Danish Pharmacovigilance Update

Year 3 #6
21 June 2012

# Decrease in the number of intoxications and suicide attempts using drugs containing acetylsalicylic acid or paracetamol

The Danish Health and Medicines Authority has prepared a status report on the development in the sale of drugs containing acetylsalicylic acid or paracetamol and the number of intoxications and suicide attempts using these drugs.[1]

Figures from the National Patient Registry (Statens Serum Institut, the National Institute for Health Data and Disease Control, SSI) show that in particular the number of suicide attempts among 12 to 20-year-old girls/young women has decreased from 2010 to 2011.

## Number of hospitalisations due to intoxication

Table 1 shows the number of intoxications resulting in admission to a somatic hospital. The intoxications include suicide attempts which are stated separately in Table 2.

The 2001-2009 period saw a generally steady increase in the number of hospitalisations due to intoxication using drugs containing acetylsalicylic acid or paracetamol. The 2009-2011 period followed the opposite trend with a decreasing number of intoxications caused by these drugs – for 12 to 20-year-old girls/young women in particular (Table 1).

## Number of suicide attempts

Table 2 shows that the number of suicide attempts among 12 to 20-year-old girls/young women was fairly constant in the years 2002-2004. The number then increased until 2010, followed by a decrease in 2011. Due to fluctuation patterns, figures for single years should be interpreted with caution. Also, in the bigger picture, it is worth noting that the population 12 to 20-year-old girls/young women is not constant.[2]

Figure 1 shows the development in the number of suicide attempts among young women and women in general using paracetamol or acetylsalicylic acid compared to the consumption of these drugs.[3]

## Possible correlation with the introduction of an age limit

As of 7 March 2011, an age limit of 18 years was introduced for buying >

**Table 1. Admissions to somatic hospitals due to intoxications caused by drugs containing acetylsalicylic acid or paracetamol**

| | *Age* | *2001* | *2002* | *2003* | *2004* | *2005* | *2006* | *2007* | *2008* | *2009* | *2010* | *2011* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Men | 0-11 years | 16 | 17 | 20 | 26 | 30 | 38 | 49 | 54 | 53 | 68 | 55 |
| | 12-20 years | 63 | 65 | 100 | 91 | 109 | 86 | 117 | 101 | 154 | 132 | 140 |
| | 21-50 years | 373 | 323 | 318 | 350 | 357 | 343 | 319 | 335 | 453 | 415 | 387 |
| | 51- years | 67 | 85 | 99 | 106 | 126 | 105 | 109 | 142 | 192 | 148 | 184 |
| | **Total** | **519** | **490** | **537** | **573** | **622** | **572** | **594** | **632** | **852** | **763** | **766** |
| Women | 0-11 years | 19 | 21 | 23 | 16 | 31 | 44 | 44 | 56 | 63 | 52 | 45 |
| | 12-20 years | 448 | 524 | 589 | 634 | 743 | 701 | 841 | 899 | 1135 | 1029 | 812 |
| | 21-50 years | 619 | 615 | 655 | 797 | 835 | 864 | 834 | 837 | 925 | 904 | 862 |
| | 51- years | 180 | 174 | 178 | 165 | 206 | 181 | 219 | 210 | 255 | 246 | 242 |
| | **Total** | **1266** | **1334** | **1445** | **1612** | **1815** | **1790** | **1938** | **2002** | **2378** | **2231** | **1961** |

Sources: The National Patient Registry

1 Drugs containing acetylsalicylic acid or paracetamol account for approx. 80% of the total sale of mild painkillers.
2 During the 2002-2011 period, the population of 12 to 20-year-old girls/young women grew from 256,239 to 308,184, i.e. an increase of 20%.
3 The comparison is based on sales figures for drugs containing paracetamol or acetylsalicylic acid sold over the counter, incl. combination products.

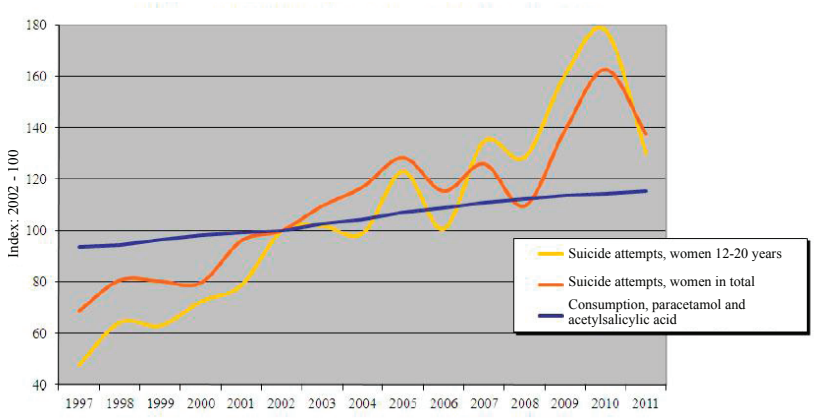
**Table 2. Admissions to somatic hospitals due to suicide attempts using drugs containing acetylsalicylic acid or paracetamol**

| | *Age* | *2001* | *2002* | *2003* | *2004* | *2005* | *2006* | *2007* | *2008* | *2009* | *2010* | *2011* |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Men | 0-11 years | 1 | 0 | 0 | 2 | 0 | 0 | 0 | 0 | 0 | 2 | 0 |
| | 12-20 years | 29 | 28 | 33 | 34 | 31 | 32 | 34 | 33 | 47 | 60 | 60 |
| | 21-50 years | 158 | 122 | 105 | 127 | 150 | 123 | 105 | 70 | 121 | 145 | 146 |
| | 51- years | 25 | 32 | 34 | 31 | 36 | 36 | 28 | 27 | 51 | 56 | 55 |
| | **Total** | **213** | **182** | **172** | **194** | **217** | **191** | **167** | **130** | **219** | **263** | **261** |
| Women | 0-11 years | 1 | 0 | 1 | 2 | 0 | 1 | 1 | 2 | 3 | 1 | 2 |
| | 12-20 years | 187 | 237 | 242 | 235 | 292 | 239 | 320 | 305 | 381 | 422 | 309 |
| | 21-50 years | 234 | 214 | 244 | 291 | 282 | 285 | 258 | 199 | 246 | 315 | 302 |
| | 51- years | 59 | 50 | 62 | 58 | 69 | 53 | 52 | 43 | 67 | 77 | 76 |
| | **Total** | **481** | **501** | **549** | **586** | **643** | **578** | **631** | **549** | **697** | **815** | **689** |

Sources: The National Patient Registry

> mild over-the-counter painkillers in pharmacies as well as in shops outside the pharmacy sector. It is a reasonable assumption that there is a correlation between the age limit and the decreasing number of cases of intoxication and suicide attempts. However, it will take a couple of years before a final conclusion can be drawn, as the figures may reflect a random fluctuation.

**Figure 1. Incidence of suicide attempts among young women using paracetamol and acetylsalicylic acid compared to the consumption of the two substance types**




Sources: The National Patient Registry and Register of Medicinal Product Statistics

# Information on adverse drug reaction (ADR) reports in the European ADR database will become generally available.

The European Medicines Agency will now publish adverse reaction reports from the European pharmacovigilance database (Eudravigilance) for around 650 types of medicine. The publication takes place due to the new EU pharmacovigilance legislation placing emphasis on increased transparency.

## Reports of suspected adverse reactions

Data in Eudravigilance have been reported by doctors, patients, companies and others suspecting that the symptoms are caused by medicine. This means that there is no certain causal relationship between the adverse reaction experienced by a patient and the medicine taken by this patient. Therefore, the information cannot be used to determine the exact risk of having an adverse reaction or as an indication of whether a medicinal product is particularly dangerous.

The known adverse reactions from the use of each individual product are described in the product information for the medicine (*www.produktresume.dk*, in Danish only) or in the package leaflet (*www.indlaegsseddel.dk*, in Danish only).

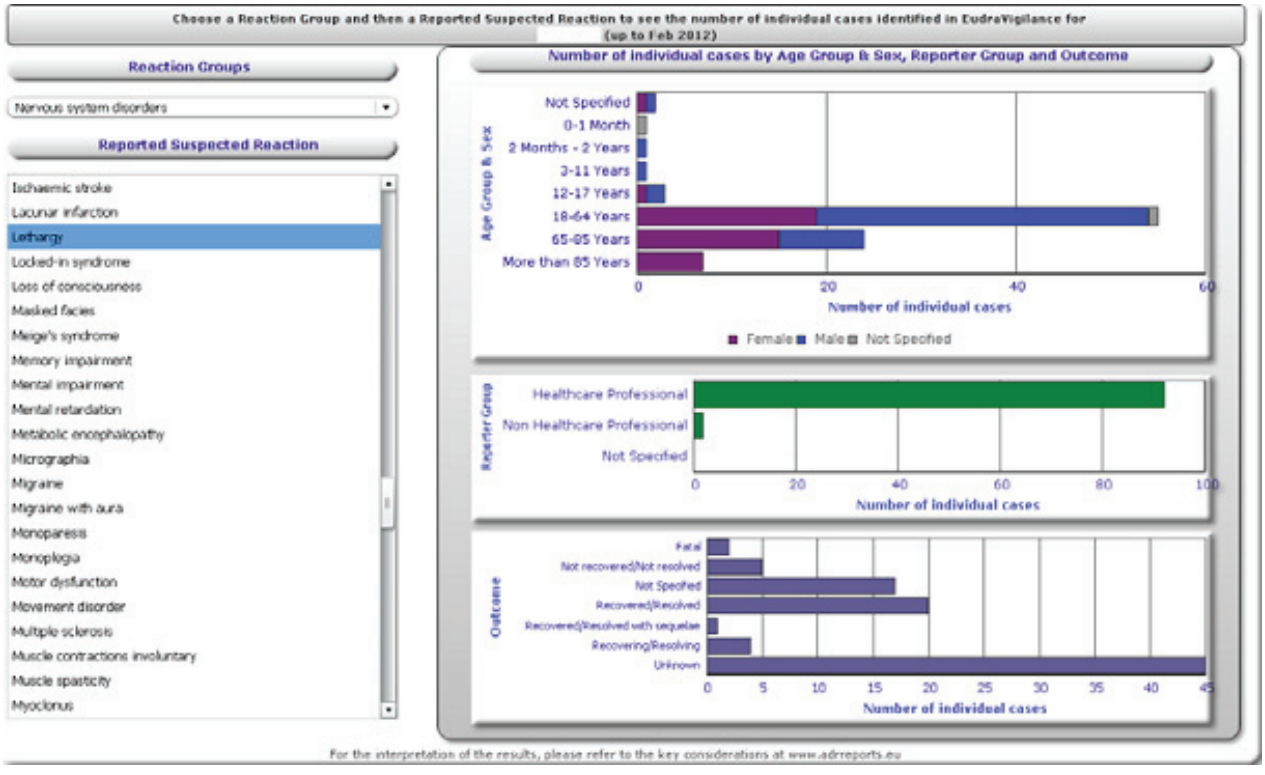
Authorities base their medicine safety assessment on reports of suspected adverse reactions, along with information from other sources – such as clinical and epidemiological studies, medical literature and knowledge of background levels of diseases.

When a medicinal product has been approved in Europe, authorities have assessed that the benefits outweigh the potential risks of the medicine, for the indications for which the medicine has been approved.

## Data for centrally approved medicines are published first

The first portion of the reports which are available now, cover medicines that have been centrally approved throughout the EU.

During the next year, the European Medicines Agency is working to publish the next portion of the reports. These reports cover suspected adverse reactions from the most common active >



> substances in medicines that have been approved by each national authority.

**Primarily serious adverse reactions**
The database primarily contains serious adverse reactions such as deaths, life-threatening conditions, disability, congenital malformations or foetal defects.

**Reports from all over the world**
Data are submitted by national authorities in the EU and by pharmaceutical companies. Therefore, the reports may originate from any country in which the medicine has been approved.

The available listings from Eudravigilance provide an insight into the total number of reports in Europe. It is not possible to distinguish between reports from each individual EU country.

Any suspected serious adverse reactions reported by doctors and others to the Danish Health and Medicines Authority will be available in Eudravigilance within 15 days from the report.

**What information is available?**
The database makes it possible to see the total number of suspected adverse reactions for each medicine – broken down by age, gender, type of adverse reaction and outcome of the adverse reaction, as seen from the example on page 3.

**Access to data**
Eudravigilance is accessed via *www.adrreports.eu*. The information is generally provided in English. During the course of 2012, the contents will be translated into all EU languages.

**Reported suspected adverse drug reactions in Denmark**
Statements of suspected adverse reactions from medicines in Denmark are generally available on the Danish Health and Medicines Authority's website: *Drug Analysis Prints: reported adverse reactions*.

The Danish statements contain all reports of suspected adverse reactions, whereas the statements from Eudravigilance at present only contain reports categorised as serious.

## Report of development of irreversible polyneuropathy in patients treated with products containing vincristine

In April 2012, the Danish Health and Medicines Authority received a report about a patient who, due to being diagnosed with a malignant disease, started treatment with Oncovin® among other products.

The patient developed neuropathic discomfort including a sense of walking on cotton wool, swollen feet, a tingling feeling in the fingers and fatigue. The dose was reduced after the second treatment. Subsequently, however, the patient still had severe adverse reactions. It was then assessed that the patient could not be treated with Oncovin®.

Around 18 months after onset of symptoms, the patient had substantial muscle wasting of arms and legs, but no paralyses. The gait was insecure and stiff, and the patient's condition was compatible with medium to severe polyneuropathy.

### Ten reports of development of neuropathy in association with vincristine

In total, the Danish Health and Medicines Authority has received ten reports of patients who developed neuropathy in association with the use of products containing vincristine.

It appears from the summary of product characteristics for the product that the incidence of neurologic adverse reactions is related to dose and age. At first, the neuromuscular manifestations most often are paraesthesias and sensory disorders. Continued treatment may cause neuropathy and, later on, serious motor disorders.

A substance with ability to reverse the neuromuscular adverse reactions is yet to be found. The adverse reactions may persist throughout the treatment, but most often disappear within weeks to months following discontinuation.

There is a high risk of neurotoxicity in patients with existing neurological disorders.

You can find a summary of product characteristics for vincristine at *www.produktresume.dk*.

**Indication for Oncovin®**
Oncovin® is indicated in certain malignant disorders, especially acute leukaemia, malignant lymphomas, solid tumours in children, and lung cancer.

## Lamotrigine does not appear to increase the risk of sudden unexpected death in patients with epilepsy

Two observational studies published in 2007 and 2010 together indicated an increased risk of sudden unexpected death in epilepsy (abbreviated SUDEP) in users of lamotrigine (e.g., Lamictal®). Therefore, the European Pharmacovigilance Working Party, PhVWP, decided to review all knowledge in the area in order to assess the risk.

The PhVWP concluded that there is no evidence to warn against an increased risk of SUDEP in patients with epilepsy using lamotrigine. By contrast, the principal risk factor for SUDEP is uncontrolled epilepsy with tonic-clonic seizures. Additional risk factors are polytherapy, male gender and young age at onset of epilepsy.

### Studies with differing results

The observational studies from 2007 and 2010 had several weaknesses. Both were case-only observations not allowing adjustment for risk factors, and the absolute number of cases was low. Moreover, the deaths had occurred during a period where the warning against concomitant use of contraceptive pills due to drug interactions had not yet been implemented.

Also, other studies turned out to indicate the opposite. An analysis of 112 clinical trials in adult patients with uncontrolled epilepsy showed that treatment with adjunctive anti-epileptics reduced the risk of SUDEP to a seventh compared with placebo. This study included 16 clinical trials where lamotrigine was used as adjunctive treatment in refractory epilepsy.

>

> Clinical trial data from the marketing authorisation holder for Lamictal® showed that the incidence rates for SUDEP with Lamictal® treatment fall within the range of the rates observed in patients with refractory epilepsy. In the trials, Lamictal® was given to precisely this group of patients.

For further information, please read the *PhVWP monthly report* from May 2012

**Indication for lamotrigine**
Used in the treatment of all types of epileptic seizures including treatment in patients with bipolar disorders and Lennox-Gastaut syndrome.

Several different mechanisms may underlie SUDEP. Most research has focused on mechanisms like seizure-related respiratory arrest, cardiac arrhythmia, cerebral depression and autonomic dysfunction. Data from an analysis of risk factors for SUDEP indicate that the higher the frequency of tonic-clonic seizures in an individual, the higher the risk of SUDEP. SUDEP usually occurs when the seizures are not witnessed and often at night.

In 2011, 31,636 persons received treatment with lamotrigine-containing medicines.

## Product information for Pradaxa® will be updated for patients and doctors in order to minimise the risk of bleeding

The European Medicines Agency (EMA) recently completed a review of the risk of bleeding with the anticoagulant Pradaxa®, in order to assess whether the latest available data on use of this product show any higher risk than previously recognised. The Agency's Committee for Medicinal Products for Human Use (CHMP) concluded that the latest data on Pradaxa® are consistent with the well-known risk of bleeding associated with anticoagulants and that the benefit-risk ratio of the product is still favourable. However, CHMP decided that the product information for Pradaxa® needs to be updated to clarify the guidance for doctors and patients in order to ensure that the product is used correctly so that the risk of bleeding is minimised.

### Updated recommendations in the product information:

- Patients should seek urgent medical attention if they fall or injure themselves during treatment with Pradaxa®, especially if they hit their head, due to the increased risk of bleeding
- Patients may not use Pradaxa® in combination with other anticoagulants (e.g., unfractionated heparin, low molecular weight heparin, heparin derivatives, oral anticoagulants) except during short periods where their treatment is being switched to or from Pradaxa®
- Pradaxa® may not be used in persons with lesions or conditions associated with a significant risk of major bleeding (e.g., gastrointestinal ulcerations, malignant neoplasms at high risk of bleeding, oesophageal varices, vascular aneurysms and others)
- Renal function should be assessed by calculating the creatinine clearance (CrCL) in all patients prior to initiation of Pradaxa®. Pradaxa is contraindicated in patients with a CrCL < 30 ml/min. See previous recommendations for the assessment of renal function in patients treated with Pradaxa in *Danish Pharmacovigilance Update from November 2011*
- For the indication atrial fibrillation, dose reduction may be necessary in patients with moderate renal impairment, see the recommendations in the summary of product characteristics for Pradaxa.

The product information for Pradaxa® will be updated shortly.

For further information about the review and the updates of the summary of product characteristics, please visit the EMA website: *Pradaxa*

*Questions and answers on the review of bleeding risk with Pradaxa (dabigatran etexilate)*

**Indication for Pradaxa®**
Pradaxa® is used for preventing venous thromboembolism in adult patients following knee and hip prosthesis surgery and for preventing apoplexy and systemic embolism in adult patients with atrial fibrillation.

# Use of medicines containing pioglitazone and risk of developing bladder cancer

*By Peter Gæde, M.D., D.M.Sc., medical secretary in the Danish Health and Medicines Authority, pg@dkma.dk*

The risk of developing bladder cancer in association with the use of medicines containing pioglitazone has been investigated in a number of observational studies with contradictory results. A recently published study in the scientific journal BMJ illustrates the issue based on data from the "UK general practice research database"[1]. This database contains structured datasets from more than 10,000,000 patients from more than 600 general practices in the UK. The study included all patients with type 2 diabetes who started using oral antidiabetics in the period 1 January 1988 through 31 December 2009. Of the 115,727 patients who met the inclusion criteria, 470 were subsequently diagnosed with bladder cancer over a total observation period of 526,559 patient years.

Based on the requirement in the overall analysis for a treatment period of minimum one year prior to development of bladder cancer, 376 patients were included in this analysis, and these patients were compared with 6,699 matching controls treated with other types of antidiabetics who were randomly selected from the database. The size of the cohort also allowed comparison of the risk of developing bladder cancer between pioglitazone and rosiglitazone. The latter has not previously been associated with an increased risk. Finally, it was possible to assess the risk based on the dose given and the duration of the treatment with these two products.

## Study results

The average treatment duration was 2.2 years for pioglitazone and 2.3 years for rosiglitazone. In general, the overall risk of developing bladder cancer was higher in patients with diabetes with an incidence of 89.4 per 100,000 patient years as opposed to 73 per 100,000 patient years in the general population in the UK. This is in line with previous results[2]. Use of pioglitazone was associated with an 83% increased risk of bladder cancer (95% confidence interval 10% to 305%), whereas no significant increase in risk was found with use of rosiglitazone.

A correlation was found between the pioglitazone dose given and the risk of developing bladder cancer, in that a cumulative dose of more than 28,000 mg was associated with an increased risk of 254% (95% confidence interval 5% to 614%). When looking at correlation with the duration of the treatment with pioglitazone, there was a 99% increased risk (95% confidence interval 14% to 345%) for treatment durations of more than 24 months.

## Study strengths and weaknesses

One of the strengths of the study as compared to previous observational studies is the very long follow-up period with a corresponding high number of bladder cancer cases. The structured data collection in the database is another strength. However, the incidence of bladder cancer is still low, a fact that is evident from the very broad confidence intervals. Another weakness of the study lies in the fact that the database described does not allow full adjustment for other risk factors for bladder cancer. This, however, applies to pioglitazone as well as rosiglitazone.

## Advice for doctors

Pioglitazone is still approved for the treatment of type 2 diabetes in Denmark. The Danish Health and Medicines Authority as well as the European Medicines Agency (EMA) assess pioglitazone on an ongoing basis. As with any other treatment, benefits must be weighed against risks prior to initiating or discontinuing a treatment. At present, several medicines for oral use as well as for injection are available for the treatment of type 2 diabetes. If, in consultation between the patient and the treatment provider, the safety profile for pioglitazone is found to be unfavorable, the patient can be switched to one of these. An updated overview of the role of each medicinal product in the treatment has just been published[3].

**Indication for pioglitazone**
Pioglitazone is an oral antidiabetic for the treatment of type 2 diabetes. The mode of action is improvement of insulin resistance via stimulation of peroxisome proliferator activated receptor gamma (PPARγ) ligand.

See Danish Pharmacovigilance Update from August 2011: *The European Medicines Agency recommends limited use of anti-diabetic medicine with pioglitazone (Actos®)*

1) Azoulay L, Yin H, Filion KB, J Assayag, Majdan A, Pollak MN, Suissa S. The use of pioglitazone and the risk of bladder cancer in people with type 2 diabetes: nested case-control study. BMJ 2012;344:e3645 doi: 10.1136/bmj.e3645
2) Larsson SC, Orsini N, Brismar K, Wolk A. Diabetes mellitus and risk of bladder cancer: a meta-analysis. Diabetologia 2006;49:2819-23
3) Inzucchi SE, Bergenstal RM, Buse J, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R, Matthews DR. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2012;55:1577-1596

# Childhood vaccinations and adverse reactions in the first quarter of 2012

One of the Danish Health and Medicines Authority's focus areas is potential adverse reactions from vaccinations. A vaccination panel has been established. The panel meets quarterly to assess the adverse reactions reported. The results are presented every quarter.

In the first quarter of 2012, there was no change in the routine childhood immunisation programme in Denmark. In the weekly newsletter EPI-NEWS from the Statens Serum Institut, the National Institute for Health Data and Disease Control, SSI, from week 20, there are new figures for the coverage of each individual vaccine in Denmark. These figures are based on a questionnaire survey showing that vaccinations are under-reported to the Danish Childhood Vaccination Database.
This means that the estimated coverage in Denmark of each individual vaccine is higher than previously estimated.

There are no data on the number of persons receiving vaccines from the immunisation programme later in life.

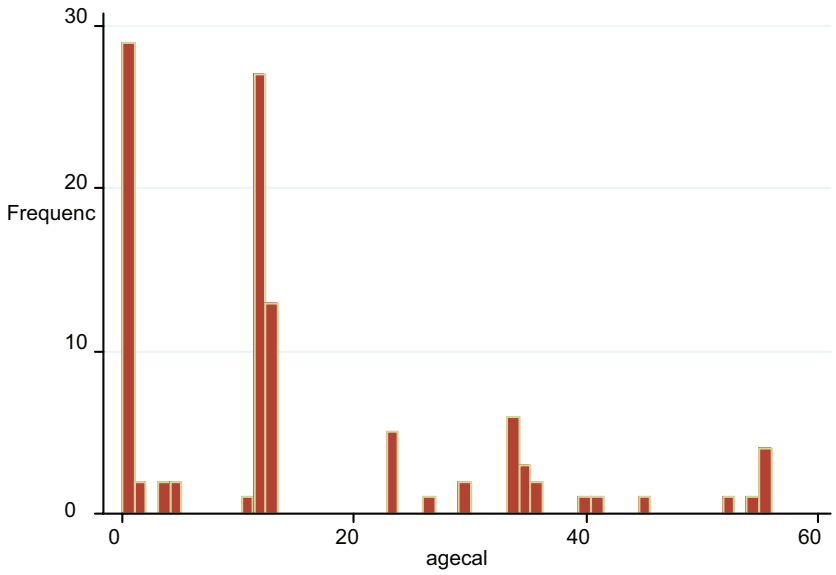
A patient experienced a serious adverse reaction if:

- The patient was hospitalised or had the hospital stay extended.
- The patient was in a life-threatening condition.
- The patient became disabled or suffered a considerable functional impairment.
- The patient died.
- Malformations or foetal defects occurred due to vaccination of the mother or the father.

This means that any person who has been briefly hospitalised (e.g., in a paediatric admission ward) with an adverse reaction will have been classified as a patient with a serious adverse reaction.

| | |
|---|---|
| DTaP-IPV booster vaccination | 85.1-86.3% |
| DTaP-IPV/Hib1 | 94.1% |
| DTaP-IPV/Hib2 | 90.6% |
| DTaP-IPV/Hib3 | 90.7% |
| MMR1 | 90.7% |

**Figure 1. Number of adverse reactions broken down by age for the person having the adverse reaction**




## Adverse reaction reports for the first quarter

In the first quarter, the Danish Health and Medicines Authority received a total of 41 reports including a total of 119 adverse reactions, which is fairly unchanged compared to previous periods.

Excluding Gardasil/Cervarix, there are no gender differences regarding frequency.

37 adverse reactions in a total of ten patients (reports) were classified as serious.

The majority of the adverse reactions reported were well-known, such as local reactions at the injection site and general malaise. Thus, general symptoms such as fatigue, fever and pain accounted for 35%, while local irritation, rash and temporary changes of the skin accounted for 24% of the adverse reactions reported. >

> The vaccines were given to persons aged 0-54 years, and 14 of the reports concerned persons over the age of 18. Adults had received Gardasil®, Cervarix®, Td booster, DTaP-IPV booster, Priorix®, and Pneumovax.

Table 1 shows the distribution of the number of reports and the number of serious reports for the various vaccines in the first quarter of 2012.

For Gardasil®, there were two cases of eczema following vaccination, as opposed to 2009, when there was a focus on this potential adverse reaction and there were many reports.

Across all vaccines, unknown adverse reactions classified as non-serious were as follows: Herpes zoster and tics.

Adverse reactions classified as serious:

1. A young man developed a high fever and elevated CRP the day after vaccination with Pneumovax and Act-Hib. For Pneumovax both are described in the product information, for Act-Hib only fever is described. Since it is a known adverse reaction, a correlation is deemed possible.

2. 12 years ago, a now middle-aged woman developed Guillain-Barré syndrome (GBS) approx. a month after vaccination with Td booster. According to the literature, there is no documentation of a possible correlation between the vaccination and the disease. Therefore, a correlation is deemed less likely.

3. A girl received a vaccination with Priorix® and Gardasil®. She immediately developed a vasovagal reaction and, in the afternoon of the same day, headache, dizziness and nausea. Priorix® was given intramuscularly. She was in recovery at the time of reporting.

4. A previously healthy girl was vaccinated with Priorix® and Gardasil® on 18.8.11, changed behaviour on 23.8.11 and was hospitalised psychotic on 5.9.11. She was assessed for encephalitis, which was disconfirmed.

   The literature does not provide evidence of a correlation between psychosis and either of the vaccines mentioned. Therefore, a correlation is deemed less likely.

>

**Table 1: (*some received more than one vaccine)**

| Vaccine | Total number of adverse reactions per vaccine* | Number of adverse reactions per vaccine with report classified as serious | Number of reports per vaccine classified as serious |
|---|---|---|---|
| Pneumovax | 6 | 2 | 1 |
| DTaP-IPV booster | 4 | 0 | 0 |
| Td booster | 7 | 1 | 1 |
| DTaP-IPV/Act-Hib | 20 | 3 | 2 (received both) |
| Prevenar13 | 10 | 1 | |
| Gardasil | 55 | 17 | 5 (2 concomitant Priorix) |
| Cervarix | 1 | 0 | 0 |
| Priorix | 16 | 13 | 3 (2 concomitant Gardasil) |
| **Total** | **119** | **37** | **10** |

> 5. Approx. three weeks following the 2nd vaccination with DTaP-IPV/Act-Hib and Prevenar13, a girl developed pyoderma gangrenosum - an inflammatory skin disease often seen along with an underlying disease such as an arthritis disorder or inflammatory bowel disease. The disease is rarely seen in children. There are only case reports of a correlation with vaccines. Based on the documentation available, a correlation with the vaccines is deemed less likely.

6. Five days following vaccination with DTaP-IPV/Act-Hib and Prevenar, a girl developed left-sided cerebral infarction. She had previously been vaccinated without experiencing adverse reactions.

   Cerebral infarctions are rarely seen in children (0.6-7.9/100,000), but there are known risk factors such as arteriopathy, heart disorders and infection. The literature does not describe a correlation between vaccination and cerebral infarction. A correlation with the vaccinations is deemed less likely.

7. Approx. three weeks following the 3rd vaccination with Gardasil®, a woman developed opticus neuritis. The incidence of this condition is approx. 6.4/100,000 in the US, most frequently in women of 20-40 years of age. Previously only isolated cases of a correlation between the vaccinations and this condition have been found; there is no epidemiological evidence. Based on the documentation available, a coincidence is deemed more likely.

8. A girl developed knee joint pain, no clinical findings. Priorix® was given on 11.10.11, Gardasil ® on 13.12.11. The symptoms started on 16.1.12. As it is stated in the product information for Gardasil® that arthralgias may occur (unknown incidence), a correlation with Gardasil® is deemed possible.

9. Approx. six months following vaccination with Gardasil®, a woman was diagnosed with ITP. In the product information, idiopathic thrombocytopenia is mentioned as a potential adverse reaction of unknown incidence. PubMed contains at least one more case report with a correlation. As a temporal correlation cannot be excluded for this case, even though the disease was not diagnosed until six months following the vaccination (sometimes diagnosed late), a correlation cannot be excluded.

10. This report was submitted by a private citizen and concerned a boy who had been vaccinated with Priorix®. The report mentions bone and neck pain, fever, allergy and a low platelet count with a risk of leukaemia. Additionally, autism is suspected. Priorix® may cause fever and thrombocytopenia, but the present basis does not allow a causality assessment of this case and it is not possible to obtain further information concerning the case.

**Overall conclusion for the first quarter of 2012**

Throughout 2011, we received 435 reports of adverse reactions associated with the immunisation programme, and thus, the number of reports for the first quarter of 2012 appears to be stable compared to 2011.

There is no clear pattern among the serious adverse reactions. There is a higher number of potentially chronic rare disorders. Please note that only two out of the ten reports assessed as serious concern children under 12 years of age. No figures are available on the number of adults vaccinated with vaccines from the immunisation programme. As of 1 April 2012, free vaccination with MMR vaccine is offered to young adults and therefore, attention needs to be paid to potential adverse reactions in this group.

The other adverse reactions reported were largely well-known, primarily with local reactions at the injection site, general malaise, fever and pain.

## New studies on antidepressants

On the Danish Health and Medicines Authority's website, you can read about two new Danish studies concerning SSRIs and *slightly increased risk of heart malformations* (in Danish only) and *increased risk of cardiac arrest associated with the use of TCA and SSRI antidepressants* (citalopram), respectively.

The Danish Health and Medicines Authority will discuss the studies in the European Medicines Agency and in the European Pharmacovigilance Working Party (PhVWP) in order to subject them to a closer assessment.

## Next issue of Danish Pharmacovigilance Update will be published in August

Due to summer holidays, Danish Pharmacovigilance Update will not be published in July. The next issue will be published on 16 August 2012. We wish all readers a great summer.

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