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DANISH MEDICINES AGENCY

Danish Pharmacovigilance Update

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In this issue

Suicidal behaviour and suicidal ideation have been reported as suspected adverse reactions to the dermatologic medicinal product Otezla® (apremilast)

The product information of the medicine Otezla® will be updated with a warning about depression, suicidal behaviour and suicidal ideation as new adverse reactions to the medicine. The update comes after the registration of several cases of suicidal ideation and suicidal behaviour following a review of reported suspected adverse reactions and clinical adverse reaction data. There were cases with and without previous depression with an uncommon frequency (≤1/1,000 to ≥1/100). The reported adverse reactions also covered cases of completed suicides.

Background leading to the product information update

Up until March 2016, a total of 65 cases of suicides and suicidal behaviour related to Otezla® had been reported worldwide – including:

- 5 completed suicides
- 4 suicide attempts
- 50 cases of suicidal ideation
- 5 cases of depression/suicidal ideation
- 1 case of suicidal behaviour

32 of the 65 cases described improvements after discontinuing treatment with Otezla®. Since marketing of the product in January 2015 up until 20 March 2016, a total of 105,000 patients have been exposed to Otezla®.

Advice for prescribers

- The benefits and risks of apremilast treatment should be considered carefully in patients with a history of psychiatric symptoms and in patients taking (other) medication that may cause psychiatric symptoms.
- If patients suffer from new or worsening psychiatric symptoms or if suicidal ideation or suicidal behaviour is identified, it is recommended to discontinue treatment with apremilast.

- Patients, relatives and caregivers should be instructed to notify prescribing healthcare staff of any changes in behaviour or mood, or signs of suicidal ideation.

Report suspected adverse reactions related to Otezla®

Otezla® was marketed in January 2015 and is therefore on the list of medicines subject to stricter reporting requirements. This means that doctors are obliged to report all suspected adverse reactions to the medicine. Suspected adverse reactions should be reported to the DKMA on the website www.meldenbivirkning.dk.

Indication for Otezla®

On 15 January 2015, Otezla® (apremilast) was authorised in Europe with the following indications: Otezla®, alone or in combination with Disease Modifying Antirheumatic Drugs (DMARDs), is indicated for the treatment of active psoriatic arthritis (PsA) in adult patients who have had an inadequate response or who have been intolerant to a prior DMARD therapy. Otezla® is also indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who failed to respond to or who have a contraindication to, or are intolerant to other systemic therapy including cyclosporine, methotrexate or psoralen and ultraviolet-A light (PUVA).

A Direct Healthcare Professional Communication (DHPC) has been sent out to relevant doctors.

Focus on reported adverse reactions to selected biological medicines

Since 1 January 2016, doctors, dentists and midwives have been obligated to, as far as possible, provide the medicine's name and batch number in ADR reports that concern selected biological medicines[1] (cf. new executive order no. 1823 of 15 December 2015).

The selected biological medicines are subject to stricter reporting requirements.

In this connection, the DKMA has put special focus on suspected adverse reactions to biological medicines and biosimilars – especially those arising from switches between reference medicinal products and biosimilars.

In Danish Pharmacovigilance Update, we have regularly reviewed the ADR reports we have received about these biological medicines: the first time in *Danish Pharmacovigilance Update, February 2016* and most recently in *Danish Pharmacovigilance Update, August 2016*.

In this month's issue, we review the ADR reports received about selected biological medicines in the third quarter of 2016.

Review of ADR reports related to selected biological medicines and consumption thereof in Q3

In the third quarter of 2016, the DKMA received 42 ADR reports* on biological medicines/biosimilars on the *List of selected biological medicinal products*[1]. Just over half of them were classified as serious (table 1).

[1] The selected biological medicines in focus appear from a list, which is updated regularly by the Danish Medicines Agency. The list is available at the DKMA website: *List of selected biological medicinal products*.

***Disclaimer**
All cases referred to in this article originate from the DKMA's database of adverse drug reactions. The cases have been forwarded to all relevant pharmaceutical companies and to the EudraVigilance database. Therefore, the pharmaceutical companies are not to report these cases the to DKMA.

Medicine	Active substance	Number of ADR reports	Number of serious ADR reports	Number of ADR reports providing batch number
Gonal-F®	follitropin alfa	2	1	1
Nivestim	filgrastim	1	1	0
Cosentyx	secukinumab	2	1	0
Benepali	etanercept	11	2	9
Enbrel	etanercept	3	3	0
Medicine not provided	etanercept	1	1	0
Remicade	infliximab	9	7	2
Remsima	infliximab	10	8	6
Name not provided	infliximab	6	4	0
Total		45[2] (42)	28 (25)	18

Table 1: ADR reports received in Q3 of 2016 about biological medicines/biosimilars by medicine/active substance and severity.

ADR reports on infliximab

The majority of ADR reports concern infliximab-containing medicines: 23 of the 42 ADR reports. Nine of them involve the reference product Remicade, and ten its biosimilar version Remsima. No medicine names were provided in the six remaining ADR reports (table 1). In two of the serious ADR reports, both Remicade and Remsima are suspected.

The serious ADR reports about Remicade describe, among other things, cases of infections (laryngitis and abscesses) as well as malignancies (Hodgkin's disease and basal cell carcinoma). These are primarily known adverse reactions described in the summaries of product characteristics (SmPCs). Given the current knowledge, the possible risk that patients receiving a TNF-antagonist may develop lymphoma or other malignancies cannot be excluded. Caution should be exercised when considering TNF-blocking therapy for patients with a history of malignancy or when considering continuing treatment in patients who develop malignancies[3].

Among the serious ADR reports about Remsima, a variety of allergic reactions are described, including urticaria and swelling and itchy mouth. Allergic reactions are known adverse reactions.

[2] One serious ADR report describes etanercept as well as infliximab (Remicade). Two other serious ADR reports describe Remicade as well as Remsima.
[3] *http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124*

The non-serious ADR reports related to infliximab also describe primarily known adverse reactions such as infections and transient visual loss. Visual loss occurring during or within two hours of infliximab infusion is described in the SmPC.

Foetal exposure
In five cases, foetuses had been exposed to Remicade. Four of the cases are described in the literature. Two of the reports describe suspected adverse reactions in the child: a newborn was diagnosed with a duplex kidney, another with a vessel anomaly.

In the SmPCs of infliximab, it is described that women of childbearing potential must use adequate contraception to prevent pregnancy and continue its use for at least six months after the last treatment. Infliximab crosses the placenta and has been detected in the serum of infants up to six months following birth. After in utero exposure to infliximab, infants may be at increased risk of infection.

The available clinical experience is too limited to exclude a risk, and administration of infliximab is therefore not recommended during pregnancy.

ADR reports in connection with switches from Remicade to Remsima

No adverse reactions have been reported in connection with switches from Remicade to Remsima in the third quarter of 2016. Almost all patients receiving infliximab in Denmark have since the summer of 2015 been treated with Remsima (figure 1.), and it should thus be assumed that only very few switch-related adverse reactions will be reported ahead.

Reports on etanercept

15 of the total of 42 ADR reports received in the third quarter concern etanercept. Three of them describe suspected adverse reactions to Enbrel, the reference product, and 11 describe suspected adverse reactions to Benepali, the biosimilar version. One report did not name the suspected product.

The serious ADR reports (6 of 15) describe suspected adverse reactions such as angioedema, multiple sclerosis and systemic lupus erythematosus – all of which are known suspected adverse reactions. Whereas multiple sclerosis-like disease is described in the SmPC as a rare adverse reaction, lupus-like syndrome is described as an uncommon adverse reaction.

The non-serious ADR reports especially describe various forms of headache as well as nausea and vomiting. These adverse reactions do not appear in the SmPC.

ADR reports in connection with switches from Enbrel to Benepali

In the third quarter, we received four reports about switches from Enbrel to Benepali.

1. One ADR report describes a patient who two weeks after switching to Benepali, the biosimilar version, experienced worsening of arthritis with joint pain and swelling. The patient was switched back to Enbrel, and the symptoms subsided.
2. Another report describes a patient who switched from Enbrel to Benepali. Immediately after the first injection, the patient developed nausea and general discomfort lasting for about one week. The half-life is 70 hours for etanercept, which corresponds to any adverse reaction symptoms disappearing during the course of one week. Thus it cannot be excluded that the symptoms are linked to the medicine.
3. The third report describes a patient who developed hypertension, dizziness, facial redness and warm ears in connection with switching to Benepali. The treatment was discontinued due to adverse reactions, and the patient was switched back to Enbrel. The ADR report notes that the suspected adverse reactions did not disappear after the switch to Enbrel.

Hypertension is not described in the SmPC, but there is a temporal association between administration of the medicine and the symptoms, and thus it cannot be excluded that the symptoms are linked to the medicine.

4. The last ADR report describes an arthritis patient who was symptom-free for a shorter period of time on Benepali compared to Enbrel. There is no information about the disease activity of arthritis, and thus it is not possible to determine if it is caused by reduced efficacy of Benepali compared to Enbrel.

Adverse event reported to the Danish Patient Safety Authority's database

An adverse event has been reported where relevant healthcare professionals had not been informed that Benepali must not be used in children under 18 years. This may potentially lead to prescription errors.

Consumption of infliximab-containing medicines in 2015 and the first three quarters of 2016

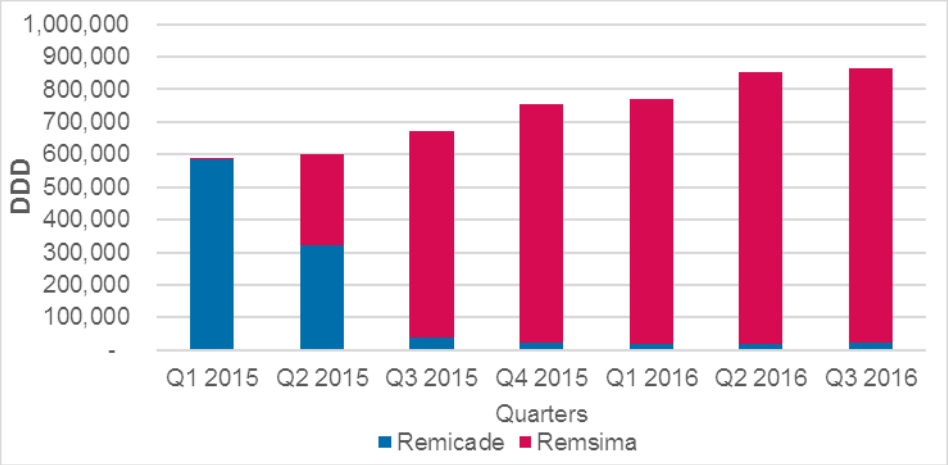

Figure 1. DDD consumption of infliximab-containing medicines broken down by Remicade and Remsima through Q1 to Q4 of 2015 and Q1, Q2 and Q3 of 2016. (Register of Medicinal Product Statistics, Danish Health Data Authority)

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. A DDD does not necessarily represent the recommended daily dose, and there may be cases where medicines are to be used in other doses than those established. 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.

Infliximab consumption increased in 2015 and continued doing so in the first three quarters of 2016. In the third quarter, the DDD consumption was approx. 850,000.

Remsima and Remicade must only be used in hospital treatment.

Remsima was marketed in March 2015. Consumption data show that the Danish regions have followed the recommendations from the Council for Use of Expensive Hospital Medicine (RADS) to switch from Remicade to Remsima. The total consumption has increased because infliximab (Remsima) appears as a first-line

product in RADS' guidelines[4] for biological treatment in the fields of rheumatology and gastroenterology. In the third quarter of 2016, the consumption of Remsima accounted for 98% of infliximab-containing medicines.

Consumption of etanercept-containing medicines from Q1 to Q3 in 2016

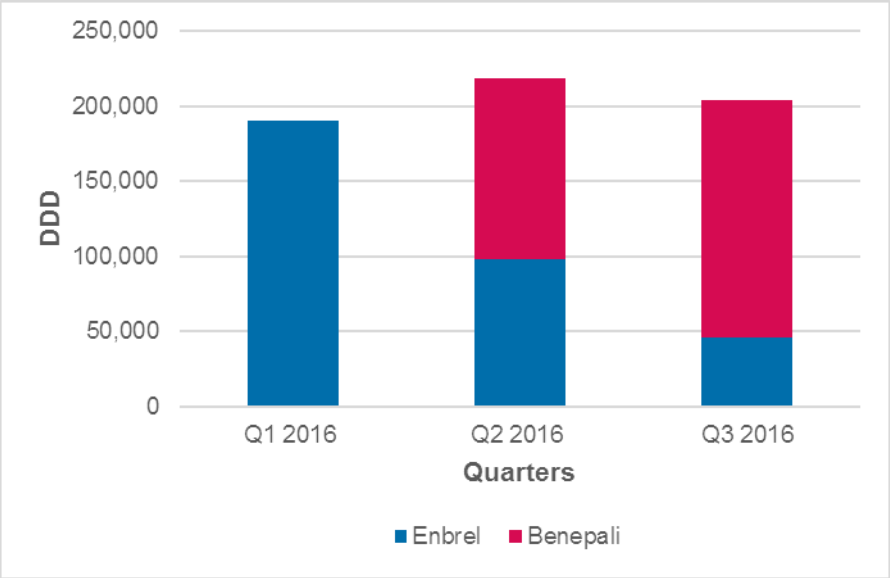

Figure 2. DDD consumption of etanercept-containing medicines broken down by Enbrel and Benepali in Q1, Q2 and Q3 of 2016 (Register of Medicinal Product Statistics, Danish Health Data Authority).

In the first quarter of 2016, Enbrel accounted for all etanercept consumption. Compared to the second quarter, Benepali consumption increased in Q3, accounting for the largest share at 77%.

Etanercept can be used in biological treatment of arthritis and psoriasis, respectively. Etanercept-containing medicines may be used in hospital treatment and in specialist practices (dermatology and rheumatology).

Benepali was marketed in February 2016. In the RADS' treatment guidelines for patients treated with etanercept, it appears that new patients and patients for whom other biological treatment has failed are to be treated with the cheapest version of the medicine (Benepali). Benepali must not be used for the treatment of children as there are no low-dose formulations of the medicine.

Furthermore, patients who are stable on etanercept treatment ought to be switched to the cheapest version of the medicine, unless there are exceptional individual patient concerns[5]. Consumption data show that the regions have switched from Enbrel to Benepali in line with he RADS' treatment guidelines.

Conclusion

Patients treated with biosimilar medicines can be expected to develop the same adverse reactions known to occur with the reference product, and our review does not suggest that the profile of adverse drug reactions of the biosimilar versions is any different from that of the reference products. Mainly known adverse reactions have been reported. For infliximab medicines, we have received approximately the same number of ADR reports about the reference product and the biosimilar version, but for etanercept medicines, we have received more about Benepali, the biosimilar version.

No connection between batch numbers and reported suspected adverse reactions has been identified. Information about batch numbers was only provided in less than

[4] *http://www.regioner.dk/radsdk/behandlingsvejledninger*
[5] *http://www.regioner.dk/services/nyheder/2016/april/rads-anbefaler-ibrugtagning-af-nyt-biosimilaert-laegemiddel*

half of the ADR reports, continuing the trend seen in our previous updates. The DKMA encourages reporters to provide batch numbers and brand names in ADR reports concerning biological medicines appearing on the *List of selected biological medicinal products*.

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:

- **Lenalidomide (Revlimid) multiple myeloma medicine:** New important advice regarding viral reactivation. Sent out 7 November 2016.
- **Apremilast (Otezla) immunosuppressant:** New advice regarding suicidal ideation and behaviour. Sent out 7 November 2016.
- **Levetiracetam-containing medicines (incl. Keppra) as 100 mg/ml oral solution for treatment of epilepsy:** Risk of medication errors leading to overdose. Sent out 21 November 2016.

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

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 on the PRAC meeting from 26-29 September 2016 concern the following products:

- **Levetiracetam (oral solution)** – medication errors associated with accidental overdose.
- **Metronidazole** – severe hepatic and neurologic toxicity in patients with Cockayne syndrome.

See EU's list of recommendations on safety signals: *PRAC recommendations on signals adopted 26-29 September 2016* as well as the *Danish translations of the product information*.

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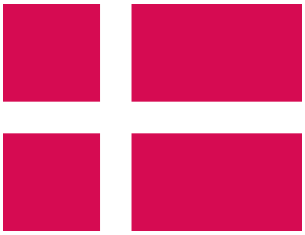
Danish Pharmacovigilance Update celebrates 7-year anniversary



We appreciate the growing interest in our newsletter and our work with the monitoring of medicine safety.

To ensure that the content of our newsletter is still relevant and appeals to our readers, we will soon be evaluating Danish Pharmacovigilance Update on the occasion of our anniversary.

The evaluation result will be published in a future issue of Danish Pharmacovigilance Update.

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