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DANISH PHARMACOVIGILANCE UPDATE

Contents

News from the EU

News from the Danish Medicines Agency

Short news

Inhaled corticosteroids and risk of pneumonia in COPD patients

The European Pharmacovigilance Risk Assessment Committee, PRAC, has completed a review and evaluation of the known risk of pneumonia with inhaled corticosteroids for the treatment of COPD.

The benefits of inhaled corticosteroids outweigh the risks

The PRAC review confirms that COPD patients treated with inhaled corticosteroids are at increased risk of pneumonia; however the PRAC finds that the benefits of inhaled corticosteroids continue to outweigh their risks. The PRAC also looked at whether there were any differences in the risk of pneumonia between corticosteroid-containing products, but did not find any evidence to support any such difference. The product information of all inhaled corticosteroids describes pneumonia as a common adverse reaction.

PRAC's recommendation after review

- Inhaled corticosteroids can be used as before, but doctors should be vigilant for symptoms of pneumonia in COPD patients as the clinical features of pneumonia could be mistaken for exacerbations of the underlying disease. Symptoms of pneumonia are fever, chills, increased mucus production and changes in the colour of mucus, deterioration in cough and shortness of breath.
- The product information will be updated to reflect the current knowledge so that the risk of pneumonia is adequately described.

Background leading to the PRAC review

The risk that COPD patients treated with inhaled corticosteroids may develop pneumonia was observed in a study conducted in 2007. The study showed that patients treated with the inhaled corticosteroid, fluticasone, were exposed to a higher risk of pneumonia compared to the placebo group. New studies and meta analyses of the substance class have since added new knowledge about the risk of pneumonia in the treatment of patients with inhaled corticosteroids. The EMA therefore found that a thorough evaluation of the currently available data was needed.

Read the press release from the EMA: *PRAC reviews known risk of pneumonia with inhaled corticosteroids for chronic obstructive pulmonary disease*

Read more about the art. 31 referral here: *PRAC reviews known risk of pneumonia with inhaled corticosteroids for chronic obstructive pulmonary disease*

News from the EU

The European Pharmacovigilance Risk Assessment Committee is reviewing gadolinium contrast agents

The European Pharmacovigilance Risk Assessment Committee, PRAC, has initiated a review and evaluation of the risk of gadolinium deposition in brain tissue following MRI scans with gadolinium contrast agents.

Gadolinium contrast agents are diagnostic products given to patients before or during MRI scans to obtain better images of organs and tissues. After administration, gadolinium agents are mostly eliminated via the kidneys. However, there is an indication that gadolinium can build up in some body tissues, including in the liver, kidneys, muscles, skin and bones.

In recent studies, there have been observations of gadolinium in brain tissue. Although there have been no reports of clinical adverse reactions relating to this deposition, the PRAC will carry out a review of the risk of brain gadolinium deposits and will evaluate the overall safety of these products.

The DKMA contributes actively to this process.

Read EMA's press release: *EMA reviewing gadolinium contrast agents used in MRI scans.*

Updated precautions for use of idelalisib (Zydelig)

The European Pharmacovigilance Risk Assessment Committee, PRAC, has started a review of the safety of idelalisib for the treatment of chronic lymphocytic leukaemia (CLL) and follicular non-Hodgkin lymphoma.

Until the review has been completed, the PRAC recommends that the following precautionary measures be followed in parallel with the guidelines currently given in the product information.

- Idelalisib should not be started as first-line treatment in CLL patients with 17p-deletion or TP53-mutation. Patients who already take idelalisib first-line should be re-evaluated to ensure that the benefits still outweigh the risks.
- Idelalisib can still be used in combination with rituximab in CLL patients who have received at least one prior therapy, and as monotherapy in patients with follicular non-Hodgkin lymphoma that is refractory to two lines of treatment.
- Patients should be informed of the risk of serious and/or fatal infections, and treatment with idelalisib should not be started in patients with generalised infection.
- All patients treated with idelalisib should receive prophylaxis with antibiotics for Pneumocystis jiroveci pneumonia (PJP) and should be monitored for respiratory signs and symptoms. Regular monitoring for cytomegalovirus infection is also recommended.

- Regular blood measurements should be taken to detect neutropenia. In case of moderate or severe neutropenia, it may be necessary to interrupt treatment with idelalisib in line with the summary of product characteristics.

Review background
The review started after a higher rate of serious and fatal adverse events was seen in three clinical trials among patients who had idelalisib added to their standard first-line treatment. Most of the deaths were related to infections such as PCP or cytomegalovirus infections. The clinical trials, which have now been stopped, included patients with another disease profile and studied another treatment regimen than the currently authorised indication.

Letters have been sent out to doctors with information about the new restrictions, and the product information will be updated.

Read the press release from the EMA: *EMA recommends new safety measures for Zydelig*.

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 in February 2016 concern the following products:

- **Bcr-abl tyrosine kinase inhibitors: Glivec (imatinib); Sprycel (dasatinib); Tasigna (nilotinib); Bosulif (bosutinib); Iclusig (ponatinib)** – hepatitis B virus reactivation
- **Duodopa (levodopa/carbidopa, intestinal gel)** – intussusception
- **Lysodren (mitotane)** - sex hormone disturbances and development of ovarian macrocysts

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

Childhood vaccinations and reported suspected adverse reactions in Q4 of 2015

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 experts from relevant clinical specialties in Denmark.

Here are the results of the review for Q4 2015.

Since adverse reactions to the HPV vaccines have attracted attention over the last years, we present our review in two sections:

1. A review of the ADR reports related to vaccines in the childhood immunisation programme – excluding the HPV vaccine.

2. A review of the ADR reports related to the HPV vaccine.

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

Reports of suspected adverse reactions to vaccines in the childhood immunisation programme (excluding the HPV vaccine) Q4 of 2015

In the fourth quarter of 2015, the DKMA received a total of 147 ADR reports about vaccines in the childhood immunisation programme (excluding the HPV vaccine). Seven of them were classified as serious[1].

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

Vaccine	Non-serious	Serious	Total
DTaP Booster	2		2
DTaP-IPV Booster	17		17
DTaP-IPV Booster / DTaP-IPV/Act-Hib	1		1
DTaP Booster / Polio vaccine "SSI"	1		1
DTaP-IPV /Act-Hib	57	3	60
DTaP-IPV /Act-Hib / Infanrix	2		2
DTaP-IPV /Act-Hib / MMR Vaxpro / Prevenar 13	1		1
DTaP-IPV /Act-Hib / Prevenar	2		2
DTaP-IPV /Act-Hib / Prevenar 13	36	1	37
Infanrix Hexa	3		3

[1] 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.

Infanrix Hexa / Prevenar 13	1		1
MMR Vaxpro	7	3[2]	10
Pneumovax	3		3
Priorix	7		7
Total	**140**	**7**	**147**

Table 1a. ADR reports by severity.

Review and assessment of the serious ADR reports
When we assess the serious ADR reports, we investigate whether it is likely that there is a causal link to the vaccine.

The result of our causality assessment is based on four categories:

- Possible
- Less likely
- Insufficient documentation
- Unclassifiable

The categories were described in *Danish Pharmacovigilance Update, January 2015*.

Vaccine	ADR description	Assessment and causality
DTaP-IPV Act-Hib	A 3-month-old child had fever in the days before vaccination. On the day of vaccination, the child developed fever again and a cough. Four days after vaccination, the child was admitted to hospital with severe respiratory problems. Infection with parainfluenza and rhinovirus were verified with complicated bacterial pneumonia and sepsis.	Neither cough, pneumonia nor sepsis are known adverse reactions of the vaccine. Fever is a known adverse reaction, but in this case may be secondary to the verified viral and bacterial infections. It is therefore considered **less likely** that it could be related to the vaccine.
DTaP-IPV Act-Hib	A 1-year-old child developed a granuloma on the thigh and aluminium allergy after vaccination. The granuloma was removed as malignancy was suspected. The changes, however, were later verified as being reactive only.	Granuloma formation is a known adverse reaction to the vaccine. Causality is considered **possible**.
DTaP-IPV/Act-Hib Prevenar13	A 13-month-old boy died 8 days after vaccination (crib death). Before vaccination, the boy had had one febrile episode, and the diagnosis of adenovirus myocarditis was made in the autopsy findings. The virus was isolated from the pericardium, brain lining and brain.	Adenovirus is known to cause serious infections and is a known aetiology in crib death. Causality with the vaccine is therefore considered **less likely**.

[2] In two of these reports Gardasil® is suspected as the primary cause of the adverse reactions. The ADR reports are described in the section about adverse reactions from HPV vaccination.

DTaP-IPV/Act-Hib	A 3-month-old child developed redness of the entire leg, extending from foot to iliac crest, on the day of vaccination. The child was admitted to hospital.	Skin reactions are known adverse reactions, and causality with the vaccine is considered **possible**.
MMR Vaxpro	Ten months after vaccination, a 2-year-old child is described as having "induration erythema".	There are too few details, and the duration of the condition is not given, but acute redness is known after vaccination. The MMR Vaxpro vaccine does not contain aluminium and normally does not induce granulomas. It is possible that redness and induration were caused by the development of a granuloma, which is an adverse reaction to one or several other vaccinations with aluminium-containing vaccines (e.g. DTaP-IPV/Act-Hib), but it cannot be concluded from the ADR report. Causality with the MMR Vaxpro is therefore considered **less likely**.

Table 1b: Description of the suspected adverse reactions as appearing in the ADR reports and the causality assessment.

Review of the non-serious ADR reports

A total of 140 ADR reports were classified as non-serious. Most of them describe local reactions, especially granulomas (103 of the ADR reports).

Most of the reports of granulomas were reported after vaccination with DTaP-IPV Act-Hib and Prevenar13. However, a few (5) were reported as suspected adverse reactions to Infanrix® Hexa.

Conclusion

In the fourth quarter of 2015, we received a total of 147 ADR reports that concerned vaccines in the childhood immunisation programme (excluding the HPV vaccine).

Seven[3] were classified as serious. In two of these reports, a causal link to the vaccine was assessed as possible.

None of the new data shift the benefit-risk balance, and the DKMA therefore still maintains that the benefits of the vaccines outweigh the possible risks.

Note! Temporary change in the Danish childhood immunisation programme

As a result of technical problems in SSI's vaccine production, it has been necessary to temporarily change the Danish childhood immunisation programme.

It is currently not possible to obtain a five-valent vaccine, which corresponds to SSI's primary vaccine DTaP-IPV /Act-Hib. Nor is it possible to obtain the six-valent vaccine that was used in

[3] In two of these reports Gardasil® is also suspected as the cause of the adverse reactions. The ADR reports are described in the section about adverse reactions from HPV vaccination.

the first temporary immunisation programme (Infanrix hexa®). A corresponding six-valent vaccine, Hexyon®, will therefore be used instead.

Children who start vaccination from the time Hexyon® is supplied are therefore to be vaccinated with this vaccine. Besides protecting against the same diseases of SSI's DTaP-IPV /Act-Hib vaccine, Hexyon® offers protection against hepatitis B as well.

It is the first time Hexyon® is used in the childhood immunisation programme, and the DKMA has therefore decided to enact stricter reporting requirements, implying that all suspected adverse reactions to the vaccine must be reported by doctors (dentists and midwives).

ADR reports about the HPV vaccine received in Q4 2015

In the fourth quarter of 2015, the DKMA received a total of 230 reports of suspected adverse reactions to the HPV vaccine, of which 141 were classified as serious.

Table 2a shows the number of reports of suspected adverse reactions related to the HPV vaccine classified as serious and non-serious.

Vaccine	Serious	Non-serious	Total
HPV vaccine	141	89	230

Table 2a. ADR reports by severity.

Number of doses sold and number of ADR reports from 2009-2015

HPV vaccine	2009	2010	2011	2012	2013	2014	2015	Total
Number of reports	288	67	43	95	512	192	822	2019
– of which serious	25	7	9	18	191	98	475	823
Number of doses sold	347,69	151,476	163,37	349,730	488,22	114,467[4]	53,781	1,668,742

Table 2b. Number of ADR reports related to HPV vaccines received from 2009 to 2015 and the share of serious reports. The number of doses sold in Denmark is also shown. (Please be aware that when the DKMA receives additional information, this may imply changes. Consequently, there may be small variations between previously published figures and the figures reported here.)

The figures above show that we received many ADR reports in 2015, and if we look at the number of doses sold, the number of ADR reports is high. We have therefore investigated these ADR reports further to find out when the reported symptoms began relative to the time of vaccination.

[4] A review of data from 2014 has implied a small change in the number of doses sold.

Reports received in the period 2009-2015 by adverse reaction onset

We have recorded the start date[5] of suspected adverse reactions of the HPV vaccine for ADR reports received in the period 2009 to 2015. In case of no onset date, the vaccine administration date is used instead. In case of no vaccine administration date, the date when the ADR report was received is used instead (table 2c).

	Year the adverse reaction started (all ADR reports)								Total
Age groups	**2003-2008**	**2009**	**2010**	**2011**	**2012**	**2013**	**2014**	**2015**	
Over the age of 18	23	28	34	44	201	417	58	23	828
18 years or younger	138	260	98	81	100	99	67	37	880
Unknown	50	46	13	23	59	71	28	21	311
Total	211	334	145	148	360	587	153	81	2019

Table 2c: ADR reports for the HPV vaccine received in the period 2009 to 2015 by age group and ADR onset date.

As shown in the above table, we received most ADR reports with adverse reaction onset in 2013, followed by 2012 and 2009. These are also the years when the most doses were sold.

Several ADR reports received in 2015 concern adverse reactions that started earlier, and several of them involve adverse reactions that started years back, (table 2c). 822 ADR reports were submitted in 2015, but only 81 (10%) of them describe adverse reactions with onset in 2015.

This can probably be ascribed to the recent years' awareness on adverse reactions; It is a well known mechanism to see rising numbers of ADR reports when there is much awareness on adverse reactions to a specific medicine.

Age distribution

The HPV vaccine is the only vaccine in the Danish childhood immunisation programme that has also been offered free of charge to women outside the childhood programme.

From August 2012 until end-2013, the HPV vaccine was offered free of charge to women from the 1985-1992 birth cohorts. From 1 January 2014, the HPV vaccine was offered to women from the 1993-1997 birth cohorts. These birth cohorts have previously been offered the HPV vaccine. The offer was available until the end of 2015.

In this quarter, we received two ADR reports about boys/men who had received the HPV vaccine.

[5] If several adverse reactions with different start dates are described, the date of the first occurring adverse reaction is used.

Table 2d shows the age distribution of the persons described in the ADR reports we received in the fourth quarter of 2015.

Number of ADR reports about persons under 18	Number of ADR reports about persons aged 18 or over	Number of ADR reports with age unknown
123[6]	94[7]	13

Table 2d. Age of the persons described in the ADR reports received.

Review and assessment of the serious ADR reports about the HPV vaccine
A total of 141 reports were classified as serious.

The classification of ADR reports after our causality assessment is as follows:

- In two of the ADR reports, causality is classified as **possible**.
- Causality was **unclassifiable** in 60 of the ADR reports. These reports either have little or no information about a temporal relationship with the vaccine and/or describe no or very few examination results.
- 21 of the ADR reports were classified as containing **insufficient documentation**. In these reports, a consistent temporal relationship between the symptoms and vaccination is described; Examinations are adequately described, but the literature provides no evidence confirming or disproving a possible association.
- In 47 of the ADR reports, causality was classified as **less likely**. They describe a non-consistent temporal relationship with the vaccine, or the literature has found no evidence of an association between symptoms and vaccination.
- In eight reports, the causality for some adverse reactions was assessed as **less likely**, for others as **insufficient documentation**.
- In three reports, causality for some of the adverse reactions was considered **less likely**, for others it was **unclassifiable**.

Symptoms most frequently described in the serious ADR report

The table below shows the six most frequent symptoms described in the 141 serious ADR reports.

[6] Includes a boy
[7] Includes a man

Adverse reaction	Number of ADR reports describing the adverse reaction (percentage)
Fatigue[8]	105 (74)
Headache[9]	98 (70)
Dizziness[10]	98 (70)
Nausea[11]	65 (46)
Abdominal pain[12]	63 (45)
Arthralgia	56 (40)

The symptoms are often described as long-lasting, and more than one/several symptoms often appear in the ADR reports.

ADR reports with no specific diagnoses suspected as adverse reactions
Similar to our previous reviews, many of the ADR reports describe symptoms such as headache, fatigue, dizziness with or without fainting, paresthesia, joint symptoms and abdominal symptoms.

Many of this quarter's ADR reports carry inadequate information, especially regarding possible examinations made, which renders causality unclassifiable.

ADR reports with specific diagnoses suspected as adverse reactions

ADR reports with causality classified as possible

1. A woman with no prior illness was diagnosed with acute meningoencephalitis 10 days after the second HPV vaccine dose. Pleocytosis of 139 cells was verified (mostly monocytes).

   The EEG was diffusely in the low-frequency domain, and no microbiological aetiology was found. The MRI scan showed several small lesions in both hemispheres which, however, were undiagnostic, and it was subsequently discussed if it was a case of acute disseminated encephalomyelitis or allergic encephalomyelitis.

   Acute disseminated encephalomyelitis is a known, yet extremely rare, possible adverse reaction of Gardasil®, cf. the summary of product characteristics. As there is a close temporal relationship between vaccination and symptoms, an association to the vaccine is considered **possible**. The woman is recovering.

2. A report describes a woman who experienced anaphylaxis in relation to vaccination. The ADR report carries few details, but anaphylaxis is a known adverse reaction in vaccination.

[8] Coded as fatigue
[9] Coded as headache
[10] Coded as dizziness
[11] Coded as nausea
[12] Coded as abdominal pain, abdominal pain lower or abdominal pain upper

ADR reports with causality classified as less likely

3. Postural Orthostatic Tachycardia Syndrome (POTS). In this quarter, altogether 24 cases of POTS verified by tilt table test were reported. A temporal relationship between symptom onset and vaccination was reported for 16 of the women, one of whom was diagnosed with POTS already in 2010. For eight of the girls/women, the temporal relationship is either uncertain or not obvious.

   For one of the above women, Complex Regional Pain Syndrome (CRPS) was also reported as suspected adverse reaction to the vaccine. Another woman was diagnosed with POTS several years before vaccination, but experienced exacerbation after vaccination.

   The European Medicines Agency's (EMA) safety review in November 2015 showed that there is no evidence confirming an association between the HPV vaccine and the POTS and CRPS syndromes, and these ADR reports are therefore classified as **less likely** to be related to the vaccine. Some of the ADR reports also describe symptoms with **unclassifiable** causality or have **insufficient documentation** to evaluate an association.

4. One report describes a woman with hypertension as suspected adverse reaction to the vaccine. There is no consistent temporal relationship with the vaccine, and causality is therefore considered **less likely**.

5. One report describes a girl developing juvenile myoclonic epilepsy as suspected adverse reaction to the vaccine. In the literature[13], there is no evidence supporting a link to HPV vaccines, and causality is considered **less likely**.

6. Two ADR reports describe women who developed hypothyroidism, one of whom also developed inflammatory intestinal condition. Another report describes a woman who developed Hashimoto's disease and psoriasis as suspected adverse reactions to the vaccine, and in a third report a woman who developed diabetes. In the literature[14], no association between any of these conditions and the HPV vaccine was found, and causality is considered **less likely**.

7. A report describes a woman who had lymph node swelling and was diagnosed with Cat Scratch Disease. This infection diagnosis may explain the symptoms, and a causal link to the vaccine is therefore considered **less likely**.

8. In another report, T-cell leukaemia in a woman occurring three years after vaccination is reported as a suspected adverse reaction to the vaccine. There is no evidence in the literature of an association between cancer and HPV vaccines. Nor is there a consistent temporal relationship between vaccination and the development of leukaemia, and causality is therefore considered **less likely**.

[13] Arnheim-Dahlstrøm L et al: Autoimmune, neurological, and venous thromboembolic adverse events after immunization of adolescent girls with quadrivalent human papillomavirus vaccine in Denmark and Sweden: cohort study. BMJ 2013 ;347():f5906

9. In an ADR report, allergies, including food and pollen allergies, are reported as suspected adverse reactions to the HPV vaccine. There is no evidence in the literature supporting such association. These conditions are relatively common, and causality is considered **less likely**.

ADR reports with causality classified as containing insufficient documentation

10. A woman developed Addison's disease shortly after vaccination.

11. Two persons developed arrhythmia. The one was treated with ablation, the other had a ECG monitor inserted (Reveal).

12. Two ADR reports described women who had narcolepsy, one of whom with cataplexy.

13. Another ADR report described a woman who developed chronic fatigue syndrome. There is little evidence in the literature supporting a connection to Gardasil® – however, one article does describe that there is no association between chronic fatigue syndrome and the HPV-vaccine[14].

14. In two ADR reports, Raynaud's disease is described as a suspected adverse reaction. It is a relatively common disorder.

In regard to the above ADR reports 10-14, there is no evidence in the literature either confirming or disproving an association, and causality is classified as **insufficient documentation**.

Review of the non-serious ADR reports
We received a total of 89 ADR reports classified as non-serious.

Similar to the serious ADR reports, the most frequent symptoms are fatigue, headache, dizziness, nausea, abdominal pain and joint symptoms.

Conclusion
We received a total of 230 reports concerning the HPV vaccine in the fourth quarter of 2015. 141 of them were classified as serious.

The volume of ADR reports is about the same as in Q3 2015. There are still only very few ADR reports (2) for which the DKMA assesses that an association to the vaccine is possible.

A total of 44 ADR reports with specific diagnoses were received. 24 of them involved POTS as a suspected adverse reaction to the vaccine.

There are still many ADR reports for which there is insufficient documentation in the literature to link the adverse reactions to the vaccine. In addition, many of the ADR reports are unclassifiable, either because the temporal relationship between symptoms and vaccinations is inadequately described, or because there is no information about e.g. examinations.

[14] Donegan K et al: Bivalent human papillomavirus vaccine and the risk of fatigue syndromes in girls in the UK. Vaccine 2013,43(9), 4961-4967.

Like our previous reviews, the vast majority of these adverse reactions concern long-term symptoms with fatigue, headache, dizziness, complaints about pain from different organ systems with no identified cause.

None of the new data shift the benefit-risk balance of the vaccine.

We still encourage doctors and patients to continue reporting suspected adverse reactions to the HPV vaccine which are used for the important assessment of the safety profile of HPV vaccines. Adverse reactions can be reported electronically at *www.meldenbivirkning.dk* (report a side effect).

Note! New HPV vaccine in the childhood immunisation programme – stricter reporting requirements

On 1 February 2016, a new HPV vaccine entered the childhood immunisation programme. The new HPV vaccine is called Cervarix®. It is the first time Cervarix® is used in the Danish childhood immunisation programme, and therefore the DKMA has decided to enact stricter reporting requirements, implying that doctors must report all suspected adverse reactions to the vaccine to the DKMA.

Public funds to research adverse reactions in HPV vaccination

The Danish Parliament has earmarked DKK 7 million for research in adverse reactions to HPV vaccination. These public funds have been appropriated for research projects that can contribute to greater knowledge about any link between the HPV vaccine and a number of serious symptoms.

For more information, please see: *Public funds to research adverse reactions to HPV vaccination (in Danish only)*

Danish case-control study among HPV vaccinated women

More knowledge is needed, and Statens Serum Institut (SSI) is therefore initiating a case-control questionnaire study to improve our understanding of any differences between the group of women who have reported serious adverse reactions from the HPV vaccine and the group of women, also vaccinated, but who have not reported any adverse reactions.

The study started in February 2016.

Further information is available in the SSI's newsletter: *EPI-NEWS NO. 4 2016*.

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 to DKMA.

Remember to record the vaccine batch number as well as the specific location on the body where the vaccine was injected as it can significantly impact the evaluation of adverse reactions. Also remember to state the product name and batch number when reporting adverse reactions to the DKMA.

Reports of granuloma formation after vaccination with aluminium adjuvant vaccines

In the past years, the DKMA has recorded an increase in the number of ADR reports about the formation of granulomas after vaccination. Less than 10% of the granulomas reported as suspected adverse reactions to the vaccines in 2015 occurred in 2015. Most of them occurred in the period 2011-2014, but has not been reported until now.

	Before 2006	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	Total
ADR report received	0	2	0	3	2	7	10	27	55	124	284	514
Granuloma occurred*	6	4	5	16	28	45	84	128	107	66	25	514

*We have reviewed the ADR reports received and recorded the onset date of the granuloma. In case of no onset date, the vaccine administration date is used instead. In case of no vaccine administration date, the date when the ADR report was received is used instead.

We assume that the increase is attributable to the past years' awareness on granulomas and aluminium-containing vaccines. In the vast majority of cases, granulomas have been reported as suspected adverse reactions to DTaP-IPV /Act-Hib vaccination, and in one case the Prevenar13 pneumococcal vaccine was co-administered. Granulomas have also been reported with other vaccines in the childhood immunisation programme, yet to a far less extent.

Since the concentration of aluminium varies between vaccines, some of which contain none, we advise those who report vaccination granuloma as adverse reactions to consider which of the vaccines they suspect to be the cause. Their suspicion could for example be justified in the vaccine's aluminium content or the injection site relative to the granuloma that has developed.

The following article provides an overview of our understanding so far of granulomas and the handling of the condition in clinical practice.

Vaccination granulomas

By Jeanne Duus Johansen, Professor, Consultant, MD, National Allergy Research Centre, Department of Dermato-Allergology, Herlev-Gentofte Hospital

Aluminium absorbed vaccines can cause severely itching subcutaneous granulomas (lumps) at the injection site. They are often observed weeks or months after vaccination and may persist for a long time.

Aluminium is used as an adjuvant stimulating the immune response and is considered necessary for inactivated vaccines to catch on. For this reason, a number of the vaccines used in Denmark are aluminium adsorbed, i.e. all vaccines against diphtheria and/or tetanus, both primary and booster DTaP-IPV /Act-Hib vaccines, vaccines against HPV, pneumococcus, hepatitis A and/or B, TBE and meningococcal group C.

Many of them are used in the Danish childhood immunisation programme, and vaccination granulomas are observed frequently in small children. For most of the children with vaccination granulomas, contact allergy to aluminium is verified.

Frequency, clinical practice and process
The risk of granuloma formation is described in the product information of several aluminium adjuvant vaccines as a known but rare adverse reaction.

The incidence rate of vaccination granulomas was approx. 1% among 76,000 Swedish children immunised against pertussis, tetanus and diphtheria with an aluminium adjuvant vaccine from Statens Serum Institut in the 1990s [Bergfors et al. 2003, Lidholm et al. 2013]. There is no similar Danish study, but vaccination granulomas have been known since the 1980s [Kaaber et al. 1992].

Vaccination granulomas are typically 1-3 cm in size, firm and located subcutaneously. There may be hyperpigmentation, hypertrichosis and/or eczema of the skin covering the granuloma. In most cases, onset occurs after the third dose of DTaP-IPV /Act-Hib, i.e. around the age of 1-2 years, but it may be observed before or after.

The symptoms are strongest in the beginning with severe itching often with observations of excoriations in the area, and sleep may be disrupted. This is followed by a period with intermittent symptoms, until the condition burns out. The symptoms may be long-lasting, and in the first major Swedish study, 75% of the children still had symptoms four years after (median) [Bergfors et al. 2003]. In the latest Danish report of vaccination granulomas in children, 84% still had symptoms 1.6 years (median) and up to 9.5 years after they consulted a dermatologist [Salik, E et al, 2016]. Exacerbation of symptoms may be seen in connection with stomach or bronchial infections.

Aluminium allergy and clinical consequences
Aluminium allergy can be observed in more than 90% of children with vaccination granulomas [Salik E, 2016; Bergfors E et al., 2013]. Aluminium allergy is a type IV allergic reaction involving T lymphocytes. The allergy is verifiable by an allergy test, epicutaneous patch test, performed by a dermatologist.

Aluminium salts are contained in a number of skin products such as antiperspirants and certain sunscreens as declared on the label. Aluminium may also be present in metal objects such as buttons and buckles. Between 10-20% of parents to children with vaccination granulomas state in questionnaires that their children have experienced rashes from one of several of the above objects [Bergfors E, 2013; Salik, E et al, 2016].

Aluminium is present in various foods, normally in small amounts. Aluminium may spill over to food from pots and kitchen utensils made of aluminium or from packaging. There is no scientific evidence that aluminium in food has an impact on the symptoms.

Several studies indicate that aluminium allergy for most children is transient or that it weakens to a point where it can no longer be verified. In a Swedish study, it was no longer possible to verify aluminium allergy in 2 out of 3 children after 5 years or longer from the first time the

allergy was verified. The longer the time, the bigger the chance that the aluminium allergy test came out negative [Lidholm A et al, 2013].

Examination, treatment and advice
The diagnosis is made based on the medical history compared to clinical findings and, if relevant, by verification of aluminium allergy by a dermatologist. Knowledge of vaccination granulomas is important to avoid unnecessary procedures (biopsies, X-ray, surgical removal, etc.)

The treatment consists of reducing the itching and thus scratching, which leads to further itching. Itching at night can be reduced if the child sleeps at cool temperatures. It is important to prevent skin scratching both during the day and the night, for example by using bandages or patches. Periodic treatment (2-3 weeks) with corticosteroids (group II) may be necessary to reduce symptoms, but it does not remove the granuloma.

There are no studies on the efficacy of various treatment measures.

(Continued) vaccination:

- Vaccination with aluminium-containing vaccines should be administered by deep intramuscular injection to reduce the risk of granulomas (SSI recommendation since 1999).
- The risk of reformation of granulomas in continued vaccination seems small according to Swedish studies: While two (8%) of 25 children with aluminium allergy developed granulomas in connection with re-vaccination, the rest tolerated vaccination [Lidholm et al, 2013].
- It is important to weigh the risk of granuloma reformation against the risk of catching a potentially life-threatening infection.
- There can be variations in the aluminium content and aluminium salts of the same type of vaccine from different manufacturers. There are no studies directly comparing the risk of granuloma formation with the different products.

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 to DKMA.

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Lithium intoxication

The DKMA has lately received several ADR reports of lithium intoxication. The ADR reports involved patients who were treated with lithium while they were dehydrated or had other risk factors.

Lithium has a narrow therapeutic index, and toxic effect begins at serum concentrations above 1.2 mmol/L.

Be aware of the following contraindications:

- Renal impairment and cardiac insufficiency
- Conditions with disturbances in fluid/electrolyte balance
- Hypothyroidism
- Addison's disease
- Pregnancy in the 1st trimester

In addition, caution should be taken in the treatment of patients:

- with somatic disease with fever (e.g. influenza)
- who are to undergo major surgery
- dieting or on low sodium diet or otherwise dehydrated.

Under these circumstances, treatment should be interrupted, or the dose should be reduced, and serum concentrations should be monitored. Due to the risk associated with dehydration, fluid should be administered parenterally in patients treated with lithium who are unconscious for a long time, who have severe vomiting and in connection with fasting before anaesthesia. Lithium treatment should be stopped 2-3 days before major surgery.

Indication for lithium
Mania and prevention of manic depressive disorder.

Hypotonic solutions for infusion may cause hyponatraemia with severe cerebral symptoms

By Christian Overgaard-Steensen, MD, PhD, Department of Neuroanaesthesiology, Copenhagen University Hospital

Cases of hyponatraemia with severe cerebral symptoms have been observed with the use of hypotonic solutions for infusion. They have been reported to the DKMA.

Hospitalised patients often have non-osmotic release of arginine vasopressin (antidiuretic hormone). This causes reduced renal water excretion[1]. When hypotonic solutions are infused there is a risk of hospital-acquired hyponatraemia. This could be dangerous due to the development of cerebral oedema and is associated with increased morbidity and mortality[2-4]. Solutions for infusion which are highly hypotonic in patients include the following products: Glukose isotonisk (5% glucose), Darrow-glukose, Kalium-natrium-glukose, Hydreringsvæske "SAD" and Rehydrex. The solutions are initially isotonic, but after infusion the glucose is metabolised and becomes highly hypotonic. Ringer's acetate and Ringer's lactate are mildly hypotonic in patients and therefore may cause minor drops in plasma sodium levels. 0.9 % NaCl (Isotonic NaCl) is initially isotonic in the patient. Cases of hospital-acquired hyponatraemia can be reduced if intravenous solutions – quantity and quality – are prescribed with the same care and monitoring practice as for other medicines.

Advice for prescribers

- Caution and close monitoring of plasma sodium levels in intravenous infusion of large quantities (e.g. 5 ml/kg/day) of highly hypotonic solutions in hospitalised patients.
- Special care with the use of highly hypotonic solutions for infusion in children since their brain is relatively large compared to the intracranial space[5,6].
- Special care should be taken in patients at risk of increased intracranial pressure, i.e. patients with affected consciousness with possible head injury or possible intracranial pathology such as meningitis, haemorrhaging, cerebral oedema or tumour. For patients in this category, even minor drops in plasma sodium levels – e.g. 3-5 mmol/l could be critical. In general, 0.9 % NaCl is used as solutions for infusion. Mildly hypotonic solutions like Ringer's lactate or Ringer's acetate and highly hypotonic solutions therefore are generally not used[7].
- Patients with secondary hyperaldosteronism (e.g. patients with liver failure) accumulate sodium in the body, and sodium restriction is therefore part of the treatment. However, these patients often have non-osmotic release of arginine vasopressin with reduced renal water excretion. Infusion of large quantities (e.g. 5 ml/kg/day) of highly hypotonic solutions could lead to overhydration and hyponatraemia. This may increase morbidity and mortality. If administration of glucose is needed, glucose solutions higher than 5% Glukose can be used.

Patients having developed hyponatraemia with severe symptoms (altered consciousness or seizures) are treated intravenously with a bolus dose of 3% NaCl 2 ml/kg over 5 minutes and repeated for maximum 3 times[8]. Plasma sodium levels and treatment are subsequently monitored to ensure sodium levels do not rise too quickly[8]

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NSAIDs should be avoided in patients at risk of heart disease

Prescribers of NSAID products should pay special attention to the increased risk of heart diseases associated with this type of medicine.

The recommendation remains that these products should be used at the lowest effective dose for as short a time as possible.

In the SmPCs of NSAID products it appears among other things that:

- Diclofenac, ibuprofen and naproxen are contraindicated in severe heart insufficiency.
- Patients with significant risk factors for cardiovascular events e.g. hypertension, hyperlipidaemia, diabetes mellitus and patients who smoke should only be treated with diclofenac after careful consideration.
- Naproxen has the lowest risk, while diclofenac is considered to have the same relatively high risk as the newer products (COX-2-inhibitors). Ibuprofen at high doses (2400mg daily) is also considered to have a relatively high risk.

For more information, please see:
New recommendations for use of diclofenac-containing painkillers (in Danish only).

NSAID – non-steroid anti-inflammatory drugs – report on consumption, reported adverse reactions and adverse events in Denmark (in Danish only).

Pregabalin and abuse potential

Several reports of misuse and potential abuse of pregabalin and epidemiological studies have raised concerns about the medicine's abuse potential.

In collaboration with Aalborg University Hospital, the DKMA has made a literature review of pregabalin to further assess the medicine's abuse potential[15]. To get an overview of pregabalin consumption in Denmark, we conducted a pharmacoepidemiological study[16] focused on identifying characteristics of patients with higher consumption than recommended.

As described in *Danish Pharmacovigilance Update, May 2015* the number of pregabalin users has risen sharply in Denmark since marketing (figure 1).

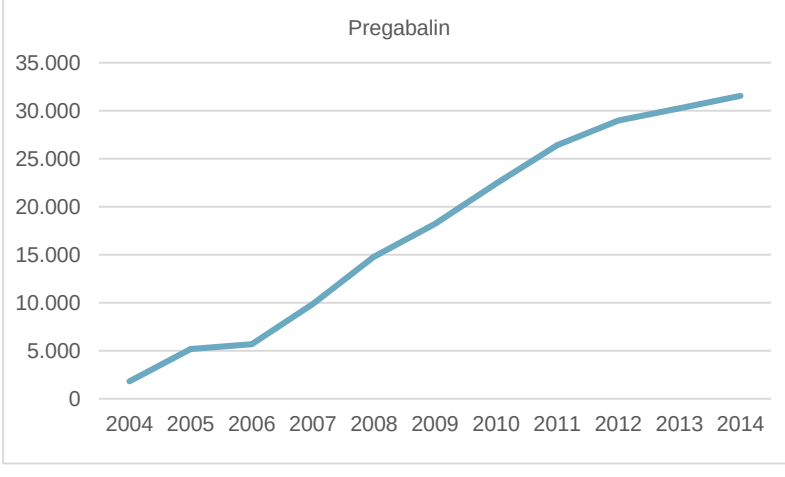

Figure (1): Number of people having redeemed at least one prescription for pregabalin in a year (Register of Medicinal Product Statistics, medstat.dk).

In Denmark, pregabalin is authorised for the treatment of neuropathic pain, epilepsy and generalised anxiety. Neuropathic pain was added to the indications in 2006. Table 1 shows that prescriptions for pregabalin in 2014 were primarily redeemed for anxiety (28.7%) and pain (30.3%). Note, however, that the indication is unknown for quite many of the prescriptions.

[15] Ole Schejerning, Mary Rosenzweig, Anton Pottegård, Per Damkier and Jimmi Nielsen, Abuse potential of Pregabalin, CNS Drugs (2016), 30:9-25

[16] Ole Schejerning, Anton Pottegård, Per Damkier, Mary Rosenzweig and Jimmi Nielsen, Use of Pregabalin – A nationwide pharmacoepidemiological drug utilization study with focus on abuse potential, Pharmacopsychiatry, 2016.

Indication noted on prescription redeemed	% of all pregabalin prescriptions redeemed in 2014
Unknown/blank	39.8
For pain	30.3
For anxiety	28.7
For epilepsy	1.1
Other	0.1

Table (1): Indications noted on redeemed pregabalin prescriptions in 2014 and 2015 (Register of Medicinal Product Statistics).

Conclusion on literature review and pharmacoepidemiological study

Pregabalin may cause euphoria and dissociative effects at doses higher than therapeutic doses. In clinical studies, 1-10% of the patients felt euphoric. Euphoria seems to be a dose-dependent adverse reaction in pregabalin use, which supports the concerns that pregabalin has an abuse potential.

In the pharmacoepidemiological study, the use of pregabalin was investigated in Danish health registers. A sharp increase in consumption is observed (as described in figure 1). However, use of pregabalin at higher doses than recommended is recorded only for a very small share of patients, and the analysis seems to indicate that there is no major abuse potential in the Danish consumption pattern (Lorenz-1[17] value of 6.1%). This analysis does not take into account any abuse in sub-populations.

Be aware of abuse in patients already receiving medicines with a known abuse potential

Doctors should always be vigilant for symptoms of abuse when pregabalin is used to treat patients who are treated concomitantly with benzodiazepines, antipsychotics and opioids.

The majority of the cases of pregabalin abuse described in the literature concerns patients with a history of abuse. The literature review shows that pregabalin has an abuse potential and that doctors should be vigilant for symptoms of abuse and should exercise caution when treating patients with a history of abuse.

[17] Lorenz value 1: This value indicates how big the abuse potential of a product is. The Lorenz value 1 is usually higher than 10% for drugs with a high abuse potential such as strong opioids and benzodiazepines and less than 5% for drugs with a minor abuse potential.

List of biological medicines and biosimilars

The list of medicines subject to stricter monitoring has been updated as of 1 March 2016.

See the list here.

The DKMA's annual pharmacovigilance report 2015

The DKMA's annual pharmacovigilance report for 2015 has just been published on our website. Here you can read about the development in the number of ADR reports, gain an insight into our focus areas and the European collaboration in the pharmacovigilance area as well as see a selection of the ADR signals we processed in 2015, and much more.

Read the *DKMA's annual pharmacovigilance report 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:

- **SGLT2 inhibitors (canagliflozin, dapagliflozin, empagliflozin)**: Updated recommendation about the risk of diabetic ketoacidosis in treatment with SGLT2 inhibitors. Sent out 14 March.
- **BCR-ABL tyrosine kinase inhibitors (imatinib, dasatinib, nilotinib, bosutinib and ponatinib)**: Reports of reactivation of Hepatitis B virus. Sent out 28 March.
- **Zydelig (idelalisib)**: Increased risk of serious adverse reactions including death, generally due to infections in first-line treatment with Zydelig for chronic lymphatic leukaemia (CLL) and recurring indolent non-Hodgkins lymphoma. Sent out 23 March.

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

Head of Pharmacovigilance and Editor-in-Chief signs off

After seven and a half years heading the DKMA's Pharmacovigilance & Medical Devices Division, Henrik G. Jensen has decided to retire.

Besides heading the DKMA's Pharmacovigilance & Medical Devices Division, Henrik was a dedicated Editor-in-Chief of Danish Pharmacovigilance Update, which was one of the first major initiatives he helped organise.

Openness and communication have always guided Henrik's work.

"In the seven and a half years I have headed the Pharmacovigilance Division, I have felt strongly about building relations and encouraging dialogue with those who are affected by our work: doctors and other health professionals, patients and the industry – each and everyone I have considered as collaboration partners in our work. And I have greatly appreciated being part of the pharmacovigilance activities in Denmark. I'm resigning after more than seven good, but also intense, years – a period where the awareness on pharmacovigilance has grown more and more. I now look forward to watching the future pharmacovigilance work from the sidelines. Not least will I keep abreast of developments through Danish Pharmacovigilance Update." Henrik G. Jensen.

Helle Harder, Head of Unit under Henrik G. Jensen, will be acting as Head of the Pharmacovigilance & Medical Devices Division and hence also takes over responsibility for Danish Pharmacovigilance Update.

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