Danish Pharmacovigilance Update

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Modafinil should only be used for the treatment of narcolepsy

The European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) has investigated the effect and safety of modafinil.

The review shows that the advantages of using modafinil-containing medicines only exceed the risks when used for the treatment of narcolepsy. For any other use, e.g. for the treatment of obstructive sleep apnoea and sleeping problems in connection with shift work, the risk/benefit balance is negative.

Modafinil-containing medicines should not be used for:

- Patients with uncontrolled hypertonia or arrhythmia.
- Children – due to the increased risk of severe skin reactions.

Doctors should continuously monitor patients undergoing treatment with modafinil due to the safety profile of modafinil, which involves a potential risk of severe skin reactions, psychiatric adverse reactions as well as hypertension and cardiac arrhythmias

For further information, please read the CHMP monthly report (p. 3): *http://www.ema.europa.eu/docs/en_GB/document_library/Committee_meeting_report/2010/11/WC500099368.pdf*

The Danish Medicines Agency has received a report of a death in connection with treatment with Ritalin (methylphenidate)

The case involves a young man, hospitalised with ventricular fibrillation, who subsequently died from a cerebral incarceration after extended resuscitation attempts. ECGs taken during the hospitalisation showed indications of the congenital heart disease WPW (Wolff-Parkinson-White syndrome). The patient had been treated with Ritalin (methylphenidate) since childhood and was also being treated for asthma. The patient had consulted a doctor specifically because of episodes of heart palpitations.

It cannot be ruled out that Ritalin contributed to the death. Therefore, the Danish Medicines Agency would like to emphasise the following recommendations from the summary of product characteristics:

- Before initiation of treatment with methylphenidate, it is important to carry out a baseline evaluation of the cardiovascular status, and detailed medical history thereof must be recorded from the patient.
- Blood pressure and pulse should be measured in connection with dose adjustment or every six months, and patients with symptoms such as palpitations, chest pain triggered by physical exertion, inexplicable fainting, dyspnoea or other symptoms indicating a heart disease during treatment with methylphenidate must immediately have their heart examined by a specialist.
- Stimulants such as methylphenidate are not recommended for children or adolescents with a history of structural cardiac deformities, cardiomyopathy, severe cardiac arrhythmia or other serious heart problems which can lead to increased vulnerability to sympathomimetic effects of a stimulant drug.

Ritalin, tabletter 10 mg.doc

Methylphenidate-containing medicines are only approved for the treatment of ADHD in children and adolescents (6-18 years old) and for the treatment of the rare disease narcolepsy.

Interaction between alcohol and certain opioids with modified release

A European review of the safety of opioids with modified release for the treatment of severe pain has disclosed the scope of interaction with alcohol.

The review indicated that patients who drink alcohol while undergoing treatment with certain types of opioids with modified release (prolonged-release tablets containing polymethacrylate-triethylcitrate) risk must faster absorption than intended of the opioid dose administered. This increases the risk of serious adverse reactions such as respiratory depression.

The above-mentioned pharmacokinetic interaction only applies to the products mentioned. In addition, the well-known pharmacodynamic interaction exists between alcohol and all types of opioid products.

Therefore, the recommendation of the European Medicines Agency (EMA) is as follows:

- The marketing authorisation for the products in question should be suspended until a more alcohol-resistant formulation has been developed.

- Patients undergoing treatment with this type of opioids with modified release should switch to another product as long as these products have the current level of instability towards alcohol.

However, it still applies to most opioids that the benefits outweigh the risks, but there is a need to harmonise the warnings against interaction with alcohol for the entire group of opioids.

For further information:

EMA's press release:
http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2010/07/WC500095005.pdf

Q&A document:
http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Modified-released_oral_opioids_31/WC500099180.pdf

In Denmark, the following opioids contain polymethacrylate-triethylcitrate which especially interacts with alcohol:

Ethirfin (morphine), prolonged-release capsules
Zomorph (morphine), prolonged-release capsules
Morphine sulphate 'Ethypharm' (morphine), prolonged-release capsules

Withdrawal of GlucaGen® Hypokit 1 mg for injection

In October 2010, Novo Nordisk A/S in Denmark withdrew a GlucaGen® Hypokit 1 mg lot for the treatment of hypoglycaemia in diabetic patients. This was exclusively GlucaGen® Hypokit 1 mg for injection bearing the lot number YW60417 and the expiry date 01/2013.

The lot has been available in the Danish market since 18 August 2010.

The Danish Medicines Agency expects most of the lots bearing this lot number to have been returned, but some patients may still have this product in their possession.

Patients are asked to contact the closest pharmacy, where they will be given a new package at no additional cost.

The reason for the withdrawal of GlucaGen® Hypokit with lot number YW60417

The hypokit consists of a prefilled syringe containing sterile water and a vial containing freeze-dried glucagon powder. The reason for the withdrawal is a production error causing the risk that a small number of vials may have been broken. Although this production error presumably only applies to a few hypokits, it is important that all units bearing this lot number are returned and replaced by new units, as it is not possible to see with certainty whether the vials are broken – and using a broken vial entails a risk of the patients not receiving the correct dose.

Corticosteroids for inhalation or intranasal use and possible risk of psychiatric adverse reactions

It has been known for a long time that systemic use of corticosteroids can cause a number of adverse reactions, including psychiatric adverse reactions and behavioural changes. In rare cases, similar adverse reactions have also been reported in connection with the use of inhaled or intranasal corticosteroids due to systemic absorption.

Therefore, the European Pharmacovigilance Working Party (PhVWP) has now reviewed the known data for the risk of psychiatric adverse reactions and has prepared harmonised wordings to reflect the above. These wordings will be implemented in all summaries of product characteristics and package leaflets during the coming months.

Among other things, the following adverse reactions will be added in the summaries of product characteristics for inhaled corticosteroids and for intranasal corticosteroids:

- Hyperactivity, dyssomnia, anxiety, depression and aggressiveness (especially in children).

Furthermore, monitoring of growth will be added in the summaries of product characteristics for intranasal corticosteroids because, as is the case for the use of inhaled corticosteroids, rare cases of delayed growth have been recorded.

Special alertness should be exercised when large doses are used for prolonged periods – patients must not change their own doses.

For further information, please read the PhVWP monthly report: *http://www.ema.europa.eu/docs/en_GB/document_library/Report/2010/11/WC500099367.pdf*

Risk of osteonecrosis of the jaw in patients who have undergone treatment with Avastin® or Sutent® with concomitant or previous use of intravenous bisphosphonates

Cases of osteonecrosis of the jaw have been reported in cancer patients in connection with treatment with Avastin® (bevacizumab) or Sutent® (sunitinib), where most patients have previously or concomitantly undergone treatment with intravenous bisphosphonates.

In the Danish Pharmacovigilance Update of 18 February 2010, we presented information about treatment with bisphosphonates and the risk of osteonecrosis of the jaw. Avastin® and Sutent® may possibly be additional risk factors for the development of osteonecrosis of the jaw.

Danish Pharmacovigilance Update, 18 February 2010

Advice for doctors:

- This potential risk should especially be considered when Avastin® or Sutent® is administered concurrently or sequentially to bisphosphonates.
- Dental examination and appropriate preventive dental treatment should be considered before start-up of treatment with Avastin® or Sutent®. If possible, invasive dental procedures should be avoided in patients who have previously received or who are receiving bisphosphonates.

The summaries of product characteristics for Avastin® and Sutent® will be updated, and a letter will be sent to health-care professionals to inform them about this risk.

For further information, please read the CHMP monthly report (p. 2): *http://www.ema.europa.eu/docs/en_GB/document_library/Committee_meeting_report/2010/11/WC500099368.pdf*

Methylphenidate (Ritalin® etc.) and the risk of abuse

Recently, the Danish Poison Control Hotline informed the Danish Medicines Agency that they have received an increasing number of calls about methylphenidate abuse. According to the Poison Control Hotline, the calls primarily involve children and adolescents – on the one hand children and adolescents undergoing treatment for ADHD and on the other hand children and adolescents who are given the medicine from other children and adolescents.

Doctors with patients undergoing treatment with methylphenidate should particularly note the following items in the summary of product characteristics:

- Methylphenidate should be used with caution in patients with a history of drug or alcohol dependency, and just like other stimulants, it may be inappropriate for the treatment of patients who have a high risk of developing drug abuse.
- Patients should be monitored closely for any signs of inappropriate use, abuse or passing on of methylphenidate.

Chronic abuse of methylphenidate may result in pronounced tolerance and psychological dependence with a varying degree of abnormal behaviour. Actual psychotic episodes may occur, especially in connection with parenteral abuse.

On the basis of the mechanism of action for methylphenidate, the Danish Medicines Agency has already introduced special rules for the sale and dispensing of this medicinal product.

Methylphenidate-containing medicine is prescription-only and subject to the duty to copy prescriptions for doctors. Methylphenidate has also been included on the Danish Medicines Agency's list of euphoriant substances.

Please find the summary of product characteristics for Ritalin here:

Ritalin, tabletter 10 mg.doc

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