Danish Pharmacovigilance Update

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Possible risk of second primary malignancies in patients treated with Revlimid® (lenalidomide)

There have been observations of a higher incidence of second primary malignancies in patients treated with lenalidomide in clinical studies conducted on the medicine's off-label use.

Based on these observations, the Committee for Medicinal Products for Human Use (CHMP) will now thoroughly review the risks and benefits of lenalidomide in its authorised indication.

At present, there is no recommendation to delay, modify or restrict the use of lenalidomide for patients treated according to the indication authorised in the EU.

Off-label use of lenalidomide is not recommended, and prescribers are therefore advised to carefully weigh the benefits and risks of any such use.

Doctors should be aware of symptoms of second primary malignancies, particularly in connection with off-label use, and should immediately report any such adverse reactions at *'Report side effects in humans'*.

Please see the *CHMP Monthly Report* (p. 5).

Revlimid® is authorised in the EU for use in combination with dexamethasone for the treatment of multiple myeloma in patients who have received at least one prior therapy.

News in brief

New contraindication for Telzir® (fosamprenavir) for HIV treatment

Due to pharmacokinetic interactions, co-administration with alfuzosin and co-administration with sildenafil for the treatment of pulmonary arterial hypertension have been added as a contraindication in the summary of product characteristics of Telzir®.

In addition, a warning has been added to section 4.4 regarding co-administration with PDE5 inhibitors (medicine used in the treatment of erectile dysfunction). Read more in the *CHMP Monthly Report* (p. 2)

New dosing recommendation for Votrient® (pazopanib) for treatment of advanced renal cell carcinoma

Several sections (4.2, 4.4 and 5.2) in the summary of product characteristics for Votrient® have been updated with information about the new dosing recommendation and warnings for patients with mild hepatic impairment. Read more in the *CHMP Monthly Report* (p. 3).

New contraindication for Xyrem® (sodium oxybate) for treatment of narcolepsy

A contraindication in patients with depression has been added to the summary of product characteristics of Xyrem®. Read more *here*.

Information about the occurrence of serious hypersensitivity reactions has been added to the summary of product characteristics of Efient® (prasugrel) for the prevention of atherothrombotic events

New warnings on the occurrence of serious hypersensitivity reactions have been added to the summary of product characteristics, section 4.8. A letter has been sent out to prescribers. Read more in the *CHMP Monthly Report* (p. 3).

Analgesic (NSAID) and risk of gastric ulcers in arthritic sufferers

By Jane Møller Hansen, Associate Professor, MD, PhD, Department of Gastroenterology, Odense University Hospital, Denmark

The consumption of nonsteroidal antiinflammatory drugs (NSAIDs) is high, especially among senior citizens. In 2009, approx. 25 percent of all persons older than 60 years redeemed a prescription for an NSAID. To this should be added an unknown consumption of OTC medicines.

Adverse reactions of NSAID treatment

While dyspepsia is a common adverse effect of NSAIDs, experienced by approx. 10 to 40 percent of all users, gastric ulcers occur for approx. 25 percent of users. Among the serious known adverse reactions of NSAIDs are gastrointestinal bleeding or perforation, suffered by one to two percent of patients treated each year. The relative risk of developing ulcer complications from the use of an NSAID is 4-7 percent. Despite a decreasing incidence of uncomplicated gastric ulcers, the incidence of ulcer complications is unchanged through the past decade, which is probably ascribable to an increase in consumption of low-dose Magnyl® (ASA) and NSAIDs.

Each year in Denmark, some 3,200 patients are hospitalised due to ulcer complications. About 80 percent of the patients who are hospitalised for treatment of bleeding ulcers, have used an ASA/NSAID in the preceding period.

Risk factors of NSAID treatment

There are a number of identified risk factors for development of ulcer complications during NSAID treatment:

- A history of ulcers is a significant risk factor, particularly if the patient has previously suffered a gastrointestinal bleed.
- Increasing age, particularly after the age of 60.
- Concomitant treatment with a number of products: Magnyl® (ASA), ADP receptor inhibitors, dipyridamole and vitamin K antagonists, the risk increases further with combination treatment.
- Concomitant treatment with steroid and selective serotonin reuptake inhibitors (SSRIs).
- Comorbidity such as heart disease, diabetes mellitus, and severe rheumatoid arthritis has also shown to be risk factors.
- The risk of ulcer complications also depends on the dose applied, just as there are differences between the NSAIDs. Ibuprofen and diclofenac are associated with the lowest risk, while piroxicam is associated with the highest.
- Moreover, the risk of ulcer complications is highest in the first period after commencement of treatment, some episodes occur after only a few days of treatment, but the risk remains present, even after a long period of treatment. Many cases of ulcer complications occur without preceding dyspepsia, which is why this symptom is not a reliable predictor of gastrointestinal toxicity.

A study conducted over a six-month period has shown that the risk of ulcer complications following NSAID treatment is 0.4 percent in patients without risk factors, whereas it is 9 percent in patients who have more than four risk factors.

Preventing NSAID-induced ulcer complications

Prior to prescribing an NSAID, it is important to evaluate the risk factors for the individual patient. If the patient has risk factors, doctors should reconsider prescribing an NSAID and consider alternative pain-relieving therapy.

Doctors who do decide to prescribe an NSAID are recommended to select one with the least risks and the lowest possible dose.

Concomitant treatment with a proton-pump inhibitor (PPI) and misoprostole reduces the risk of NSAID-induced ulcers by 50-60 percent, but does not eliminate the risk. The efficacy of misoprostole increases with the dose applied, but there are often adverse effects associated with treatment, in particular diarrhoea, which is why a PPI is often recommended as prophylactic therapy.

Helicobacter pylori (Hp) is an independent risk factor for gastric ulcers. Eradication of Helicobacter pylory alone is not adequate prophylaxis for continued NSAID treatment in patients who have had NSAID-induced ulcers. It has been documented that eradication of Hp in

NSAID-naive patients may reduce the risk of NSAID-induced ulcers.

Treatment with COX-2 inhibitors is associated with a lower risk of ulcers than the non-specific NSAIDs. The protective effect of COX-2 inhibitors is neutralised when used concomitantly with Magnyl® (ASA). Furthermore, COX-2 inhibitors are associated with an increased risk of cardiovascular episodes. Therefore, these products are not recommended in patients at risk of or with a history of cardiovascular diseases.

Before prescribing an NSAID, doctors are advised to

1. Evaluate the patient's risk factors
2. Reconsider the indication/ alternative treatments if there are risk factors
3. Select the NSAID with the least risks and the lowest possible dose
4. Prophylactic ulcer therapy if there are risk factors: 1-2 risk factors: NSAID + PPI, COX-2 inhibitor (if no cardiovascular risks).
   >2 risk factors of history of gastrointestinal bleeding: alternative pain-relieving therapy, COX-2 inhibitor + PPI (if no cardiovascular risks).

References

Bardou M, Barkun AN. Preventing the gastrointestinal adverse effects of nonsteroidal anti-inflammatory drugs: from risk factor indication to risk factor intervention. Joint Bone Spine 2010; 77: 6-12

Danish College of General Practitioners, 2009. Clinical guidelines for general practitioners: Dyspepsia, assessment and treatment of adults with upper gastrointestinal tract symptoms. (Danish title: Dyspepsi, udredning og behandling af voksne med symptomer fra øvre mave-tarm-kanal)

Swedish study raises suspicion about link between Pandemrix® (the H1N1 vaccine) and the sleep disorder narcolepsy in children and adolescents.

A recently completed Swedish registry study has shown that children and adolescents under the age of 20 have a four times higher risk of developing the sleep disorder narcolepsy if they have received the influenza vaccine Pandemrix® compared to those who are not vaccinated. The results from this study are in line with the results of a similar Finnish study. Read more about the Finnish study in *Danish Pharmacovigilance update, February 2011*.

In the Swedish study, 1:33,000 vaccinees developed narcolepsy – in the Finnish study, it was 1:12,000. Most cases were seen in the period immediately after vaccination. Neither the Swedish nor the Finnish study has shown an increased risk for adults.

No reports of narcolepsy in Denmark

In Denmark, we have had no reports of narcolepsy after vaccination with Pandemrix®.

The Danish Medicines Agency, the Danish National Board of Health and the Danish State Serum Institute have discussed the new research results from Sweden and Finland, finding that there is no immediate cause for concern in Denmark, but we will follow the ongoing investigations of the potential link between Pandemrix® and narcolepsy.

Read more on the Agency's website *here*.

Pandemrix® was used as vaccination against A(H1N1) – the pandemic flu – in 2009/2010. It has not been used in Denmark since the pandemic in 2009/2010.

In Denmark, the Danish National Board of Health recommended to only vaccinate children who were more vulnerable to severe or serious influenza, unlike in Sweden where the vaccine was offered to all children and adolescents regardless of their health condition. In Denmark, 20,800 children and adolescents younger than 18 were vaccinated.

Narcolepsy is a rare sleep disorder involving sudden sleep attacks, occurring in about ten in a million each year. The cause of illness is not yet established, but it is suspected to be caused by genetic and environmental factors, including infections.

Reports of blood clots from the use of Vivaglobin®

The Danish Medicines Agency has been made aware of a few reports of serious cases of blood clots related to the use of Vivaglobin®.

None of the reports are from Denmark.

The risk of arterial and venous blood clots after intravenous use of immunoglobulin products is known, but reports suggest that subcutaneous use of Vivaglobin® may also be associated with the risk of developing blood clots. Laboratory tests carried out by CSL Behring revealed pro-coagulation activity in some batches of Vivaglobin®. However, the clinical significance of these findings is uncertain at present.

The Danish Medicines Agency recommends exercising caution when prescribing Vivaglobin® to patients who are predisposed to developing blood clots. Alternate treatment should be considered for patients with such risk factors.

Be aware of symptoms of thromboembolic events such as shortness of breath, pain and swelling in the extremities, focal neurological signs, chest pain, etc.

Vivaglobin® is not authorised for intravenous use. Intravenous use may be associated with an increased risk of blood clots and should therefore be avoided. The batches concerned are no longer distributed by CSL Behring. CSL Behring will continue to distribute batches with low pro-coagulation activity. The national European regulatory authorities will work closely to avoid supply problems to the extent possible.

The Danish Medicines Agency will continue to monitor reports of thromboembolic events in connection with intravenous and subcutaneous immunoglobulin products.

Read more on the Agency's website *here*.

Vivaglobin® is a human antibody, which is used to treat immunoglobulin deficiency.

Vivaglobin® is authorised for the treatment of primary immunodeficiency (PID) and replacement therapy in myeloma or chronic lymphatic leukaemia with severe secondary hypogammaglobulinaemia and recurrent infections. Vivaglobin® is given subcutaneously (injected under the skin).

It appeared from the reports of blood clots related to the use of Vivaglobin® that the patients had risk factors such as pre-existing cardiovascular diseases, a history of blood clots, obesity, use of oral oestrogen, hyperlipoproteinemia, in-dwelling catheter and immobilisation, etc. Hyperviscosity, hypercoagulation disorders and several cardiac diseases may also increase the risk of blood clots in immunoglobulin administration.

Childhood vaccination and adverse reactions in 2010

Adverse reactions experienced from vaccination are one of the Danish Medicines Agency's focus areas.

We have had positive experience with establishing a vaccination panel as part of the monitoring of adverse reactions after vaccination with the influenza vaccine Pandemrix®. We therefore set up a similar vaccination panel to assess the potential adverse reactions associated with the Danish childhood immunisation programme.

You can read about the first results below.

Adverse reaction reports in 2010 related to the childhood immunisation programme

We do not know exactly how many children were vaccinated in 2010, but some 60,000 children were born in Denmark in 2010, and according to the Danish State Serum Institute, between 80 and 90 percent were vaccinated (depending on vaccine type), which is about the same as in previous years.

In 2010, the Danish Medicines Agency received a total of 168 reports related to the Danish childhood immunisation programme. 55 of the reports were classified as serious (e.g. cramps and high fever).

The majority of the reported adverse reactions, which relate to the childhood immunisation programme, involved known and non-serious adverse effects, such as local reactions at the injection site.

All children who experienced serious adverse reactions fully recovered, with the exception of two cases of narcolepsy and one case of autism. For these three children, the Danish Medicines Agency found it less likely that the adverse effects were linked to the vaccine.

	Total number of reports *	Number of reports classified as serious
Act-Hib	1	1
DTaP/IPV Booster	15	0
DTaP/IPV/Act-Hib	40	22
Gardasil	53	5
MMF vaccine	1	1
MMR	1	1
Prevenar	23	14
Prevenar13	9	6
Priorix	21	5
DTa Booster	4	0
Total	**168**	**55**

Table 1: Number of adverse reaction reports by vaccine type in 2010. On 15 April 2010, Prevenar (7-valent) was replaced by the 13-valent pneumococcal vaccine Prevenar13. The programme is otherwise unchanged compared to 2009. *One report may cover several suspected adverse reactions.

Table 1 shows the number of reports and the number of serious reports distributed between the different vaccines in the childhood immunisation programme.

The number of reported adverse reactions is the same for boys and girls, whose reports related to the Gardasil® HPV vaccine have been extracted from the statistics – Gardasil® is primarily given to girls.

In 2009, there was much focus on the new vaccine Gardasil®, and already in 2010, there were considerably fewer reports for this vaccine compared to 2009 – probably because focus on the vaccine declined. In particular, the number of reported cases of atopic dermatitis, which saw increased attention in 2009, had fallen in 2010.

The childhood immunisation programme as a focus area

In order to maintain safety of vaccination, it is important to obtain the right knowledge about the balance between benefits and risks of vaccination. In future, the Danish Medicines Agency will thus publish quarterly reports on all evaluations of reported adverse reactions related to the Danish childhood immunisation programme.

New improved e-forms for reporting suspected adverse reactions

In February 2011, we launched a revised version of our electronic e-forms (in Danish) for adverse reaction reporting. The e-forms have been improved and simplified, and the design has changed. See the e-forms *here*.

Like the previous versions, there are two e-forms for health professionals:

- E-form for reporting suspected adverse drug reaction from *medicines*
- E-form for reporting suspected adverse drug reaction from *vaccines*.

Are the response times too long when you report adverse drug reactions?

If you experience long response times or other problems when you complete the e-forms, it may be because you are using Windows Internet Explorer 6.0 as browser. Windows Internet Explorer 6.0 does not support the e-forms. You can fix this by upgrading to the newest version of Windows Internet Explorer or by using another browser, e.g. *Mozilla Firefox*.

Our aim is to make it as simple as possible to complete the e-forms, and we would appreciate hearing about your experience with reporting suspected adverse reactions via our e-forms. Please write to *FOS-BIV-TAST@dkma.dk* or ring +45 4488 9757.

The Danish Medicines Agency's annual pharmacovigilance report 2010

In May, we will be sending out our annual pharmacovigilance report for 2010. Here you can read about the development in the number of reports in general, see the top 10 most frequently reported adverse reactions and gain insight into our various campaigns and focus areas.

The report will be available in Danish first. As soon as it has been translated, we will send it out automatically to our subscribers. The report will also be placed on our website: *www.dkma.dk.*

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