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In this issue

Focus on reported adverse reactions to biological medicines

Since 1 January 2016, doctors, dentists and midwives have been obliged, as far as possible, to 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).

In this connection, the Danish Medicines Agency (DKMA) has put special focus on suspected adverse reactions to biological medicines and biosimilars – especially those arising from switches between biological medicines and biosimilars.

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

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

Review of ADR reports and consumption of selected biological medicines in Q2 of 2016

In the second quarter of 2016, the DKMA received 87 ADR reports on biological medicines/biosimilars appearing from the *List of selected biological medicinal products*. Just over half of them were classified as serious (table 1).

[1] The selected biological medicines in focus appear from a list updated regularly by the Danish Medicines Agency and placed on DKMA website: *List of selected biological medicinal products*.

Medicine name	Active substance	No. of ADR reports	Number of serious reports	Number of ADR reports providing batch number
Omnitrope	Somatropin	1	0	0
Cosentyx	Secukinumab	5	2	2
Repatha	Evolocumab	2	1	0
Enbrel	Etanercept	7	3	2
Medicine name not provided	Etanercept	2	1	0
Remicade	Infliximab	34	13	1
Remsima	Infliximab	39	25	32
Medicine name not provided	Infliximab	1	1	0
TOTAL		**91**[2] [3]**(87)**	**46**[3]**(44)**	**37**

Table 1: ADR reports received in Q2 of 2016 about biological medicines/biosimilars by medicine/active ingredient and severity.

ADR reports on infliximab

As in our last review, the majority of ADR reports concern infliximab-containing medicines: 72 out of 87 ADR reports. 34 of them involved the reference product Remicade, and 39 the biosimilar version Remsima (one report did not provide the medicine name) (Table 1).

28 of the 34 ADR reports on Remicade are from a study where patients with ulcerative colitis were treated with Remicade (*Study P04808AM3*).

The ADR reports on Remicade classified as serious describe infections and infusion-related reactions. These are primarily known adverse reactions described in the summaries of product characteristics (SmPCs). The cases described in the serious ADR reports on Remsima include infections, neuropathy and depression.

The non-serious ADR reports related to infliximab also described primarily known adverse reactions such as fatigue, headache and infections.

ADR reports in connection with switches from Remicade to Remsima

Adverse reactions caused by switches from reference product to biosimilar version have only been reported for infliximab-containing medicines.

In the second quarter, we received two reports (one serious and one non-serious) that described suspected adverse reactions caused by switches:

1. After switching from Remicade to Remsima, a patient developed hypertension and polycythaemia and had transitory cerebral ischaemia (TCI). The patient was treated concomitantly with methotrexate. Both Remsima and methotrexate were reported as suspected causes of the adverse reactions.
2. In another report, a patient developed an upper respiratory tract infection in connection with switching from Remicade to Remsima.

Hypertension is a known adverse reaction of infliximab, and in the SmPC for methotrexate, cerebral thromboembolism is indicated as a rare adverse reaction. TCI may also be related to polycythaemia. Polycythaemia is not a known adverse reaction to either of the medicines, but is seen in elevated disease activity.

[2] One serious ADR report describes Cosentyx, Enbrel as well as Remicade.
[3] Two of the serious ADR report describe Remicade as well as Remsima.

Upper respiratory tract infections are known adverse reactions to infliximab-containing medicines.

Reports on etanercept

Nine of the 87 ADR reports received in the second quarter concern etanercept – seven of them describe adverse reactions of the reference medicine Enbrel, and in two of the ADR reports, no medicine name was provided (Table 1).

The serious adverse reactions (four out of seven) describe suspected adverse reactions such as infections (urosepsis and peritonsillar abscess) as well as development of malignant diseases (skin and lung cancer). Infection is a known adverse reaction to etanercept treatment. The SmPC for Enbrel describes that cases of various forms of malignancies from Enbrel use have been reported.

The non-serious ADR reports also described primarily known adverse reactions such as infections and (pain) reactions at the injection site.

We received no ADR reports about Benepali in the second quarter of 2016.

Consumption of infliximab-containing medicines

As mentioned, we received most ADR reports about infliximab-containing medicines.

Figure 1 shows the consumption of infliximab-containing medicines in 2015 and Q1 and Q2 of 2016.

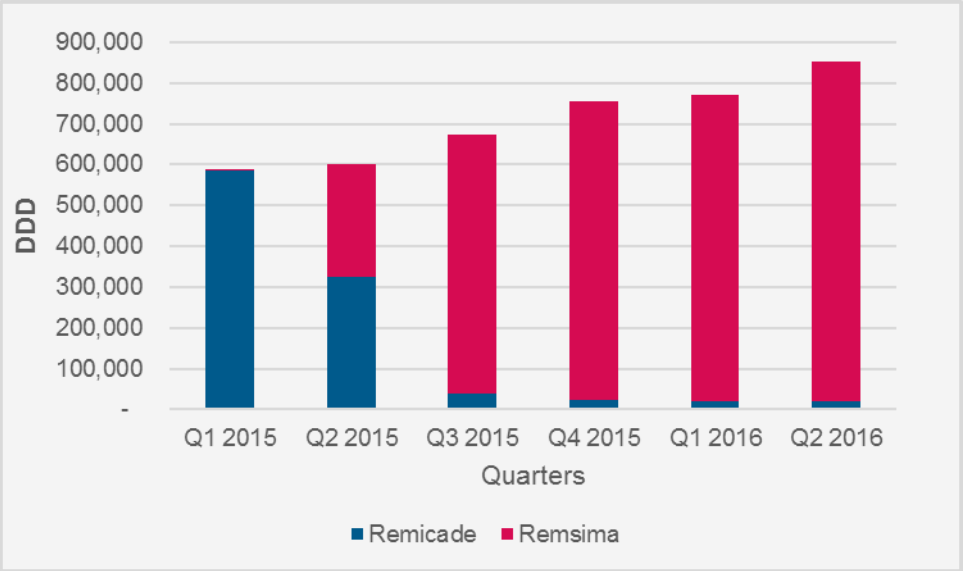

Figure 1. DDD consumption[4] of infliximab-containing medicines broken down by Remicade and Remsima through Q1 to Q4 of 2015 and Q1 and Q2 of 2016. (Data from the Danish Health Data Authority)

Infliximab consumption increased throughout 2015 and into Q1 and Q2 of 2016.

Remsima and Remicade must only be used in hospital treatment.

Remsima was marketed in March 2015. Consumption data reveals that the Danish regions have followed the recommendation issued by the Council for Use of Expensive Hospital Medicine (RADS) to switch from Remicade to Remsima. The consumption has also increased because infliximab (Remsima) appears as a first-line product in RADS' guidelines[5] for biological treatment in the fields of rheumatology and gastroenterology. In the second quarter of 2016, the consumption of Remsima accounted for 98% of infliximab-containing medicines.

[4] 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.

[5] *http://www.regioner.dk/radsdk/behandlingsvejledninger*

Consumption of etanercept-containing medicines

Figure 2 shows the consumption of etanercept-containing medicines in Q1 and Q2 of 2016.

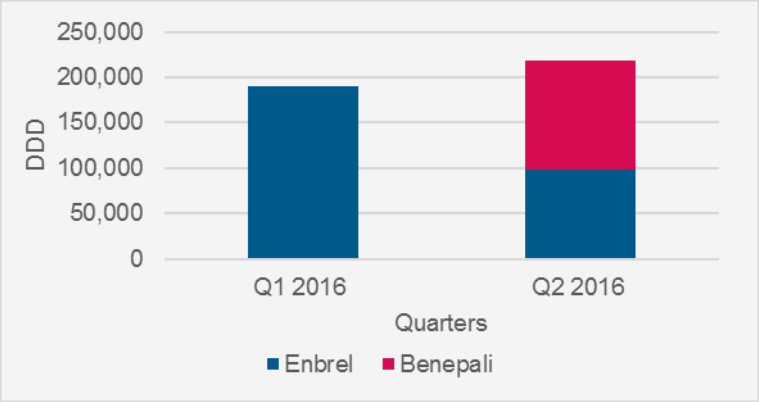

Figure 2. DDD consumption of etanercept-containing medicines broken down by Enbrel and Benepali in Q1 and Q2 of 2016. (Data from the Danish Health Data Authority)

In the first quarter of 2016, Enbrel accounted for all etanercept consumption. In the second quarter of 2016, the consumption of etanercept-containing medicines rose, and Benepali consumption accounted for 55%.

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. RADS has announced that new patients and patients for whom biological treatment has failed, who, according to the RADS' treatment guidelines are to be treated with etanercept, should be treated with the cheapest version of the medicine (Benepali). 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[6]. Consumption data show that the regions have started switching from Enbrel to Benepali.

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 Remsima's profile of adverse drug reactions is any different from its reference product Remicade. Mainly known adverse reactions have been reported.

In April 2016, the Danish Medicines Agency sent out information about the new executive order, which provides that reports of suspected adverse reactions of selected biological medicines must, as far as possible, include information about medicine name and batch number. Ahead, we expect that relatively more ADR reports about biological medicines/biosimilars on the list will include details about batch number, and we will track the progress. No connection between the adverse reactions described so far and the individual Remsima batches has been identified.

Allopurinol and serious adverse reactions

The DKMA has received 20 ADR reports of serious skin reactions in connection with allopurinol treatment in the period 1979-2015. The ADR reports describe adverse reactions such as generalised exfoliative dermatitis, eosinophilia reactions and

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

systemic symptoms, erythema multiforme and erythema nodosum, Stevens-Johnson syndrome and toxic epidermal necrolysis, which are all described in the product information for allopurinol.

Allopurinol should be used with particular caution in elderly patients and kidney patients

Among the 20 ADR reports, three deaths were reported caused by serious skin disorders[7]. The latest death associated with allopurinol treatment was reported in 2015 while the other deaths were reported years back. The latest report describes an elderly man who developed exfoliative skin disorder – a known, but rare, adverse reaction of allopurinol treatment. The patient received concomitant medication, including diuretics, antihypertensives and benzodiazepines. The patient had nephropathy and was on haemodialysis.

Allopurinol consumption

The number of persons treated with allopurinol has increased over the past 10 years, and in 2015, the number of persons who redeemed at least one prescription for allopurinol was 52,871 (see Figure 1). More men than women are treated with allopurinol.

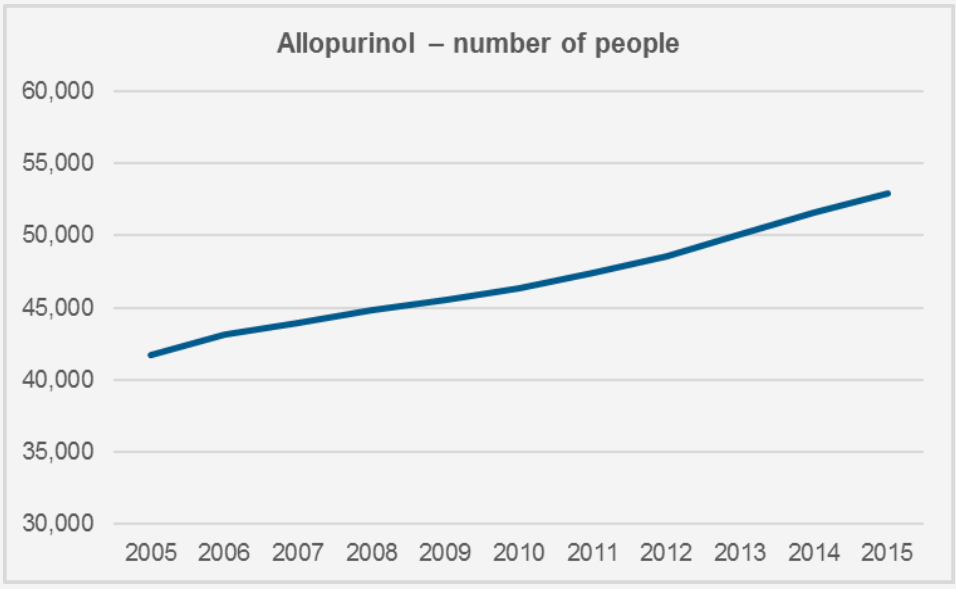

Figure 1: Number of people having redeemed at least one prescription for allopurinol, 2005-2015.

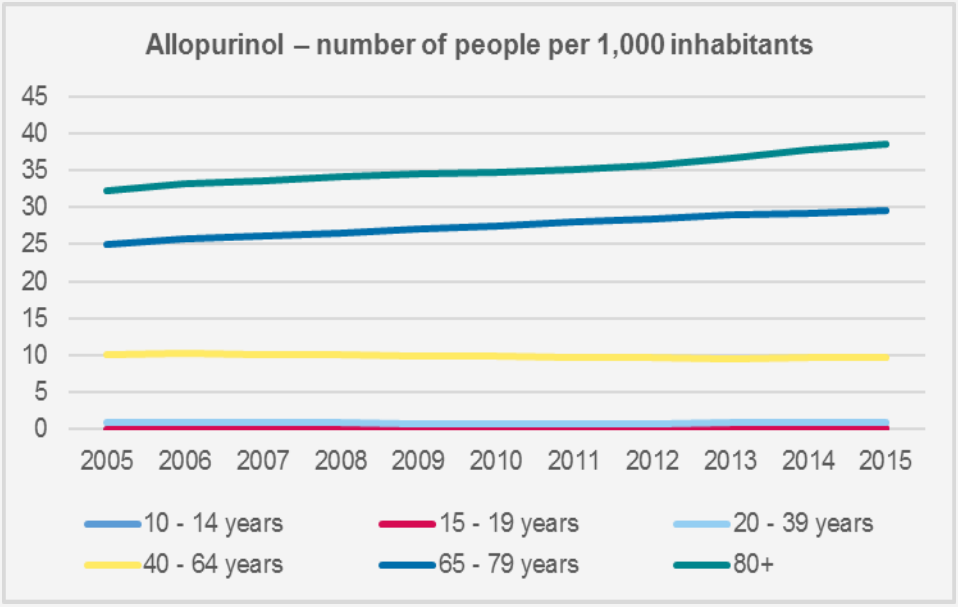

Figure 2: Number of people having redeemed at least one prescription for allopurinol by age (Medstat 2016).

[7] The Danish Medicines Agency has received a total of eight ADR reports of deaths in connection with allopurinol treatment of which three described cases of preceding severe skin conditions.

As can be seen from figure 2, allopurinol is primarily used for the treatment of people over 65 years – a population where the prevalence of renal impairment is generally higher compared to younger people.

Doctors should be particularly aware of the following:

- Allopurinol may cause severe grade 4 skin reactions like Stevens-Johnson syndrome, exfoliative dermatitis and toxic epidermal necrolysis.
- Allopurinol is contraindicated in patients with severe renal impairment with creatinine clearance < 0.33 ml/s (20 ml/min).
- Elderly patients and patients with renal disease should be treated cautiously with allopurinol since the elimination of oxypurinol (the active metabolite of allopurinol) may be reduced.

Indication for allopurinol
Prevention and treatment of gouty arthritis.

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.

Hormonal emergency contraception containing levonorgestrel (Norlevo, Levodonna) and interaction with liver enzyme inducing medicine

The contraceptive effect of hormonal levonorgestrel-containing contraceptives can be reduced if used concomitantly with certain liver enzyme inducers and herbal remedies. It applies to the concomitant use of medicines against fungi, epilepsy, tuberculosis and HIV as well as herbal remedies containing Hypericum perforatum.

The lowest effective dose of levonorgestrel in emergency contraception has not been determined, but for persons taking these enzyme inducers, it is important to ensure that the contraception is sufficient.

Advice for prescribers

- Women seeking emergency contraception who have used enzyme-inducing medicine within the last four weeks, are advised to use a non-hormonal emergency contraceptive, i.e. a copper intrauterine device (Cu-IUD).
- Copper coils (Cu-IUD) can be used as a non-hormonal emergency contraception. A Cu-IUD may prevent pregnancy, provided it is inserted in the uterus within five days after unprotected intercourse.

- If the use of copper coil is not possible, women are advised to double the usual dose of levonorgestrel from 1.5 mg to 3 mg to compensate for the reduction in plasma levonorgestrel concentration. The tablet must be taken as soon as possible, preferably within 12 hours after the unprotected intercourse, and no longer than 72 hours after the intercourse.

  No increased risk of adverse reactions is expected from the higher dose for women who take a double dose of Norlevo or Levodonna under these circumstances. However, the specific combination of a double dose of levonorgestrel during concomitant use of an enzyme inducer has not been studied so users or healthcare professionals are encouraged to report any adverse reactions occurring with use of a double dose.

- Exposure during pregnancy of some enzyme-inducing medicines has been associated with birth defects, so it is important to exclude pregnancy and provide advice on reliable forms of regular contraception for women taking these medicines.

Background to the recommendations

The recommendations come from the EMA on the basis of interaction studies. Data from studies of levonorgestrel-containing hormonal contraceptives have indicated that plasma levonorgestrel levels are consistently reduced by concomitant use of liver enzyme inducers, mainly inducers of CYP3A4 enzymes. A recent study with levonorgestrel-containing[8] emergency contraception showed that concomitant administration of efavirenz reduces plasma levels of levonorgestrel (AUC) by around 50%. Other hepatic enzyme-inducing medicines may produce similar reductions in plasma levels. This reduction in plasma levonorgestrel levels may reduce contraceptive efficacy of levonorgestrel-containing emergency hormonal contraceptives.

For more information, please see the Direct Healthcare Professional Communication (DHPC) on the website of the Danish Medicines Agency. *Levonorgestrel-containing emergency hormonal contraception (Norlevo, Levodonna)*

Levonorgestrel-containing emergency contraception

Levonorgestrel-containing emergency contraceptives are tablets for emergency contraception to be taken within 72 hours after unprotected intercourse or failure of a contraceptive method. Efficacy is highest if the tablet is taken soon after unprotected intercourse and diminishes with later use (from 95% within 24 hours to 58% if started between 48 and 72 hours).

Medicines which affect levonorgestrel levels

- Certain medicines to treat epilepsy (e.g. barbiturates, primidone, phenytoin or carbamazepine)
- Certain medicines to treat tuberculosis (e.g. rifampicin, rifabutin)
- Certain medicines to treat HIV (e.g. ritonavir, efavirenz)
- Certain medicines to treat fungal infections (e.g. griseofulvin)
- Herbal remedies containing St John's wort (Hypericum perforatum)

[8] Carten ML, et al, (2012) Pharmacokinetic Interactions between the Hormonal Emergency Contraception, Levonorgestrel (Plan B), and Efavirenz. Infectious Diseases in Obstetrics and Gynecology, article ID:137192

Confusion between batch numbers and ATC codes of medicines

At the DKMA, we have received several ADR reports where the medicine's batch number (production number) has been confused with the medicine's ATC code (classification code).

For certain medicines, it is particularly important to provide the medicine's batch number in the ADR report. Batch numbers are used to identify possible safety and quality problems among the individually manufactured batches (productions) of medicines. At present, there is special focus on the registration of batch numbers of biological medicines and biosimilars. Likewise, it is important to provide the batch number in connection with the reporting of suspected adverse reactions to vaccines.

The difference between batch number and ATC code

While the ATC code is unique for the medicine, the batch number is unique for each individually manufactured batch of a medicine. The batch number will therefore always be different for each manufactured batch of a medicine, but the ATC code is the same for the same active ingredient.

Only the batch number should as far as possible be provided in ADR reports

The ATC system is used to classify medicines according to their active ingredient and area of impact. Each medicine has a unique ATC code. The ATC code is construed according to a specific classification system administered by the WHO. The ATC code is not required to appear on the medicine package. The ATC code appears from the medicine's summary of product characteristics, but there is no requirement to provide the ATC code in ADR reporting.

The batch number is used to identify a specific batch (production) of a medicine. When a company manufactures a medicine, the specific batch is allocated a batch number. Each time a new batch of a certain medicine is manufactured, that batch is given a new batch number.

The batch number always appears on the medicine package. The structure and length of the number may vary substantially, but it is usually referred to as batch or lot on the package. For biological medicines and biosimilars as well as vaccines, healthcare professionals must, as far as possible, provide the batch number when they report suspected adverse reactions to the DKMA.

Most recent Direct Healthcare Professional Communications (DHPCs)

Below is a list of the most recent DHPCs that have been sent out to relevant doctors and healthcare professionals with safety information and updated recommendations about medicines:

- **Riociguat (Adempas) for treatment of pulmonary hypertension:** New contraindication in patients with pulmonary hypertension associated with idiopathic interstitial pneumonias. Sent out 4 July.
- **Levonorgestrel-containing emergency hormonal contraception (Norlevo, Levodonna):** New advice for users of hepatic enzyme-inducing medicines. Sent out 5 August.
- **Antineoplastic agent idelalisib (Zydelig):** Updated advice after EMA's conclusion on safety review. Sent out 22 August.

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 meetings in June and July 2016 concern the following products:

- **Riociguat** – Increased mortality and serious adverse events in certain patients in a clinical trial
- **Ferrous sulfate** – Mouth ulceration
- **Proton pump inhibitors** – Elevated circulating levels of Chromogranin A

See EU's list of recommendations on safety signals: *PRAC recommendations on signals June 2016* and *PRAC recommendations on signals July 2016* as well as the *Danish translations of the product information from June* and *Danish translations of the product information from July*.

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