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Contents

News from the EU

News from the DHMA

Short news

News from the EU

Assessment of risk of serious anaphylactic reactions from treatment with ferumoxytol (Rienso)

The ferumoxytol-containing medicine Rienso is a newer iron preparation for intravenous treatment of iron deficiency anaemia in adult patients with chronic kidney disease (CKD). It is well-known that parenterally administered iron preparations can cause hypersensitivity reactions, including serious and potentially fatal anaphylactic reactions. The recommendations in the medicine's product information have recently been updated after a review of the entire product group. Rienso was not included in this group review because it was not authorised at the start of the review, but the product information of Rienso has been updated with the newest recommendations in line with the other products.

During an ongoing routine assessment of the benefits and risks of Rienso, the European Pharmacovigilance Risk Assessment Committee (PRAC) has identified a signal concerning an increased risk of anaphylactic reactions from the medicine. Until the assessment of the risk of anaphylactic reactions to Rienso compared to other intravenous iron preparations has finished, the DHMA calls the attention of doctors to continue complying with the current recommendations:

Current recommendations for IV iron preparations

- IV iron-containing products must not be used in patients with hypersensitivity to the active substance, the product itself or one or more of its excipients.
- The risk of hypersensitivity is increased in patients with known allergies (including drug allergies) and in patients with immune or inflammatory conditions (e.g. systemic lupus erythematosus, rheumatoid arthritis) as well as in patients with a history of severe asthma, eczema or other atopic allergy. In these patients IV iron-containing products should only be used if the benefits of treatment are assessed to clearly outweigh the potential risks.
- To minimise the risks, IV iron-containing products should be administered in compliance with the dosage and administration instructions for e.g. the rate of infusion described in the summary of product characteristics of the individual products.
- IV iron-containing products should only be administered by staff trained to diagnose and manage anaphylactic/anaphylactoid reactions and only when resuscitation facilities are available.
- Patients should be informed of the risk of hypersensitivity before each administration. They should be informed of relevant symptoms and the importance of seeking medical attention if a reaction subsequently occurs.
- Patients should be closely observed for signs and symptoms of hypersensitivity reactions during and for at least 30 minutes following each injection of an IV iron-containing product.
- IV iron-containing products should not be used during pregnancy, unless it is clearly necessary. The treatment should be limited to the 2nd and 3rd trimesters, and should only be used if the benefits clearly outweigh the potential risks to the mother and the foetus. The risks to the foetus may be serious, covering anoxia and foetal distress.

A letter will also be sent to relevant specialist physicians informing them about the problem.

At present, the DHMA has not received any reports of suspected adverse reactions to Rienso.

For further information, please see EMA's press release here: *Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 5-8 May 2014*.

News from the EU

The European Medicines Agency, EMA, has started a review of the benefits and risks of using ivabradine (Corlentor®/Procoralan®)

EMA has started a new review of the benefits and risks of Corlentor®/Procoralan® used in systematic treatment of chronic stable angina pectoris in adults with coronary artery disease and in treatment of chronic heart failure.

Review background
EMA has started the review based on the preliminary results of a study (the SIGNIFY study). The SIGNIFY study investigated if treatment with Corlentor®/Procoralan® in patients with ischaemic heart disease reduces the rate of cardiovascular events – e.g. myocardial infarction – compared to placebo treatment. The patients enrolled in the trial received up to 10 mg twice daily, which is higher than the present recommended dose of 7.5 mg twice daily. The results from the SIGNIFY study showed that a number of patients with symptomatic angina (CCS class II or higher) had a small but significant increase in the combined risk of cardiovascular death or non-fatal myocardial infarction.

The conclusion from EMA's review will be published in Danish Pharmacovigilance Update when available.

Read more in EMA's press release *Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 5-8 May 2014*.

Read more about the *SIGNIFY study*.

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[1].

The list of signals leading PRAC to recommend further measures is published on the website of the European Medicines Agency (EMA) every month.

The most important recommendations on safety signals from the PRAC meeting in April 2014 concern the following products:

- Adalimumab - missed dose due to malfunction of the pre-filled pen device.
- Clindamycin – drug interaction with warfarin leading to international normalised ratio (INR) increased.
- Fentanyl patches – accidental exposure – the DHMA is presently following up on the problem.
- Levonorgestrel-releasing intrauterine device (IUD) – risk of uterine perforation, final study results of EURAS-IUD study.
- Simvastatin – risk of myopathy and rhabdomyolysis associated with high doses.

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

1 The fact that a signal has been assessed does not mean that there is a causal link to the medicine.

Nalmefen (Selincro®) and psychiatric adverse reactions

In May 2014, the DHMA received an adverse drug reaction (ADR) report concerning Selincro®, which described insomnia, anxiety, suicidal ideation and the hearing of own thoughts in a man a few hours after he had taken 18 mg of the medicine.

The man had no previous history of psychiatric symptoms. The symptoms lasted for a day, and the man is well today and has stopped taking the medicine.

As at 30 April 2014, the DHMA had received 28 reports for Selincro®, of which four are serious[2]. In three of the serious reports, psychiatric symptoms are described – including anxiety – as suspected adverse reactions to the medicine.

Number of users of Selincro® and ADR reports

Year	2013	As of 30 April 2014
Number of reports	5	28
Number of users*	743	–

**Number of users having redeemed at least one prescription for Selincro®.[1] Selincro® was marketed in 2013.*

Doctors should be aware of the following:

- In clinical studies, confusion and rare cases of hallucinations and dissociation have been reported. The majority of these reactions were mild or moderate, were associated with treatment initiation and were of short duration (a few hours to a few days). Most of these adverse reactions resolved during continued treatment and did not recur upon repeated administration (see the summary of product characteristics).
- While these symptoms had a short duration, they could represent alcoholic psychosis, alcohol withdrawal symptom or comorbid psychiatric disease.
- Selincro® has not been studied in patients with unstable psychiatric disorders. Caution should be taken when Selincro® is prescribed to patients with comorbid psychiatric disease such as moderate to severe depression.
- Selincro® should only be prescribed in conjunction with continuous psychosocial support focused on treatment adherence and reducing alcohol consumption.
- Selincro® should only be prescribed to patients who continue to have a high alcohol consumption two weeks after the first assessment.

The DHMA will continue to closely monitor adverse reactions related to Selincro®. Selincro® was marketed in February 2013, and it is therefore on the list of medicines subject to stricter monitoring, which means that doctors are obliged to report all suspected adverse reactions to the medicine. See the list of medicines subject to stricter reporting requirements on the DHMA's website: *Medicines with stricter reporting requirements for doctors, dentists and veterinarians*.

Indication for Selincro®
Selincro is indicated for the reduction of alcohol consumption in adult patients with alcohol dependence who have a high alcohol consumption, without physical withdrawal symptoms and who do not require immediate detoxification.

1 The analysis related to drug consumption has been prepared in collaboration with Data Delivery and Medicinal Product Statistics at Statens Serum Institut, National Institute for Health Data and Disease Control (SSI).

2 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.

All cases referred to in this article originate from the Danish Health and Medicines Authority's database of adverse drug reactions. 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.

ADR reports for the HPV vaccine

Since the HPV vaccine became part of the Danish childhood immunisation programme in 2009, the DHMA has had increased focus on the monitoring and evaluation of the reports of suspected adverse reactions associated with the vaccine.

Since 2009, we have received 1095 reports of suspected adverse reactions to the HPV vaccine. In the first two years after the vaccine was marketed, it was subject to stricter reporting requirements, which meant that doctors were obliged to report all suspected adverse reactions to the vaccine to the DHMA. This could explain the many reports in 2009, see table 1.

In 2013, focus on the vaccine intensified again after several girls/women experienced various symptoms after vaccination. While some of these girls were diagnosed with POTS (Postural Orthostatic Tachycardia Syndrome), others are still waiting for a diagnosis.

This renewed attention may explain why the reporting rate for the vaccine increased sharply in 2013 and the beginning 2014 (see table 1).

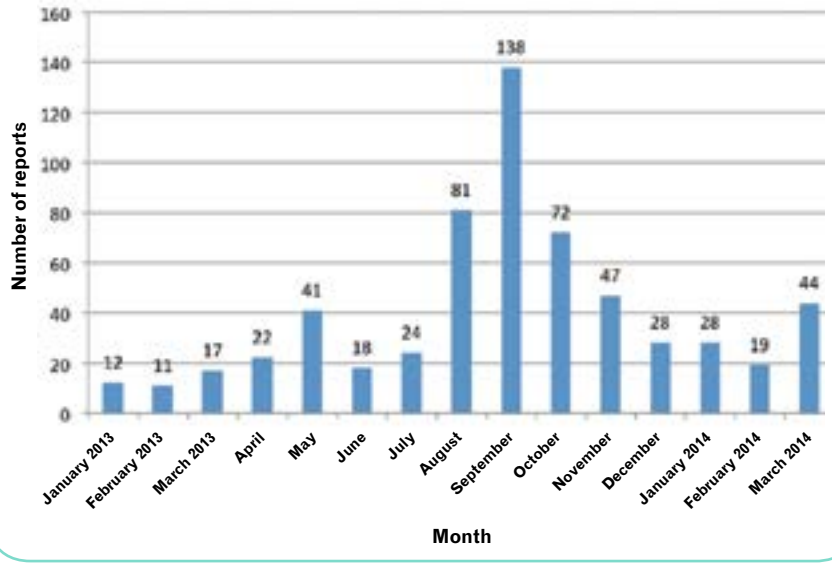

Figure 1: The total number of reports submitted for the HPV vaccine by months from January 2013 to March 2014.

In the period 2009-2012, we received 493 reports in total, of which 56 were categorised as serious. In 2013, we received five times as many reports than in 2012. The increase peaked over the summer and autumn 2013 when the HPV vaccine was exposed widely in the media (figure 1).

This renewed attention is why we have featured separate articles on the status of reports related to the HPV vaccine in Danish Pharmacovigilance Update since June 2013. This present status covering the period 1 December 2013 to 31 March 2014 is a follow-up on the previous articles in Danish Pharmacovigilance Update from *June 2013*, *September 2013* and *January 2014*.

HPV vaccine	2009	2010	2011	2012	2013	Q1 2014	Total
Number of reports	288	66	43	96	511	91	1.095
Number of serious reports	25	5	8	18	177	24	257
Number of doses sold	347,690	151,476	163,374	349,730	488,224	38,640	1,539,134

Table 1. Number of ADR reports involving the HPV vaccine received from 2009 to 31 March 2014, broken down by serious and non-serious reports. The number of doses sold in Denmark is also shown. (Please be aware that when the DHMA receives additional information, this may imply changes. Consequently, there may be variations between previously published figures and the figures reported here.)

Number of ADR reports related to the HPV vaccine received in the period from 1 December 2013 to 31 March 2014

During this period, we received a total of 119 reports, of which 91 were reported in the first three months of 2014. 32 of the reports were classified as serious[1].

The figures include all ADR reports related to the HPV vaccines Gardasil®, Cervarix® and Silgard® that we received in this period. In Denmark, Gardasil® is the vaccine used the most, which could explain that 31 of the total 32 reports in this period is related to Gardasil® – the last report carried no mention of the HPV vaccine given.

For the period December 2013 to March 2014, the number of reports was lower that in autumn 2013, but still higher than before the summer 2013.

New reports of previously occurring adverse reactions

Not all adverse reactions are reported at the time they occur. Among the 32 reports categorised as serious, there were several adverse reactions that started before 2013.

Table 2 shows the year the adverse reactions started. Two of the reports did not mention when the adverse reactions started.

Reports by age

Figure 2 shows the ADR reports by the age the girls had when the adverse reactions started.

As described previously in *Danish Pharmacovigilance Update, January 2014*, the HPV vaccine is the first vaccine included in the Danish childhood immunisation programme that is also offered free of charge to women outside the child vaccination programme. This is reflected in the age distribution of the reports.

In August 2012, a temporary offer was introduced, offering HPV vaccination free of charge to women born from 1985-1992 (i.e. 20 to 27-year-olds in 2012). The offer expired on 31 December 2013.

Since 1 January 2014, the HPV vaccine has been offered to women born from 1993-1997 (17 to 21-year-olds). The new offer expires on 31 December 2015[2].

Year when ADR started	Number of reports
2009	5
2010	4
2011	3
2012	2
2013	14
2014	2
Unknown	2
Total	**32**

Table 2: Year when the serious adverse reactions started of those described in the current period.

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.

2 *http://www.ssi.dk/Aktuelt/Nyheder/2014/2014%201%20epinyt%201-2%20HPV.aspx*

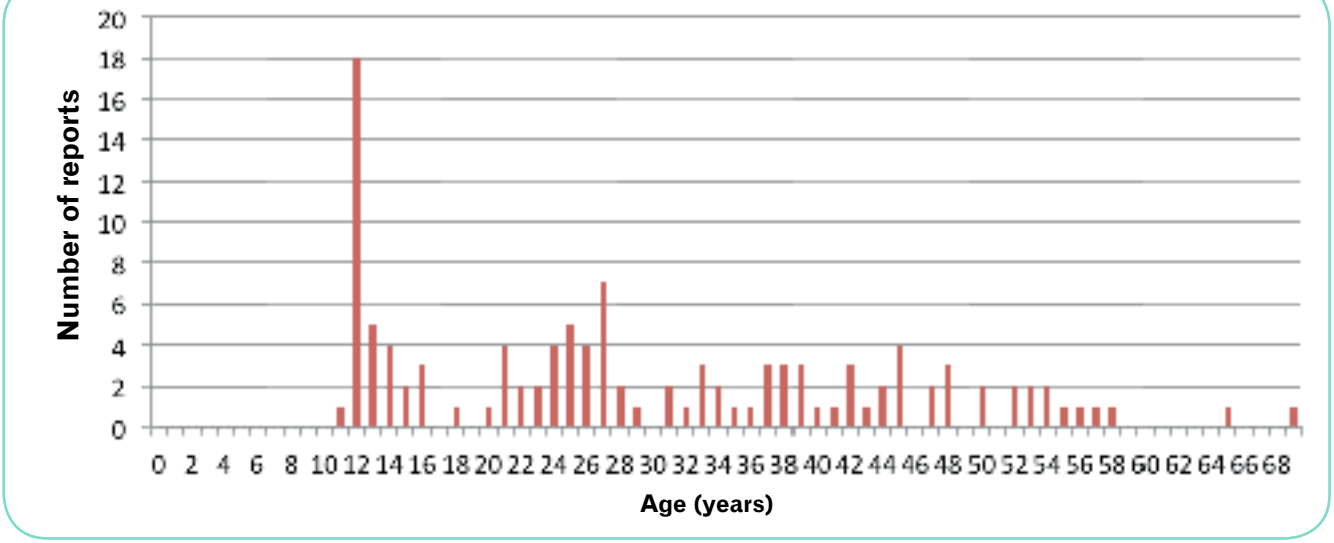

Figure 2: Reports received from 1 December 2013 to 31 March 2014 by age at vaccination. An additional three reports did not mention the age.

Review of the serious reports

The 32 reports that were classified as serious are described in table 3 together with the results of the causality assessment. The table indicates whether the adverse reactions are known and described in the summaries of product characteristics of the HPV vaccines. If an adverse reaction is known, it does not necessarily imply that it was caused by the vaccine.

The DHMA's results of the causality assessment of the serious adverse reports appear in the last column of table 3. A causality between the HPV vaccine and a suspected adverse reaction has been assessed in the following way:

- Possible
- Less likely
- Not possible to assess based on the available information.[3]

If information is missing to assess causality, we try to obtain it. We may receive additional information after this statement.

3 If a diagnosis has not been made, it is often difficult to assess causality.

Conditions	Possible adverse reaction(s)	Number	Described as possible ADR in the SPC	Results of causality assessment
Allergic reactions	A woman developed anaphylaxis immediately after vaccination.	1	Yes	Possible
Several different symptoms within several different System Organ, Classes without a diagnosis being made	Reports of women/girls who had long-term symptoms going from dizziness, headache, paresthesia, muscle/joint pain, faster heart rate, fluctuating pulse, fatigue, orthostatic intolerance etc. Almost all have been examined to varying extents by their own GP, privately practising neurologists, or in hospital without a diagnosis being made.	10	No	It is not possible to assess 9 of these, as no diagnosis has been made. 1 has been assessed as less likely
POTS	Described in both cases are symptoms suggestive of POTS. Diagnosis has been verified by tilt table test.	2	No	Possible
Symptoms from the heart	A girl experienced faster heart rate and shortness of breath about 6 months after vaccination. No diagnosis has been described.	1	No	Not possible to assess.
Mostly symptoms from muscles and skeleton	There is a description of a woman who suffered back pain, which is a very common disorder, in connection with vaccination.*	1	No	Less likely
	A woman experienced pains in her legs which were treatment refractory. Later, her own doctor informed us that the symptoms were present when the woman was vaccinated.	1	No	Less likely
	A girl developed muscle weakness and short-sightedness. No diagnosis has been made yet.	1	No	Not possible to assess
Mostly neurological symptoms	A girl fainted in connection with the vaccination.	1	Yes	Possible
	Mostly neurological symptoms have been described such as dizziness and fainting over longer periods after vaccination of a girl and two women. No diagnoses have been made.	3	No	Not possible to assess
	Multiple sclerosis (MS): * 1. 8 days after vaccination a woman developed symptoms suggestive of MS, which she had diagnosed. 2. 4 months after vaccination a woman developed symptoms suggestive of MS, but she does not yet fulfil the criteria thereof. The patient is still monitored.	2	No	Less likely
	A girl developed narcolepsy/cataplexy 3 months after vaccination. *	1	No	Less likely
	A girl had cramps during her sleep 2 days after vaccination. No diagnosis has been made yet.	1	No	Not possible to assess

	A woman had pain and developed neurological symptoms after the third vaccination. The neurological symptoms have not been specified further, and no diagnosis has been made.	1	No	Not possible to asses
Symptoms from the ears	3 months after vaccination a woman developed unilateral deafness.*	1	No	Less likely
Psychiatric symptoms	A girl developed psychosis 5 days after vaccination. *	1	No	Less likely
Autoimmune symptoms	A woman developed arthritis 6 weeks after vaccination. *	1	No	Less likely
	A girl who had previously been treated for Polyarteritis nodosa had a relapse a few days after vaccination. *	1	No	Less likely
	A woman developed symptoms of Wegener's granulomatosis 2 months after vaccination. *	1	No	Less likely
	A woman developed Henoch-Schonlein Purpura 6 days after vaccination.*	1	No	Less likely

*Table 3. Overview of the 32 suspected serious reports in the period from 1 December 2013 to 31 March 2014 and conclusions on the causality assessment. The table provides overview, and not all clinical information that the assessments are based on appear in the table. An * indicates that the literature has no description of causality between the adverse reactions and the vaccine.*

The vast majority of the serious adverse reactions to the HPV vaccine from 1 December 2013 to 31 March 2014 covered unexpected reactions.

There were two new reports on the diagnosis POTS. An additional number of reports (10) described symptoms in vaccinated girls such as headache, dizziness, fatigue, etc. In these reports, paraesthesia was also described. Most of these girls were examined by their own doctor, hospital or by a privately practising specialist with no diagnosis being made. Some of the described symptoms could be suggestive of autonomic dysfunction, for others, the POTS diagnosis was ruled out.

In epidemiological studies, no increased incidence rate of multiple sclerosis has been found in girls or women vaccinated with the HPV vaccine compared to people who were not given the vaccine. For this reason, it is considered most likely that the cases reflect pure coincidences with vaccination (1).

There were no other accumulated disorders.

There were reports describing neurological disorders and autoimmune diseases, but still no immediate pattern can be seen in these reports. There is no evidence in literature of a causality between the vaccine and these cases.

Review of the non-serious reports

87 (73%) of the reports related to the HPV vaccine that we received in this period described adverse reactions that were classified as non-serious.

The most frequently reported adverse reactions were local discomfort at the injection site (redness, pain, swelling) as well as headache and dizziness – all of them well-known adverse reactions described in the vaccines' summaries of product characteristics.

Among the unexpected non-serious adverse reactions were cases of periodontitis, paresthesia and herpes zoster infection.

Overall conclusion on reports submitted from 1 December 2013 to 31 March 2014

Compared to the latest statement of reported adverse reactions related to the HPV vaccine in *Danish Pharmacovigilance Update, January 2014*, the period from 1 December 2013 to 31 March 2014 did not show significantly different symptoms. There were two new cases of POTS, but several girls/women still remain to be diagnosed.

Generally, the number of reports is decreasing, but still higher than the period before 2013.

As of 31 March 2014, the accumulated number of POTS cases after HPV vaccination was 25 in Denmark. In the background population, the disease occurs most prevalent in women between 15 and 50 years of age. The prevalence is not known precisely, but in the USA it is estimated that half a million women suffer from POTS. This would correspond to approx. 7000-8000 women in Denmark having the disease. But not nearly as many have been diagnosed with the disease.

As at 31 September 2013, 33 possible cases of POTS or postural tachycardia cases had been reported as a possible adverse reaction to the Gardasil®-vaccine worldwide. Six of them were from Denmark. An additional 19 cases of POTS were thus reported from September 2013 to March 2014. There are treatments for POTS.

In 2013-2014, there were no accumulation of reports involving POTS cases in other countries than Denmark.

Both the DHMA and the rest of the EU are closely monitoring adverse reactions (including POTS) related to the HPV vaccine. The overall conclusion of the HPV vaccine is still that the benefits outweigh the possible risks.

New studies on adverse reactions to the HPV vaccine

Among the reported serious adverse reactions to the HPV vaccine, there have been reports of a number of different autoimmune and neurological conditions, yet with no pattern. It is not possible to determine based on the individual ADR reports if the vaccine could possibly cause these conditions in general.

In a study from 2013 (1), 954,182 Swedish and Danish women (age: 10-18) were monitored. 301,366 of them had received the HPV vaccine, the rest had not. The two groups were compared through patient registries in respect of autoimmune, neurological disorders and thromboembolic conditions, and no increased incidence rate was found for the group of vaccinated women for any of the conditions. In a case-control study, no increased incidence rate of autoimmune conditions was observed after HPV vaccination (2).

In regard to celiac disease, facial palsy and epilepsy, the incidence was lower among those vaccinated.

The HPV vaccine Gardasil® and Complex Regional Pain Syndrome

In April, the European Pharmacovigilance Risk Assessment Committee (PRAC) assessed an ADR signal on a rare condition known as Complex Regional Pain Syndrome (CRPS), characterised by local burning pain, sensory disturbances, tremor and weakening, etc. as a possible adverse reaction to the HPV vaccine Gardasil®. The ADR signal came from the Japanese authorities which had received several reports of CRPS cases in women vaccinated with Gardasil®. PRAC concluded that there was no basis to suspect the Gardasil® vaccine as the cause of CRPS.

Attention will still be paid to CRPS in the safety monitoring of Gardasil®.

The HPV vaccine was included in the Danish childhood immunisation programme on 1 January 2009. This means that all 12-year-old girls have been offered the vaccine since January 2009 for free, and the vaccines must be given before they turn 18. In addition, catch-up programmes have run for young girls and women.

Indication for Gardasil®

Gardasil® is a vaccine that can be used from the age of nine for the prevention of:

– premalignant genital lesions (cervical, vulvar and vaginal) and cervical cancer causally related to certain oncogenic Human Papillomavirus (HPV) types.

– genital warts (condyloma acuminata) causally related to specific HPV types.

References

1) Arnheim-Dahlström L et al: Autoimmune, neurological, and venous thromboembolic adverse events after immunisation of adolescent girls with quadrivalent human papillomavirus vaccine in Denmark and Sweden: cohort study BMJ 2013;347:f5906

2) Arnheim-Dahlström L et al: Autoimmune disorders and quadrivalent human papillomavirus vaccination of young female subjects. J Intern Med. 2014 Apr;275(4):398-408

All cases referred to in this article originate from the Danish Health and Medicines Authority's database of adverse drug reactions. 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.

Short news

Danish Health and Medicines Authority's annual pharmacovigilance report 2013

Our annual report 2013 has just been published in Danish on the DHMA website. Among other things you can read about the development in the number of ADR reports, see the top 5 of the medicines that generated the most reports to us as well as get an overview of the various campaigns, focus areas and the European collaboration in the pharmacovigilance area.

Read the *Danish Health and Medicines Authority's annual pharmacovigilance report 2013.*

New report from the DHMA about the users and adverse reactions of antiepileptics in Denmark

The DHMA has just finished a report on users and adverse reactions of antiepileptics in Denmark.

The report contains an analysis of the number of users of the medicines and the suspected adverse reactions that have been reported to the DHMA from 2003-2012. In addition, the report includes a review of the newest publications in the area.

Read the DHMA's report, which is in Danish only: *Users and adverse reactions of antiepileptics in Denmark (Danish title: Brugere og bivirkninger af antipileptika i Danmark)*.

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