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DANISH PHARMACOVIGILANCE UPDATE

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News from the Danish Medicines Agency

Short news

SGLT2 (sodium-glucose co-transporter 2) inhibitors and development of life-threatening atypical ketoacidosis in patients with type 2 diabetes

The European Medicines Agency (EMA) has completed its review and assessment of SGLT2 inhibitors, advising healthcare professionals to pay close attention to the risk of diabetic ketoacidosis in patients treated with any medicine of this class.

Diabetic ketoacidosis – a serious and life-threatening condition

Diabetic ketoacidosis is a serious and often life-threatening condition usually developing in patients with type 1 diabetes with high blood sugar levels (>13.9 mmol/l or 250 mg/dl).

Observations of diabetic ketoacidosis have now also been made in patients with type 2 diabetes. The patients observed were all taking SGLT2 inhibitors and had blood sugar levels that were not particularly high.

Because blood sugar levels are not high at the time when patients with type 2 diabetes treated with SGLT2 inhibitors develop diabetic ketoacidosis, there is a risk that diagnosis and thus treatment, is delayed.

Three SGLT2 inhibitors are presently available on the EU market (canagliflozin, dapagliflozin and empagliflozin) as single ingredient products or in combination products with metformin. The product names are: Ebymect, Edistride, Forxiga, Invokana, Jardiance, Synjardy, Vokanamet and Xigduo.

EMA's recommendations to health professionals:

- Patients taking SGLT2 inhibitors should be made aware of the symptoms of diabetic ketoacidosis. Symptoms include rapid weight loss, nausea and vomiting, stomach pain, excessive thirst, fast and deep breathing, confusion, unusual sleepiness or tiredness, a sweet smell to the breath, a sweet or metallic taste in the mouth, or a different odour to urine or sweat.
- Patients should contact their doctor if they have any of the above symptoms.
- If diabetic ketoacidosis is suspected, treatment with SGLT2 inhibitors should be stopped immediately.
- Healthcare professionals should exercise caution in patients with risk factors for ketoacidosis such as: a) low reserve of insulin-secreting cells, b) conditions that lead to dehydration or restrict food intake, c) a sudden reduction in insulin or d) an increased requirement for insulin due to illness, surgery or alcohol abuse.

- Treatment with SGLT2 inhibitors should also be suspended temporarily in patients who are in hospital for major surgical procedures or because of serious, life-threatening illness.

Read the press release from the EMA: *SGLT2 inhibitors: PRAC makes recommendations to minimise risk of diabetic ketoacidosis.*

Indication
Sodium-glucose co-transporter 2 (SGLT2) inhibitors are used in combination with diet and exercise in the treatment of patients with type 2 diabetes, either alone or in combination with other antidiabetic medicines.

New recommendations to minimise the risk of PML in connection with treatment with natalizumab (Tysabri)

The EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has completed its review of the risk of the rare brain disease known as progressive multifocal leukoencephalopathy (PML) related to the use of the multiple sclerosis medicine natalizumab based on which it has resolved to update the recommendations for use.

New studies suggest that early detection and treatment of PML when the disease is till asymptomatic are critically important to limit the degree of brain damage and resulting disability caused by the disease. Asymptomatic cases of PML can be detected on an MRI scan.

The risk factors for PML are:

- Presence of antibodies against JC virus
- Treatment with natalizumab for longer than 2 years
- Use of immunosuppressant medicines before starting natalizumab.

Patients who have all mentioned risk factors are at higher risk of PML.

In respect of patients who have not been treated with immunosuppressants prior to starting natalizumab, there is a connection between the level of JC virus present (index) and the risk of PML. Thus, the risk of PML is small, and lower than previously estimated, at antibody index values of 0.9 or less, whereas the risk increases substantially in patients with index values above 1.5, especially in patients treated with natalizumab for longer than 2 years. These patients are therefore also considered at higher risk of PML.

Advice for prescribers

- If PML is suspected, treatment with natalizumab should be stopped until PML has been ruled out.
- The PRAC recommends that more frequent MRI scans (e.g. every 3 to 6 months) be considered for patients at higher risk of PML.
- In patients at higher risk of developing PML, treatment with natalizumab should only be continued if benefits outweigh the risks.
- For patients who have a low antibody index and have not used immunosuppressant medicines before, it is recommended to repeat the antibody test every 6 months once the patients have taken natalizumab for longer than 2 years.
- In patients who tested negative for JC virus antibodies, the antibody test should be repeated every 6 months.

Read the recommendations from the EMA: *Updated recommendations to minimise the risk of the rare brain infection PML with Tysabri.*

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 at the PRAC meeting in January 2016 concerns the following medicinal product:

- **Oxybutynin (Kentera)** – psychiatric disorders

See EU's list of recommendations on safety signals: *PRAC recommendations on signals January 2016* as well as the *Danish translations for the product information*.

Special focus on reported adverse reactions to biological medicines and biosimilars

In the autumn of 2015, an action plan was implemented about *better monitoring of biological medicines, biosimilars and vaccines* (in Danish only).

The action plan sets up a special focus area for adverse reactions to biological medicines and biosimilars with particular focus on suspected adverse reactions arising from switches between biological medicines and biosimilars.

A biological medicinal product differs from other types of medicinal products by being manufactured from a biological material (from human beings, animals or plants) or by means of gene technology. A biosimilar medicinal product is a new version of an existing biological medicinal product (the reference product) which must have been authorised (in the EU) for at least 10 years.

The implementation of the action plan is managed by the Danish Medicines Agency (DKMA) in collaboration with a working group composed of representatives from patient organisations, pharmaceutical industry associations, regions, etc. The action plan runs until end-2016.

Increased monitoring of biological medicines and biosimilars

On 1 January 2016, a new executive order on reporting of adverse reactions of medicinal products, etc. was implemented (executive order no. 1823 of 15 December 2015). It repeals the previous executive order no. 381 of 9 April 2014 on reporting of adverse reactions of medicinal products, etc. A new provision has been written into the executive order, providing for ADR reports from doctors, dentists and midwives to include information, whenever possible, about the medicine's name and batch number when ADR reports concern biological medicines appearing on a specific list prepared by the DKMA.

The rule applies to biological medicines whose substance is also contained in a biosimilar version – in which case both the biological medicine and the biosimilar will appear on the list. Biological medicinal products authorised for cancer indications only are not on the list – see the list in table 1.

The list is updated regularly by the DKMA and is available at *www.dkma.dk*.

Trade name	Active substance	Date of marketing
Eprex®	Erythropoietin	1 January 1991
Retacrit	Erythropoietin	11 January 2010
Bemfola	Follitropin alfa	9 June 2014
Gonal-F®	Follitropin alfa	12 April 2004
Genotropin®	Somatropin	26 March 1990
Omnitrope®	Somatropin	5 November 2007
Neupogen®	Filgrastim	22 April 1991

Nivestim	Filgrastim	5 September 2011
Zarzio	Filgrastim	11 July 2011
Remicade	Infliximab	22 September 1999
Inflectra	Infliximab	16 February 2015
Remsima	Infliximab	2 March 2015

Table 1: Brand name, active substance and marketing date of authorised biosimilar products and reference medicinal products

Consumption of infliximab-containing medicines

From the list of biological medicines in table 1, infliximab-containing medicines generated the most attention in 2015 when the biosimilar Remsima was marketed in Denmark. We have therefore chosen to look closer at the consumption and adverse reactions of infliximab.

Data from the Register of Medicinal Product Statistics, delivered by the Danish Health Data Authority, shows that the DDD[1] consumption increased in 2015 and that Remsima is clearly the most used medicinal product from Q3.

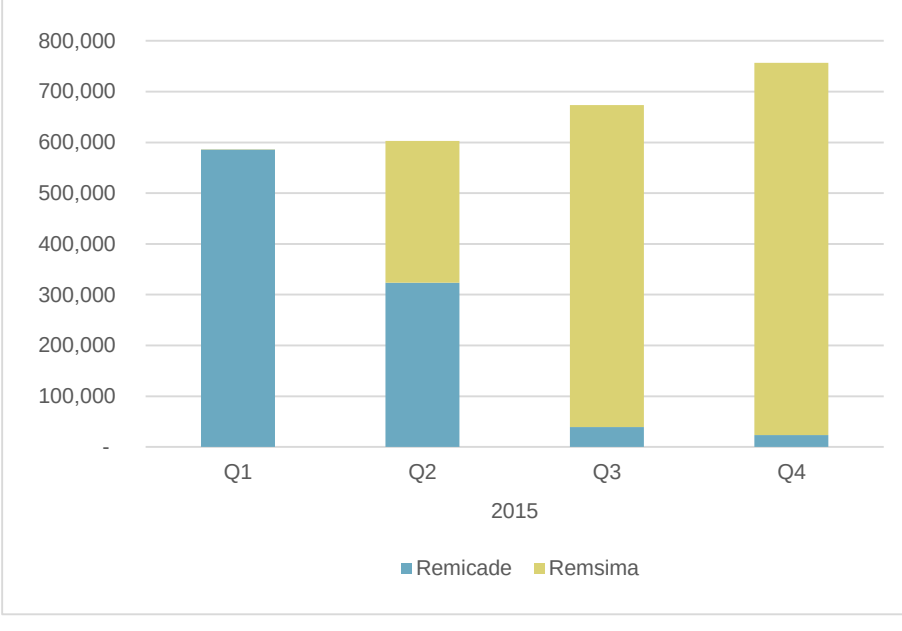

Figure 1: DDD consumption of infliximab-containing medicines broken down by Remicade and Remsima from Q1 to Q4 of 2015.

[1] DDD = Defined Daily Doses. One DDD corresponds to the dose consumed by an adult per day when the medicine is used for its initially authorised indication. It is not possible to provide figures on how much of the volume sold has been used. Data on hospital sales are not personally identifiable, but are reported to the Register of Medicinal Product Statistics by level of department.

Remsima is a biosimilar version of the biological medicinal product Remicade. Remsima was marketed in Denmark in March 2015. It is thus evident from the consumption data that the Danish regions have followed the recommendation from the Council for Use of Expensive Hospital Medicine (RADS) to switch from Remicade to Remsima. The lower price of infliximab (Remsima) has made it a first-line product in RADS' guidelines[2] for biological treatment in the fields of rheumatology and gastroenterology. The guidelines are only available in Danish.

Adverse reactions reported for biological medicines and biosimilars in 2015

In 2015, we received a total of 132 reports of suspected adverse reactions to the medicines in table 1.

The ADR reports are distributed between the medicinal products as follows:

Trade name	Active substance	Number of reports
Omnitrope®	Somatropin	2
Neupogen®	Filgrastim	2
Gonal-F®	Follitropin alfa	3
Not provided	Infliximab	6
Remicade	Infliximab	55
Remsima	Infliximab	64
Total		**132**

Table 2. Reports broken down by brand names.

The reports in 2015 of suspected adverse reactions to infliximab are shown in figure 2.

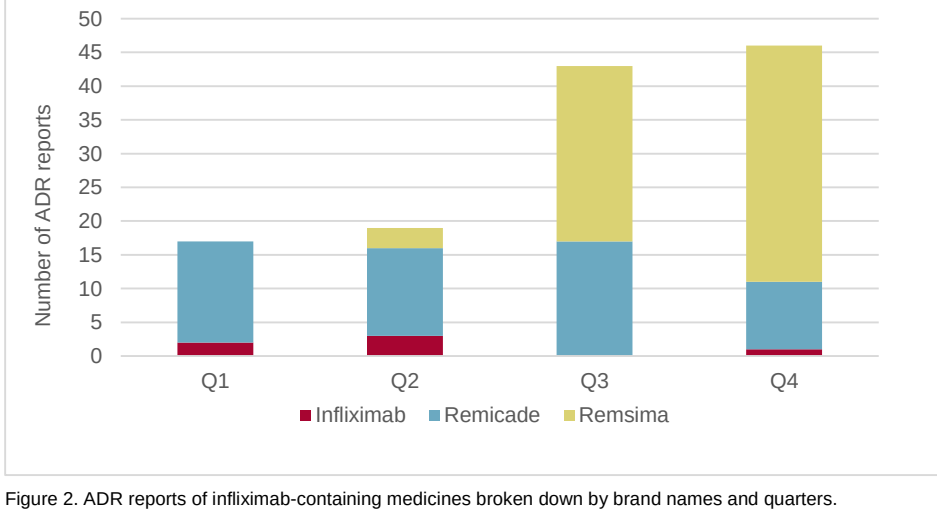

Figure 2. ADR reports of infliximab-containing medicines broken down by brand names and quarters.

[2] *http://www.regioner.dk/medicinsite/rads/behandlingsvejledninger*

The number of ADR reports increased over the year led by Remsima in particular. Taking consumption into account, it is evident that the rise in ADR reports is related to an increase in consumption.

The rise in Remsima ADR reports is also likely to have occurred because it is a new medicinal product, which means there is more focus on its adverse reactions and efficacy.

Reports about Omnitrope®, Neupogen and Gonal F®

- We received two reports related to Omnitrope®. The first describes a child who developed a number of birth marks, the other a child who experienced pain and a tingling sensation at the injection site.
- Two other ADR reports concerned well-known adverse reactions such as fever and allergic reaction to Neupogen.
- We received three ADR reports about Gonal F®. Two of them describe known adverse reactions such as headache and oedema. The third ADR report involved an adult who died suddenly of myocarditis. The patient was undergoing fertility treatment with a number of different medicines. There is no evidence in the literature of a link between myocarditis and Gonal F®.

ADR reports about infliximab with no brand name given

We received six ADR reports about infliximab that did not provide the brand name of the medicinal product given. All these ADR reports are so-called literature cases that have been submitted by the companies marketing the medicines containing infliximab. The companies, which are obliged to monitor the literature, have identified articles which describe suspected adverse reactions occurring in treatment with infliximab.

The literature cases included a fatal outcome caused by encephalitis after reactivation of varicella zoster virus (VZV). Infection – including reactivation of VZV – is a known adverse reaction of TNF alpha inhibitors. In this group, cases of malignancies were also observed as suspected adverse reactions. The risk of malignancies in patients treated with a TNF-blocking agent cannot be excluded[3].

Remicade ADR reports

We received 55 ADR reports about Remicade, and 19 (35%) were classified as serious[4].

Among the serious ADR reports were descriptions of various infections and development of malignancies. These are adverse reactions described in the SPCs.

[3] Summary of product characteristics for infliximab-containing products: *http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124&source=homeMedSearch&keyword=infliximab&category=human&isNewQuery=true*

[4] 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 36 non-serious ADR reports include observations of known adverse reactions, including infusion-related reactions, skin reactions, symptoms from the nervous system such as dizziness and memory problems as well as general reactions such as discomfort and infections.

Remsima ADR reports

We received altogether 64 ADR reports about Remsima, of which 36 were classified as serious (56%). The most frequently described adverse reactions in the serious ADR reports are allergic reactions (anaphylactic reactions and hypersensitivity) and skin reactions such as urticaria and angioedema. In this group, infections such as pneumoniae were also observed as suspected adverse reactions.

A review of the allergic reactions found reports of acute infusion-related reactions requiring treatment that occurred after initiation of biological treatment with infliximab – both among patients who had not previously been treated with infliximab and those who had previously been treated with Remicade.

The incidence rate of allergic reactions should be assessed taking into account the relatively high number of patients who were started on infliximab-treatment in 2015. When new medicines, like Remsima, are placed on the market, it is expected that there will be increased focus on incidence rates of adverse reactions and ADR reports.

Anaphylactic reactions are known adverse reactions to treatment with biological medicines. Although they can occur any time during a treatment course, they are most common in the beginning of treatment. In addition, it cannot be ruled out that a patient with no history of allergic reactions from Remicade treatment can experience such reactions with Remsima due to small variations in the manufacturing process, although it is unusual.

The 28 non-serious ADR reports described general symptoms such as fever, fatigue, rash and gastrointestinal tract problems, e.g. nausea.

ADR reports about switches from Remicade to Remsima

As mentioned earlier, the action plan puts special focus on adverse reactions related to switches between biological medicines and biosimilars.

In 2015, we recorded 11 cases that described adverse reactions having occurred in connection with switches from Remicade to Remsima. The 11 cases are:

- A patient who had previously been treated with Remicade had an allergic reaction when switching to treatment with Remsima.
- A patient experienced a flare-up of the underlying disease (rheumatoid arthritis) a couple of weeks after switching to Remsima.
- A patient experienced a flare-up of the underlying disease (swollen and aching joints) immediately after switching to Remsima.
- A patient’s symptoms of Crohn’s disease got worse (immediately after switch to Remsima). The treatment continued, and the adverse reactions abated a little.

- A patient developed erythema nodosum two to three days after switch to Remsima. Erythema nodosum is not described in the SPCs of infliximab-containing medicines, but erythema nodosum after treatment with Remicade has been reported to us before.
- A woman developed various symptoms including muscle and tendon pain of the arms, bradycardia and vaginal ulcers shortly after switching to Remsima.
- A patient had sinusitis, sores and rash a week after switching to Remsima.
- A patient developed a rash immediately after switching to Remsima.
- A patient was admitted to hospital for assessment of skin rash and visual disturbances after switching to Remsima.
- A patient had a headache, swollen hands and feet as well as joint pain in arms and legs for about three days after switching to Remsima. The patient experienced this again at the second infusion. The patient did not experience adverse reactions to treatment with Remicade.
- A patient with Crohn's disease experienced progressive abdominal pain 1-1½ months after switching from Remicade to Remsima.

Conclusion on the ADR reports overall

Different problems have been presented above, including flare-up of the underlying disease immediately after switching from a biological medicinal product to a biosimilar version as well as suspected adverse reactions such as allergic reactions and infections.

Immunogenicity is expected in treatment with any biological medicine. In some patients, the immune system will perceive the drug as "foreign" and starts to develop antibodies. These antibodies can lead to lack of efficacy or adverse reactions, e.g. infusion reactions. It is therefore quite common and expected for this to occur also with biosimilar medicines. The authorisation of the product is based on clinical data which have compared the immunogenicity of the biosimilar and the original medicinal product directly. The immunogenicity of a biosimilar version is not accepted to be higher.

People treated with biosimilar medicinal products can be expected to develop the same adverse reactions known to occur with the reference product. Reference is made to the relevant SPCs.

Batch numbers not adequately provided in the ADR reports

As mentioned earlier, a new provision has been written into the executive order, providing for ADR reports from doctors, dentists and midwives to include information, whenever possible, about the medicine's name and batch number when ADR reports concern biological medicines appearing on the list prepared by the DKMA.

In our review, a batch number was provided in one of three ADR reports for Gonal-F®, in none of the two Neupogen® reports, in both ADR reports for Omnitrope®, in 51 of the 64 ADR reports for Remsima, but only in one of the 55 ADR reports for Remicade.

Adverse events related to infliximab medicines

Extracts from the database of adverse events managed by the Danish Patient Safety Authority showed that during 2015, reports of adverse events involving Remicade and Remsima had been received.

Among them were reports of patients who received treatment with Remicade a few days after being vaccinated. In one case, this led to influenza-like symptoms that lasted for about one week.

The SPC for Remicade states that use of live vaccines could result in clinical infections, including disseminated infections. Concurrent administration of live vaccines and Remicade is therefore not recommended.

Three reports described events of insecurity exhibited by patients or staff in connection with switches between Remicade and Remsima. In two cases, the patients had not been informed that a switch had been made from Remicade to Remsima. The patients felt unsafe when they subsequently discovered the switch. The third event described a nurse who, only after the infusion of infliximab, discovered that she had given Remsima instead of Remicade.

The reports suggest that patients and staff lack information about biosimilar medicines.

Conclusion

The vast majority of the suspected adverse reactions reported in relation to the use of the described biological medicines and biosimilars are known adverse reactions described in the summaries of product characteristics. Based on the ADR reports received in 2015, there is nothing to suggest that the risk profiles of the biosimilar medicinal products are any different from those of their reference products.

In acknowledgement of the request for more information, the DKMA has prepared a list of frequently asked questions related to treatment with biosimilar medicinal products[5].

Additional information material will follow in 2016, targeting healthcare professionals and patients, respectively. The information for patients will be prepared jointly with the relevant patient organisations.

The DKMA continues its monitoring of reports of adverse reactions from biological medicines and biosimilars and will provide quarterly reviews of the ADR reports here in Danish Pharmacovigilance Update.

[5] *http://laegemiddelstyrelsen.dk/en/special/biological-and-biosimilar-medicinal-products/frequently-asked-questions*

Development in the number of melatonin users younger than 25 years of age from 2007-2015

In December 2013, the DKMA (previously the Danish Health and Medicines Authority) published a report with an analysis of users of melatonin (magistral preparation of melatonin and Circadin®) from 2007 to 2012 among users younger than 25 years of age.

It is described in the Danish Health and Medicines Authority's guideline on medical treatment of children and adolescents with psychiatric disorders[6] that melatonin can be used to treat e.g. comorbid dyssomnia in psychiatric disorders in children and adolescents. The above-mentioned report found that the vast majority of melatonin-users under 25 years had a diagnosis covered by this guideline.

The DKMA has regularly followed up on the analysis with respect to the number of users.

Increase in the number of users younger than 25 years from 2007-2015

Table 1 shows the number of users under 25 years having redeemed at least one prescription for magistral preparation of melatonin or Circadin® from 2007-2015.

	2007	2008	2009	2010	2011	2012	2013	2014	2015
Magistral preparation of melatonin	-	-	-	-	3,818	5,221	6,089	6,943	8,501
Circadin®	80	898	1,643	2,323	2,899	3,354	3,471	4,017	4,809
Melatonin users in total[7]	80	898	1,643	2,323	6,391	8,078	9,031	10,279	12,381

Table 1. Number of users aged 0-24 years of magistral preparation of melatonin and Circadin® from 2007-2015. (Register of Medicinal Products Statistics, Danish Health Data Authority)

The number of users of magistral preparation of melatonin younger than 25 years has grown by 1,558 from 2014 to 2015; the 22% increase is higher than the year before of 14%. The number of Circadin® users has increased as well; by 20% in the same period.

The number of melatonin users younger than 25 years has grown by 2,102 from 2014 to 2015. The largest increases are found in the age groups of 15-19 years and 20-24 years (data not shown).

Reported suspected adverse reactions in 2015 related to melatonin-containing medicines

In 2015, the DKMA received nine reports of suspected adverse reactions to melatonin. One ADR report describes suspected adverse reactions in a child who after starting melatonin treatment presented with increased irritability, irascibility and short temper at

[6] Guideline no. 9194 of 11 April 2013

[7] The total is not equal to the sum of users of magistral preparation of melatonin and Circadin®, because some children/adolescents have been prescribed both magistral preparation of melatonin and Circadin®.

school and at home. The treatment was stopped after a few weeks, and the symptoms disappeared.

In the SPC for Circadin®[8], aggression and agitation appear as known adverse reactions.

Doctors should be aware of the following:

- Prescription of melatonin is reserved for medical specialists in the fields of child and adolescent psychiatry, neurology or paediatrics[9].
- Magistral preparations of medicinal products are subject to stricter reporting requirements, implying that doctors are obliged to report any suspected adverse reactions observed in persons they are or have been treating. Adverse reactions occurring as a result of medication errors are, however, exempted[10].

Conclusion

While the number of melatonin users younger than 25 years continues to grow, the number of ADR reports received is low.

Adverse reactions can be reported electronically at *www.meldenbivirkning.dk* (report a side effect).

The DKMA intends to repeat the analysis from 2013 using data from 2015 to find out if the majority of users under 25 years still have a diagnosis covered by the Danish Health and Medicines Authority's guideline on medical treatment of children and adolescents with psychiatric disorders.

The DKMA will look at the literature on the safety of using melatonin-containing medicines in children.

Read the previous analysis from 2013: *Melatonin users younger than 25 years of age (in Danish only).*

Indication for melatonin
Circadin® is indicated as monotherapy for the short-term treatment of primary insomnia characterised by poor quality of sleep in patients who are aged 55 or over.

[8] *www.produktresume.dk (Danish website)*
[9] Guideline no. 9194 of 11 April 2013
[10] Danish executive order no. 1823 of 15 December 2015

Beware of interactions between miconazole and warfarin – new, serious ADR reports

In response to several ADR reports of increased INR – including a case of life-threatening bleeding after concomitant use of the blood-thinning medicine Warfarin and the antifungal medication miconazole – we called attention to this known interaction in Danish Pharmacovigilance Update, October 2015.

New serious cases

In January this year, the Danish Patient Safety Authority received two new reports about patients who were admitted to hospital with adverse reactions caused by interactions between warfarin and miconazole. Since October 2015, the DKMA has also received two new ADR reports that describe adverse reactions caused by interactions between these two medicines.

Known interaction

Warfarin is known to interact with many types of medicines. The three antimycotics fluconazole, voriconazole and miconazole interact with warfarin by inhibiting the CYP2C9 enzyme, which clinically is the most important enzyme involved in the metabolism of warfarin. Warfarin plasma concentration thus increases.

The interaction between miconazole and warfarin is described in the authorised Danish summary of product characteristics of Brentan oral cavity gel. It is also mentioned in the package leaflet and on Pro.medicin.dk.

It may seem surprising that the interaction produced by warfarin and a topically applied antifungal medication can be so severe and occur so quickly. However, Brentan oral cavity gel is absorbed systemically, and the plasma half-life is 20-25 hours, so interactions should be expected. The situation is otherwise with Brentan 2% miconazole nitrate for application on the skin, which does not result in measurable plasma concentrations (bioavailability <1%).

Advice for doctors and dentists

If Brentan oral cavity gel and warfarin are used concomitantly, the anticoagulant effect should be carefully monitored and titrated. An alternative could be to use another antifungal medication not interacting with warfarin and having therapeutic activity against the relevant microorganisms.

Also see *Danish Pharmacovigilance Update, October 2015*.

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:

- **TachoSil (human fibrinogen/human thrombin)** – new recommendations to reduce the risk of intestinal obstruction. Sent out 27 January 2016.

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

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