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DANISH MEDICINES AGENCY

Danish Pharmacovigilance Update

NO. 1 • VOLUME 8 • JANUARY 2017

In this issue

Withdrawal syndrome when discontinuing drug treatment for Parkinson's disease and restless legs syndrome

The European Pharmacovigilance Risk Assessment Committee, PRAC, decided in November 2016 to update the summaries of product characteristics (SmPCs) for pramipexole-containing medicines (Sifrol, etc.) with information that patients discontinuing pramipexole treatment are at risk of developing dopamine agonist withdrawal syndrome. Pramipexole is authorised for the treatment of Parkinson's disease and restless legs syndrome.

Doctors are advised to be aware of the following:

- Withdrawal syndrome may occur when treatment with dopamine agonists (including pramipexole) is tapered off or discontinued. Symptoms of dopamine agonist withdrawal syndrome include apathy, anxiety, depression, fatigue, perspiration and pain. The symptoms could be severe.
- Patient should be informed about this before tapering off the dopamine agonist and monitored regularly thereafter.
- It may become necessary to resume or increase the dose of pramipexole temporarily if symptoms persist.

The SmPCs of pramipexole already describe that the dose should be decreased gradually in connection with treatment discontinuation due to the risk of developing a neuroleptic malignant syndrome. However, depending on the initial dose, this gradual dose reduction only takes a few weeks, which is not always enough to prevent dopamine agonist withdrawal syndrome.

Knowledge about dopamine agonist withdrawal syndrome

The scientific evidence for dopamine agonist withdrawal syndrome (DAWS) suggests a general class effect of dopamine agonists [1,2,3]. However, the adverse reaction has so far only been adopted for pramipexole.

Symptoms of dopamine agonist withdrawal syndrome present when patients are tapered off dopamine agonist treatment. Tapering off treatment may become necessary, for example if the patient experiences unacceptable adverse reactions, if the patient has no clinically relevant effect of the treatment, or if, in Parkinson's

disease, the patient starts a new type of treatment for motor symptoms. The syndrome has also been seen in the treatment of restless legs syndrome.

One of the symptoms of dopamine agonist withdrawal syndrome is depression, which is common in Parkinson's disease. However, antidepressants have no effect on depression induced by dopamine agonist withdrawal syndrome. Nor can levodopa alleviate the problem even though the mechanism is lack of dopaminergic stimulation. In some cases, dopamine agonist withdrawal syndrome wears off without intervention over weeks or months, but according to the literature, the symptoms may persist for more than a year in a significant proportion of patients.

In some cases of severe, persistent symptoms, it may become necessary to resume treatment with a dopamine agonist, possibly at a lower dose.

References

[1] Dopamine agonist withdrawal syndrome in Parkinson disease. Rabinak CA1, Nirenberg MJ. Arch Neurol. 2010 Jan; 67(1):58-63. doi: 10.1001/archneurol.2009.294.

[2] Dopamine agonist withdrawal syndrome (DAWS) symptoms in Parkinson's disease patients treated with levodopa-carbidopa intestinal gel infusion. Solla P, Fasano A, Cannas A, Mulas CS, Marrosu MG, Lang AE, Marrosu F. Parkinsonism Relat Disord 2015. 21(8):968-971.

[3] Clinical features of dopamine agonist withdrawal syndrome in a movement disorders clinic. Pondal M, Marras C, Miyasaki J, Moro E, Armstrong MJ, Strafella AP, Shah BB, Fox S, Prashanth LK, Phielipp N, Lang AE. J Neurol Neurosurg Psychiatry. 2013 Feb;84(2):130-5.

Danish educational material for doctors, patients and pharmacies now available on the DKMA website

Every authorised medicine must have a summary of product characteristics (SmPC) and a package leaflet (PL) that describe its properties and its conditions for use. For some medicines, the authorities may also require that educational material is prepared for doctors, patients or pharmacies. The content of the educational material and a list of its intended target groups are prepared by the marketing authorisation holder and assessed by the DKMA.

Examples of educational material:

- Information for doctors providing treatment guidelines
- Prescription checklist
- Special instructions for use or patient card for handout.

The educational material about medicines supplements the information in the SmPC and PL.

The DKMA has published educational material for human medicines on its website since November 2016.

The list of published educational material covers only material about human medicines authorised via the national procedure, the mutual recognition procedure and the decentralised procedure. The list is not complete, but will be updated when new material has been assessed in the future.

The list is available here: *Educational material for human medicines authorised via the national procedure, the mutual recognition procedure and the decentralised procedure (in Danish only)*.

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

The most important safety signals discussed at the PRAC meeting from 28 November - 1 December 2016 concern the following products:

- **Phenprocoumon** – calciphylaxis
- **Methylphenidate** – priapism
- **Proton pump inhibitors** – gastric polyps
- **Vildagliptin; Vildagliptin, metformin** – pemphigoid

See EU's list of recommendations on safety signals: *PRAC recommendations on signals adopted 28 November - 1 December 2016* as well as the *Danish translations of the product information*.

ADR signals
An ADR signal reflects a new possible causal relationship between an adverse reaction and a medicine or a new angle on a known adverse reaction, e.g. that it is more common than described previously.

ADR signals can come from a multitude of sources, including ADR reports, clinical studies or scientific literature.

The DKMA monitors Danish ADR reports to detect possible new ADR signals. Signals about new possible adverse reactions are forwarded in the EU system to the European Pharmacovigilance Risk Assessment Committee (PRAC), which then assesses the signal.

The PRAC assesses if there is sufficient documentation to establish causality and, for example, if changes to the medicine's product information are warranted.

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:

- **Cometriq (cabozantinib):** Outdated package leaflets in some packs of Cometriq. Sent out 22 December 2016.

The DHPCs are available at the DKMA website – most of them in Danish only: *Direct Healthcare Professional Communication (DHPC) sent to healthcare professionals*.

Danish Pharmacovigilance Update is published by the Danish Medicines Agency
www.dkma.dk
Editor-in-Chief:
Janne Lehmann Knudsen (JALK)
Editor:
Nina Vucina Pedersen (NVP)
ISSN 1904-2086