Danish Pharmacovigilance Update Year 4 #2
21 February 2013

Cardiovascular monitoring when initiating and re-initiating treatment with fingolimod (Gilenya®)

When re-initiating Gilenya® (fingolimod) after a treatment break, there is a risk of affecting the heart and the atrioventricular conduction just as when initiating treatment (see *the Danish Health and Medicines Authority's website* and *Danish Pharmacovigilance Update, May 2012)*. Therefore, the same first dose monitoring as for treatment initiation should be repeated*.

As a doctor you should be aware of the following when re-initiating treatment:
The same first dose monitoring as for treatment initiation should be repeated if treatment is interrupted for

- 1 day or more during the first 2 weeks of the treatment
- more than 7 days during weeks 3 and 4 of the treatment
- more than 2 weeks after the first month of the treatment

If the treatment interruption is of shorter duration than the above, the treatment should be continued with the next dose as planned.

- Patients requiring pharmacological intervention at the time of the first dose should be hospitalised and monitored overnight. In these patients, it is recommended to repeat the first dose monitoring after the second dose.

The summary of product characteristics and the package leaflet have been updated with the recommendations, and a letter of information has been sent to doctors.

On the Danish Health and Medicines Authority's website you can find a *list of direct safety information (DHPC)* for doctors and other healthcare professionals as from 2013.

* First dose monitoring: All patients starting treatment with Gilenya should have their heart activity monitored continuously for at least six hours after receiving the first dose. The monitoring should be extended in special situations, e.g. if the patient develops bradycardia.

Read more in the summary of product characteristics (in Danish only) *here*.

Indication for Gilenya® (fingolimod)
Used for disease-modifying treatment as monotherapy in highly active relapsing-remitting multiple sclerosis in the following adult patients:

– Patients with high disease activity in spite of treatment with a beta-interferon.
– Patients with severe rapidly developing relapsing-remitting multiple sclerosis, defined by 2 or more disabling attacks in one year and with 1 or more gadolinium-enhancing lesions in cranial MRI or a significant increase in the T2 lesion burden as compared to a previous recent MRI.

Adverse Drug Reaction Manager assists the Capital Region of Denmark with adverse reaction reporting

Based on the national *action plan for a strengthened pharmacovigilance* (in Danish only), Bispebjerg Hospital introduced an Adverse Drug Reaction (ADR) Manager function in 2011. The ADR Manager function was handled by doctors in the Department of Clinical Pharmacology, and during the 1-year project period, the ADR Manager handled adverse reaction reporting for five medical departments. The project was intended to increase the number of reports and also to support doctors in the clinical departments who often find it difficult to allocate the time required for reporting. The project period saw a fivefold increase in the number of adverse reactions reported, and the average time spent by doctors on reporting dropped from 30 minutes to 3 minutes. The ADR Manager function proved so effective that resources were allocated at the end of 2012 to extend the initiative to cover the entire Capital Region of Denmark.

The function is currently being implemented

Today, the ADR Manager function is open to all hospital doctors in the region, and the implementation which, among other things, includes an information campaign is aimed at informing doctors in the clinic that this function is available. The implementation work is headed by a consultant doctor from the Department of Clinical Pharmacology supported by a pharmacist who will assist with the implementation process and the recording of adverse reactions.

The ADR Manager is available by telephone, email or fax

In future, as in the project period, hospital doctors may contact the ADR Manager by telephone, email or fax in case of a suspected adverse reaction and provide information about the patient's civil registration number, the medicinal product and the suspected adverse reaction. The ADR Manager will then collect additional information electronically via OPUS, LABKA II, web1000 and EPM and report the adverse reaction to the Danish Health and Medicines Authority.

Liver function monitoring recommended due to the risk of liver diseases from the use of Revlimid® (lenalidomide)

The European Medicines Agency, EMA, has decided that a letter must be sent to doctors and other healthcare professionals to inform them about the risk of liver diseases from the use of Revlimid® (lenalidomide). The decision is based on reports of severe hepatic injuries, including fatal cases, in patients with multiple myeloma treated with lenalidomide in combination with dexamethasone. The severe hepatic injuries reported are acute hepatic failure, toxic hepatitis, cytolytic hepatitis, cholestatic hepatitis and mixed cytolytic/cholestatic hepatitis.

As a doctor you should be aware of the following:

- Lenalidomide is excreted through the kidneys. It is important to adjust the dose of lenalidomide in patients with renal impairment to avoid high plasma levels which may increase the risk of more serious haematological adverse reactions or hepatotoxicity.
- The mechanism of severe drug-induced hepatotoxicity remains unknown, and risk factors may be an existing viral liver disease, elevated hepatic enzymes and possible treatment with antibiotics.
- Liver function monitoring is recommended, especially in case of a history of or an ongoing viral liver infection, or when lenalidomide is combined with medicines associated with hepatic dysfunction.

Indication for Revlimid® (lenalidomide)
Used in the treatment of multiple myeloma, a rare cancer of the bone marrow, in combination with dexamethasone following failure of at least one previous treatment.

Reports of adverse reactions concerning psychological changes in patients treated with levodopa

In December 2012, the Danish Health and Medicines Authority received three reports of patients who became psychotic when treated with Duodopa®. The reports described that the patients had hallucinations. The patients had been treated with the product for up to 5 years. Today, two out of the three patients do not have hallucinations. It has not been possible to obtain information about the current state of the third patient.

The DHMA has received a total of 40 reports concerning psychological changes in patients in association with the use of products containing levodopa.

In addition to those mentioned above, the reports received also comprise adverse reactions such as depression, anxiety and confusion.

As a doctor you should be aware of the following:

- Psychiatric disorders such as hallucinations, confusion, depression etc., are known to occur during treatment with Duodopa®. Therefore, all patients treated with Duodopa® should be monitored carefully for the development of depression with suicidal tendencies and other serious mental disorders.
- Patients with previous or existing psychoses should be treated with caution.

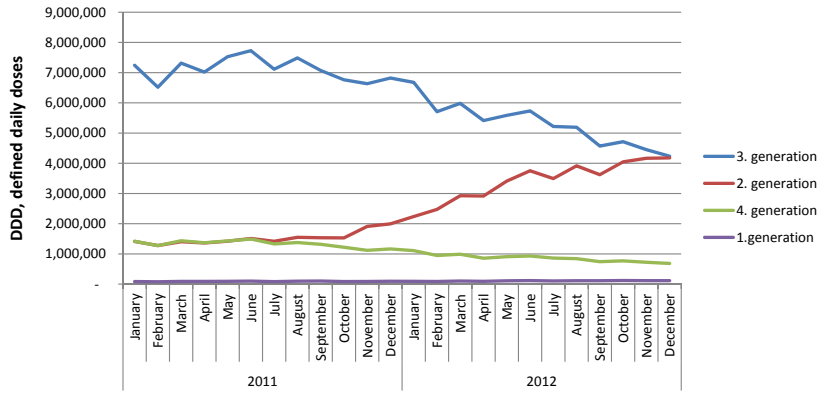
Indication for levodopa
Used in the treatment of advanced levodopa-responsive Parkinson's disease with severe motor fluctuations and hyper-/dyskinesia when other available combinations of Parkinson drugs have not given satisfactory results.

Doctors in Denmark continue to follow recommendations for contraceptive pills

In September 2012, *the Danish Health and Medicines Authority's website* reported that doctors in Denmark followed the recommendations to prescribe the older types of contraceptive pills (2nd generation pills), because these pills are associated with the lowest risk of blood clots.

The French authorities have asked The European Pharmacovigilance Risk Assessment Committee (PRAC), to review the safety of newer 3rd and 4th generation contraceptive pills focusing on the risk of blood clots. In this connection, the Danish Health and Medicines Authority has looked into the most recent figures from the Danish Register of Medicinal Product Statistics on the sale of contraceptive pills in Denmark. The figures are shown in Figure 1.

Figure 1: The sale of contraceptive pills (stated in defined daily doses, DDD) by type in 2011-2012.



Source: The Danish Register of Medicinal Product Statistics (SSI).

Steady rise in the sale of 2nd generation contraceptive pills

The figure shows a continuous significant increase in the sale of 2nd generation contraceptive pills with a corresponding decrease in the sale of the new types of contraceptive pills with the highest risk of blood clots (3rd and 4th generation).

The Danish Health and Medicines Authority will continue to monitor the development in the consumption of contraceptive pills in Denmark and follow the PhVWP review.

As a doctor you should be aware of the following:

The DHMA's recommendations remain unchanged:

- In general, 2nd generation contraceptive pills should be the first choice.
- You should assess benefits and risks for women who have used 3rd and 4th generation contraceptive pills without problems over a longer period of time. In any case, you should ensure that the so-called precautions are still observed.
- Prior to starting contraceptive pills, you should ensure that the woman is examined, that her medical history is established and that she is informed about the risk of blood clots and the associated early symptoms.
- You should follow up on the treatment based on the applicable medical guidelines on a continuous basis, especially in the start-up phase where the risk is highest, and in case the woman changes to another brand.

You can find further information here (in Danish only):

Contraceptive pills – Consumption and the risk of blood clots

Consumption of contraceptive pills and the risk of blood clots (update)

IRF (Institute for Rational Pharmacotherapy): Questions and answers on hormonal contraceptives and thrombosis

The European Pharmacovigilance Risk Assessment Committee (PRAC) is reviewing the safety of acne medicines containing cyproterone and oestrogen (Diane® Mite and others)

The European Pharmacovigilance Risk Assessment Committee (PRAC), has initiated a review of the safety of acne medicines containing cyproterone and oestrogen (Diane® Mite and others). The review is based on a decision by the French authorities to remove these drugs from the market within the next three months as a consequence of examining their own data for the risk of blood clots.

The French announcement will have no immediate consequences for the use of Diane® Mite and similar medicines in Denmark, but the pending PRAC review will be followed closely, and the outcome will also be binding for Denmark.

Read more on *the Danish Health and Medicines Authority's website* See also *the EMA's press release*

Risk of cardiovascular adverse reactions in patients with essential thrombocythaemia (ET) in association with anagrelide hydrochloride (Xagrid®)

The summary of product characteristics for Xagrid® has been updated following a review of all cardiac adverse reactions reported in patients under 50 years of age treated with anagrelide hydrochloride. A statement has been added stating that serious cardiovascular adverse reactions may occur in patients without any suspected heart disease and with normal previous cardiovascular investigations.

The update of the summary of product characteristics for Xagrid® does not alter the current benefit/risk ratio for anagrelide hydrochloride in the context of its therapeutic indication as a second-line treatment for at risk essential thrombocythaemia (ET) patients.

As a doctor you should be aware of the following:

- Serious cardiovascular adverse reactions including cases of cardiomyopathy, cardiomegaly, congestive heart failure and cardiac arrhythmia have been reported.
- Anagrelide hydrochloride should be used with caution in patients of any age with known or suspected heart disease. Moreover, serious cardiovascular adverse reactions have also occurred in patients without suspected heart disease and with normal pre-treatment cardiovascular examinations.
- Anagrelide hydrochloride is an inhibitor of cyclic AMP phosphodiesterase III and because of its positive inotropic effects, a pre-treatment cardiovascular examination (including further investigation such as echocardiography, electrocardiogram) is recommended. Patients should be monitored during treatment for evidence of cardiovascular effects that may require further cardiovascular examination and investigation.

A letter of information has been sent to doctors and other healthcare professionals.

On the Danish Health and Medicines Authority's website you can find a *list of direct safety information (DHPC)* for doctors and other healthcare professionals as from 2013.

Indication for Xagrid® (anagrelide hydrochloride)
Used for the reduction of elevated platelet counts in at risk essential thrombocythaemia (ET) patients when other treatment has proven ineffective or resulted in unacceptable adverse reactions. Anagrelide hydrochloride should only be used when the treatment is managed by doctors with specific knowledge of treatment of essential thrombocythaemia.

An at risk essential thrombocythaemia patient is defined by one or more of the following characteristics:
– > 60 years of age or
– a platelet count of > 1000 x 10^9/l or
– a history of thrombo-haemorrhagic events.

Direct safety information (DHPC*) for doctors and other healthcare professionals will be made available on the Danish Health and Medicines Authority's website

Providing timely information to doctors and other healthcare professionals is of paramount importance whenever new information emerges about the safety of a medicine. According to the applicable rules, the information is sent directly from the pharmaceutical company to the doctors following approval by the DHMA of the contents of the letter. It has proven problematic that the letters are not publicly available. Also, a need for separating these letters from other correspondence from the companies has been identified.

Therefore, the DHMA will make future direct safety announcements – also known as Direct Healthcare Professional Communication (DHPC) – available on the website.

The DHPCs serve the purpose of supporting safe and effective use of medicines. As of 1 May 2013, the envelopes used for DHPCs will bear the following text printed in black font on a yellow background: "Ny sikkerhedsinformation om brugen af medicin – i samarbejde med Sundhedsstyrelsen" (New safety information on the use of medicine – prepared in collaboration with the Danish Health and Medicines Authority, in Danish only). This step is to ensure that the letters are readily identifiable.

On the Danish Health and Medicines Authority's website you can find more *information about DHPC* and an *overview of announcements issued as from 2013*.

**Direct Healthcare Professional Communication.*

Ny sikkerhedsinformation om brugen af medicin
- i samarbejde med Sundhedsstyrelsen

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