Danish Pharmacovigilance Update #4

Volume 5
30 April
2014

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New restrictions on the use of domperidone-containing medicines (Motilium® etc.)

The EU has just finished a new review of the benefits and risks of using domperidone-containing medicines, concluding that the use of the medicine should be restricted.

The new restrictions for use of domperidone imply the following changes:

- In future, domperidone will only be authorised to relieve symptoms of nausea and vomiting.
- Domperidone will no longer be indicated in epigastric sense of fullness, upper abdominal discomfort and regurgitation of gastric contents.
- The maximum dose of domperidone is three times daily in respect of 10 mg tablets, and twice daily in respect of 30 mg suppositories in adults and children weighing 35 kg or more.
- Domperidone in 10 mg tablets and 30 mg suppositories, the formulations authorised in Denmark, should not be used in children weighing less than 35 kg as it is not possible to ensure a precise dose per kg.
- Domperidone should generally not be used for longer than one week.
- Domperidone must not be given to patients with moderate or severe impairment of liver function, patients with existing heart rhythm abnormalities or patients at high risk due to an underlying heart disease or electrolyte imbalance.
- Domperidone should not be used with other medicines that can affect the heart rhythm or with medicines that can reduce the breakdown of domperidone in the body, thus increasing the risk of overdose and adverse reactions.

Events leading to the new restrictions

The risk of cardiac adverse reactions with domperidone has been reviewed several times in the EU, leading to revised product information with warnings and precautions for use in patients with certain heart diseases. The latest review included a thorough evaluation of e.g. published literature, study data and reported adverse reactions. Data showed that domperidone was associated with a small, increased risk of serious and potentially life-threatening cardiac adverse reactions, particularly when given to patients older than 60 years, when given at doses exceeding 30 mg daily or when given to patients treated concomitantly with certain other medicines.

In Denmark, no cardiac adverse reactions have been reported after treatment with domperidone.

For further information, please see EMA's press release here: *PRAC recommends restricting use of domperidone*.

News from the EU

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 PRAC to recommend further measures is published on the website of the European Medicines Agency (EMA) every month.

The most important recommendations on safety signals from the PRAC meeting in March 2014 concern the following products:

- **Goserelin** – long duration flushing and hyperhidrosis.
- **Tenofovir** – acute kidney injury caused by co-administration with NSAIDs.

See the list on EMA's website. *PRAC recommendations on signals.*

1 The fact that a signal has been assessed does not mean that there is a causal link to the medicine.

News from the DHMA

The DHMA has made guidance documents on contraceptive pills and the risk of blood clots available to prescribers and users of contraceptive pills

On the basis of the EU's latest review of the risk of venous thromboembolism (VTE) with contraceptive pills and other combined hormonal contraceptives[1], the DHMA and the other European drug regulatory authorities have jointly prepared guidance documents for prescribers and users of contraceptive pills.

The guidance documents include:

- A prescriber checklist to facilitate consultations prior to prescribing the products
- A card for users providing information about the products and the symptoms of blood clots to be aware of

The material is available in Danish from our website *Guidance documents for prescribers and contraceptive pill users (in Danish only)*.

The DHMA's recommendations are unaltered

The conclusions from the EU's latest review comply with previous data, and our recommendations for prescribing and using contraceptive pills are unaltered.

The DHMA recommendations on contraceptive pills:

- Second generation contraceptive pills should be first choice when prescribing combined hormonal contraceptives.
- Even when women who have used third and fourth generation pills for a long period without problems should doctors carefully weigh the benefits and risk of continuing these products. The risks of VTE associated with the different types of contraceptive pills are estimated as follows:
  - First and second generation contraceptive pills, 5-7 cases of VTE each year per 10,000 users of contraceptive pills
  - Third and fourth generation contraceptive pills, 9-12 cases of VTE each year per 10,000 users of contraceptive pills
  - Contraceptive patch and contraceptive vaginal ring, 6-12 cases of VTE each year per 10,000 users of contraceptive pills
- Before a woman starts taking contraceptive pills, the doctor should ensure that she is examined, that her medical history is taken and that she is informed of the risk of blood clots and their early warning signs.
- Doctors should regularly follow-up on the treatment in relation to the applicable medical guidelines, being particularly alert in the beginning of treatment when the risk is highest, and in situations when the woman takes a break from the pill or switches to another brand.

Read the article in *Danish Pharmacovigilance Update, February 2014* on the consumption of contraceptive pills, which shows that prescribers and patients adhere to the DHMA's recommendation to use second generation contraceptive pills as first choice.

Further reading in Danish

The DHMA's letter with recommendations sent to the Organization of General Practitioners *Information from the Danish Health and Medicines Authority on the European review of the risk of thromboembolism in users of contraceptive pills (in Danish only)*.

The EU's latest review and assessment of contraceptive pills published on our website *EU's Pharmacovigilance Risk Assessment Committee confirms benefits of all contraceptive pills (in Danish only)*.

Further reading in English

EMA's press release available from the EMA website: *PRAC confirms that benefits of all combined hormonal contraceptives (CHCs) continue to outweigh risks*

1 Combined hormonal contraceptives contain two types of hormones, an estrogen and a progestogen, and are available as pills, patches and vaginal rings.

Short news

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:

- **HIV medicine saquinavir** (Invirase): New recommendations on ECG monitoring of treatment naive patients

- **Lenograstim** (Granocyte®): Risk of capillary leak syndrome in patients with cancer and in healthy donors

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

All cases referred to in this article originate from the Danish Health and Medicines Authority's database of adverse drug reactions. The cases have been forwarded to all relevant pharmaceutical companies and to the EudraVigilance database. Therefore, pharmaceutical companies should not report these cases to the Danish Health and Medicines Authority.

Danish Pharmacovigilance Update is published by the
Danish Health and Medicines Authority
www.dhma.dk
Editor-in-Chief:
Henrik G. Jensen (HGJ)
Editor:
Nina Vucina Pedersen (NVP)
ISSN 1904-2086

Sundhedsstyrelsen
Danish Health and Medicines Authority