Danish Pharmacovigilance Update #8

Year 4
26 September
2013

Contents

News from the EU

News from the Danish Health and Medicines Authority

News from the EU

Filgrastim (Neupogen) and pegfilgrastim (Neulasta) are associated with risk of capillary leak syndrome

Thirty-eight cases of capillary leak syndrome (CLS) in association with the use of pegfilgrastim and/or filgrastim have been reported worldwide.
No Danish cases have been reported to the Danish Health and Medicines Authority (DHMA). The reports primarily concerned patients undergoing chemotherapy, but also included a healthy donor undergoing peripheral blood stem cell mobilisation. Four of these patients received pegfilgrastim, while 34 patients received filgrastim. The episodes varied in severity and frequency.

CLS is characterised by hypotension, hypoalbuminaemia, oedema and haemoconcentration, and may be fatal. The symptoms often have a rapid onset.

As a doctor you should be aware of the following:

- Patients and healthy donors should be informed about and monitored for signs and symptoms of CLS, and symptomatic treatment should be initiated immediately if symptoms occur.
- Patients should be advised to seek medical attention if they experience symptoms of CLS.

The summary of product characteristics will be updated, and letters of information have been issued to relevant doctors. See the letter on the DHMA's website: *List of issued DHPC letters (in Danish only).*

Indication for filgrastim (Neupogen) and pegfilgrastim (Neulasta)
Filgrastim (Neupogen) and pegfilgrastim (Neulasta) are recombinant granulocyte colony-stimulating factors (G-CSF) used to stimulate the proliferation and differentiation of granulocytes, particularly polymorphonuclear, in various forms of chemotherapy-induced neutropenia. Filgrastim is also used to help release blood stem cells from the bone marrow of healthy donors.

Use of bromocriptine (Parlodel®) for prevention or suppression of lactation is to be reassessed

Following post-marketing reports of rare, but serious cardiovascular, neurological and psychiatric adverse reactions (ADRs) associated with the dopamine receptor agonist bromocriptine (Parlodel®), the European Medicines Agency, EMA, has initiated a review of the benefits and risks of bromocriptine when used for preventing or suppressing lactation in women following childbirth.

Bromocriptine is also approved for other indications such as Parkinsonism. However, the benefit/risk ratio will only be reassessed for prevention or suppression of lactation, where ADRs should be seen in light of the fact that lactation is a natural process that eventually stops after a period of time without breastfeeding an infant.

Read more about the review on the EMA's website. *Bromocriptine-containing medicines indicated in the prevention or suppression of physiological lactation post-partum*

News from the EU

Pregnancy prevention programme during treatment with Erivedge

Erivedge may cause foetal death or severe congenital malformations if used in pregnant women. Therefore, Erivedge may not be used during pregnancy.

A pregnancy prevention programme (PPP) has been developed for use during treatment with Erivedge. The PPP describes measures required prior to initiation of and during treatment with Erivedge. The measures comprise, among other things, restrictions on prescription and dispensing as well as contraception and pregnancy tests. The PPP is available at *www.erivedge-ppp.dk*.

As a doctor you should be aware of the following:

- Erivedge has teratogenic effects. It may cause foetal death or severe congenital malformations and may not be used during pregnancy. It is important that all patients are informed about this.
- Women of child-bearing potential must use contraception during and after treatment. Men must also use contraception during and after treatment, since Erivedge can be present in sperm.
- Inform the patients that Erivedge may never be passed on to another person, and that they must ensure safe disposal of any unused capsules at the end of treatment (in accordance with local requirements – e.g. by returning them to the pharmacy)
- All patients, including men and women of non-child-bearing potential, must receive the patient information brochure and the reminder card that describe the measures of the PPP to be followed
- All patients must complete and sign a verification of counselling form.

Letters with this information have been issued to relevant doctors. See the letter on the Danish Health and Medicines Authority's website: *List of issued DHPC letters (in Danish only).*

Indication for Erivedge
Erivedge is indicated for the treatment of adult patients with symptomatic, metastatic basal cell carcinoma or locally advanced basal cell carcinoma inappropriate for surgery or radiotherapy.

News from the EU

Risk of hypermagnesaemia from the use of the parenteral nutrition preparations Numeta G13E and G16E

Due to reports of hypermagnesaemia (without clinical symptoms) in preterm infants, the manufacturer voluntarily recalled the parental nutrition preparation Numeta G13E in the EU this spring. Numeta G13E is approved as parenteral nutrition for premature newborns.

The authorities have now reviewed the available data on the risk of hypermagnesaemia with Numeta G13E and G16E from clinical studies, articles and reports.

Numeta G13E suspended due to an increased risk of hypermagnesaemia

The authorities concluded that the administration of Numeta G13E may lead to an increased risk of hypermagnesaemia, particularly in preterm infants, since their kidneys are still immature. As symptoms of hypermagnesaemia in premature newborns may be difficult to identify, there is also a risk that the condition may not be detected until it causes serious complications. Therefore, Numeta G13E has been suspended from the European market.

The benefits of Numeta G16E still outweigh the risks

For Numeta G16E, the benefits are still assessed to outweigh the risks. There is a potential risk of hypermagnesaemia when administering Numeta G16E to children aged 0 to 2 years, particularly children with reduced renal function and newborns of mothers who were receiving supplemental magnesium prior to delivery.

As a doctor you should be aware of the following:

- Serum magnesium levels, along with other electrolyte levels should be monitored when initiating treatment and at appropriate intervals thereafter
- Be aware of signs of hypermagnesaemia such as generalised weakness, respiratory failure, hypotension and arrhythmias. Hypermagnesaemia may also cause non-specific symptoms such as nausea, vomiting and flushing. Clinical symptoms may not be identifiable until development of severe hypermagnesaemia.
- In case of elevated serum magnesium levels or clinical signs of hypermagnesaemia, the infusion of Numeta G16E should be stopped or infusion rate reduced and alternative fluids, nutrition and electrolytes administered as deemed appropriate.

Read more about the review on the European Medicines Agency's website. *Numeta G13%E and Numeta G16%E emulsion for infusion*

News from the EU

Be aware of the bleeding risk factors associated with the use of the new oral anticoagulants Eliquis®, Pradaxa® and Xarelto®

In recent years, the oral anticoagulants Eliquis® (apixaban), Pradaxa® (dabigatran etexilate) and Xarelto® (rivaroxaban) have been approved for indications where vitamin K antagonists or low molecular weight heparins (LMWH) have been used for decades. Clinical studies and experience have shown that major bleeding events, including those leading to death, are not limited to the use of vitamin K antagonists/LMWH, but also constitute a considerable risk in association with the use of the above-mentioned new oral anticoagulants.

Furthermore, adverse reaction reports indicate that knowledge of the product information regarding handling of the risk of bleeding is important.

As a doctor you should be aware of the following:

Observe the dosage recommendations, warnings and precautions for use in order to minimise the risk of bleeding. This comprises:

- A thorough assessment of benefits and risks in patients with lesions, conditions and/or treatment (such as NSAIDs and platelet inhibitors) increasing the risk of major bleeding.
- In addition, clinical surveillance for symptoms of bleedings is recommended throughout the treatment period, particularly in patients with an increased risk of bleeding.

Contraindications common to Eliquis®, Pradaxa® and Xarelto®:

Eliquis®, Pradaxa® and Xarelto® have different contraindications, but the following contraindications are common to these three drugs:

- Active clinically significant bleeding
- Lesion or condition, if considered a significant risk factor for major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms with a high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities.
- Concomitant treatment with any other anticoagulant, e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin etc), heparin derivatives (fondaparinux etc), oral anticoagulants (warfarin and others), except when switching therapy to or from the drug, or when UFH is given at doses necessary to maintain an open central venous or arterial catheter.

See the respective product information for Eliquis®, Pradaxa® and Xarelto® for information about additional contraindications specific to each drug. The product information for each drug also includes advice on treatment in the event of bleeding complications. See product information in Danish at *www.produktresume.dk*

There is currently no specific antidote available for Eliquis®, Pradaxa® or Xarelto®.

Letters with the above-mentioned information have been issued to relevant doctors. See the letters on the Danish Health and Medicines Authority's website: *List of issued DHPC letters (in Danish only)*

News from the EU

Lariam® and neuropsychiatric adverse reactions

Use of Lariam® (mefloquine) is associated with a risk of serious neuropsychiatric disorders. The most common neuropsychiatric adverse reactions (ADRs) include abnormal dreams, insomnia, anxiety and depression. Additionally, cases of hallucinations, psychosis, suicide, suicidal thoughts and self-endangering behaviour have been reported in association with the use of Lariam®.

As a doctor you should be aware of the following:

- Be aware of neuropsychiatric reactions from the use of Lariam® for malaria prophylaxis and replace the drug immediately if neuropsychiatric reactions occur.
- Do not prescribe Lariam® for malaria prophylaxis in patients with active or a history of psychiatric disturbances.

Please note: Due to the long half-life of mefloquine, ADRs may occur and persist for up to several months after discontinuation.

Letters with this information have been issued to relevant doctors. See the letter on the Danish Health and Medicines Authority's (DHMA's) website: *List of issued DHPC letters (in Danish only)*

Indication for Lariam®
Treatment and prophylaxis of malaria caused by Plasmodium falciparum strains that are resistant to other malaria drugs.

The DHMA has received a total of 146 reports concerning Lariam®. The ADRs most frequently reported are depression (32 cases), anxiety (28 cases) and nightmares (23 cases).

In Denmark, Lariam® is sold in a quantity of 3-4,000 DDD per year.

You can report ADRs at *http://laegemiddelstyrelsen.dk/en/topics/side-effects-and-trials/side-effects/report-a-side-effect-or-incident/humans*

Use of short-acting beta-agonists for obstetric indications

Short-acting beta-agonists are primarily used for the treatment of asthma. Also, higher doses may be used for the treatment of acute tocolysis (labour inhibition) in pregnant women. There is a known risk of cardiovascular adverse reactions with high doses of beta-agonists. Therefore, the European Medicines Agency, EMA, has reviewed the safety and efficacy of beta-agonists when used as tocolytics.

After the review, the EMA concluded that:

- Oral products and suppositories should not be used, since the risk outweighs the benefit associated with tocolytic treatment.
- The available data showed that injectable forms of beta-agonists are effective for tocolysis in the short term (up to 48 hours) when the treatment is managed by specialists, the pregnant woman and the foetus are monitored continuously, and other guidelines in the product information are observed.

In Denmark, only the injection form of salbutamol (Ventoline®) is approved for tocolysis.

Read more about the review on the EMA's website. *Short-acting beta-agonists*

Psychotic or manic symptoms emerging during use of methylphenidate and atomoxetine

In July 2013, the Danish Health and Medicines Authority (DHMA) received two adverse reaction (ADR) reports concerning patients who developed psychotic or manic symptoms in association with the use of methylphenidate and atomoxetine.

One of the reports concerned a 16-year-old patient diagnosed with ADHD who had been undergoing treatment with Ritalin® and Strattera® for 18 months. The patient was hospitalised acutely in an agitated condition and with visual hallucinations. The drugs were discontinued, and the symptoms disappeared.

The other report concerned a 23-year-old patient diagnosed with ADHD who, after a pregnancy, resumed treatment with Ritalin®. She developed a mania 1-2 days following initiation of treatment which was then discontinued. The treatment was resumed later, but the patient developed the same symptoms, after which the treatment was discontinued permanently. The patient had previously had a stress-triggered psychosis.

ADR reports concerning methylphenidate and atomoxetine

In total, the DHMA has received 40 reports of patients who developed psychotic or manic symptoms in association with the use of methylphenidate and/or atomoxetine.

As a doctor you should be aware of the following:

Emergence of psychotic symptoms or mania in children and adolescents with no history of psychotic illness or mania may be due to treatment with methylphenidate or atomoxetine in normal doses.

- If psychotic or manic symptoms occur in patients, the possibility of a causal relationship with methylphenidate and/or atomoxetine should be considered, and discontinuation of the treatment may be relevant.

Indication for atomoxetine and methylphenidate

Atomoxetine is indicated for the treatment of ADHD in children of 6 years and older, in adolescents and in adults as part of a comprehensive treatment programme. Methylphenidate is indicated as part of a comprehensive treatment programme for ADHD in children aged 6 years or older, when remedial measures alone are insufficient. Methylphenidate is also used for the treatment of narcolepsy.

Adverse reaction reports concerning the HPV vaccine from 1 January through 9 September 2013

HPV vaccination – a part of the Danish childhood immunisation programme

On 1 January 2009, Gardasil® was included in the Danish childhood immunisation programme. This means that all 12-year-old girls have been offered the vaccine free of charge since January 2009. Already in October 2008, doctors started vaccinating girls born in 1993, 1994 and 1995 as part of a pilot programme running until the turn of the year 2009/2010. Additionally, HPV vaccination became available free of charge as of 27 August 2012 for all young women born between 1985 and 1992 (the offer ends on 31 December 2013).

Since the inclusion of HPV vaccination in the Danish childhood immunisation programme, the Danish Health and Medicines Authority (DHMA) has continuously monitored and assessed reports of potential adverse reactions (ADRs) from the use of the vaccine. Earlier this year, the DHMA prepared a listing of the reports of potential ADRs from Gardasil® received by the DHMA during the period 1 January 2009 through 31 December 2012. See *Danish Pharmacovigilance Update, 27 June 2013*.

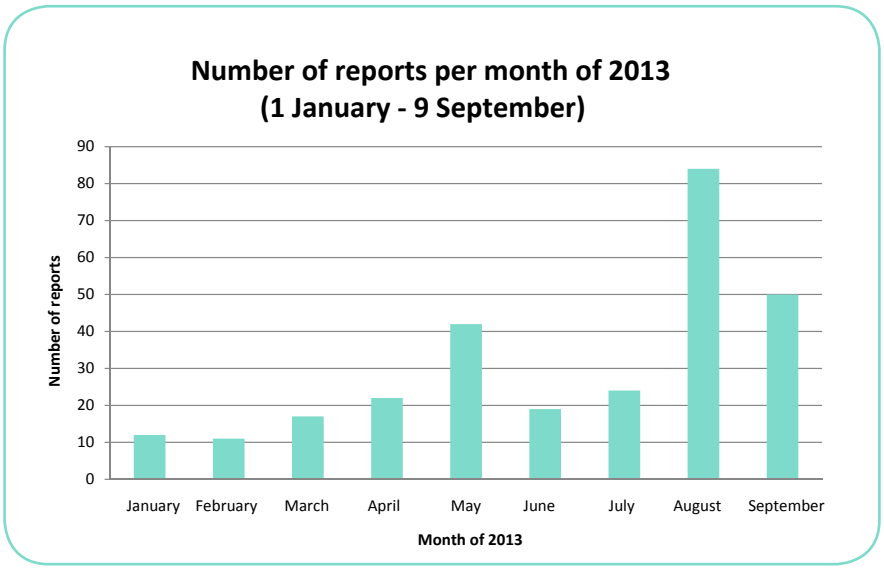

Figure 1: The total number of ADR reports concerning the HPV vaccine received by the DHMA from 1 January through 9 September 2013.

ADR reports concerning the HPV vaccine received from 1 January through 9 September 2013

During the summer of 2013, the HPV vaccine received wide media coverage in Denmark, and potential ADRs have been the subject of increasing attention since then. The increased attention is also apparent from the overall reporting statistics concerning ADRs from the HPV vaccine, since the statistics comprise an increased number of reports concerning serious[1] as well as non-serious ADRs (Figure 1). As appears from this listing, the reports constitute an important part of the monitoring. The majority of the ADRs reported are already known and described in the summary of product characteristics for the vaccine. In outline, the listing shows that:

- The DHMA received more reports of suspected serious ADRs from the HPV vaccine during the period 1 January through 9 September 2013 as compared with the past four years.
- Most of the reports concerned non-serious, known ADRs.
- The suspected serious ADRs most frequently reported were fainting or dizziness, headache and general malaise, possibly accompanied by other more non-specific symptoms.
- During the above-mentioned period, the DHMA received four reports describing the diagnosis of Postural Orthostatic Tachycardia Syndrome (POTS). This is a new type of suspected ADR from the HPV vaccine.

1 A serious ADR is defined as an ADR 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 "bekendtgørelse nr. 826 af 1. august 2012 om indberetning af bivirkninger ved lægemidler m.m. (the Danish executive order no. 826 of 1 August 2012 on the reporting of ADRs from medicinal products etc., in Danish only).

The DHMA maintains its assessment that the benefits of the vaccine outweigh the risks.

As part of its routine monitoring and based on the most recent ADR reports concerning POTS and similar symptoms associated with the use of the HPV vaccine, the DHMA has requested that the European Medicines Agency, EMA, investigates this as a potential newly identified ADR.

All ADR reports concerning the HPV vaccine (Gardasil®/Silgard® and Cervarix®)[2] received by the DHMA during the period 1 January through 9 September 2013 are included below. In Denmark, Gardasil® accounts for the majority of the HPV vaccines administered, and this is reflected by the fact that all reports categorised as serious concern Gardasil® or just the HPV vaccine with no indication of the name.

Number of reports, ADRs and doses sold

Table 1 shows the numbers of reports and ADRs received by the DHMA since 2009. The table also shows the number of doses sold in Denmark.

As appears from the table, each report often comprised several ADRs.

The total sale during the period amounted to more than 1.3 million vaccine doses. A total of three doses are needed per vaccinee in order to obtain the desired prevention.

Reports of suspected ADRs received in 2013

During the period 1 January through 9 September 2013, the DHMA received a total of 281 reports comprising 80 reports of suspected serious ADRs from HPV vaccines. The individual suspected serious ADRs are described in Table 3 below.

HPV vaccine	2009	2010	2011	2012	2013 till 9 Sep	Total
Number of reports	287	48	38	95	281	749
Of these, number of serious reports	25	5	6	17	80	133
Number of ADRs	524	140	107	251	1538	2560
Number of doses sold (till 31 July 2013)	347,690	151,476	163,374	349,730	379,830	1,392,101

Table 1 The number of reports following HPV vaccination, the number of reports concerning serious ADRs and the total number of ADRs received up to and including 9 September 2013 and, in the last row, the number of doses sold per year in Denmark up to and including 31 July 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.

The DHMA has not received any reports of deaths among HPV vaccinees, but the number and share of the reports categorised as potential serious ADRs are significantly higher in 2013 as compared with the past four years – see Table 1.

However, not all of the ADRs emerged in 2013. Table 2 shows the year of onset of serious ADRs reported in 2013. Seven of the reports do not specify the time of onset. For some women, the time of onset is prior to the introduction of the routine vaccinations, which may be explained by the fact that a few women participated in studies concerning the HPV vaccine.

ADR year of onset	Number of reports
2004	1
2005	1
2006	1
2007	2
2008	2
2009	9
2010	6
2011	2
2012	22
2013	27
Year unknown	7

Table 2: Year of onset of the 80 serious ADRs reported to the DHMA in 2013.

Age at onset of symptoms

The HPV vaccine is the first vaccine which, in addition to being a part of the Danish childhood immunisation programme, is also given to an age group past childhood.

As appears from Figure 2, many of the reports concerned adult women, of whom some are not included in the target group for the immunisation programme.

Figure 2 shows that there is a notable accumulation of reports among women in their twenties. As of August 2012 and up until the end of 2013, HPV vaccination is temporarily offered to women born

2 Gardasil® and Silgard® are identical vaccines from the same vaccine manufacturer.

in 1985-1992 (i.e. 20-27-year-olds in 2012). The number of reports of suspected ADRs in 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 approx. 366,000 HPV vaccinations were given to women in their twenties during the period 2012 through June 2013. During that period, the DHMA received a total of 167 ADR reports from this group of vaccinees[3].
The reported suspected ADRs for this group were mostly non-serious ADRs (as for other age groups). The suspected non-serious ADRs most frequently reported were headache, dizziness and nausea. There was no significant difference between the suspected serious ADRs reported for this age group and the ones reported for other age groups.

According to the Danish childhood immunisation programme, HPV vaccination is recommended to 12-year-old girls. Therefore, not surprisingly, the highest number of reports concerned 12-year-olds.

Figure 3 shows the number of reports by reporter type in 2012 and 2013, respectively[4]. As appears from this figure, the increasing number of reports were submitted by vaccinees (or their relatives) as well as by doctors.

In 2012, vaccinees (or their relatives) only reported non-serious ADRs.
In 2013, 37 of the 109 reports from vaccinees have been classified as serious.

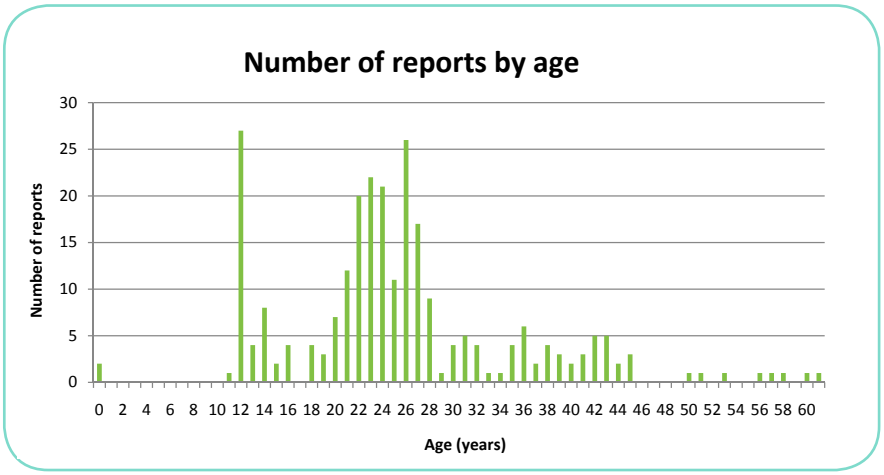

Figure 2: The number of reports received in 2013 through 9 September 2013 by age. Additionally, the DHMA received 18 reports that do not specify age.

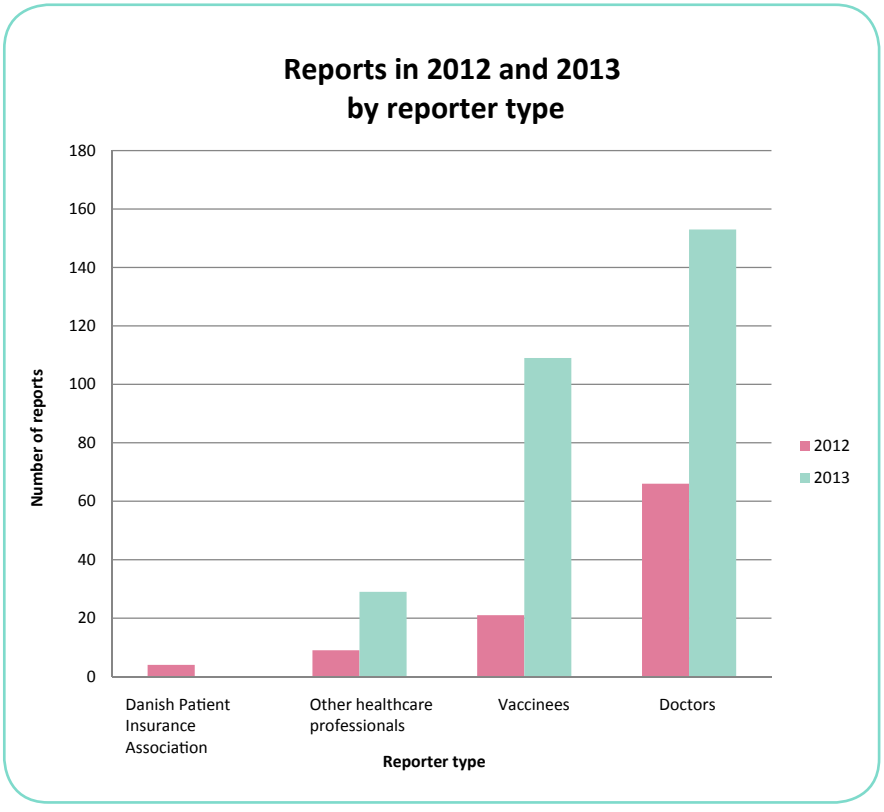

Figure 3: The number of reports in 2012 and 2013 by reporter type

3 Furthermore, the DHMA received a number of reports that do not specify the woman's age and/or the time of vaccination.

4 A few reports (5 in 2012 and 10 in 2013) were submitted by a vaccinee (or a relative) as well as by a doctor. These reports are included twice in the figure, which is why the total is higher than the number of reports received.

Reports of suspected serious ADRs received in 2013

All serious ADRs received by the DHMA during the period 1 January through 9 September 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 suspected ADRs from the HPV vaccine appears from the last column of Table 3. A possible correlation between the vaccine and an 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 as 'Not possible to assess'. In such cases, an attempt will be made to collect the missing information.

As mentioned above, the number of reports of suspected serious ADRs increased in recent months – and most of these ADRs are not described in the summary of product characteristics.

Several reports described non-specific symptoms such as headache, dizziness with or without paraesthesias, fatigue etc. Most ADRs reported were assessed by the GP, in a hospital or by specialist practitioners, but without reaching a final diagnosis. It is very difficult to assess a possible causal relationship (causality), when a final diagnosis is not available.

The reports comprised a wider variety of diagnoses as compared with previous listings. Four women/girls have been diagnosed with Postural Orthostatic Tachycardia Syndrome (POTS) since the last listing. POTS is an exclusion diagnosis confirmed by a tilt table test where the heart rate changes rapidly. The causal mechanisms in POTS remain unclear, but the condition has been described following, e.g., rapid growth in teenagers, infectious diseases or severe traumas such as car accidents. The hallmark symptom of POTS is an increase in heart rate following a change from supine to upright position.

Two women have been diagnosed with premalignant conditions. In one of the women, it happened very shortly after the vaccination, and the other woman had been diagnosed with HPV infection prior to the vaccination.

Two women had migraine attacks directly after the vaccination and have had migraine more frequently since then.

There were two cases of myasthenia gravis diagnosed more than a year after the vaccination.

Three women experienced isolated paraesthesias after the vaccination.

Two women were diagnosed with multiple sclerosis.

One woman experienced anaphylaxis.

Some of the serious ADRs reported are rare diseases that are most likely not causally related to the vaccination. With respect to neurological disorders and autoimmune conditions reported, there is no clear pattern. Many of the reports concerned adult women in whom these conditions occur more frequently than in children.

Organ system	Potential ADR(s)	Number	Described as a potential ADR in the SPC	Result of the causality assessment
Cancer/premalignant condition	Vulvar dysplasia	1	No	Less likely
	Endometrial dysplasia, diagnosed 20 days after the 1st vaccination	1	No	Less likely
Haematological conditions	Idiopathic thrombocytopenic purpura	1	Yes	Possible disorders
Allergic reactions	Anaphylaxis	1	Yes	Possible
	Swelling of the throat	1	Yes (allergic reaction)	Possible
General conditions	Reports concerning long-term symptoms varying from dizziness, headache, paraesthesias, heart palpitations, irregular pulse, fatigue etc.	25	No	Not possible to causality assess sufficiently without a diagnosis

>

	Almost all vaccinees were investigated varying degrees by the GP/a neurologist/ a hospital without reaching a diagnosis.			
POTS	Long-term symptoms are stated in all the reports - the diagnosis has been confirmed by a tilt table test	4	No	Possible
Other symptoms without a diagnosis	Dizziness, mood swings, liver problems etc. – receiving Lamictal	1	No	Not possible to assess
	Leg pain, absent menstruation, weight gain	1	No	Not possible to assess
	Acne, irregular menstruations, infertility	1	No	Less likely
	Short-term paralysis of hand 3-4 days after vaccination, weakness in leg	1	No	Not possible to assess
	Malaise 10 days before the 2nd vaccination, worsened after vaccination, hospitalised with pain, rash, swollen lymph glands	1	No	Not possible to assess
Primarily neuro-logical symptoms	Fainting in association with vaccination	1	Yes	Possible
	Severe epileptic seizure on the day of vaccination (had not had any seizures for a long time), subsequently worsening of the epilepsy	1	No	Possible
	Rolandic epilepsy 5 days after vaccination	1	No	Less likely
	Hypersomnia 14 days after vaccination – not narcolepsy	1	No	Less likely
	Women known to have migraine, who suffered severe attacks in association with vaccination	2	No	Possible
	Migraine development 3-4 months after vaccination	1	No	Less likely
	Chronic headache	1	No	Less likely
	Severe headache and sensory disturbances 4.5 months after the final Gardasil vaccination	1	No	Less likely
	TCI 14 days after vaccination	1	No	Less likely
	Paraesthesias in the arm after vaccination– (followed by paraesthesias in the lower limbs)	1	Pain is described paraesthesia is not	Possible
	Paraesthesias in both femurs	1	No	Not possible to assess
	Paraesthesias in the face, arms and legs – also receiving Valdoxan, for which paraesthesia is a possible ADR	1	No	Less likely
	Multiple sclerosis, pseudo attack (Uhthoff's phenomenon) 4-5 hours after vaccination Symptoms lasted a month. History of Guillain-Barré syndrome	1	No	Possible
	Multiple sclerosis – very little information	1	No	Not possible to assess
	Multiple sclerosis 6 days after the 2nd vaccination	1	No	Less likely

>

	Transversal myelitis 1 week after vaccination	1	No	Possible
	Reduced sensation in legs and prickling sensation. MRI shows myelitis. Onset approx. sensation. MRI shows myelitis. Onset approx. 3 years after Gardasil vaccination	1	No	Less likely.
	Lingual nerve injury (acute right hypoglossal nerve paralysis) 2 weeks after vaccination	1	No	Possible
	Neuromyelitis optica	1	No	Less likely
	Approx. 1 month after the 2nd Gardasil vaccination severe vertigo, headache, photophobia and phonophobia. Assessed without finding the cause	1	No	Less likely
Respiratory illness	Worsening of asthma 1 month after Gardasil	1	No	Less likely
	First time asthma 17 days after the 2nd Gardasil	1	No	Less likely
Suspected autoimmune disorders	Interstitial nephritis The patient also had influenza symptoms prior to renal disease	1	No	Less likely
	Ulcerative colitis with various subsequent symptoms	1	No	Less likely
	Iritis	1	No	Less likely
	Schönlein-Henoch purpura	1	No	Less likely
	Chilblain Lupus Erythematosus approx. 2 months after vaccination	1	No	Less likely
	Myastenia gravis	2	No	Less likely
	Joint affection occurred immediately after vaccination	1	Yes	Possible
	Connective tissue disease with no name – little information	1	No	Not possible to assess
	Retinal vasculitis approx. 4 months after vaccination	1	No	Less likely
	Pemphigus vulgaris 1 month after vaccination	1	No	Less likely
Infection	Clinical meningitis 3 weeks after vaccination	1	No	Less likely
	High fever on the day of vaccination	1	Yes	Possible
Malformations	Acrania, diaphragmatic hernia, hypoplastic adrenal gland and hypoplastic lungs – induced abortion week 19. Received the 1st dose of Gardasil corresponding to a gestational age (GA) of 1-2 weeks.	1	No	Less likely
Premature birth	corresponding to GA 25; vaccinated corresponding to week 4, history of cone biopsy	1	No	Less likely
Abortion	Spontaneous abortion week 3-4, week 6 and dead foetus week 13	3	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.

Reports of suspected non-serious ADRs received in 2013

The DHMA received a total of 201 reports of suspected non-serious ADRs during the period 1 January through 9 September 2013. The suspected non-serious ADRs most frequently reported were headache (9%), dizziness (7%), local reactions at the injection site (redness, pain, swelling) (6%), nausea (5%), fatigue (5%), paraesthesias (3%), fever (3%), extremity pain (3%), muscle pain (3%) and influenza-like symptoms (2%). All these symptoms, except for paraesthesias, are known ADRs that are mentioned in the summary of product characteristics.

The DHMA's overall assessment

The vaccine serves its purpose, i.e. to be an essential element in the prevention of cervical cancer. In rare cases, the vaccine may cause serious ADRs. However, the DHMA – as the authorities in the rest of Europe – presently assesses the benefits to outweigh the risks of the vaccine[5].

As part of our routine monitoring and based on the most recent ADR reports concerning POTS and similar symptoms associated with the use of the HPV vaccine, the DHMA has requested that the EMA investigates this as a potential newly identified ADR.

Particulars concerning studies on HPV vaccination

The suspected serious ADRs reported comprise a number of various autoimmune and neurological disorders, but with no pattern. Whether or not the vaccine could cause such diseases cannot be determined based on the individual reports, and studies and scientific literature do not support such a correlation.

Arnheim-Dahlström L et al. have presented an abstract of a study[6], in which the authors follow 954,182 Swedish and Danish women (aged 10-18 years), of whom 301,366 had been HPV vaccinated, and the rest had not. Through the patient registries, the two groups were compared with regard to autoimmune, neurological and thromboembolic disorders, and increased incidence among the vaccinees was not observed for the conditions and disorders mentioned. For coeliac disease, facial paresis and epilepsy, the incidence was lower among the vaccinees as compared with the group of non-vaccinees. It cannot be ruled out that women at risk of these disorders had opted out of vaccination.

In a recently published study[7], Grimaldi-Bensouda L et al. did not find an increased incidence of autoimmune disorders after HPV vaccination.

Even though these studies do not demonstrate a correlation between the vaccine and autoimmune disorders, continued monitoring is important. In this connection, it is also important to focus on the fact that more adult women are now vaccinated, and that special circumstances may apply to the adults. The DHMA will continue to monitor the development and assess the possibility of a correlation between the vaccine and the incidence of autoimmune disorders.

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.

Particulars concerning POTS

The condition POTS may occur in both genders, but occurs most frequently in women aged 15-50 years. The exact prevalence is not known. However, half a million women are deemed to suffer from POTS in the USA corresponding to an estimated number of approx. 7,000-8,000 women in Denmark.

Figures from the Danish National Patient Registry shows that 96 patients diagnosed with POTS were hospitalised during the period 2006-2012.

Until May 2013, only 24 cases of POTS were reported worldwide after vaccination with Gardasil/Silgard®. This number should be seen in the light of the 170 million vaccine doses sold globally (corresponding to approx. 60 million vaccinees).

5 The benefits of vaccination are described on the DHMA's website (in Danish only); *http://www.sst.dk/stophpv*

6 Arnheim-Dahlström, L. et al. Occurrence of adverse events after quadrivalent HPV vaccination in Denmark and Sweden, Karolinska Institutet, Stockholm and Statens Seruminstitut, Copenhagen, EUROGIN, 2012, Prague, Czech Republic,8--11th July 2012 (abstract)

7 Grimaldi-Bensouda L et al., Autoimmune Disorders and Quadrivalent Human Papillomavirus Vaccination of Young Females. 29th International Conference on Pharmacoepidemiology and Therapeutic Risk Management.Montreal, Canada, August 25-28, 2013 (abstract)

In addition to the four Danish reports from 2013 describing the diagnosis of POTS, one additional vaccinated woman has been diagnosed with POTS this year. This latter report is not included in the table, since it was received before 2013. Since the exact incidence and prevalence of this disease 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.

In the total of five women who have been diagnosed with POTS, the symptoms started between 1 and 30 days after the second or third HPV vaccination, respectively.

If a person is diagnosed with POTS or experiences symptoms of POTS (e.g. elevated heart rate and fainting), he/she must seek medical attention in order to be started on a treatment.

The reports may lead to knowledge of new potential ADR signals. It remains unclear whether there is a causal relationship between POTS and the HPV vaccination or the temporal association with the vaccination is merely coincidental for this relatively common disorder which is known to have its onset in the very age group vaccinated.

The DHMA will continue to focus on this issue and will inform about the results of the EMA investigation when available.

Important to report potential ADRs

It is important that doctors and patients continue to be aware of reporting potential ADRs from HPV vaccines.

The Danish reports are included as part of the basis for the Europe-wide assessment of the safety of the HPV vaccines.

Everyone can report ADRs to the DHMA at *http://laegemiddelstyrelsen.dk/en/topics/side-effects-and-trials/side-effects/report-a-side-effect-or-incident/humans*

The next overall listing of ADRs from the HPV vaccine will cover the period up until 1 January 2014 and will be published the last Thursday of January 2014.

All cases referred to in the articles in the Danish Pharmacovigilance Update 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.

Danish Pharmacovigilance Update is published by:
Danish Health and Medicines Authority
http://www.sundhedsstyrelsen.dk/English.aspx
Editor-in-Chief:
Henrik G. Jensen (HGJ)
Editor:
Nina Vucina Pedersen (NVP)
ISSN 1904-2086