Danish Pharmacovigilance Update Year 3 #3
15 March 2012

A new registry study has investigated the frequency of malformations in newborns after treating the mother with antidepressants (SSRI) during the pregnancy

Last year, in cooperation with Statens Serum Institut, National Institute for Health Data and Disease Control (SSI), the Danish Health and Medicines Authority initiated a registry study to determine whether the use of SSRI products in pregnant women leads to changes in the frequency of malformations.

The registry study covers approx. 950,000 children – including approx. 11,000 children born to mothers who have redeemed prescriptions for an SSRI product either around the start of pregnancy or in early pregnancy.

The registry study concludes that:

- The frequency of malformations in general is slightly increased in children born to mothers redeeming prescriptions for SSRI products around the start of pregnancy or in early pregnancy. The frequency is 3.1% compared to 2.4% in other women.

- The specific type of SSRI products has no major impact on the slightly increased prevalence of malformations.

- The prevalence is slightly increased for most categories of malformations. Despite the fact that the study comprises nearly 1 million children, it cannot be determined with sufficient certainty if the frequency of specific malformations is particularly increased.

As the increased prevalence of malformations cannot be uniquely ascribed to a biological effect of SSRI products, it is a theoretical possibility that the women who redeem prescriptions for SSRI products differ from other women in ways that may explain the increased prevalence.

Advice for doctors
In compliance with the guidelines in the area, the Danish Health and Medicines Authority maintains its recommendation that the decision to medically treat depression in pregnant women should be made only in consultation with a specialist in psychiatry and after other non-medical options have been considered. In the individual case, the potential beneficial and harmful effects of treatment should be weighed against the risks involved for the pregnant woman and unborn child if a depression is not treated adequately.

The results of the study will be presented to the European Pharmacovigilance Working Party, PhVWP, and discussed together with the other knowledge in the area.

Furthermore, it is expected that the study will be published with peer-review in a respected international medical journal in mid-2012.

Read the full announcement *New data on antidepressants of the SSRI type and prevalence of malformations in newborns*.

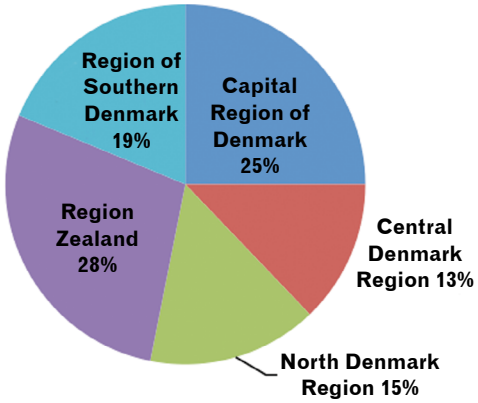
The first results from a new study on Pradaxa® (dabigatran etexilate)

In August 2011, a relatively new anti-coagulant, Pradaxa® (dabigatran etexilate), was approved for the prevention of apoplexy in patients with non-valvular atrial fibrillation.

In this connection, the Danish Health and Medicines Authority (the former Danish Medicines Agency) entered into a cooperation agreement with the Thrombosis Centre in Aalborg to start a study with the aim of mapping the consumption and the safety profile for this new medicine. Below, we will present the first results.

The report briefly describes the status of the consumption of Pradaxa® based on the first available data from the Register of Medicinal Product Statistics Furthermore, we summarise the adverse reactions reported to the Danish Health and Medicines Authority's adverse reaction database concerning Pradaxa® in the period 22 August 2011 through 23 February 2012. Finalised reports from the Danish Health and Medicines Authority's adverse reaction database were considered.

Figure 1. The quantity consumption expressed in DDD (defined daily doses) per 1,000 inhabitants per day distributed on the five regions in Denmark.



The consumption of Pradaxa®

Since Pradaxa was introduced on 22 August 2011 and up until the end of 2011, 4,610 persons have redeemed at least one prescription for Pradaxa®, 45% of these persons being women, and 55% men. Of those having redeemed at least one prescription, 19% are under 65 years, 37% are between 65-74 years and 43% are 75 years or above.

Among the users (1,017) started on a treatment with Pradaxa®, roughly a fifth has not redeemed a prescription for other blood-thinning medication in the period from 1 January 2009. In the previous period (1 January 2009 to 22 August 2011), half (52%) of the new users redeemed a prescription for warfarin alone or warfarin and clopidogrel and/or aspirin.

The quantity consumption per inhabitant is highest in Region Zealand and the Capital Region of Denmark, as shown in Figure 1.

Reported suspected adverse reactions concerning Pradaxa®

In the period 22 August 2011 through 23 February 2012, we received 52 adverse reaction reports for patients having experienced adverse reactions from the use of Pradaxa®.

All of the adverse reactions except for one have been reported by doctors. The reports concern 27 men and 25 women aged between 43 and 95 years – and with a median age of 76 years.

Among the total 52 reports are four deaths in connection with treatment with Pradaxa®. One case appears to have been caused by treatment failure – the patient had a cerebral infarction. Another case concerns fatal bleeding per rectum. In a third case, Pradaxa® was used off-label, and the patient died from a suspected bleeding. In the last case, it is still uncertain whether the patient had taken Pradaxa® at all before the time of death.

The 48 non-fatal adverse reaction reports cover 85 adverse reactions, as shown in Table 1. The number of serious adverse reactions is shown in parenthesis.

Of the suspected adverse reactions, 44% are gastrointestinal adverse reactions, see Table 2. There is an over-representation of bleedings and thromboses and their sequelae, e.g. dyspnoea caused by pulmonary embolism, renal failure due to renal infarction etc. These adverse reactions appear in varying chronological order after initiating Pradaxa®. >

> 22 serious cases of bleedings have been observed, mostly concerning the gastrointestinal tract. In addition, five serious cases of thromboses (the brain, kidneys, spleen and lungs) have been observed. Furthermore, five cases of non-serious bleedings have been observed.

Table 1. Adverse reactions by organ system

Organ system	Total no. of adverse reactions (serious adverse reactions)
Symptoms from the blood and lymphatic system	4 (4)
Symptoms from stomach and intestines	38 (24)
General symptoms and reactions	5 (1)
Infections	3 (2)
Injuries and intoxication	1 (1)
Symptoms related to metabolism and nutrition	2
Symptoms from the nervous system	6 (4)
Kidney and urinary tract symptoms	5 (5)
Symptoms from the genitalia	1 (1)
Airway symptoms	8 (3)
Symptoms from the skin	7 (1)
Surgical and medical procedures	1
Symptoms from vessels	4 (4)

Table 2a. Serious adverse reactions concerning the gastrointestinal tract

Types of gastrointestinal symptoms	No. of adverse reactions
Haematochezia	5
Rectal bleeding	5
Gastrointestinal bleeding	2
Melaena	2
Gastric bleeding	1
Intestinal bleeding	1
Gastric ulcer	1
Duodenal ulcer perforation	1
Intestinal ischaemia	1
Upper gastrointestinal bleeding	1
Dysphagia	1
Acute abdomen	1
Gastrointestinal necrosis	1
Haemorrhagic diarrhoea	1
Total	**24**

Table 2b. Non-serious adverse reactions concerning the gastrointestinal tract

Types of gastrointestinal symptoms	No. of adverse reactions
Abdominal pain	5
Dyspepsia	2
Oral bleeding	2
Xerostomia	1
Diverticuli	1
Oral pain	1
Diarrhoea	1
Enlarged uvula	1
Total	**14**

The conclusion of the first results

The picture of the adverse reactions reported emphasises the importance of assessing the patient's risk of bleeding, including continuous monitoring of the patient's renal function, as Pradaxa® is secreted through the kidneys. In addition, it is also important to take risk factors for bleeding into consideration, e.g. gastrointestinal ulcer, and other medicines that affect haemostasis, e.g. Plavix®, acetylsalicylic acid (ASA) and NSAIDs. Also, doctors should consider carefully whether a well-treated patient should be switched from medicine containing warfarin or phenprocoumon to Pradaxa®.

Interaction between Victrelis (boceprevir) and ritonavir-boosted HIV protease inhibitors

A pharmacokinetic study in 39 healthy volunteers assessed the interactions between Victrelis and ritonavir-boosted HIV protease inhibitors. The study showed that co-administration of boceprevir and ritonavir in combination with atazanavir or darunavir or lopinavir resulted in:

- A significant drop in the exposure to the HIV protease inhibitors with a reduction in mean-trough-value of 49% with atazanavir/rtv, 59% with darunavir/rtv, and 43% with lopinavir/rtv.
- A reduction in the exposure of boceprevir of 45% with lopinavir/rtv and 32% with darunavir/rtv. However, co-administration with atazanavir/rtv did not lead to a significant change in the exposure of boceprevir.

Based on these pharmacokinetic data, item 4.5 in the summary of product characteristics for Victrelis was updated as follows:

- It is not recommended to co-administer boceprevir and darunavir/rtv or lopinavir/rtv.
- Co-administration of atazanavir/ritonavir with boceprevir resulted in lower exposure of atazanavir which may be associated with lower effect and loss of HIV control. This co-administration might be considered on a case by case basis if deemed necessary, in patients with suppressed HIV viral loads and with HIV viral strain without any suspected resistance to the HIV regimen. Increased clinical and laboratory monitoring is warranted.

These pharmacokinetic drug interactions may be clinically significant in HIV-HCV co-infected patients through a potential reduction of the effect of these drugs when co-administered. Therefore, doctors should inform patients in combination treatment with a HIV protease inhibitor and boceprevir about the new findings. Also, patients should be advised to contact their doctor prior to stopping the treatment with one of these two drugs.

There are no data on pharmacokinetic drug interactions with other ritonavir-boosted protease inhibitors.

Read *EMA's press release*.

At the time of approval of the marketing authorisation for Victrelis (boceprevir), only data on drug interactions for ritonavir showing no significant interaction were available. Therefore, the Committee for Medicinal Products for Human Use, CHMP, concluded there was a need for further studies of drug interactions for boceprevir, an oral hepatitis C virus (HCV) NS3/4A protease inhibitor, and ritonavir-boosted HIV protease inhibitors.

Review of Vivaglobin® completed

The European Medicines Agency, EMA, has reviewed data on Vivaglobin® in order to explain the serious cases of blood clots that have been reported in association with the use of Vivaglobin®, see *Danish Pharmacovigilance Update, April 2011*.

This review concluded that the blood clots were caused by the manufacturing process for Vivaglobin®. This has led to a change in the manufacturing process and the quality control of the product.

In Denmark, we have not received any reports of blood clots in association with the use of Vivaglobin®.

Read *EMA's press release*.

New contraindications and warnings for blood pressure medicine containing aliskiren (Rasilez® and Rasilez® HCT)

The European Medicines Agency, EMA, has just completed a reassessment of the effect and safety of aliskiren. The background for the reassessment was an early discontinuation of a clinical study, ALTITUDE, due to lack of efficacy of aliskiren and an increased prevalence of apoplexy, renal adverse reactions, hyperkalaemia and hypotension among patients treated with aliskiren. The study and the problems are detailed in *Danish Pharmacovigilance Update, January 2012*.

Based on the reassessment EMA recommends to update the product information with a general warning against combining aliskiren containing medicines with ACE inhibitors or angiotensin receptor blockers (ARBs).

In addition, EMA recommends that:

- Treatment with aliskiren containing medicine is contraindicated in patients with diabetes mellitus (type 1 or type 2) or renal impairment (GFR < 60 ml/min/1.73 m^2) taking medicine of the ACE inhibitor or ARB types.
- Doctors must stop aliskiren-based treatment and must not initiate a new treatment with aliskiren in patients taking an ACE inhibitor or an ARB, who have either diabetes mellitus or renal impairment (GFR <60 ml/min/1.37 73 m^2).
- For all other patients, doctors should carefully consider the advantages and disadvantages of continued treatment with blood pressure medicine containing aliskiren in combination with ACE inhibitors or ARBs.

At the earliest possible opportunity, the summary of product characteristics for Rasilez® and Rasilez® HCT will be updated with the changes above.

Read *EMA's press release*.

Statins and myopathy/rhabdomyolysis

The Danish Health and Medicines Authority has reviewed all adverse reaction reports received up until 31 January 2012 related to statins.

Statins can cause myopathy manifested as muscle pain, soreness or weakness with creatine kinase (CK) above ten times the upper limit of normal (ULN). Myopathy sometimes takes the form of rhabdomyolysis with or without acute renal failure secondary to myoglobinuria.

The Danish Health and Medicines Authority has received a total of 441 reports of muscle-related adverse reactions – including elevated blood levels of myoglobin and creatine (phospho) kinase and renal impact following treatment with statin.

Table 1

Adverse reaction	No. of reports describing adverse reactions		
Myopathy			18
Myalgia			260
Other muscle-related adverse reactions	Impaired mobility	1	
	Muscle atrophy	2	
	Muscle disease	1	
	Muscle fatigue	11	
	Muscle rigidity	1	
	Muscle spasms	45	
	Muskel firmness	1	
	Muscle contractions	1	
	Muscle weakness	40	201
	Muscle and skeleton discomfort	4	
	Muscle and skeleton pain	7	
	Muscle and skeleton stiffness	12	
	Myositis	27	
	Polymyositis	2	
	Neck pain	3	
	Extremity pain	40	
	Feeling of muscle heaviness	3	
Rhabdomyolysis			45
Elevated blood level of creatine (phospho) kinase			30
Elevated blood level of myoglobin			2
Renal impact, renal impairment or renal failure			14

Table 1 lists the number of muscle-related adverse reactions (570) in the 441 reports. A single report may describe several adverse reactions, and several of the adverse reactions below are found in one and the same report.

The risk of myopathy/rhabdomyolysis is rare and dose-related. The incidence in clinical studies, in which the patients were carefully monitored and certain interacting drugs were excluded, has been 0.02% at 20 mg, 0.08% at 40 mg, and 0.53% at 80 mg.

Advice for doctors

When treatment with statin is initiated or the dose is increased, all patients must be informed about the risk of myopathy and instructed to contact the doctor immediately, in case they experience muscle pain, soreness or weakness.

- If muscle pain, weakness or cramps occur while the patient is being treated with a statin, the CK levels are to be measured.
- If these levels turn out to be significantly elevated (> 5 x ULN) and are not following tough exercise, the treatment should be stopped. If the CK levels go back to normal, re-initiation of statin or initiation of an alternative statin may be considered with the lowest documented dose and careful monitoring.
- If the muscular symptoms are serious and cause daily discomfort even with CK levels < 5 x ULN, the treatment must be stopped. If the symptoms resolve during the treatment break, but return after re-initiation, dose reduction or discontinuation should be considered.

The U.S. Food and Drug Administration updates the product information for statins in the USA

The U.S. Food and Drug Administration, FDA, recently decided to update the product information for statins with information on cognitive adverse reactions in the form of memory problems and confusion as well as a risk of increased blood glucose. In addition, recommendations have been revised to remove the need for routine periodic monitoring of liver enzymes in patients, and there are specific warnings regarding concomitant use of lovastatin and other medicines that can cause myopathy/rhabdomyolysis.

The Danish Health and Medicines Authority is aware of the new announcements made by the FDA and the current discussions in the area and will follow the development in the area.

Read *FDA's announcement.*

The benefits from the use of medicine containing orlistat still outweigh the potential risks

The benefits of taking medicine containing orlistat outweigh the potential risk of serious liver injuries. This is the conclusion of the Committee for Medicinal Products for Human Use, CHMP, in a study of medicines with the ingredient orlistat that has just been completed. The study included the centrally approved products Xenical® and Alli® and the nationally approved generic drugs with the same ingredient. CHMP launched the study in August 2011 based on several reports of cases of serious liver injuries.

Reported cases of serious liver injuries

From January 1997 to January 2011, a total of 21 cases of serious liver injuries were reported worldwide, for which a relationship to treatment with Xenical® cannot be excluded, however, other factors may have contributed to the liver injuries, such as the underlying disease, other diseases or other medicines.

Nine cases of liver failure have been reported in association with the use of Alli® between May 2007 and January 2011. Here too, other factors may have caused the liver injuries.

The number of cases should be seen in the light of the consumption of Xenical® and Alli®, for which the total estimated number of patients worldwide is more than 53 millions.

The conclusion from CHMP is based on the fact that the number of liver injuries associated with treatment with orlistat was small, and in most cases there were other factors that were more likely causes of the liver injuries.

CHMP is of the opinion that the benefit of the use of medicine containing orlistat continues to outweigh the risks when treating patients with a BMI ≥ 28 kg/m2.

Identical information for all medicines containing orlistat

CHMP has recommended to harmonise the product information so that information on these rare liver injuries is identical for all medicines containing orlistat.

Read *EMA's press release*.

Known adverse reactions

Liver injuries such as hepatitis, cholelithiasis, and changes in the liver enzyme levels, are known adverse reactions for medicines containing orlistat, which are described in the product information for the medicines.

Indication for orlistat (Xenical® and Alli®)

When used with a light, low-calorie diet, Xenical® is indicated in obese patients with a BMI ≥ 30 kg/m^2 or overweight patients with a BMI ≥ 28 kg/m^2 with associated risk factors.

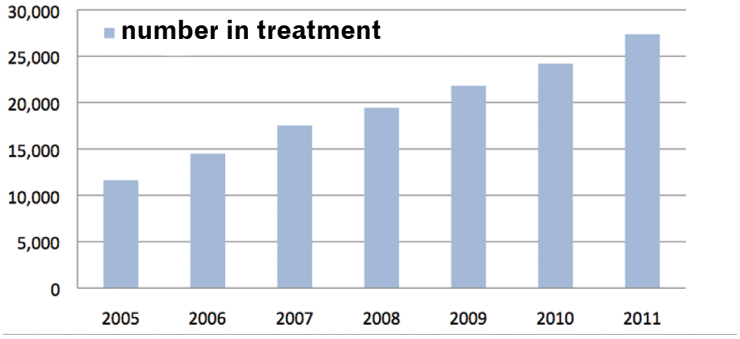
Alli® is indicated for weight loss in overweight adults with a BMI ≥ 28 kg/m^2 in combination with a light, low-calorie, low-fat diet.

Adverse reactions when using gestagen-containing intrauterine contraceptives (Mirena®)

In recent years, the Danish Health and Medicines Authority has received a large number of reports concerning intrauterine devices (IUDs) containing the gestagen levonorgestrel and marketed in Denmark under the trade name Mirena®. In 2011 Mirena® was the product for which the Danish Health and Medicines Authority received the highest number of adverse reaction reports (111 reports). At present, our adverse reaction database contains a total of 593 reports concerning Mirena®. The vast majority of these reports have been forwarded to the Danish Health and Medicines Authority by the company marketing Mirena®.[1]

Mirena® was approved for marketing in Denmark in 1993, and the use has increased in recent years as shown in Figure 1.

Figure 1. Number of women being treated with hormone IUD.



The vast majority of the adverse reactions reported are well-known

The majority of the reports describe adverse reactions that are known and included in the product information for the medicine. Table 1 shows the ten most frequently reported adverse reactions from hormone IUDs.

The most frequently reported adverse reaction in association with the use of Mirena® is bleeding, and it is well-known that most women experience changes in their bleeding pattern after IUD insertion. Within the first 90 days, 22% of the women experience prolonged bleeding, while 67% experience irregular bleeding. However, these numbers decrease to 3% and 19%, respectively, after the first year of use.

IUD rejection or dislocation is also frequently reported and appears from the summary of product characteristics as a common adverse reaction experienced by 1/10 to 1/100 of women in treatment. Systemic adverse reactions caused by gestagen, such as acne and headache, are also well-known.

No reason for further initiatives at the present time

At the present time, the adverse reactions reported do not give rise to further initiatives, and the information in the summary of product characteristics and the package leaflet for Mirena® continues to be adequate:

- In order to ensure correct insertion of hormone IUDs and thus prevent rejection/dislocation as well as to maximise the contraceptive effect, the insertion instructions should be followed closely. It is recommended that Mirena® insertion is done only by experienced or adequately trained doctors.

- The woman must be examined 4 to 12 weeks after insertion and then once annually or more often if clinically indicated.

The Danish Health and Medicines Authority will continue to closely monitor the development.

The summary of product characteristics (in Danish) for Mirena® are available here: *www.produktresume.dk*

Table 1. Reported adverse reaction

	Number
Vaginal bleeding	106
Pain	85
IUD rejection	51
Genital bleeding	44
IUD dislocation	41
Acne	25
Headache	21
Ectopic pregnancy	20
Menorrhagia	19
Migraine	18

Indication for Mirena®
Mirena® is an intrauterine device (IUD) with the gestagen levonorgestrel and is approved for birth-control and for the treatment of menorrhagia and protection against endometrial hyperplasia during oestrogen therapy.

1) Data extracted up until 17 February 2012

Childhood vaccinations and adverse reactions in the fourth quarter of 2011

In the fourth quarter of 2011, there was no change in the routine childhood immunisation programme in Denmark. It is estimated that the figure of 80-90 per cent of children being vaccinated, depending on the vaccine, is unchanged.

In this period, the Danish Health and Medicines Authority (the former Danish Medicines Agency) received a total of 43 reports. Four reports concerned persons over the age of 18 who had received Gardasil® and Pneumovax®.

Excluding Gardasil® there are no gender differences regarding frequency.

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 38%, and local irritation, rash and temporary changes of the skin accounted for 31% of the adverse reactions reported.

14 reports were classified as serious.

Table 1 shows the distribution of the number of serious reports for the various vaccines in the fourth quarter of 2011.

For Gardasil®, there were no occurrences of eczema following vaccination, as opposed to 2009, when there was focus on this potential adverse reaction and for that reason, inter alia, many reports.

In the fourth quarter, there were also reports of unknown adverse reactions, all of which however were classified as non-serious: alopecia, herpes zoster, dermal cyst, and migraine.

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

Vaccine	Number of reports per vaccine classified as serious
Pneumovax	1
DTa-pertussis-polio (DTaP-IPV) booster	2
DTaP-IPV/Act-Hib	7*
Prevenar 13	(received both vaccines)
Gardasil	3
Priorix	1
Tetanus	0
Total	**14**

Adverse reactions reported as serious were:

1. A pregnant woman develops ulcerative colitis a month after the last Gardasil® vaccination; alopecia areata is developed five months after that vaccination. The child is born with a branchial fistula. There are no previous reports of the development of ulcerative colitis after Gardasil®, which is why a relationship is deemed to be less likely.

2. Child with a branchial fistula born to the above woman. The last Gardasil® vaccination was given in the 6th week of gestation. Literature describes no such malformations after Gardasil® vaccination, which is why a relationship is deemed to be less likely.

3. 35 days following commencement of Gardasil® vaccination, a 13-year-old girl develops monosymptomatic Chorea Minor. This condition may present after a group A streptococcal infection, and no descriptions have been found about development of this condition after Gardasil® vaccination. A relationship is deemed to be less likely.

4. Severe swelling and redness after DTaP-IPV booster vaccination. Arthus reaction is suspected, and the child was hospitalised for observation. A relationship to the vaccine is likely.

5. An 81-year-old woman develops severe swelling, redness, and necrosis at the injection site after Pneumovax vaccination. A relationship is deemed to be likely.

6. A 1-year-old boy develops pertussis despite vaccination. It is known that not all vaccinees are seroconverting, and this case is due to vaccine failure.

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8. A 1-year-old boy develops ADEM (acute demyelinating encephalomyelitis) 2-3 weeks after DTaP-IPV/Act-Hib and Prevenar13 vaccination and respiratory infection. The literature does not provide evidence of a relationship between the vaccines mentioned and ADEM. There was a concomitant viral infection, and a relationship to the vaccines is therefore deemed to be less likely.

9. A 1-year-old child, where the mother reports unprovoked falls in the days following DTaP-IPV/Act-Hib and Prevenar13 vaccination. The child's doctor reports these falls as petit mal. No examinations were performed. The attacks disappeared spontaneously, and it is deemed to be less likely that this is a case of epilepsy.

10. On the day of DTaP-IPV/Act-Hib and Prevenar13 vaccination, a 2-month-old child develops fever cramps. A relationship is deemed to be likely.

11. In a 1-year-old child, itchy nodules are reported as an adverse reaction from DiTeKiPol/Act-Hib and Prevenar13 vaccines. Was evaluated in the paediatric admission ward due to itchy eczema in the nodule area. Occurrence of nodules is a known adverse reaction from the vaccines. A relationship is deemed to be likely.

12. A 5-year-old boy develops Henoch-Schonlein purpura (HSP) two days after DTaP-IPV booster vaccination. The disease is most frequently reported in this age group, and is often seen after infection. No case reports describing a relationship between HSP and DTaP-IPV booster have been found in the literature, and such a relationship is therefore deemed to be less likely.

13. A premature boy born at the gestational age of 25 6/7 weeks is vaccinated at the age of 3 ½ months with DTaP-IPV/Act-Hib and Prevenar13. Two days after the vaccination, he develops group B streptococcal meningitis. A correlation is deemed to be less likely.

14. Approx. one month after his vaccination with Priorix®, a 12-year-old boy develops spontaneously disappearing thrombocytopenia. It is known that thrombocytopenia has an incidence of 0.087-4 cases per 100,000 vaccine doses. A relationship between the vaccine and the symptoms is therefore deemed to be likely.

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