LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY

NO. 11 • VOLUME 6 • DECEMBER 2015

DANISH PHARMACOVIGILANCE UPDATE

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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.

At the PRAC meeting in November 2015, there were no signals for which the PRAC considered it necessary to make any changes to marketing authorisations or product information.

See EU's list of recommendations on safety signals: *PRAC recommendations on signals November 2015.*

Childhood vaccinations and reported suspected adverse reactions in Q3 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 Q3 2015.

Since adverse reactions to the HPV vaccine 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 adverse reactions to vaccines in the childhood immunisation programme (excluding the HPV vaccine) Q3 of 2015

In the third quarter of 2015, the DKMA (formerly the Danish Health and Medicines Authority (DHMA)) received a total of 117 ADR reports about vaccines in the childhood immunisation programme (excluding the HPV vaccine). 14 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
DT booster	3		3
DTaP-IPV Booster	5	1	6
DTaP-IPV Booster / DTaP-IPV/Act-Hib	1		1
DTaP-IPV /Act-Hib	43	4	47
DTaP-IPV /Act-Hib / Infanrix Hexa	2		2
DTaP-IPV /Act-Hib / Infanrix Hexa / Prevenar 13	2		2
DTaP-IPV /Act-Hib / MMR Vaxpro / Prevenar 13	5		5
DTaP-IPV /Act-Hib / Prevenar	2		2

[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.

DTaP-IPV /Act-Hib / Prevenar 13	16	3	19
Infanrix Hexa	4	1	5
Infanrix Hexa / Prevenar 13	2	1	3
MMR Vaxpro	7	3	10
Pneumovax	7		7
Polio vaccine "SSI"	1		1
Prevenar	0		0
Prevenar 13	2	0	2
Priorix	1	1	2
Total	**103**	**14**	**117**

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
- Missing/insufficient documentation
- Unclassifiable

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

Vaccine	ADR description	Assessment and causality
Infanrix Hexa	A 1-year-old girl developed pertussis. The girl had been vaccinated with two doses.	Most likely this is a case of vaccine failure, which is a known phenomenon.
Infanrix-Hexa Prevenar13	A 6-month-old boy developed a lump at the injection site, had fever and vomited in connection with vaccination. His asthma was aggravated, and he later developed milk and gluten intolerance.	Local reactions, fever and vomiting are known adverse reactions, and causality with the vaccine is considered **possible**. The vaccines have neither been observed to aggravate existing asthma nor to induce allergies, and an association to these symptoms is considered **less likely**.
DTaP-IPV/Act-Hib	A 3-year-old girl, who was fully immunised with three doses, developed pertussis.	Most likely this is a case of vaccine failure, which is a known phenomenon.
DTaP-IPV/Act-Hib	A 1-year-old boy developed a granuloma on his thigh around the area of the injection site. The boy was admitted to hospital.	Granuloma formation is a known adverse reaction, and causality is considered **possible**.

MMR VAX-PRO	About one month after vaccination, a 12-year-old girl developed papillitis/ papilledema.	There is a temporal relationship with vaccination, but it is not possible to find other case reports in the literature describing a similar development of papillitis/papilledema after MMR vaccination. On the available basis, the ADR report is classified under the category **insufficient documentation**.
DTaP-IPV/Act-Hib Prevenar 13	A 3-month-old girl developed fever and purpura on the lower extremities on the day of vaccination.	The symptoms were interpreted as "discolored leg syndrome", which is an adverse reaction known to occur especially with the DTaP-IPV/Act-Hib vaccine. A causal relationship with the vaccine is therefore considered **possible**.
DTaP-IPV/Act-Hib	A 1-year-old girl developed an itching granuloma in connection with vacci-nation. She was admitted to hospital.	Granuloma formation is a known adverse reaction, and causality is therefore considered **possible**.
Gardasil and Priorix	A 12-year-old girl developed multiple symptoms.	The ADR report is included in the review of adverse reactions to the HPV vaccine below.
MMR vaxpro	Seven days after vaccination, a 13-year-old girl developed gastroenteritis and pancreatitis.	There are several case reports of pancreatitis after MMR vaccination, and causality is therefore considered **possible**.
Prevenar13 DTaP-IPV Act-Hib	In the evening on the day of vaccination, a 1-year-old girl had fever and febrile seizures.	Causality is considered **possible** since fever is a known adverse reaction, and there is a consistent temporal relationship between vaccination and adverse reaction.
DTaP-IPV Booster	A few hours after vaccination, a 5-year-old boy developed excessive redness and swelling of the arm in which the vaccination was given.	Causality is considered **possible** since these are known adverse reactions to the vaccine.
DTaP-IPV/Act-Hib	A 4-month-old boy developed a granuloma and was verified with aluminium allergy after vaccination. He was admitted to hospital.	Causality is considered **possible** since granuloma formation and aluminium allergy are known adverse reactions to the vaccine.
Prevenar13 DTaP-IPV/Act-Hib	A 1-year-old boy developed aluminium allergy and granuloma formation at the injection site. The boy was admitted to hospital.	Causality is considered **possible** since granuloma formation and aluminium allergy are known adverse reactions.
MMR vaxpro	A 14-month-old boy developed a rash and fever five days after vaccination. The boy was admitted to hospital.	Causality is considered **possible** since these are known adverse reactions to the vaccine.

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 103 ADR reports were classified as non-serious. The vast majority of them are local reactions, especially granulomas, which is described in 76 cases.

Most of the ADR reports about granulomas were reported after vaccination with DTaP-IPV Act-Hib and Prevenar13. However, a few (8) were reported as suspected adverse reactions to Infanrix® Hexa.

Conclusion

In the third quarter of 2015, we received a total of 117 ADR reports that concerned vaccines in the childhood immunisation programme (excluding the HPV vaccine).

14 of them were classified as serious. In most of these ADR reports, a causal link to the vaccine was assessed as possible. Many of the ADR reports describe known adverse reactions.

One single report described a patient who developed papilledema in temporal association with the vaccine. However, no corresponding descriptions are found in the literature, which means that there is no evidence to support this.

There are no new data shifting the benefit-risk balance, and therefore the DKMA assesses that the benefits of the vaccines still outweigh the possible risks.

ADR reports about the HPV vaccine received in Q3 2015

In the third quarter of 2015, the DKMA (formerly the Danish Health and Medicines Authority (DHMA)) received a total of 205 reports of suspected adverse reactions to the HPV vaccine, of which 119 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	119	86	205

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	to 30 Sept. 2015	Total
Number of reports	288	67	43	95	512	192	593	1790
– of which serious	25	7	9	18	186	98	323	666
Number of doses sold	347,690	151,476	163,374	349,730	488,224	114,467	45,914	1,660,875

Table 2b. Number of ADR reports related to the HPV vaccine received from 2009 to 30 September 2015, broken down by serious and non-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 within a relatively short period of time, and if we look at the number of doses sold in 2015, the number of ADR reports is high. We have therefore looked closer into these ADR reports to find out when the reported symptoms began.

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

We have recorded the start date[2] of suspected adverse reactions of the HPV vaccine for ADR reports received in the period 2009 to 30 September 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, see table 2c.

Age group	Year the adverse reaction started (all ADR reports)								Total
	2003-2008	2009	2010	2011	2012	2013	2014	2015	
Over the age of 18	22	25	30	41	181	375	45	18	737
Under the age of 18	136	258	97	81	100	97	65	34	868
Unknown	34	24	3	4	37	57	13	13	185
Total	192	307	130	126	318	529	123	65	1790

Table 2c: ADR reports for the HPV vaccine received in the period 2009 to 30 September 2015 by ADR start date.

As shown in the above table, we have 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. From August 2012 until end-2013, the HPV vaccine was offered free of charge to women from the 1985-1992 birth cohorts (see below).

We received many ADR reports in 2015 (table 2b). Most of the ADR reports concern adverse reactions that started before 2015 (table 2c); several of them involve adverse reactions that started years before, but were not reported until now.

A sizeable share of them can probably be ascribed to the recent period's awareness on adverse reactions; it is a well known mechanism that ADR reports increase in step with rising awareness on adverse reactions to a specific medicine. It happened in 2009 as well when the media focused heavily on atopic dermatitis as a suspected adverse reaction to the vaccine.

Age distribution

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

From August 2012 until end-2013, the HPV vaccine was, as mentioned above, offered free of charge to women from the 1985-1992 birth cohorts. Since 1 January 2014, the HPV

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

vaccine has been offered to women from the 1993-1997 birth cohorts. These birth cohorts have previously been offered the HPV vaccine. The offer is available until the end of 2015.

Table 2d shows the age distribution of the girls/women from the ADR reports we received in the third 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, age unknown
122	72	11

Table 2d. Age of the girls/women from the ADR reports received.

Review and assessment of the serious ADR reports about the HPV vaccine
A total of 119 ADR reports were classified as serious.

One woman was vaccinated with Cervarix®, two ADR reports did not mention the vaccine used, and the remaining 116 ADR reports state that the girls/women were vaccinated with Gardasil® or Silgard®.

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

- In two ADR reports, a causal link to the vaccine was assessed as **possible**.
- In 42 of the ADR reports, a causal link to the vaccine was assessed as **less likely**. They have received this classification either because the reported adverse reactions were unknown and there was no temporal association with the vaccine or because another present disease could more likely explain the symptoms.
- Causality was **unclassifiable** in 32 of the ADR reports. In these ADR reports, the information is either very scarce or the reports failed to indicate a time interval between vaccination and symptom onset.
- In 38 ADR reports, there is **insufficient documentation** to link the reactions to the HPV vaccine. The temporal relationship is consistent, but the adverse reactions are not described in the literature.
- Five of the ADR reports either describe symptoms for which an association to the vaccine is considered **less likely** or symptoms with **insufficient documentation** to link it to the vaccine.

ADR reports with specific diagnoses suspected as adverse reactions
We received a total of 33 ADR reports with specific diagnoses as suspected adverse reactions.

Idiopathic thrombocytopenic purpura (ITP)
Two ADR reports describe patients who were verified with ITP shortly after vaccination. ITP is mentioned in the summary of product characteristics as a known adverse reaction to the vaccine, and causality is therefore considered **possible**.

POTS

Five ADR reports involved POTS as a suspected adverse reaction to the vaccine. Four of them describe a consistent temporal relationship with the vaccine. Based on the safety review conducted by the European Medicines Agency (EMA) in November 2015, which showed that there is no evidence of an association between the HPV vaccine and the syndromes POTS and CRPS, the causality assessment in respect of the POTS diagnosis is changed to **less likely**. However, four of the ADR reports describe many other symptoms for which there is **insufficient documentation** to link them to the vaccine.

In the last ADR report, causality is considered **less likely** because there is no consistent temporal relationship between vaccination and symptom onset.

Infections

Five other ADR reports describe specific diagnoses: meningococcus meningitis, intrauterine abscess, osteomyelitis, infected eczema and genital herpes.

In quite many ADR reports, no specific diagnosis is made, but they describe symptoms seen in e.g. upper respiratory tract infections and urinary tract infections.

These ADR reports are classified as **less likely**.

Uveitis, myocarditis, pericarditis

Three cases of respectively uveitis, myocarditis, pericarditis as suspected adverse reactions have been reported. With reference to the literature, there is **insufficient documentation** to establish causality.

Narcolepsy/hypersomnia

In three ADR reports, narcolepsy/hypersomnia is reported as a suspected adverse reaction to the vaccine. It is assessed for all of them that there is **insufficient documentation** in the literature to establish causality.

CRPS

Two cases of Complex Regional Pain Syndrome have been reported as a suspected adverse reaction to the vaccine. As mentioned earlier, the European Medicines Agency (EMA) published a safety review in November, which showed that there is no evidence of an association between the HPV vaccine and the syndromes POTS and CRPS. Against this background causality is considered **less likely**.

Rheumatoid arthritis/juvenile idiopathic arthritis

Two ADR reports describe patients who developed rheumatoid arthritis/juvenile idiopathic arthritis as suspected adverse reactions to the vaccine. There are epidemiological studies that go against an association with the HPV vaccine, and causality is considered **less likely**.

Pregnancy/neonatal

The same woman has been reported to have aborted two foetuses with chromosomal abnormalities, one of which with a heart defect.

There is an ADR report describing a child who was born about 14 months after the mother had received the last Gardasil® vaccine dose. The child was asphyxic and irritable and subsequently developed allergy and a rash.

Another child was born with optic hypoplasia reported as a suspected adverse reaction to the mother's HPV vaccination.

A case of extrauterine pregnancy has also been reported as a suspected adverse reaction to HPV vaccination.

There are no descriptions in the literature that HPV vaccination or other vaccination of pregnant women can cause chromosome abnormalities in foetuses or optic hypoplasia; other causes are considered more likely. For the other ADR reports, there is no consistent temporal relationship, and therefore causality is considered **less likely**.

Thrombosis

A case of portal vein thrombosis with the presence of JAK2 mutation was reported. Causality with the vaccine is considered **less likely** as JAK2 mutation is a known risk factor for thrombophilia, and in the literature there is no description of an association between thrombus formation and HPV vaccination.

Fibromyalgia

A case of fibromyalgia has been reported as a suspected adverse reaction to HPV vaccination. There is **insufficient documentation** in the literature in support of such causality.

Facial paralysis

There is an ADR report of a patient who developed facial paralysis two months after vaccination. Shortly before the vaccination, the patient had had a cold, and an association to a viral infection is considered more likely.

Epilepsy

An ADR report describes a patient who developed epilepsy after vaccination. The time of onset is not indicated in the report. Pursuant to the literature, the occurrence of epilepsy is not higher in HPV vaccinees than non-vaccinees. Causality is therefore considered **less likely**.

Adenoma

We received an ADR report about a patient who developed a large hepatic adenoma after vaccination. Causality with the vaccine is considered **less likely**. No other cases of adenoma have been described in the literature as a suspected adverse reaction to the vaccine.

Another girl was diagnosed with thyroid adenoma after vaccination. Causality with the vaccine is considered **less likely** in this case also.

Review of the non-serious ADR reports

Like the preceding quarters, the most commonly reported adverse reactions are fatigue, headache and dizziness, syncope and joint pain.

Conclusion

We received a total of 205 ADR reports that concerned the HPV vaccine in the third quarter of 2015. 119 of them were classified as serious. The number of ADR reports is high, but has fallen by one third since Q2 of 2015 (308).

Like the previous quarter, the many ADR reports could be attributable to the considerable awareness on and discussion of adverse reactions suspected as being caused by the HPV vaccine because many of the ADR reports we have received in the last quarters describe suspected adverse reactions with earlier onset.

We received a total of 33 ADR reports with specific diagnoses. They cover a diversity of diagnoses, and causality with the vaccine was considered possible in only two of the ADR reports.

There are still many ADR reports for which there is insufficient documentation in the literature to link the symptoms described to the vaccine. Like previous accounts, 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.

There are also many ADR reports with inadequate information, e.g. poorly indicated time of onset, lack of test results, etc. These ADR reports are assessed to be unclassifiable.

In November 2015, the European Medicines Agency (EMA) published a safety review, confirming that there is no evidence to suggest a possible association between HPV vaccination and the syndromes of POTS and CRPS. It also announced that it found no reason to change the information for use of the vaccines. The DKMA has subsequently changed the causality for these ADR reports to "less likely" in compliance with the report.

There are still a few ADR reports for which the DKMA assesses that causality to the vaccine is possible. Against this background the DKMA's recommendations remain unchanged.

We maintain our recommendation for doctors and patients to carefully report suspected adverse reactions to the HPV vaccine to ensure a continued monitoring and evaluation of the vaccine's safety profile. Adverse reactions can be reported electronically at *www.meldenbivirkning.dk* (report a side effect).

Reports of suspected adverse reactions related to influenza vaccines

The season has begun for influenza and influenza vaccination, and we therefore focus intensely on reports of adverse reactions suspected to be caused by the current influenza vaccines. In the following, we will review the reports of suspected adverse reactions received from 1 August to 30 November 2015.

This season's vaccines
This season, people will be vaccinated with vaccines from two manufacturers, Fluarix® and Vaxigrip®. They are considered equal protection against influenza.

Free influenza vaccination is offered to risk groups
The offer for free influenza vaccination to people at risk of developing severe influenza disease started on 1 October 2015 and runs until 31 December 2015.

Pregnant women in the 2nd and 3rd trimesters and people with immunodeficiency and their household contacts can, however, be vaccinated free of charge until the end of February 2016.

Vaccination is recommended and offered at no cost to the following groups:

- Persons aged 65 years and over.
- Chronically ill persons, upon assessment of a doctor, who have:
    - chronic lung disease
    - with cardiovascular disease (with the exception of isolated hypertension)
    - diabetes 1 or 2
    - congenital or acquired immunodeficiencies
    - affected respiration due to reduced muscular strength
    - chronic liver and kidney impairment
    - other chronic diseases which imply that influenza is a serious health risk according to a doctor's assessment.
- Obese patients (BMI > 40)
- Persons with other serious diseases which imply that influenza is a serious health risk according to a doctor's assessment.
- Women in the second or third trimesters of pregnancy.
- Household contacts of severely immunosuppressive patients according to a doctor's assessment.

In addition, persons on disability retirement can be vaccinated free of charge.

ADR reports about the influenza vaccine from 1 August to 30 November 2015

In this report, we have analysed reports of suspected adverse reactions to the influenza vaccine in the period from 1 August to 30 November 2015. There are 26 ADR reports, of which four are classified as serious[3].

Sales figures are not included in this report because the number of doses sold for the vaccines in question are not available before the beginning of 2016.

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 split into four categories:

- Possible
- Insufficient documentation[4]
- Less likely
- Unclassifiable (not possible to assess because of inadequate information)

The table describes the adverse reactions and assesses causality

Vaccine	ADR description	Causality assessment of the adverse reactions
Vaxigrip®	In relation to vaccination, a citizen developed severe swelling and redness around the injection site on the left upper arm. The citizen was treated with antibiotics. Some weeks after, the citizen returned with pain in the left upper arm, and ultrasound imaging revealed a blood clot in the arm. There is no information in the report about the citizen's current health status.	The influenza vaccine may have caused a blood clot in the arm in response to an inflammatory impact on the vein. Causality is therefore considered **possible.**

[3] 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.

[4] This category contains the reports for which it was not possible to determine whether or not there is a possible connection between the reaction and the vaccine because of insufficient documentation. Reports in this category concern symptoms occurring in temporal association with vaccination, where the vaccinee has no other immediate factors that may explain the symptoms (other disease, other medicine, etc.), but where there is no evidence in the literature or other available data that can confirm a causal relationship.

Fluarix®	In temporal association to vaccination, a citizen developed sensory disturbances such as uncharacteristic shooting pain and a burning sensation on different areas of the body. There were also problems with raising the right leg, which resulted in a limping gait. The citizen was diagnosed with myelitis. He has since recovered considerably.	Myelitis can be a complication of infection and is described after vaccination. In this case, there is a temporal relationship between the vaccination and inflammation of the spinal cord, and causality is therefore considered **possible**.
Influenza virus (the report does not indicate the vaccine used)	Two days after vaccination, a younger citizen developed influenza-like symptoms. The symptoms lasted for three weeks, and immediately thereafter he developed symptoms of diabetes (thirst, urge to urinate, visual disturbances). He was subsequently diagnosed with diabetes mellitus type 1.	Influenza-like symptoms can occur in immediate association with vaccination. Normally, these symptoms subside without treatment in one to two days' time. The citizen's symptoms lasted for three weeks, so it is most likely that he contracted an infection. Infections have previously been suggested to cause type 1 diabetes. No literature has established that vaccination with seasonal influenza increases the occurrence of diabetes mellitus type 1. Against this background causality is considered **less likely**.
Fluarix®	An elderly citizen was admitted to hospital as she felt unwell and had redness of the neck and face. Symptom onset was 10 minutes after the vaccine was given, and an allergic reaction was suspected. The citizen had experienced similar reactions when in contact with perfume or when eating almonds. At the time of reporting, the citizen had recovered.	Allergic reactions are known to occur in association with influenza vaccination. It is described that the symptoms occurred in temporal relation with the vaccination, and causality is therefore considered **possible**.

Review of the non-serious ADR reports

The non-serious ADR reports mainly describe cases of fever, rash, arthralgia and reactions ad the injection site (redness, itching, swelling, etc.).

Most of these reactions are known adverse reactions to influenza vaccination, and the reactions normally disappear without treatment in one to two days' time.

Conclusion
In the period from 1 August to 30 November 2015, the DKMA received a total of 26 reports of suspected adverse reactions to seasonal influenza vaccines. Four were classified as serious.

The serious ADR reports describe different symptoms such as sensory disturbances, blood clot, etc. The serious ADR reports have undergone our causality assessment, and in three cases the DKMA assessed it likely that they are related to the vaccine.

The DKMA still assesses that the benefits of the influenza vaccines outweigh the possible risks.

Nasal glucocorticoids indicated in children under 18 years of age have become prescription-only

Nasal glucocorticoids indicated in children under 18 years have been made prescription-only after growth retardation has been observed in children treated with nasal glucocorticoids.

Nasal glucocorticoids are authorised for the treatment of allergic rhinitis and nasal polyps. They can be grouped in 1st generation glucocorticoids (beclomethasone, budesonide and triamcinolone) and 2nd generation glucocorticoids (fluticasone propionate, fluticasone furoate and mometasone).

Nasal spray containing budesonide, triamcinolone, fluticasone and mometasone is authorised for treatment in both children and adults.

The products have a comparable efficacy and safety profile[5,6]. It is especially in long-term treatment with high doses of nasal glucocorticoids that systemic adverse reactions can develop in rare cases. Systemic adverse reactions include Cushing's syndrome, reduced adrenal cortex function, neuropsychiatric adverse reactions, cataract, glaucoma as well as growth retardation in children.

[5] SmPCs for beclomethasone, budesonide, triamcinolone, fluticasone proprionate, fluticasone furoate, mometasone.
[6] The diagnosis and management of rhinitis: an updated practice parameter. Wallace DV, Dykewicz MS, Bernstein DI, Blessing-Moore J, Cox L, Khan DA, Lang DM, Nicklas RA, Oppenheimer J, Portnoy JM, Randolph CC, Schuller D, Spector SL, Tilles SA; Joint Task Force on Practice; American Academy of Allergy; Asthma & Immunology; American College of Allergy; Asthma and Immunology; Joint Council of Allergy, Asthma and Immunology. J Allergy Clin Immunol. 2008 Aug; 122(2 suppl): S1-S84.

A study has shown growth retardation in children

A study conducted by one of the manufacturers has shown a small growth retardation of an average of 0.27 cm/year (95% CI -0.48 to -0.06 cm/year) in children aged 5 to 9 years treated with nasal glucocorticoids daily for one year.

Growth in children should be monitored

Due to the risk of growth retardation, it is recommended that doctors monitor the growth in children treated with nasal glucocorticoids in the same way that growth in children treated with glucocorticoids for inhalation is monitored.

Prescription-only from 7 December 2015

The DKMA has therefore decided to make nasal glucocorticoids when indicated in children subject to prescription, by changing its dispensing status from HA (*over-the-counter medicine, sold in pharmacies only*) to dispensing status B *(prescription medicine to be dispensed one time only on the same prescription.* Nasal glucocorticoids will still be available over the counter when indicated in adults, but the dispensing will be changed from status HA *(over-the-counter medicine, sold in pharmacies only)* to dispensing status HA18 *(over-the-counter medicine, sold in pharmacies only, minimum age 18 without prescription)*. The changes entered into force on 7 December 2015.

The following glucocorticoid-containing products are now subject to the prescription-only requirement:

- Budesonide nasal spray 32 microgram/dose from Sandoz
- Fluticasone propionate nasal spray 50 microgram/dose from Teva
- Nasacort nasal spray 55 microgram/dose from Sanofi-aventis, Orifarm or 2Care4
- Rhinocort Aqua nasal spray 32 microgram/dose from Astra Zeneca

The following glucocorticoid-containing products for nasal use, must in future only be dispensed over the counter to persons aged 18 and over:

- Flonase nasal spray 50 microgram/dose from GlaxoSmithKline
- Flixonase nasal spray 50 microgram/dose, 60 dose package from GlaxoSmithKline
- Beconase nasal spray 50 microgram/dose from GlaxoSmithKline, 2Care4 or Europharm.
- Triamcinolonacetonid nasal spray 55 microgram/dose from Sanofi-aventis

Read the announcement from the DKMA on its website (in Danish only): *Nasal spray with corticosteroids for children is made prescription-only (Næsespray med binyrebarkhormon til børn gøres receptpligtige).*

Most recent Direct Healthcare Professional Communications (DHPCs)

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:

- **Insuman (human insulin) (100Ui/ml):** Shortage in supply of 3 ml cartridges and pre-filled pens. Sent out 30 November 2015.

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

Danish Pharmacovigilance Update is published by the Danish Medicines Agency
www.dhma.dk
Editor-in-Chief:
Henrik G. Jensen (HGJ)
Editor:
Nina Vucina Pedersen (NVP)
ISSN 1904-2086