Danish Pharmacovigilance Update Year 3 #8
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New definition of adverse reactions due to new European legislation on pharmacovigilance

As of 3 August 2012, a new definition of adverse reactions has been introduced in *the Danish executive order on the reporting of adverse reactions from medicinal products etc. (in Danish only)*

The new definition of adverse reactions has been introduced throughout the EU in association with the implementation of new European legislation on pharmacovigilance. The new European pharmacovigilance legislation aims to strengthen patient safety by improving the present system used for monitoring safety of medicines in Europe. Information on the new legislation is available on *the Danish Health and Medicines Authority's website.*

Definition of adverse reactions expanded to include all noxious and unintended reactions to medicinal products

The definition of an adverse reaction has been expanded to include "a response to a medicinal product which is noxious and unintended", whereas the prior definition was limited to "a response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function".

Thus, the new definition of adverse reactions includes noxious and unintended reactions from the use of a medicinal product in accordance with the approved summary of product characteristics and reactions resulting from medication errors, incorrect use, abuse, and off-label use of medicinal products. The broader definition will ensure the availability of more information on potential risks for use in assessing the safety of medicinal products and ultimately for the benefit of patient safety.

Does the new definition cause a change in doctors' reporting duty?

The duty of doctors to report suspected adverse reactions of medicinal products is more or less unchanged, with the exception that the reporting duty does not apply to suspected adverse reactions resulting from medication errors. Doctors and dentists may, but do not have to, report this type of adverse reactions to the Danish Health and Medicines Authority. Information on the obligation to report is available on *the Danish Health and Medicines Authority's website.*

Adverse events must still be reported to the Danish Patient Safety Database, and the reports are then processed by the Danish National Agency for Patients' Rights and Complaints.

The Danish Health and Medicines Authority cooperates with the Danish National Agency for Patients' Rights and Complaints, among others, regarding information on adverse reactions and adverse events from the use of medicinal products.

Decline in the number of elderly people over 79 years of age receiving Pradaxa 150 mg

In May 2012, the Danish Health and Medicines Authority focused on Pradaxa (dabigatran exexilate) dosing in association with treating the new indication "prevention of apoplexy in patients with non-valvular atrial fibrillation (AF)". Data from the Danish Register of Medicinal Product Statistics for the period 22 August 2011 through 31 December showed that approx. 10% of all Pradaxa users over 79 years of age (121 users) were prescribed the large packages with Pradaxa 150 mg capsules.

The Authority warned against this development and has followed up to detect possible changes in the prescription pattern.

Table 1. New users of Pradaxa* aged 75-79 and 80+ years distributed by months (Sept. 2011-July 2012).

Age groups	Month	No. of new users of Pradaxa*	Number (percentage) redeeming 150 mg the first time
75-79 years	2011-09	129	93 (72 %)
	2011-10	169	115 (68 %)
	2011-11	207	120 (58 %)
	2011-12	177	92 (52 %)
	2012-01	151	88 (58 %)
	2012-02	116	71 (61 %)
	2012-03	135	69 (51 %)
	2012-04	106	59 (56 %)
	2012-05	115	53 (46 %)
	2012-06	119	43 (36 %)
	2012-07	97	37 (38 %)
80+	2011-09	237	36 (15 %)
	2011-10	292	34 (12 %)
	2011-11	329	26 (8 %)
	2011-12	268	17 (6 %)
	2012-01	266	12 (5 %)
	2012-02	199	7 (4 %)
	2012-03	245	7 (3 %)
	2012-04	218	3 (1 %)
	2012-05	192	7 (4 %)
	2012-06	178	4 (2 %)
	2012-07	161	6 (4 %)

***only new users of 110 mg and 150 mg, packages of 60 and 3 x 60, deemed to suffer from AF**
Source: The Danish Register of Medicinal Product Statistics, the Statens Serum Institut, National Institute for Health Data and Disease Control (SSI)

Data from the Danish Register of Medicinal Product Statistics and the Danish National Patient Registry

In this follow-up study, patients using Pradaxa® for the new indication were selected on the basis of data from the Register of Medicinal Product Statistics as well as the National Patient Registry. The data run was performed by the Statens Serum Institut, National Institute for Health Data and Disease Control (SSI), for the Danish Health and Medicines Authority.
Firstly, new users who redeemed a prescription for a large package of (60 and 3 x 60) Pradaxa 110 mg and 150 mg capsules were extracted from the Register of Medicinal Product Statistics. Of these, the study only includes users who have previously redeemed a prescription for the older anticoagulants Marcoumar® and Marevan® and people who, according to data from the two registers, have not redeemed a prescription for Pradaxa up to 21 days after knee or hip surgery.

Only a minority of elderly people receive the high strength dose

Data were extracted for the period 22 August 2011, i.e., from the marketing date, up until the end of July 2012. The results are shown in Table 1. There has been a large decline in the number of elderly people over 79 years of age receiving the high strength dose. Since February 2012, only a minority of elderly people, corresponding to >

> between 1 and 4%, have been prescribed the high strength dose as compared to 10% on average before the turn of the year. Also, there is a downward trend in the share of users aged 75-79 years receiving the high strength dose of 150 mg (Table 1).

Recommendations
The Danish Health and Medicines Authority continues to recommend doctors to follow the dose recommendations in the summary of product characteristics and to take into consideration the patient's renal function, as Pradaxa® is secreted through the kidneys and contraindicated in patients with severe renal impairment (CrCL <30 ml/min.). Pradaxa users over 74 years of age account for just below half of all Pradaxa users, and we continue to receive many adverse reaction reports concerning serious bleedings. Therefore, doctors must also take into consideration other risk factors for bleeding, e.g. gastric ulcer, and other medicines that affect the haemostasis, e.g. Plavix® (clopidogrel), acetylsalicylic acid (ASA) and NSAIDs.

New recommendations for dosing, duration and precautions when treating patients with nosocomial (hospital-acquired) pneumonia with Doribax® (doripenem)

Following a recently completed evaluation, the European Medicines Agency (EMA) has updated the recommendations for the treatment of patients with nosocomial pneumonia, including ventilator-associated pneumonia, with Doribax® (doripenem):

- Recent studies indicate that the currently approved dose of 500 mg every 8 hours as one or four hours of infusion is not sufficient in all patients.
- A dose of doripenem of 1 g every eight hours infused over four hours may be considered in patients with creatinine clearance >150 ml/min and/or infections caused by non-fermenting gram-negative pathogens (e.g. Pseudomonas spp., Acinetobacter spp.).
- A treatment duration of 10-14 days is usually required.
- Doctors should exercise caution when selecting antibacterial and dose in patients with late ventilator-associated pneumonia (disease onset after more than five days of hospitalisation) and for other cases of nosocomial pneumonia where pathogens with reduced sensitivity such as Pseudomonas spp. and Acinetobacter spp. are suspected or detected.
- When Pseudomonas aeruginosa is suspected or confirmed as the cause of the pneumonia, concomitant treatment with an aminoglycoside may be indicated.

Read *EMA's press release*

Indication for Doribax®
Used in the treatment of serious nosocomial pneumonia (including ventilator-associated pneumonia), complicated intra-abdominal and urinary tract infections caused by bacteria sensitive to doripenem.

Cases of symptomatic hypocalcaemia in patients undergoing treatment with Xgeva® (denosumab)

In August, a letter was sent to health-care professionals to inform them about cases of symptomatic hypocalcaemia, including fatal cases, among patients undergoing treatment with Xgeva® (denosumab). Symptoms of these cases included among others altered mental status, seizures and QTc prolongation.

Hypocalcaemia may occur any time during treatment with denosumab, but most often occurs within the first six months of treatment.

Doctors must pay attention to the following recommendations to minimise the risk of hypocalcaemia:

- Pre-existing hypocalcaemia must be corrected prior to initiation of treatment
- Supplements of calcium and vitamin D is required in all patients, unless hypercalcaemia is present
- If hypocalcaemia occurs, additional calcium supplementation may be necessary
- Patients with severe renal impairment (creatinine clearance <30 ml/min) or patients receiving dialysis have an elevated risk of developing hypocalcaemia. Monitoring of calcium levels in these patients is recommended.

In Denmark, we have not received any reports of adverse reactions related to hypocalcaemia in association with Xgeva®.

Indication for Xgeva®
Used in the prevention of skeletal-related events (pathological fracture, radiation to bone, spinal cord compression or bone surgery) in adults with bone metastases from solid tumours.

Revatio (sildenafil) has been approved in the EU for the treatment of children, but should only be used in the recommended low doses

Revatio has been approved for the treatment of paediatric patients in the EU. In the USA, a long-term clinical paediatric trial including 234 patients showed that children receiving high doses of Revatio had a higher risk of death than children receiving lower doses, and that low doses of Revatio are not effective in improving the exercise capacity.

Based on this, the U.S. Food and Drug Administration (FDA) has issued a warning against the use of Revatio in the treatment of pulmonary arterial hypertension in children aged 1-17 years. Subsequently, the product information in the USA has been updated with information stating that the use of Revatio is not recommended in paediatric patients and information on results of the trial.

The European product information already specifies how to use Revatio in paediatric patients, including dosing and special precautions.

The benefits of Revatio outweigh the risks

The results of the above trial were assessed by the Committee for Medicinal Products for Human Use (CHMP) in April 2012. According to the CHMP, the benefits of Revatio still outweigh the risks when used in accordance with the product information.

The European Medicines Agency (EMA) continues to warn against off-label use of Revatio in children and the use of higher doses than recommended. The EMA awaits the final results of the trial and will issue new recommendations, if necessary.

In Denmark, we have not received any reports of adverse reactions in children undergoing treatment with Revatio.

The paediatric indication for Revatio®
Revatio is a phosphodiesterase-5 inhibitor used in the treatment of pulmonary arterial hypertension (PAH). In the paediatric population, efficacy in terms of improvement of exercise capacity or pulmonary haemodynamics has been shown in primary pulmonary hypertension and pulmonary hypertension associated with congenital heart disease.

For further information:
FDA Drug Safety Communication: FDA recommends against use of Revatio in children with pulmonary hypertension

Report of development of pulmonary fibrosis associated with the use of the active substance amiodarone (Cordan® and others)

The Danish Health and Medicines Authority has received an adverse reaction report concerning a patient who developed pulmonary fibrosis in association with the use of Cordan®. The patient had received Cordan® 100 mg x 2 for 2 1/2 years when being diagnosed with pulmonary fibrosis. Today, the patient is affected by the pulmonary impairment.
The Danish Health and Medicines Authority has received a total of 33 Danish reports of pulmonary fibrosis in association with the use of amiodarone.

Patients undergoing treatment should be monitored

Medicines containing amiodarone may cause serious adverse reactions affecting the lungs, liver, thyroid gland, skin and peripheral nervous system as specified in the summaries of product characteristics. As these reactions may be delayed, patients undergoing long-term treatment should be monitored closely.

Pulmonary toxicity (alveolar/interstitial pneumonitis or fibrosis etc.) is a common adverse reaction from the treatment.

Advice for doctors

- Dyspnoea and/or non-productive cough in patients undergoing treatment with amiodarone may be caused by pulmonary toxicity such as interstitial pneumonitis. Therefore, chest X-rays are required in patients developing functional dyspnoea either isolated or associated with a deterioration in their general health (fatigue, weight loss, fever).

- The use of amiodarone should be reassessed, since interstitial pneumonitis most often is reversible after early discontinuation of amiodarone (the clinical signs usually disappear within three to four weeks, and X-rays and the objective pulmonary function are improved over several months), and corticosteroid therapy should be considered.

You can find summaries of product characteristics for amiodarone (in Danish only) at *www.produktresume.dk*.

Indication for Cordan® amiodarone
Used in the prevention and treatment of supraventricular and ventricular tachyarrhythmias, when other antiarrhythmics are ineffective.

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