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DANISH MEDICINES AGENCY

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In this issue

Starting in this issue, Danish Pharmacovigilance Update will bring a quarterly focus selected from our monitoring of the childhood immunisation programme. This quarter, we have decided to look at Danish ADR reports of thyroid disorders (thyroiditis in particular) in connection with vaccination with HPV vaccines.

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 at the PRAC meeting in May 2016 concern the following products:

- **Natalizumab** – Necrotising retinitis
- **Warfarin** – Calciphylaxis

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

Childhood vaccinations and reported suspected adverse reactions in Q1 of 2016

Every three months, the reports of suspected adverse reactions to vaccines in the Danish childhood immunisation programme are reviewed and assessed by the Danish Medicines Agency (DKMA) and a vaccination panel composed of a number of experts.

Here, we bring the results of the review for Q1 2016.

The review covers primary vaccines in the childhood immunisation programme as well as booster vaccines (re-vaccination).

ADR reports about vaccines in the childhood immunisation programme

In the first quarter of 2016, the DKMA received a total of 313 reports of suspected adverse reactions to vaccines in the childhood immunisation programme, of which 70 were classified as serious[1].

Table 1a shows the number of ADR reports classified as serious and non-serious by vaccine.

Vaccine reported	Non-serious	Serious	Total
Diphtheria tetanus polio vaccine / measles mumps and rubella	0	1	1
DT booster	5	0	5
DTaP-IPV Booster	4	0	4
DTaP-IPV Booster / DTaP-IPV/Act-Hib / Prevenar	1	0	1
DTaP-IPV Booster / DTaP-IPV/Act-Hib / Prevenar 13	2	0	2
DTaP-IPV /Act-Hib	38	4	42
DTaP-IPV /Act-Hib / Infanrix Hexa	5	0	5
DTaP-IPV /Act-Hib / Infanrix Hexa / Prevenar 13	3	1	4
DTaP-IPV /Act-Hib / MMR Vaxpro / Prevenar 13	1	0	1
DTaP-IPV /Act-Hib / Prevenar	3	0	3
DTaP-IPV /Act-Hib / Prevenar 13	115	4	119
Hexyon	1	0	1
Infanrix Hexa	2	1	3
Infanrix Hexa / Prevenar 13	6	0	6
MMR	0	1	1
MMR Vaxpro	5	1	6
Pneumovax	5	0	5
Prevenar 13	4	0	4
Gardasil/Silgard	41	57	98
Cervarix	2	0	2
Main total	**243**	**70**	**313**

Table 1a. Reports broken down by severity and vaccine.

[1] An ADR 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.

Summary and conclusion to Q1 ADR reports

In this quarter, we note the following:

- There was an increase in the number of reports of adverse reactions after vaccination with DTaP-IPV/Act-Hib/Prevenar 13 and after DTaP-IPV/Act-Hib. Almost all of these ADR reports describe granulomas, of which the vast majority are assessed as non-serious. Most of the children were vaccinated several years before ADR report submission. The increasing number of reports likely reflects the public's increased awareness on vaccination granulomas and not an increase in actual numbers.
- Three ADR reports describe that the vaccination granuloma was removed surgically in full anaesthetic, although the literature indicates that they should resolve spontaneously.
- Three cases of vaccine failure and development of pertussis have been reported. The remaining ADR reports classified as serious include either known adverse reactions such as fever some with febrile seizures (4 cases – all in connection with DTaP-IPV/Act-Hib (+/- Prevenar 13)), or ADR reports in which an association is assessed as less likely based on either temporal relationship or symptomatology.
- For HPV vaccines, a decline in the number of ADR reports is recorded since the last quarter.
- In this quarter, we received altogether 57 ADR reports classified as serious – none of them was causality assessed to be possible adverse reactions.
- The majority of ADR reports still describe long-term headache, long-term dizziness and long-term fatigue, which do not appear as known adverse reactions in the product information. One ADR report describes the sleep disorder Kleine-Levin syndrome; It is considered that there is insufficient documentation to assess causality. This quarter recorded eight ADR reports of Postural Orthostatic Tachycardia Syndrome (POTS), one of fibromyalgia and one of hypothyroidism in connection with HPV vaccination.
- Many of the ADR reports about the HPV vaccine still lack information about relevant examinations such as X-rays, specialist examinations, scans, blood tests, etc., and/or the results thereof.

None of the new ADR reports shift the benefit-risk balance of the childhood vaccines.

Featured quarterly focus

Background

Thyroiditis is a relatively common condition and one of the most common conditions affecting the thyroid gland.

The incidence rate of hypothyroidism, irrespective of cause, is around 33 per cent per 100,000 person-years (1). The lifetime risk of developing hypothyroidism in Denmark is 2.7% (4.1 in women versus 1.3 in men) (1).

Autoimmunity plays a significant role in thyroiditis (especially in the case of postpartum thyroiditis and Hashimoto's thyroiditis). However, it is generally a polygenic, multifactorial disease, whereby genetically susceptible individuals are exposed to an exogenous factor that triggers an immune response (2).

Hashimoto's thyroiditis is an autoimmune condition occurring six times more often in women than men. While hyperthyroidism occurs early in the disease course, hypothyroidism occurs late in the disease course.

Thyroid antibodies are verifiable in up to 10% of the population (2).

Vaccination and thyroiditis

The literature holds descriptions of thyroiditis after vaccines other than HPV vaccines, e.g. influenza vaccine (3,4), however, there are no epidemiological studies confirming any association to this vaccine.

Excess incidence of thyroid conditions has been reported after HPV vaccination in one single article (5) involving a cohort study of 189,629 women. Although an increased rate ratio of Hashimoto's thyroiditis was found in the HPV-vaccinated group, it was assessed to be a random finding since no temporal relationship with the vaccine was established.

A further two studies have investigated the occurrence of autoimmune conditions, including thyroiditis, and an association, if any, to the HPV vaccine (6,7). Grimaldi-Bensouda et al. found no thyroiditis/thyroid conditions after exposure to HPV vaccine. The other study (8) is a major cohort study conducted in Denmark and Sweden including 997,585 girls/women aged between 10-17 years, of which 296,826 received a total of 696,420 HPV vaccine doses (Gardasil) and were observed for six months. Here as well, no excess incidence of thyroiditis or other thyroid conditions after the vaccine was found (table 1b). Thus, it is assessed that there is no evidence in the literature suggesting an association between thyroid diseases and HPV vaccine.

Incidences of thyroid disease	Unvaccinated			Occurring within 180 days after HPV vaccine administration		
	Person-years:	No. of cases	Incidence rate (95%CI)	Person-years:	No. of cases	Incidence rate (95%CI)
Graves' disease	2,373,554	237	9.99 (8.79-11.34)	229,914	27	11.74 8.05-17.12)
Hashimoto's disease	2,371,666	560	23.61 (21.73-25.05)	229,751	50	21.76 (16.49-25.71)
Other hyperthyroid conditions	2,373,629	250	10.53 (9.30-11.92)	229,946	23	10.00 (6.65-15.05)
Hypothyroidism	2,368,919	1018	42.97 (40.41-45.70)	229,563	79	34.41 (27.60-42.90)

Table 1b. Extract from table in the article by Arnheim-Dahlström L et al (7), showing no difference in occurrence of thyroid disease between vaccinated and unvaccinated girls/women.

Danish ADR reports

In Denmark, there has been a large increase in the number of reports of possible adverse reactions to the Gardasil/HPV vaccine in the past years. Many have reported reactions such as fatigue, headache and dizziness, which are symptoms seen in a condition like hypothyroidism. For this reason, considerably many have been screened for this condition, and the Danish Health and Medicines Authority's guideline on examination of HPV-vaccinated people (8) recommends to measure thyroid levels.

Until 1 May 2016, a total of 15 ADR reports describing various thyroid conditions after vaccination with Gardasil have been submitted in Denmark. The average age of the women is 21 years.

Often, the ADR reports only indicate the finding of hypothyroidism or hyperthyroidism without mentioning any examination results.

The DKMA has received two ADR reports of benign thyroid nodules in patients who had neither hypothyroidism nor hyperthyroidism.

The ADR reports often fail to indicate any temporal relationship between vaccination and symptom onset or time of diagnosis. Based on the available data, there is no clear picture of a temporal association, if any.

Conclusion

More than 600,000 Danish women have been vaccinated, and thyroid conditions are relatively common as mentioned. The number of thyroid conditions/thyroiditis reported as suspected adverse reactions to the HPV vaccine is assessed to be no higher than expected in the general population.

At present, there is therefore no signal in the reported adverse reactions concerning thyroid diseases.

Read more about the HPV vaccine on the DKMA website: *HPV vaccination protects against cervical cancer (in Danish only)* and *Adverse reactions from the HPV vaccine*

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Important notes

Always remember to record the vaccine batch number in connection with vaccination as well as the specific location on the body where the vaccine was injected. Batch number and product name are important details when you report suspected adverse reactions to the DKMA as it can significantly impact the evaluation of the medicine's safety.

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.

Analysis of contraceptive pills with focus on users and ADR reports of blood clots in Denmark

The DKMA has published a new report about contraceptive pills. In the report, we review the scientific literature on contraceptive pills and thromboembolic complications.

Besides the literature review, the report looks at contraceptive pill consumption among women who redeemed a prescription for contraceptive pills in the period 2011-2014 and analyses reports of suspected adverse reactions to contraceptive pills in the same period.

Summary of report conclusions

- The literature review showed that the risk of venous thromboembolism (VTE) depends more on the type of progesterone contained in the contraceptive pill than the dose of oestrogen. Women using 3rd and 4th generation contraceptive pills have a higher risk of VTE compared to women using 2nd generation pills. The risk of VTE is highest at the beginning of treatment.

  The literature review also showed that the risk of AMI and cerebral arterial thromboembolism (ATE) is especially impacted by the oestrogen dose; The higher the oestrogen dose in contraceptive pills, the higher the risk.
- A switch between different generations of contraceptive pills or between same generation products without a pause, so-called 'switch use', seems not to increase the woman's risk of VTE.
- The number of women redeeming a prescription for contraceptive pills has dropped by 9% in the period 2011-2014.
- Before 2011, most women used 3rd generation contraceptive pills. Over the period, the number of women using 3rd generation contraceptive pills has decreased, while the number of women using 2nd generation pills has increased, to the extent that most women used 2nd generation pills in 2014.
- About 11% of new users[2] redeemed the latest prescription in 2014 for 3rd or 4th generation contraceptive pills. New users in 2014 who chose 3rd and 4th generation contraceptive pills may have done so because they want to use contraceptive pills with a low oestrogen dose[3] (3rd and 4th generation pills), or contraceptive pills with anti-androgenic effects (4th generation pills), or because the women before 2011 used the said contraceptive pill generations with few adverse reactions only.
- Almost 7% of the switches made by non-new users in the period were from 2nd generation contraceptive pills to 3rd or 4th generation pills. One explanation could be adverse reactions to 2nd generation contraceptive pills. The analysis showed that the vast majority of women switching from 2nd generation contraceptive pills chose a generation that they had previously redeemed a prescription for.
- During the period 2011-2014, there were 406 reports of suspected adverse reactions to contraceptive pills. It is assessed that 238 (59%) concern blood clots.

[2] In this analysis, a new user is classified as a user having redeemed at least one prescription for contraceptive pills in 2014 but not in the preceding three years (2011-2013).
[3] 2nd generation contraceptive pills with low dose oestrogen were not marketed until 2015.

- Around 18% of the ADR reports of blood clots described that the women who were subsequently screened for thrombophilia proved to have heterozygous or homozygous factor V Leiden. The mutation is present in about 6.6% of the Danish population. Other risk factors are also described in the ADR reports, e.g. overweight, smoking, immobilisation in temporal association with the blood clot, etc.

The analysis does not alter the DKMA's previous recommendation to prescribe 2nd generation contraceptive pills as first choice in general.

Advice for prescribers
Doctors should always inform women who have used 3rd and 4th generation pills for a long period of time about the benefits and risks. If a woman has never tried 2nd generation contraceptive pills before, there is good reason for doctors to recommend a product switch at the next prescription renewal and then take action as required by the woman's experience with the new product. In any case, it is important to ensure continuous compliance with any risk-related precautions for use (see the product information).

The analysis of reported suspected adverse reactions to contraceptive pills shows that it remains important to take a detailed medical history and perform an objective examination prior to prescribing contraceptive pills. It is also important that women receive thorough advice about which symptoms to be alert to and respond to.

Read the report here: *Analysis of contraceptive pills (in Danish only)*

Focus on reported adverse reactions to selected biological medicines

Adverse reactions to biological medicines and biosimilars have been selected as a special focus area, with particular focus on suspected adverse reactions arising from switches between 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 that ADR reports from doctors, dentists and midwives should include information, whenever possible, about the medicine's name and batch number when ADR reports concern selected biological medicines. The selected biological medicines in special focus appear from a regularly updated list. See *the list (in Danish)*.

The focus area was previously discussed in *Danish Pharmacovigilance Update, February 2016* in an article reviewing the ADR reports that the DKMA received about selected biological medicines in 2015.

ADR reports
In the first quarter, the DKMA received 39 ADR reports about biological medicines/biosimilars on the above-mentioned list.

Medicine	Active substance	No. of ADR reports	Number of serious ADR reports	Number of ADR reports with indication of batch number
Omnitrope	somatropin	1	1	0
Cosentyx	secukinumab	1	1	1
Zarzio	filgrastim	1	1	0
Repatha	evolocumab	1	0	0
Enbrel	etanercept	5	3	1
Remicade	infliximab	6	5	0
Remsima	infliximab	24	12	17
TOTAL		**39**	**23**	**19**

Table 1: ADR reports received in Q1 of 2016 about biological medicines/biosimilars broken down by medicine/active substance and severity.

As can be seen from table 1, there have only been a few reports about the medicines Omnitrope, Cosentyx, Zarzio and Repatha.

We received five ADR reports about Enbrel, but remain to receive ADR reports about its biosimilar equivalent Benepali.

30 of the 39 ADR reports concern infliximab, of which six Remicade and 24 Remsima.

17 of the 24 Remsima ADR reports stated the batch numbers. This can only be said for two of the remaining ADR reports (Table 1). Thus there is more focus on stating batch numbers for biosimilar medicines.

Consumption of infliximab-containing medicines

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

This is also the only medicine for which the ADR reports describe adverse reactions occurring in connection with switches from reference product to biosimilar version.

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

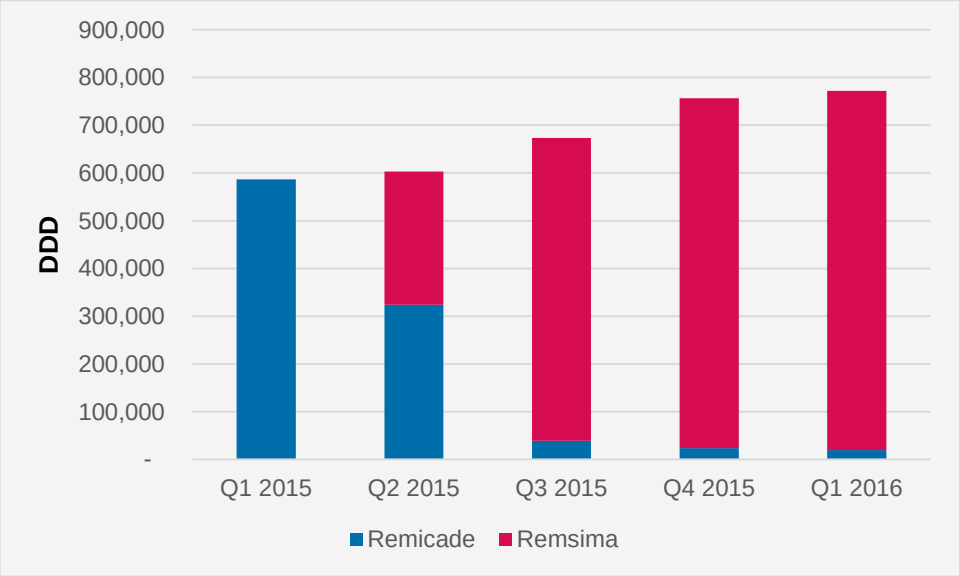

Figure 1. Quarterly DDD[4] consumption of infliximab-containing medicines broken down by Remicade and Remsima in Q1-Q4 of 2015 and Q1 of 2016.

[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.

Infliximab consumption increased in 2015 and is still increasing moderately in Q1 2016. The total consumption of infliximab-containing medicines in Q1 of 2016 was DDD 771,823.

Remsima was marketed in March 2015. It is evident from the consumption data that the Danish regions have followed the recommendations from the RADS (Rådet for Anvendelse af Dyr Sygehusmedicin (Council for Use of Expensive Hospital Medicine)) to switch from Remicade to Remsima. The increase in consumption is furthermore caused by the lower price of infliximab (Remsima) which has made it a first-line product in RADS' guidelines for biological treatment in the fields of rheumatology and gastroenterology. In the first quarter of 2016 the consumption of Remicade remained low, whereas the consumption of Remsima accounted for 97% of infliximab-containing medicines.

ADR reports about switches from Remicade to Remsima

In the first quarter of 2016, we received five ADR reports (one serious and four non-serious) describing suspected adverse reactions caused by switches:

- A patient experienced that the medicine had no effect as the disease in question exacerbated.
- A patient's hands, feet, and jaws started swelling. The patient had rheumatoid arthritis.
- A patient had a relapse of muscle and joint pain about four weeks after infusion. The symptoms disappeared after switching back to Remicade.
- A patient experienced general discomfort, generalised myalgia, arthralgia and exacerbation of known polyneuropathy. The patient switched from Remsima to another product because of the adverse reactions.
- A patient had myalgia, depressive thoughts, internal restlessness/urge to move and exacerbation of psoriasis disease, and Remsima was discontinued.

The ADR reports about switches from Remicade to Remsima in this review especially describe muscle and joint pain, which are known adverse reactions appearing in the summary of product characteristics.

Other ADR reports about infliximab-containing medicines

Among the serious ADR reports about Remsima are accounts of allergic reactions, muscle and joint pain, infections, etc., and among the serious ADR reports about Remicade are accounts of various infections and development of cancer. They are mostly known adverse reactions described in the concerned summaries of product characteristics.

The non-serious reports mainly describe known adverse reactions such as fever, fatigue and headache.

Conclusion

People treated with biosimilar medicinal products can be expected to develop the same adverse reactions known to occur with the reference product, and this review does not suggest that Remsima's adverse reaction profile is different from that of the reference product Remicade.

If the biological medicine has no effect, it could be because the existing disease has progressed, or because the active substance no longer has any effect on the patient's disease.

All ADR reports carried information about the medicine's name, and the medicine's batch number was provided in 19 of them.

In April 2016, the DKMA sent out information to health professionals, advising them to provide the details of names and batch numbers in ADR reports of biological medicines. Ahead, we expect that 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 adverse reactions and the individual Remsima batches has been identified.

Important notes
Batch number and product name are important details when you report suspected adverse reactions to the DKMA as it can significantly impact the evaluation of the medicine's safety.

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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:

- **Remifentanil hydrochloride (Ultiva):** Supply difficulties. Sent out 25 April.
- **Canagliflozin-containing medicines (Ivokana and Vokanamet):** Risk of lower limb amputation. Sent out 29 April.
- **Aprotinin (Trasylol):** New information about indication and safety after market relaunch. Sent out 26 May.
- **Haloperidol (Serenase) and alfentanil (Rapifen):** Delivery and supply difficulties. Sent out 16 June.
- **Thalidomide (Thalidomide Celgene):** New important advice regarding viral reactivation and pulmonary hypertension. Sent out 20 June.

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

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