Danish Pharmacovigilance Update #1

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Contents

News from the Danish Health and Medicines Authority

The HPV vaccine and reported suspected adverse reactions

HPV vaccination was included in the Danish childhood immunisation programme in January 2009.
The Danish Health and Medicines Authority (DHMA) has continuously monitored, assessed and published reports of suspected adverse drug reactions (ADRs) from the HPV vaccine. The most recent articles concern reports of suspected ADRs from 2012 and from the period 1 January through 9 September 2013 (see *Danish Pharmacovigilance Update, 27 June 2013* and *Danish Pharmacovigilance Update, 26 September 2013*).

This listing is a follow-on to the two previously published listings and concerns the suspected ADRs from the HPV vaccine reported during the period 10 September through 30 November 2013.

Over the summer and in the autumn of 2013, ADRs from the HPV vaccine received much attention. As expected, the increased attention is reflected in the overall reporting frequency for the HPV vaccine for the period where the number of reports increased markedly (Figure 1). This applies both to reports of suspected ADRs classified as serious[1] and to the ones classified as non-serious. However, the increased number of reports should be seen in the light that the consumption of the HPV vaccine increased compared to the previous years (Table 1).

In outline, the listing for 2013 shows:

- That the DHMA received more reports of suspected serious ADRs from the HPV vaccine in 2013 as compared to the past four years.
- That the serious ADRs most frequently reported were severe and long-term cases of fainting/dizziness, headache and general malaise – in some cases accompanied by other more non-specific symptoms.
- That, since the last listing, the DHMA has received four additional reports concerning the diagnosis of Postural Orthostatic Tachycardia Syndrome (POTS). At present, the DHMA has recorded a total of 16 Danish reports where the patients have been diagnosed with POTS. Furthermore, the DHMA has received two reports of symptoms suspected to be caused by POTS. Therefore, these patients have been referred to further assessment.

Based on the ADR reports concerning the diagnosis of POTS and the symptoms coinciding with this diagnosis, the DHMA has requested that the European Medicines Agency, EMA, investigates POTS as a new potential ADR from the HPV vaccine. The investigation is not yet complete. The DHMA will report on the results of the investigation as soon as they are available.

Number of reports and doses sold during the period 2009 through November 2013

The listing includes all ADR reports concerning the HPV vaccine, i.e. Gardasil®/Silgard® and Cervarix®. In Denmark, however, Gardasil® accounts for the majority of the HPV vaccines administered, and thus most of the ADR reports concern Gardasil®. All of the reports of suspected serious ADRs received during the above-mentioned period concerned Gardasil® except for two reports concerning Cervarix®.

Table 1 shows the number of reports received by the DHMA from 2009 through 30 November 2013 by year and seriousness. The table also shows the

HPV vaccine	2009	2010	2011	2012	2013 till 30/11	Total
Number of reports	288	66	43	96	477	970
Number of reports concerning serious ADRs	25	6	8	18	164	221
Number of doses sold	347,690	151,476	163,374	349,730	476,239	1,488,509

Table 1 The number of reports of serious ADRs from the HPV vaccine, the number of reports concerning serious ADRs received from 2009 through 30 November 2013 and, in the last row, the number of doses sold per year in Denmark up to and including 30 November 2013. (Please note that when the DHMA receives additional information, it may cause changes. This means that there may be minor differences in accumulated numbers between previous publications and the above-mentioned).

1. A serious adverse reaction is defined as an adverse reaction which is fatal, life-threatening, causes or prolongs hospitalisation, or causes permanent or significant disability or inability to work, or which is a congenital anomaly or birth defect cf. section 3(4) of Danish executive order no. 826 of 1 August 2012 on the reporting of adverse reactions from medicinal products etc. (bekendtgørelse nr. 826 af 1. august 2012 om indberetning af bivirkninger ved lægemidler m.m.) (in Danish only).

The vaccine prevents cervical cancer
Gardasil® is a so-called tetravalent vaccine, i.e. it protects against four types of HPV viruses (types 6, 11, 16 and 18). The vaccine protects against approx. 70% cases of cervical cancer and 90% cases of anogenital warts.

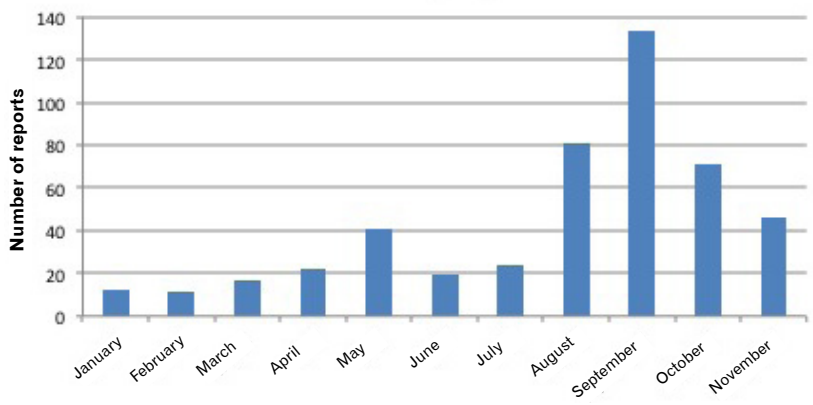

Figure 1: The total number of ADR reports concerning the HPV vaccine received by the DHMA from 1 January 2013 through 30 November 2013.

number of doses sold in Denmark up to and including 30 November 2013. For the entire period, the number of vaccine doses sold was just below 1.5 million (three doses per vaccinee). The number and proportion of serious vaccine reports were higher in 2013 (up to and including 30 November) compared to the previous four years.

Reports received in 2013

Number of reports per month

As shown in Figure 1, the number of reports increased markedly over the summer and in the autumn of 2013.

The number of new reports per month is now decreasing and approaching the level seen before the summer of 2013. The decreasing trend was apparent as from October 2013 and continued in December 2013 where the DHMA received 27 reports concerning the HPV vaccine. As reports received in December are still being processed, they are not included in this listing.

New reports of previously occurring ADRs

Not all ADRs are reported at the time of their occurrence.

Year of onset of the ADR	Number of reports 1/1-30/11 2013
2004	1
2005	1
2006	1
2007	2
2008	7
2009	17
2010	15
2011	9
2012	46
2013	50
Unknown	12

Table 2: Year of onset of serious ADRs reported to the DHMA in 2013.

Table 2 shows the year of onset of the serious ADRs reported in 2013. A few reports of suspected serious ADRs do not specify the time of onset. For a few women, the onset of the ADR experienced dates back to before the introduction of the HPV vaccine in the immunisation programme because they participated in studies of the HPV vaccine.

ADR reports concerning the HPV vaccine received during the period 10 September through 30 November 2013

During the period 10 September through 30 November 2013, the DHMA received a total of 201 reports of suspected ADRs from the HPV vaccine comprising 81 reports of ADRs classified as serious.

The assessment of the individual suspected serious ADRs are described in Table 3. The DHMA has received no reports of death in HPV vaccinees.

Reports by age

Figure 2 shows the number of reports of suspected ADRs by age for persons vaccinated during the period 10 September through 30 November 2013.

The number of reports concerning adult women in their twenties must be compared to the number of vaccinations in this group. According to the Statens Serum Institut, National Institute for Health Data and Disease Control, a total of 428,513 HPV vaccinations had been given to women of these years of birth as of 24 November 2013.

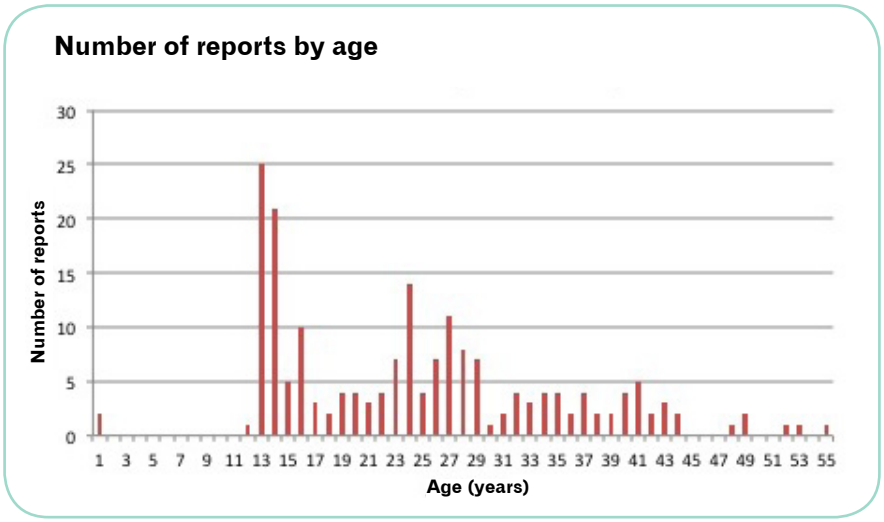

Figure 2: The number of reports received from 10 September through 30 November 2013 by age. Additionally, the DHMA received 9 reports that do not specify age.

The HPV vaccine is the first vaccine to be included in the Danish childhood immunisation programme and also offered free of charge to women who are not in the target group for the immunisation programme, and this is reflected by the age dispersion of the reports. As of August 2012 and up until the end of 2013, HPV vaccination was temporarily offered to women born in 1985-1992 (i.e. 20-27-year-olds in 2012).

As of 1 January 2014, HPV vaccination is offered free of charge to women born in 1993-1997. The new offer is open until the end of 2015[2].

Review of suspected serious reports

All serious ADRs received by the DHMA during the period 10 September through 30 November 2013 appear from Table 3. It also appears whether the ADRs reported are known, i.e. described in the summaries of product characteristics for the HPV vaccines.

The DHMA's assessment of the reported suspected ADRs classified as serious appears from the last column of Table 3. A correlation between the HPV vaccine and a suspected ADR was assessed as follows:

- Possible
- Less likely
- Not possible to assess based on the available information.

Reports lacking important information such as diagnosis were categorised

2: *http://www.ssi.dk/English/News/News/2014/2014%20-%2001%20-%20EPI-NEWS%201-2%20Extend-edn%20opportunity%20for%20HPV.aspx*

Disorder	Potential ADR(s)	Number	Described as a potential ADR in the SPC	Result of the causality-assessment
Cancer/premalignant condition	Tumour in the back of unknown nature	1	No	Less likely
Allergic reactions (2nd vaccination)	Urticaria (1st vaccination) /angiooedema	1	Yes	Possible
General symptoms	Reports concerning long-term symptoms such as dizziness, headache, paraesthesias, heart palpitations, irregular pulse fatigue etc. In addition, one is being assessed for POTS. Almost all vaccinees were investigated to varying degrees by the GP/a neurologist/a hospital without being diagnosed.	33	No	31 were not possible to causality assess sufficiently without a diagnosis. 2 occurred more than 6 months after vaccination and were deemed less likely
POTS	Long-term symptoms are stated in all the reports. The diagnosis has been confirmed. by a tilt table test.	4	No	3 possible 1 less likely
Chronic fatigue syndrome	Symptoms of chronic fatigue syndrome some months after vaccination	1	No	Less likely
Primarily neurological symptoms	Guillain-Barré syndrome emerging 15 months after vaccination	1	Yes	Less likely
	Trigeminal neuralgia emerging 6 weeks after vaccination	1	No	Less likely
	Transversal myelitis 6 weeks after vaccination	1	No	Possible
	Facial paresis emerging 4 days, 13 days and 6 months after vaccination	3	No	1 possible/2 less likely
	Absence epilepsy emerging in between the 1st and the 2nd vaccination	1	No	Less likely
	Seizure of unknown nature on day 1 after the 3rd vaccination. Diagnosed with epilepsy 3 years later.	1	No	Less likely
	A little less than 2 years after the 3rd vaccination seizure phenomenons with limpness, loss of tone and episodes of generalised convulsions.	1	No	Less likely
	Unilateral deafness approx. 2 years after vaccination	1	No	Less likely
	Tinnitus and hearing loss developed. Initially, the diagnosis was Mb. Ménière, but this was changed to nerve inflammation by an ear, nose and throat specialist. Only little additional information.	1	No	Not possible to assess
	Onset of severe migraine after the 2nd vaccination	1	No	Possible
	Multiple sclerosis, only little information	1	No	Not possible to assess

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	A girl developed arm paresis distally to the injection site a few hours after vaccination. Disappeared spontaneously	1	No	Possible
	Opticus neuritis 2 years after vaccination, multiple sclerosis developed 3 years later	1	No	Less likely
	Examined for multiple sclerosis (MS) 10 years ago. Was vaccinated and developed symptoms compatible with MS for a couple of days, which was confirmed.	1	No	Less likely
	Developed papilloedema, blurred vision, observation for multiple sclerosis 6 weeks after vaccination, but this cannot be confirmed by examinations. The patient has also had a trauma	1	No	Not possible to assess
	9 days after the 1st vaccination blood clot in brain, only little information	1	No	Not possible to assess
	Syncope in association with the 1st vaccination, afterwards frequent syncopes several times a month.	1	Yes/No	Possible
	Developed depression on the day of his 2nd vaccination.	1	No	Less likely
	A month after vaccination multiple symptoms comprising impaired muscle function, loss of balance, nerve problems, spasms in the hands, legs, head, hip pain. Diagnosed with a functional disorder	1	No	Less likely
Cardiac ADRs	Supraventricular tachycardia after the 3rd vaccination	1	No	Less likely
Suspected autoimmune disorders	Diabetes mellitus, diagnosed 2.5 years after vaccination and diabetes mellitus diagnosed 6 weeks after vaccination	2	No	Less likely
	Renal disease (glomerulonephritis)	1	No	Less likely
	Reactive arthritis (antigen HLA-B27 positive), febrile episode in association with the onset of symptoms	1	No	Less likely
	Hyperthyroidism	2	No	Less likely
Infection	Pneumonia – atypical	1	No	Less likely
	High fever on the day of vaccination	1	Yes	Possible
	7 days after vaccination, subfebrile and breathlessness – interpreted as a virus disease. Assessed without finding the aetiology. Still tired	1	No	Less likely
	11-13 days after vaccination high fever and rigidity in the neck, develops subsequently sensory disturbances. No diagnosis availabe.	1	No	Not possible to assess
	Fever and lymph gland tumour on the same day, treatment with antibiotics initiated, developed a rash (interpreted as triggered by antibiotics), subsequently tired, headache. Only little information	1	Yes/No	Not possible to vurdere
	Back pain after vaccination. Inflammation (discitis) detected, bacteria (Photobacterium nucleatum) identified in blood culture	1	No	Less likely

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Malformation	Malformation of toes	2	No	Less likely
Caesarean section	A pregnant woman was vaccinated at the time of 3 weeks gestational age and gave birth to a healthy child by Caesarean section	1	No	Less likely
Abortion	Spontaneous abortion week 3-4 followed by a missed abortion	1	No	Less likely
Complaints from the musculoskeletal system	Severe lower back pain emerged 5 days after vaccination	1	No	Less likely
	Pain in the arm and shoulder 14 days after vaccination, no result of assessment	1	No	Not possible to assess
Hepatic impairment	Elevated liver values and swelling a month after vaccination. Interpreted as a virus infection	1	No	Less likely

Table 3 Overview of the individual serious reports and the result of the causality assessment. As this is an overview, it does not include all the clinical information on which the assessments are based.

as 'Not possible to assess'. An attempt will be made to collect the missing information.

Most of these suspected serious ADRs do not appear from the summary of product characteristics for the HPV vaccine.

Relatively many reports concerned vaccinees without a specific diagnosis which made causality assessment more difficult. The symptoms varied among individuals, with many of them, however, having been extensively assessed with scans and lumbar puncture. It is important for the further work on assessing the ADRs to continue the efforts to provide diagnoses to the extent possible.

Several reports described non-specific symptoms such as headache, dizziness with or without paraesthesias, fatigue etc. Most patients were assessed by the GP or in a hospital/by specialist practitioners, but without reaching a final diagnosis. It is very difficult to assess whether there is a causal relationship between the HPV vaccination and these symptoms, when a final diagnosis is not available. Several of these reports may be compatible with autonomic dysfunction/POTS.

POTS is a relatively new diagnosis, and the causal mechanisms of the development of POTS remain unclear. For example, the condition has been described following rapid growth in teenagers, infectious diseases and severe traumas. It is known that the condition may emerge following, e.g., a virus infection. POTS is characterised by a dramatic increase in the heart rate following a change from the supine to the upright position and a labile blood pressure in the upright position. The typical symptoms are dizziness, marked fatigue and faintings. Not all sufferers experience fainting. POTS may be diagnosed with a tilt table test. POTS occurs in both genders, but most frequently in girls/women aged 15-50 years. The exact prevalence is not known. Figures from the Danish National Patient Registry shows that 96 patients diagnosed with POTS were hospitalised during the period 2006-2012. POTS also occurs in non-vaccinees in the same age group.

According to the most recent Periodic Safety Update Report, 24 reports of cases of POTS following vaccination with Gardasil®/Silgard® had been recorded worldwide as of 31 May 2013. At that time, approx. 127 million doses of Gardasil®/Silgard® had been distributed worldwide.

As described, the DHMA has currently recorded a total of 16 Danish reports where the patients have been diagnosed with POTS. Furthermore, the DHMA has received two reports of symptoms suspected to be caused by POTS. Therefore, these patients have been referred to further assessment.

Since the exact incidence and prevalence of the disease POTS are not known, it is difficult to determine whether the numbers are increased in HPV vaccinees. However, in many of the women/girls, the symptoms started shortly after the vaccination.

Once the results of the European Medicines Agency's investigation of a possible correlation between the HPV vaccine and POTS are available, the DHMA will report on them.

Three vaccinated women were diagnosed with multiple sclerosis at varying time intervals after the vaccination. The disease is suspected in a fourth woman, however, she does not meet the diagnostic criteria.

A woman developed transversal myelitis six weeks after the vaccination. A case of Guillain-Barré syndrome emerged more than a year after the vaccinations. Three cases of facial paresis emerged, again at varying time intervals from the vaccinations to the onset of symptoms.

Some of the suspected serious ADRs reported are rare diseases that are most likely not causally related to the vaccination. There were reports of various known neurological disorders and autoimmune conditions, but with no clear pattern among them. Many of the reports concerned adult women in whom these conditions occur more frequently than in children.

In a Scandinavian study, 1 million Danish and Swedish girls including 300,000 HPV vaccinees were examined. The study comprised a variety of 53 diagnoses including autoimmune and neurological diseases and blood clots, but not POTS. The researchers investigated whether the incidence of disease in the girls was elevated in the HPV vaccinees as compared to the non-HPV vaccinees. The results did not indicate that HPV vaccination was the cause of serious diseases[3].

Non-serious reports

The most frequently non-serious ADRs reported (a total of 120 reports) were headache, dizziness, nausea, fatigue, paraesthesias, syncope, fever, extremity pain, muscle and joint pain, local reactions at the injection site (redness, pain, swelling), concentration disturbances and migraine. These ADRs are mentioned in the summary of product characteristics except for paraesthesias, concentration disturbances and migraine. The non-serious ADRs reported more or less corresponds to that category of ADRs in the listing for the period 1 January 2013 through 9 September 2013.

The DHMA's overall assessment

According to the DHMA's assessment the vaccine serves its purpose by being an essential element in the prevention of cervical cancer. As described, the vaccine may, in rare cases, cause serious ADRs. However, the DHMA as well as the authorities in the rest of Europe assesses the benefits of the vaccine to outweigh the potential risks.

The DHMA will maintain the increased focus on reported suspected ADRs concerning the HPV vaccine.

Important to report potential ADRs

It is important that doctors and patients continue to be aware of reporting suspected ADRs from the HPV vaccine. The Danish reports are included as part of the basis for the Europe-wide assessment.

Everyone can report ADRs to the DHMA at *Report side effects in humans*

The DHMA expects to publish the next listing of reported suspected ADRs concerning the HPV vaccine in Danish Pharmacovigilance Update, May 2014.

Overviews of reported suspected ADRs

The DHMA publishes listings of reported suspected ADRs from HPV vaccines on an ongoing basis in the form of so-called 'Drug Analysis Prints' (DAPs). DAPs are available on the Danish Health and Medicines Authority's website:[4]. The most recent listing was published on the website on 3 January 2014.

Indication for Gardasil®

Gardasil® is a vaccine to be used from the age of 9 years for the prevention of:

- premalignant genital lesions (cervical, vulvar and vaginal) and cervical cancer causally related to certain oncogenic types of human papillomavirus (HPV).
- condylomas (condyloma acuminata) causally related to specific types of HPV.

3 *http://www.bmj.com/content/347/bmj.f5906*

4 *http://sundhedsstyrelsen.dk/en/medicines/safety/side-effects/drug-analysis-prints-reported-adverse-reactions*

Labetalol (Trandate®) and hepatic impairment

In December 2013, the Danish Health and Medicines Authority (DHMA) received a report concerning a woman who developed hypertension a few days after having given birth. She was started on 100 mg Trandate® daily. Following four months of treatment she developed symptoms of hepatitis, and the product was discontinued. Other causes of hepatitis, including viral causes, were ruled out. During the following two months the hepatic impairment gradually abated, and the woman is healthy today.

Reports of hepatic impairment in association with the use of drugs containing labetalol

The DHMA has received a total of three reports of hepatic impairment in patients in association with the use of drugs containing labetalol.

Doctors should pay attention to the following:

- Treatment with labetalol may result in elevated liver values and, in very rare cases, hepatitis and icterus.
- If hepatic function tests indicate hepatic injury or the patient is diagnosed with jaundice, labetalol should be discontinued and not re-initiated.

Indication for labetalol

Arterial hypertension.

All cases referred to in the article originate from the Danish Health and Medicines Authority's adverse reaction database. The cases have been forwarded to all relevant pharmaceutical companies and to the EudraVigilance database. Therefore, pharmaceutical companies should not report these cases to the Danish Health and Medicines Authority.

Tenofovir disoproxil (Truvada®) and renal insufficiency

The Danish Health and Medicines Authority has received a total of six reports of renal impairment in association with the use of drugs containing tenofovir disoproxil. Three of these reports describe that the patients developed renal impairment to an extent that necessitated dialysis.

Doctors should pay attention to the following:

- Close monitoring of the renal function (serum creatinine and serum phosphate) is recommended prior to the intake of Truvada® every 4 weeks during the first year and, thereafter, every 3 months. Consider more frequent monitoring of the renal function in patients with a history of renal dysfunction or patients having a risk of renal dysfunction.
- Exposure to emtricitabine and tenofovir may increase significantly when Truvada® is given to patients with moderate to severe renal impairment, since emtricitabine and tenofovir are primarily eliminated through renal excretion. It is necessary to adjust the dose interval for Truvada® in patients with moderate renal impairment (creatinine clearance between 30 and 49 ml/min: dose every 48 hours). See the summary of product characteristics for Truvada®.
- Truvada® is not recommended in patients with severe renal impairment (creatinine clearance < 30 ml/min) or patients requiring haemodialysis, since the appropriate dose reductions are not obtainable with the combination tablet.
- Use of Truvada® should be avoided in case of concomitant or recent use of a nephrotoxic drug. The renal function should be monitored once weekly if concomitant use of Truvada® and nephrotoxic drugs is unavoidable.

Indication for Truvada®
Truvada® is a fixed dose combination of emtricitabine and tenofovir disoproxil fumarate. It is indicated for the antiretroviral combination treatment of HIV-1 infected adults.

All cases referred to in the article originate from the Danish Health and Medicines Authority's adverse reaction database.
The cases have been forwarded to all relevant pharmaceutical companies and to the EudraVigilance database. Therefore, pharmaceutical companies should not report these cases to the Danish Health and Medicines Authority.

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