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Ivabradine (Corlentor/Procoralan) and risk of heart problems

The European Medicines Agency (EMA) has carried out a review of Corlentor/Procoralan (ivabradine) after the SIGNIFY study was completed.

The EMA assesses that the benefits still outweigh the risks in the authorised indications.

The study found a small but significant increase of cardiovascular death or non-fatal heart attack in patients with symptomatic angina, based on which the EMA has now prepared a number of recommendations aiming to reduce the risk of heart problems – including heart attack and bradycardia.

Updated recommendations for ivabradine:

- In patients with coronary heart disease without heart failure, ivabradine should be used only to alleviate symptoms as no beneficial effect has been indicated for the cardiovascular endpoints.
- Symptomatic treatment in patients with chronic stable angina pectoris should only be initiated at a resting heart rate of >70.
- The starting dose should not exceed 5 mg twice a day, and the maximum maintenance dose should not exceed 7.5 mg twice a day.
- Treatment should be stopped if angina symptoms have not been alleviated within three months, or if there is only limited improvement, and no clinically significant reduction in the heart rate is indicated.
- Concomitant treatment with diltiazem or verapamil is now contraindicated.
- Before starting treatment and in connection with any dose adjustment, it should be considered to perform a series of heart rate measurements, ECG or outpatient 24 hour monitoring to determine the heart rate.
- Patients who are treated with ivabradine should be monitored for any development of atrial fibrillation since ivabradine increases the risk of atrial fibrillation.
- If, during treatment, the heart rate drops below 50 beats per minute at rest or if the patient experiences symptoms of bradycardia, the dose should be reduced (lowest possible dose is 2.5 mg twice daily) and should be discontinued if there is no improvement.

Background to the recommendations

The SIGNIFY study investigated if treatment with ivabradine in patients with coronary heart disease without heart failure reduced the number of events such as heart attacks compared with placebo. The study showed that in a subgroup of patients who had symptomatic angina there was a small but significant increase in the risk of cardiovascular death or non-fatal heart attack and a higher risk of bradycardia with ivabradine compared with placebo. The EMA review also included further safety/efficacy data which indicated that patients treated with ivabradine had an increased risk of atrial fibrillation compared with control patients. The patients in the SIGNIFY study were started on and treated with higher doses than recommended, but it was assessed that the events could not be ascribed to this alone.

DHPCs with the new recommendations will be circulated, and the product information for ivabradine will be updated.

Read the EMA's press release here: PRAC recommends measures to reduce risk of heart problems with Corlentor/Procoralan (ivabradine)

Indication for ivabradine:
Ivabradine is used for symptomatic treatment of chronic stable angina pectoris and chronic heart failure.

No consistent evidence of an increased risk of heart problems with testosterone medicines

The European Medicines Agency (EMA) has completed a review of the benefit-risk balance of testosterone-containing medicines. The review followed concerns about new data showing a possible increased risk of cardiovascular events – particularly myocardial infarction in men with pre-existing cardiovascular disease who were treated with testosterone[1, 2, 3].

The result of the review showed evidence in the area to be inconclusive. Whereas some of the available studies indicate an increased risk, other studies do not[4, 5, 6, 7]. The studies also have limitations that make it difficult to draw any firm conclusions.

Testosterone deficiency can in itself increase the risk of cardiovascular events.

Based on its review, the EMA makes the following recommendations:

- Testosterone replacement therapy should only be given when hypogonadism has been confirmed by clinical symptoms and laboratory tests. Testosterone levels should be measured regularly during treatment as should haemoglobin, haematocrit, liver function and blood lipid profile.
- In patients suffering from severe cardiac, hepatic, or renal insufficiency or ischaemic heart disease, treatment with testosterone could cause severe complications characterised by oedema with or without congestive cardiac failure. In such cases, treatment must be stopped immediately.
- Testosterone could cause the blood pressure to rise and should be used cautiously in patients with hypertension.
- There is limited experience with testosterone replacement therapy in patients older than 65 years of age. Physiological testosterone levels decrease with age. Presently there is no consensus on age-specific testosterone reference values, but the use of testosterone in healthy older men is not an authorised indication in the EU.

  Read the EMA's press release here: No consistent evidence of an increased risk of heart problems with testosterone medicines

1 Finkle et al. "Increased risk of non-fatal myocardial infarction following testosterone therapy prescription in men." PLoS One. 2014.

2 Vigen et al. "Association of testosterone therapy with mortality, myocardial infarction, and stroke in men with low testosterone levels." JAMA. 2013 Nov 6;310(17):1829-36.

3 Xu L, Freeman G, Cowling BJ,Schooling CM. Testosterone therapy and cardiovascular events among men: a systematic review and meta-analysis of placebo-controlled randomized trials. BMC Med. 2013;11:108.

4 Baillargeon J, Urban RJ, Kuo Y-F, et al. Risk of myocardial infarction in older men receiving testosterone therapy. Ann Pharmacother 2014; 48: 1138-44.

5 Corona G, Maseroli E, Rastrelli G, et al. Cardiovascular risk associated with testosterone boosting medications: a systematic review and metaanalysis. Expert Opin Drug Safety 2014; 13: 1327-51.

6 Tan R, Cook KR, Reilly WG. Testosterone therapy is not associated with higher risk of myocardial infarction or stroke: the low T experience. Abstract Book of the 2014 Annual Meeting of the American Association of Clinical Endocrinologists (AACE), p. 238, abstract #1353. Available at: https://www.aace.com/files/late-breaking-abstracts-2014.pdf

7 Hildreth KL, Barry DW, Moreau KL, et al. Effects of testosterone and progressive resistance exercise in healthy, highly functioning older men with low-normal testosterone levels. J Clin Endocrinol Metab 2013; 98: 1891-1900.

Indication:
Testosterone replacement therapy for male hypogonadism when testosterone deficiency has been confirmed by clinical features and biochemical tests.

Testosterone is indicated in adult men.

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[1].

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

At the PRAC meeting in October, no recommendations were made to change any product information or initiate other risk minimisation measures.

See the full report on safety signals: 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.

ADRs related to thyroid hormone replacement therapy: Remember the clinical picture at dose optimisation

Many inquiries and ADR reports about Eltroxin and Euthyrox

Periodically, the DHMA receives many inquiries and ADR reports about Eltroxin and Euthyrox (levothyroxine = hormone T4) used to treat hypothyroidism. Most of the inquiries are from patients who describe clinical symptoms suggestive of hyperthyroidism or hypothyroidism – some of which are severe. However, many of the patients do not interpret these symptoms this way. Rather they experience them to be adverse reactions to the medicine caused by, for example, the active substances. The patients often describe their TSH values as being inside the normal range, which means that neither patient nor doctor suspects that the dose might not be optimal.

Some ADR reports describe cases where patients experience symptoms of hyperthyroidism and hypothyroidism at the same time. In these cases, the cause is more unclear. It is known, however, that not all patients regain full quality of life after treatment with T4.

The volume of reports pointing in the same direction, prompts us to make doctors aware that the therapeutic range for thyroid hormones is narrow, and that optimal doses should not be based on laboratory values alone, but on a clinical evaluation of the individual patient as well.

Doctors should be aware of the following:

- Eltroxin has a small therapeutic window. Optimal doses are based on clinical evaluation and on blood tests for monitoring of thyroid function. During the initial titration period, it is necessary to proceed cautiously with titration and ensure monitoring in order to avoid the consequences of over-treatment or under-treatment. The symptoms of over-dosing can be compared to many of the signs seen in endogen thyrotoxicosis. See the summary of product characteristics for Eltroxin (in Danish).

- If a patient treated with Eltroxin or Euthyrox does not adequately regain euthyroid state, other treatment alternatives should be considered. For further information, please see the article published by the Institute for Rational Pharmacotherapy in 2013 (in Danish only): Behandling af hyper- og hypotyreose (Treatment of hyperthyroidism and hypothyroidism).

Treatment with citalopram and methadone and risk of QT prolongation

In spring 2014, the DHMA received an ADR report about a younger man who, for several years, had been treated with citalopram for anxiety and, for some months, had used methadone due to a history of abuse.

During hospitalisation (control of existing diabetes), the patient suffered a seizure and clinical heart failure. He was resuscitated and transferred to a coronary department. An ECG showed prolonged QT interval. Citalopram and methadone were discontinued, and the QT interval subsequently normalised.

ADR reports of QT prolongation in treatment with methadone and citalopram or escitalopram
The DHMA has received a total of ten ADR reports. In one of them, QT prolongation was coded as a possible adverse reaction to methadone, and in nine of them, QT prolongation was coded as a possible adverse reaction to citalopram or escitalopram.

Doctors subscribing citalopram should be aware of the following:

- If a patient with a stable heart disease is to be treated, an ECG should be considered before initiating treatment.
- Citalopram is contraindicated for use with other medicines known to prolong the QT interval.
- Citalopram may cause a dose-dependent prolongation of the QT interval. Cases of QT interval prolongation and ventricular arrhythmia including torsade de pointes have been reported after marketing. This is particularly seen in female patients with hypokalaemia, pre-existing QT prolongation or other cardiac diseases.
- Caution is advised in patients with bradycardia, or in patients with recent acute myocardial infarction or uncompensated heart failure.
- Electrolyte disturbances such as hypokalaemia and hypomagnesaemia increase the risk for malignant arrhythmias and should be corrected before initiation of treatment.
- If signs of cardiac arrhythmia occur during treatment, the treatment should be discontinued, and an ECG should be performed.

When subscribing methadone:

- There have been reports of QT prolongation and torsade de pointes in patients treated with methadone. Most of these cases occurred at high doses (> 200 mg daily). Therefore, methadone should be administered cautiously in people at risk of developing QT prolongation, e.g. persons with a history of conduction abnormalities, persons with advanced heart disease, ischaemic heart disease and persons treated with other products known to prolong the QT interval.
- ECG should be checked for all patients who receive more than 150 mg daily and in case there are other risk factors for QT prolongation.

Indications:

Methadone:
Methadone replacement therapy and severe pain.

Citalopram
Major depressive episodes. Panic disorder with or without agoraphobia. Prevention of recurring depressive episodes.

Short news

Most recent Direct Healthcare Professional Communications (DHPCs)

Below is a list of the most recent DHPCs that have been (or soon will be) sent out to relevant doctors and healthcare professionals with safety information and updated recommendations about medicines:

- **Ustekinumab (Stelara) for treatment of psoriasis:** Risk of exfoliative dermatitis and skin exfoliation.
- **Leuprorelin (Eligard) for treatment of prostate cancer:** Risk of lack of efficacy due to incorrect reconstitution and administration process.

Read the DHPCs on the DHMA website: List of circulated DHPCs.

Danish Pharmacovigilance Update celebrates 5-year anniversary

Danish Pharmacovigilance Update was issued the first time in November 2009, and this year we celebrate its fifth anniversary with more than 3000 subscribers to the Danish and the English version.

We are delighted to see the great interest in our newsletter and notably the interest in the pharmacovigilance area, which we continually strive to improve through the launch of various initiatives.

New methods for processing Danish ADR data

Much has happened in the last two years. We implemented a new IT system capable of making advanced statistical data processing of Danish ADR reports.. The system allows comparison of large data volumes and can help identify medicines whose risk profiles turn out differently than expected. Each week, the system generates a list of possible signals based on a number of criteria, and all signals on the list are reviewed. We go through as many as 300 Danish ADR signals every week. A signal occurs when we identify a new possible causal relationship between an event (usually an adverse reaction) and a certain type of medicine. A signal could also reflect a new angle on an already known causality. In addition to picking up new signals, we also keep a vigilant eye on appropriate use of medicines in clinical practice. This involves checking if a particular type of medicine is prescribed to the right patients, and if established precautions for use of the medicine are observed so that patients avoid discomforts and adverse reactions. ADR reports are a cornerstone in this work.

In our future issues of Danish Pharmacovigilance Update, we will describe some of the ADR signals and problems related to safe use of medicines that we work with.

We hope the interest in Danish Pharmacovigilance Update will continue to grow.
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