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DANISH PHARMACOVIGILANCE UPDATE

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Short news

High-dose ibuprofen/dexibuprofen may cause small increased cardiovascular risk

The European Pharmacovigilance Risk Assessment Committee (PRAC) has completed a review of systemic ibuprofen and cardiovascular risk, concluding that high-dose ibuprofen is associated with a small increased risk of cardiovascular effects such as AMI and apoplexy. For doses of or above 2400 mg daily, an increase in the risk similar to the risks seen with COX-2 inhibitors and diclofenac was observed.

No increase in cardiovascular risk is seen with ibuprofen at doses of up to 1200 mg daily, which is the highest recommended dose for over-the-counter preparations.

Interaction between ibuprofen and acetylsalicylic acid

The PRAC also reviewed a possible interaction between ibuprofen and the cardioprotective effect of low-dose acetylsalicylic acid (ASA). It concluded that in vitro studies suggest that the effect of ASA is reduced when taken concurrently with ibuprofen. However, it is uncertain whether it reduces the benefits of ASA in preventing cardiovascular effects. Occasional use of ibuprofen should not affect the benefits of ASA.

Concurrent treatment with an NSAID product, including ibuprofen/dexibuprofen and ASA is generally not recommended due to the potentially increased risk of bleeding.

Dexibuprofen

The risk applies also to products that contain dexibuprofen for systemic use. High-dose dexibuprofen is defined as doses ≥ 1200 mg daily.

Advice for prescribers

- Treatment should always take place at the lowest effective dose for the shortest period of time.
- The generally recommended dose for ibuprofen in adults is maximum 1800 mg daily distributed over 3-4 doses. The dose can be increased up to 2400 mg daily, but for short term-use only (4-6 weeks).
- Patients with serious heart disease or circulatory conditions or a history of AMI or apoplexy should only be treated with ibuprofen upon careful consideration, and high doses (2400 mg daily) should be avoided.
- Long-term treatment with ibuprofen should only be initiated upon careful consideration in patients with risk factors for cardiovascular diseases, especially if high, daily doses (2400 mg daily) are required.
- High-dose dexibuprofen is defined as doses ≥ 1200 mg daily.

The summaries of product characteristics of ibuprofen and dexibuprofen will be updated to implement and harmonise the above recommendations across the European countries.

EU recommends further measures to minimise risk of osteonecrosis of the jaw with zoledronic acid and denosumab

The EU Pharmacovigilance Risk Assessment Committee, PRAC, has concluded a review of periodic safety update reports (PSURs) for denosumab (Prolia, Xgeva) and the bisphosphonate zoledronic acid (Zometa, Zoledronic acid Medac, and other nationally authorised products). Bisphosphonates are used to prevent bone loss and reduce the risk of bone fractures induced by various diseases, including osteoporosis and cancer.

Further risk-minimising measures – patient reminder cards and updating of the information in the summaries of product characteristics

During the PRAC review, it was decided to update and clarify the information about the known adverse reaction osteonecrosis of the jaw (ONJ) in the product information of the concerned products and to introduce a patient reminder card. These measures are to ensure that doctors as well as patients are sufficiently informed about the risk of ONJ associated with intravenous bisphosphonates and denosumab. The updates are consistent with the measures introduced for the bisphosphonate zoledronic acid (Aclasta) in March 2015. Similar measures will be effected for other intravenous bisphosphonates for the treatment of osteoporosis and the prevention of cancer-induced bone complications.

Osteonecrosis of the jaw (ONJ) – a known adverse reaction to denosumab and zoledronic acid

Osteonecrosis of the jaw (ONJ) is a known adverse reaction to these medicines. The condition occurs when the jaw bone is exposed and becomes necrotic. The aetiology of ONJ is not clear, but it may be associated with impaired remodelling of bone. The known risk factors for ONJ include:

- Prior treatment with bisphosphonates
- The potency of the bisphosphonate used (higher risk for highly potent products)
- Route of administration (higher risk in parenteral administration)
- Cancer and co-morbid disorders (e.g. anaemia, coagulopathy, infection)
- Other concomitant treatment (e.g. chemotherapy, antiangiogenic treatment, corticosteroids or radiation therapy to the head and neck)
- Smoking
- Present or pre-existing dental disease, poor oral hygiene, invasive dental treatment (e.g. dental extractions) as well as poorly maintained dental implants.

Read more in the PRAC's press release on further measures to prevent ONJ: *Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 7-10 April 2015.*

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 signal discussed on the PRAC meeting in March 2015 concerns the following product:

- Aripiprazole – aggression and related events

See EU's list of recommendations on safety signals: *PRAC recommendations on signals.*

Warfarin Orion must not replace Marevan and Waran

The DHMA has abolished generic substitution with the blood-thinning medicine Warfarin Orion. Consequently, Danish pharmacies must no longer dispense Warfarin Orion in replacement of Marevan or Waran.

Several ADR reports about elevated INR

Lately, the DHMA has received several ADR reports describing patients who after being switched from their blood-thinning medicine Marevan to Warfarin Orion experienced unintended elevated INR levels and thus an increased risk of bleeding.

Therefore, the DHMA has decided with immediate effect to remove Warfarin Orion from the list of medicines that can be mutually substituted for Marevan and Waran.

At present, it is uncertain whether the increases in INR levels were caused by the blood-thinning product Warfarin Orion, or whether there are other explanations, and the DHMA's decision is thus a precautionary measure. There have been no observations suggesting problems with the quality of Warfarin Orion.

Advice for prescribers

- Some patients treated with Warfarin Orion should have their blood-thinning treatment evaluated once more. Check as necessary the INR levels in patients who have been treated with Marevan or Waran and have switched to Warfarin Orion.
- Patients who are already taking Warfarin Orion at sufficient effect and with stable INR levels can continue treatment with Warfarin Orion.

A Direct Healthcare Professional Communication (DHPC) has been sent out to relevant doctors. Read the DHPC here (in Danish only): *Important information to doctors and other healthcare staff about all patients in anticoagulant treatment with warfarin – extra check-up may be needed.*

Clozapine and reports of deaths

As part of our pharmacovigilance activities, we have focus on antipsychotic drugs among other products. Over the past five years, we have received eight ADR reports describing fatal outcomes in connection with the antipsychotic medicine clozapine. The most recent ADR report is from February 2015. In this issue of Danish Pharmacovigilance Update, we provide a brief overview of the ADR reports of deaths in clozapine treatment.

Since 1977, we have received a total of 33 ADR reports that describe deaths suspected as adverse reactions to clozapine[1]. It is important to follow the current summary of product characteristics for clozapine-containing medicines and the current guideline in the area *Behandling med antipsykotiske lægemidler til personer over 18 år med psykotiske lidelser nr. 9276 af 6. maj 2014 (in Danish only)* (Guideline no. 9276 of 6 May 2014 on treatment with antipsychotics in people over 18 years suffering from psychotic disorders), which provides for close monitoring due to the risk of life-threatening adverse reactions such as agranulocytosis and myocarditis.

Review of the 33 reported deaths related to clozapine treatment

Age and gender distribution of the 33 patients who died while being treated with clozapine:

Gender

- Women (17)
- Men (15)
- Gender unknown (1)

Age

- Age unknown (8)
- Age 22-40 (14)
- Age 41-60 (6)
- Age over 61 (5)

Reported cause of death in the 33 patients

Cause of death	Number
Drug intoxication (sudden death)	7
Sudden death (cause of death not determined)	6
Myocarditis	4
Pulmonary embolism	4
Agranulocytosis	2
Paralytic ileus	1
Malignant neuroleptic syndrome	1
Megacolon	1

[1] In three of the 33 reports, clozapine is not indicated as the primary suspected medicine having caused the death.

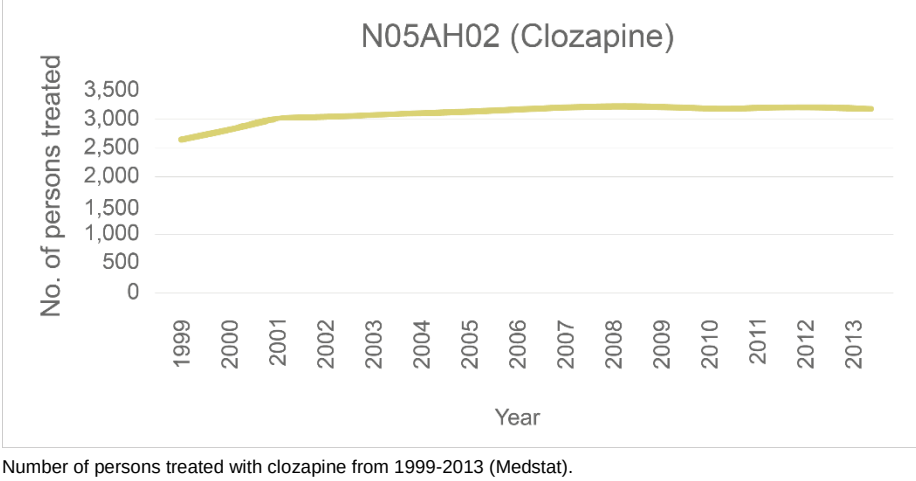
Pulmonary fibrosis	1
Multiple organ failure, pulmonary infection, sepsis	1
Hepatomegaly	1
Chronic obstructive pulmonary disease	1
Respiratory failure and hyponatraemia	1
Ileus	1
Sepsis and pneumonia	1

Indications reported for clozapine use in the 33 patients:

- Schizophrenia (16)
- Psychotic anxiety (1)
- Bipolar disorder (1)
- Psychotic disorder (1)
- Not provided (14)

Co-medication/polypharmacy/treatment with several antipsychotics
22 of the 33 patients who died were treated with several different medicinal products. 19 of the 22 patients were treated concomitantly with two or more antipsychotics, and 15 of the 22 patients were treated concomitantly with a benzodiazepine. Seven of the 33 patients were treated concomitantly with another medicine, whereas the last four ADR reports did not describe use of other medicines.

The number of clozapine users is stable
The number of people taking clozapine medication has since 1999 remained stable at around 3,000 (2,723 persons in 1999 and 3,252 in 2013).



Number of persons treated with clozapine from 1999-2013 (Medstat).

Treatment guideline

It is well-known that treatment with antipsychotics can cause numerous adverse reactions, including arrhythmia. Mortality increases when antipsychotics are taken together with sleeping pills and tranquillisers, and polypharmacy generally increases the risk of adverse reactions.

Caution is advised when combining clozapine with benzodiazepines at the beginning of treatment and during escalation of the dose since clozapine is highly sedating and causes the blood pressure to drop, which can also happen with benzodiazepines.

Danish and international data indicate that the risk of death is higher when several antipsychotics are taken concomitantly. The DHMA's old Guideline no. 9763 of 28 June 2007 on treatment with antipsychotics in people over 18 years highlights the importance to carefully monitor treatment efficiency and development of possible adverse reactions and avoid the concomitant use of several antipsychotics. Likewise, the DHMA has advised against concomitant treatment with sleeping pills and tranquillisers.

In compliance with the DHMA's present guideline "Behandling med antipsykotiske lægemidler til personer over 18 år med psykotiske lidelser *no. 9276 of 6 May 2014 (in Danish only)"*, doctors should be aware of the following:

- Avoid concomitant treatment with antipsychotics and benzodiazepines after the acute phase (1-2 weeks) as treatment increases the risk of serious adverse reactions.
- There is no evidence that concomitant treatment with several antipsychotics increases efficacy. On the contrary, polypharmacy causes more adverse reactions.

According to the summary of product characteristics of clozapine (Leponex® etc.) doctors should pay special attention to the following:

- Close monitoring of patients in clozapine treatment is required due to the risk of developing life-threatening adverse reactions.
- Prescribers must comply fully with the required safety measures
- At each consultation, a patient receiving clozapine must be reminded to contact the treating physician immediately if any kind of infection begins to develop. Particular attention must be paid to flu-like complaints such as fever or sore throat and to other evidence of infection, which may be indicative of neutropenia or, in the worst case, agranulocytosis.

Clozapine should be prescribed under strict medical supervision in accordance with official recommendations.

See *the summary of product characteristics for clozapine (Leponex® m.fl.) (in Danish only).*

Indication for clozapine (Leponex®)

Treatment-resistant schizophrenia
Leponex is indicated in treatment-resistant schizophrenic patients and in schizophrenia patients who have severe, untreatable neurological adverse reactions to other antipsychotic agents, including atypical antipsychotics. Treatment resistance is defined as a lack of satisfactory clinical improvement despite the use of adequate doses of at least two different antipsychotic agents, including an atypical antipsychotic agent, prescribed for adequate duration.

Psychosis during the course of Parkinson's disease
Leponex is also indicated in psychotic disorders occurring during the course of Parkinson's disease, in cases where standard treatment has failed.

Aubagio® under strict monitoring

The medicine Aubagio® (teriflunomide) was marketed in Denmark on 14 November 2013 for the treatment of adult patients with relapsing remitting multiple sclerosis (MS). Because the medicine is still new and became a first-choice medicine[2] in February 2014, the DHMA has chosen to monitor the safety of Aubagio® more strictly.

The DHMA has investigated consumption and prepared an overall analysis of the ADR reports reported up until 31 December 2014.

There are 71 ADR reports, of which nine were classified as serious[3].

Description of the reported adverse reactions

Review of the symptoms described in the serious ADR report
Below, we go through the most important symptoms described in the serious ADR reports.

Symptoms from the nervous system
A patient had a grand mal seizure while being treated with Aubagio®. The patient had not had seizures before, but one episode had been observed where the patient had been distant and difficult to contact. There is no information about predisposition to epilepsy in

[2] Treatment guideline including drug recommendation for disease-modifying treatment of multiple sclerosis from the Danish Council for the Use of Expensive Hospital Medicines version 3, November 2013.
[3] A report is serious when one or more of the adverse reactions are serious. A serious adverse reaction caused by a medicine for human use is a reaction that results in death, is life-threatening, requires hospitalisation or prolongation of hospitalisation, or which results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

the family. Grand mal seizure is not a known adverse reaction to the medicine, however, degenerative disease may, in itself, be a predisposition to epilepsy.

Another report describes a patient who had a seizure, and the report describes that it cannot be excluded that it is a suspected adverse reaction to Aubagio®.

A third report was about a patient who developed symptoms from a number of different organ systems, including the nervous system in the form of affected consciousness. The patient participated in a run and in this connection, he was severely dehydrated implying e.g. that his consciousness was affected, he had convulsions and developed aspiration pneumonia – mainly suspected adverse reactions that have not been described previously.

Symptoms from the eye
The DHMA has received several ADR reports about patients who developed optic neuritis, iritis and iridocyclitis as suspected adverse reactions to Aubagio®. These are not known adverse reactions to the medicine, but is has been described that MS can predispose to optic neuritis and iridocyclitis.

Infections
Some reports described patients who got infections as suspected adverse reactions to the medicine. One patient developed high fever and was hospitalised for two days. The medicine was discontinued, and he was discharged with no fever. Another patient developed persistent sinusitis. For this patient, the medicine was also discontinued.

Adverse reactions in the form of infections like influenza, urinary tract infection, bronchitis, sinusitis, etc. are well-known and described in the medicine's summary of product characteristics (SPC). Furthermore, the SPC describes that in placebo-controlled studies, no increase in serious infections was observed in patients treated with teriflunomide.

Due to the immunomodulatory effect of teriflunomide, it should be considered to suspend teriflunomide if a patient develops a serious infection, and the benefits and risks should be reassessed prior to re-initiation of therapy.

Patients receiving teriflunomide should be instructed to report symptoms of infections to a physician, and if they have active acute or chronic infections treatment should not be started.

Symptoms from the liver
In several ADR reports, it is described that the patient's liver enzymes were elevated.

It is known that the medicine may affect the liver. Elevated liver enzymes typically develop within the first six months of treatment.

Liver enzymes should be assessed before initiation of teriflunomide therapy – every two weeks during the first 6 months of treatment, and every 8 weeks thereafter or as indicated by clinical signs and symptoms such as unexplained nausea, vomiting, abdominal pain, fatigue, anorexia, or jaundice and/or dark urine. For ALT elevations between 2- and 3-fold the upper limit of normal, monitoring must be performed weekly.

Teriflunomide therapy should be discontinued if liver injury is suspected, and discontination of teriflunomide therapy should be considered if liver enzyme elevations 3-fold the upper limit of normal are confirmed.

Teriflunomide is contraindicated in patients with severe hepatic impairment and should be used with caution in patients who consume substantial quantities of alcohol.

Review of the symptoms described in the non-serious ADR report

Below, we go through the three most frequent symptoms described in the non-serious ADR reports.

Alopecia
The most frequently occurring symptom described in these reports are alopecia (19). Most of the reports simply describe that the patient suffered hair loss. In a few of the reports, the degree of hair loss is described as e.g. extensive or mild.

In the SPC for Aubagio®, it is described that in clinical trials alopecia was reported as occurring more frequently in patients treated with teriflunomide compared to patients who received no treatment. In these trials, alopecia was reported as hair thinning, decreased hair density, hair loss, sometimes associated with hair texture change.

In clinical trials, alopecia occurred most often during the first 6 months and stopped in 87 % of patients who continued treatment. Discontinuation because of alopecia occurred for only a very small percentage of patients in treatment.

Diarrhoea
Diarrhoea is the second-most frequent symptom reported as suspected adverse reaction in the non-serious ADR reports and was described in 12 reports.

Diarrhoea occurring during treatment is a known and very common adverse reaction to Aubagio®. Most often it is mild to moderate and transient.

Paraesthesia
Paraesthesia is the third-most frequent symptom and found in five ADR reports. It is a known and common adverse reaction to Aubagio®.

Consumption of Aubagio®

Since treatment with Aubagio® is reserved for hospitals, consumption is stated in defined daily doses (DDDs). One DDD corresponds to the dose consumed by an adult per day when the medicine is used for its primary authorised indication. The DDD measure enables the comparison of consumption between different medicines.

The table shows the consumption of teriflunomide in the hospital sector in 2013 and 2014[4]

Period	DDD consumption
Q4 2013[5]	5,600
Q1 2014	27,776
Q2 2014	42,588
Q3 2014	48,356
Q4 2014	58,100

Consumption increased throughout 2014, as expectable, because the product is new on the market, and because it became a first-choice medicine in the beginning of 2014.

Conclusion

The DHMA has reviewed the ADR reports that concerned suspected adverse reactions to teriflunomide Aubagio® that were reported since marketing of the product and up until 31 December 2014.

Some of the symptoms reported as suspected adverse reactions in the serious ADR reports are known. Other symptoms have not previously been described, but MS is known to predispose to these symptoms.

In the non-serious ADR reports, the three most frequently reported symptoms were alopecia, diarrhoea and paraesthesia. These symptoms are known adverse reactions of the medicine.

In this review, none of the new data shift the medicine's benefit-risk balance.

See the summary of product characteristics for *Aubagio®*.

[4] Consumption figures have been supplied by Data Delivery and Medicinal Product Statistics at Statens Serum Institut, National Institute for Health Data and Disease Control (SSI).
[5] Marketed in Denmark in November 2013

Influenza vaccines and reports of suspected adverse reactions

For the 2014/2015 influenza season, the DHMA is publishing reports of suspected adverse reactions to the influenza vaccines together with a review of the serious ADR reports.

This season employed two vaccines (Fluarix and Vaxigrip) from two different manufacturers. Both vaccines contain components of inactivated influenza vaccine and are considered equal for protection against influenza.

In *Danish Pharmacovigilance Update, December 2014*, we published a review of ADR reports received in the period of 1 August to 30 November 2014. In this present review, we are publishing the ADR reports that we received in the period of 1 December 2014 to 31 March 2015.

ADR reports from 1 December 2014 to 31 March 2015

The DHMA received a total of 16 ADR reports. Four of them were classified as serious[6].

Review and assessment of the serious reports

When we assess the serious ADR reports, we investigate whether it is likely that there is a causal connection to the vaccine.

The result of our causality assessment is split into three categories:

- Possible
- Insufficient documentation[7]
- Less likely
- Unclassifiable (not possible to assess because of inadequate information)

[6] A report is serious when one or more of the adverse reactions are serious. A serious adverse reaction caused by a medicine for human use is a reaction that results in death, is life-threatening, requires hospitalisation or prolongation of hospitalisation, or which results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

[7] This category contains the reports for which it was not possible to determine whether or not there is a possible connection between the reaction and the vaccine because of insufficient documentation.
Reports in this category concern symptoms occurring in temporal association with vaccination, where the vaccinee has no other immediate factors that may explain the symptoms (other disease, other medicine, etc.), but where there is no evidence in the literature or other available data that can confirm a causal relationship.

Vaccine	ADR description	Assessment and causality
Vaxigrip	On the same day of vaccination, a citizen experienced pain in the upper left arm, corresponding to the proximal part of m. triceps. Two months after, she still had the same pain and was sore corresponding to where the triceps muscle attaches to the scapular. The citizen was later diagnosed with left-side tendinitis caput longum sin. The citizen was also treated with Imurel® for the indication of rheumatoid arthritis (RA).	It is known from the literature that incorrect administration could cause tendinitis. The report does not mention whether the vaccine was administered incorrectly. As mentioned, the patient had RA, but since there is a temporal relationship between vaccination and the symptoms, causality is considered **possible**.
Vaxigrip	Four days after vaccination, an elderly citizen suddenly experienced a decrease in hearing. The citizen was subsequently examined by an ear specialist who assessed the decrease in hearing to be age-related.	There is a temporal relationship with the influenza vaccination, but a decrease in hearing is not a known adverse reaction to the vaccine, and the patient's decrease in hearing has been described as age-related by a specialist. Causality is considered **less likely.**
Fluanrix®	14 months after vaccination, a middle-aged citizen experienced episodes of an overwhelming need to sleep. The citizens was referred to a specialist and was diagnosed with hypersomnia, but without signs of narcolepsy.	Tiredness is a known adverse reaction to the vaccination. Tiredness occurs in close temporal association to the vaccination and is transient. It is not described in the literature that hypersomnia or narcolepsy may occur as a suspected adverse reaction to Fluanrix®. The symptoms did not occur until 14 months after the patient was vaccinated. Against this background causality is considered **less likely**.

Seasonal influenza (2009) and Pandemrix®	Three to four months after vaccination with Pandemrix® and seasonal influenza vaccine, a patient was diagnosed with multiple sclerosis. The patient was vaccinated in 2009.	Scientific articles have been published in which no connection has been established between Pandemrix and other influenza vaccines and multiple sclerosis. Causality is therefore considered **less likely.**

Table 1: Description of the adverse reactions in the serious ADR reports and subsequent causality assessment.

Review of the non-serious ADR reports

The most frequent adverse reactions described in the non-serious ADR reports are fever and muscle pain. These are known adverse reactions described in the concerned summaries of product characteristics.

Conclusion

In the period 1 December 2014 to 31 March 2015, the DHMA received 16 reports of suspected adverse reactions to the influenza vaccines. Four were classified as serious. In the corresponding four months last year, the DHMA received 11 reports of suspected adverse reactions to the influenza vaccines.

Among the serious ADR reports were symptoms such as a decrease in hearing and hypersomnia. The serious ADR reports have undergone our causality assessment, and in one report, causality was considered possible.

The non-serious reports mainly describe known adverse reactions to the vaccines.

No optimal protection from this season's influenza vaccines

This season's most common influenza virus circulating among the Danes and making them ill has been influenza A H3N2. It has changed its genetic material to such a degree that this season's influenza vaccines have not provided optimal protection[8]. The WHO has therefore decided to change which influenza A H3N2 virus it recommends for inclusion in next season's influenza vaccines[9].

[8] News, SSI of 7 April 2015 (www.ssi.dk)

[9] SSI weekly influenza news (Influenzanyt, uge 10, 2015, www.ssi.dk)

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:

- Hydroxyzine – new restrictions on the use of hydroxyzine-containing medicines to further minimize the known risk of QT prolongation.
- Insuman – temporary shortage supply of cartridges and pre-filled pens
- Imnovid (pomalidomide) – new important advice to minimise the risk of serious hepatotoxicity, interstitial lung disease and cardiac failure
- Xofigo – change in the radium 223 standard
- Zovirax – global supply problems for eye ointment 3% – change in the dispensing status: only to be dispensed to hospitals and prescribed by eye specialists
- The DHMA has abolished generic substitution between the blood-thinning medicine Warfarin Orion and Marevan/Waran.

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

Danish Health and Medicines Authority's annual pharmacovigilance report 2014

Our annual report 2014 has just been published on the DHMA website. Here you can read about the development in the number of ADR reports, gain an insight into our focus areas and the European collaboration in the pharmacovigilance area as well as see a selection of the ADR signals we processed in 2014, and much more.

Read the *Danish Health and Medicines Authority's annual pharmacovigilance report 2014*.

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