the H1N1 influenza vaccine Pandemrix®. But, it is also interesting to take a look at the international experience with Pandemrix®, and the European Medicines Agency (EMA) has published international pandemic updates on an ongoing basis.

The last update was published on 3 June this year. This update states that:

- A total of 11,014 reports of suspected adverse reactions to Pandemrix® were registered in the European EudraVigilance database.
- At least 131.7 million doses of Pandemrix® have been distributed.
- At least 30.7 million people have been vaccinated with Pandemrix®.
- The side effects from Pandemrix® can especially be classified within the following System Organ Classes: General Disorders and Administration, Nervous System Disorders, Gastrointestinal Disorders and Musculoskeletal Disorders.

The Danish experience is consistent with international experience.

In fall 2009, marketing authorisations were issued to several other vaccines for prevention of influenza H1N1. EMA's pandemic pharmacovigilance update establishes that Pandemrix® provided a large part of the experience gained, as this product accounts for 2/3 of the vaccine consumption and similarly 2/3 of all adverse reaction reports.

Although the flu season is over for now, the work on monitoring side effects from Pandemrix® is far from complete. Different studies are launched with the aim of extending knowledge of the side effects. For example, one study is generating further information on occurrence of diseases sometimes connected with the vaccination, such as the Guillain-Barré syndrome.

In addition, an evaluation is launched of the cooperation between different European authorities and institutions during the pandemic.

See the latest Danish and European status updates on Pandemrix® here:

Side effects from Pandemrix® from 23 January to 18 April 2010

Nineteenth pandemic pharmacovigilance update

Specification of story on gadolinium-containing MR contrast agents in Danish Pharmacovigilance Update, 15 April 2010

In the story on gadolinium-containing MR contrast agents, medium-risk agents (Vasovist®, Primovist® and MultiHance®) and low-risk agents (Dotarem®, ProHance® and Gadovist®) (Danish Pharmacovigilance Update 15 April, page 3), we wrote that:

'Patients with severe kidney problems and patients who are scheduled for or have recently received a liver transplant should not be given these contrast agents'.

Instead, the recommendation should be:

After a careful individual assessment of benefits and risks in each patient, the gadolinium-containing agents can be given in the lowest dose possible. Moreover, there should be at least 7 days between scans where a gadolinium-containing contract agent is used. This applies to patients with severe kidney problems, patients who are scheduled for or have recently received a liver transplant and children under 1 year old.

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