Danish Pharmacovigilance Update Year 4 #6
27 June 2013

The benefits of medicines for the treatment of acne (Diane® Mite and others) continue to outweigh the risks of use within the indication

The European Pharmacovigilance Risk Assessment Committee (PRAC) has reviewed the safety of medicines containing cyproterone and oestrogen, (Diane® Mite and others*) for the treatment of acne.

The PRAC concluded that the benefits of this type of medicines continue to outweigh the risks, provided that they are used in the approved group of patients and that the risk of blood clots is minimised.

As a doctor you should be aware of the following:

- These medicines should only be used for the treatment of moderate to severe acne related to androgen sensitivity and/or hirsutism in women of childbearing potential.
- The medicines should only be used for the treatment of acne when topical therapy or treatment with antibiotic tablets have failed.
- The medicines have not been approved exclusively for contraception. Since they act as contraceptive pills, they should not be used in combination with contraceptive pills, as that would expose the woman to an increased amount of oestrogen and thus increase the risk of blood clots.

The risk of blood clots is low. As is the case for contraceptive pills, the risk has been known for many years and is well-described in the product information. See the summary of product characteristics for Diane® Mite (will be revised at the earliest possible opportunity, in Danish only): *Diane Mite, coated tablets.doc*

Background of the safety review

The European review was initiated upon request from the French authorities following a national French analysis which gave rise to concern about the risk of blood clots and extensive off-label use, where the medicine was used exclusively as contraception.

The product information will be updated

Based on the review, the product information will be updated with harmonised indication text as well as updated warnings and recommendations.

DHPC (Direct Healthcare Professional Communication) letters with this information have been issued to relevant doctors. The letter is available on the Danish Health and Medicines Authority's website (in Danish only): *Cyproterone (Diane Mite).*

New indication for Diane® Mite

Treatment of moderate to severe acne related to androgen sensitivity (with or without seborrhoea) and/or hirsutism in women of childbearing potential.

For the treatment of acne, Diane® Mite should only be used when topical therapy or systemic antibiotic treatment has failed.

Since Diane® Mite acts also as a hormonal contraceptive, it should not be used in combination with other hormonal contraceptives.

* As of January 2013, the following products with the combination of cyproterone acetate (2 mg) and ethinylestradiol (0.035 mg) are available on the Danish market: Diane® Mite, Dianova Mite, Feminil® Mite, Vreya®, Zyrona and cyproterone acetate/ethinylestradiol "ratiopharm".

The EMA recommends restrictions in the use of retigabine (Trobalt®)

The EMA's Committee for Medicinal Products for Human Use (CHMP) recommends using the drug retigabine (Trobalt®) against epilepsy only in patients where other antiepileptics have proved inadequate or have not been tolerated.

Adverse reactions seen in clinical long-term studies

The new recommendation is due to observations of blue-grey discolouration/pigmentation of the skin, lips and nails and pigmentation of ocular tissue, including the retina, in clinical long-term studies. The changes have been seen in patients following long-term treatment with retigabine, typically after more than two years of treatment. The pigment changes in the ocular tissue may entail a risk of visual impairment.

As a doctor you should be aware of the following:

- Follow the new recommendations for Trobalt®. This means, among other things, using Trobalt® only in patients where other medicines have failed, and based on a thorough assessment of benefits and risks, and scheduling the patients for regular ophthalmological examinations.
- Patients currently receiving treatment should be assessed at a routine (non-urgent) appointment. The benefit/risk ratio should be re-assessed, and patients should be informed of the risk of pigmentation with long-term treatment.
- A comprehensive ophthalmological examination (including visual acuity test, slit-lamp examination and mydriatic ophthalmoscopy) should be performed at treatment start and at least every 6 months thereafter while treatment is ongoing. Patients already undergoing treatment with retigabine should be scheduled for an ophthalmological examination.
- If retinal pigment changes or visual impairment are detected, treatment with Trobalt® must only be continued after a careful re-assessment of the benefit/risk ratio. The same is the case in patients who develop discolouration of the nails, lips or skin.

Patients must not discontinue their treatment with Trobalt® without prior agreement with their doctor. Discontinuation of the treatment will increase the risk of epileptic seizures.

In 2011, Trobalt® was approved as an adjunctive treatment of partial seizures with or without secondary generalisation in adult epilepsy patients aged 18 or more.

In 2012, Trobalt® was used for the treatment of 62 patients in Denmark.

DHPC (Direct Healthcare Professional Communication) letters with this information will be issued to relevant doctors. DHCP letters are available on the Danish Health and Medicines Authority's website. *List of issued DHPC letters (in Danish only)*

Thiazides and hyponatraemia – reports to the Capital Region of Denmark's Adverse Drug Reaction Manager at the Department of Clinical Pharmacology at Bispebjerg Hospital

By Nanna Borup Johansen, MD, PhD, Department of Clinical Pharmacology, Bispebjerg Hospital

Hyponatraemia is a well-known adverse reaction (ADR) from the use of thiazides. Therefore, levels of electrolytes, especially serum potassium and sodium, should be checked on a regular basis. Still, several patients are hospitalised with hyponatraemia as a suspected ADR from the use of thiazides.

Many patients are treated with thiazides

Many patients are treated with thiazides – either as monotherapy or combined with another antihypertensive.

According to information from the Danish Statens Serum Institut, National Institute for Health Data and Disease Control, 82,232 persons over 80 years of age and 220,759 persons aged between 65 and 79 years redeemed at least one prescription for a thiazide diuretic in 2012 (the numbers include combination products (e.g. a number of antihypertensives combined with thiazides)).

Hyponatraemia from the use of thiazides comprised in ADR reports to the Capital Region of Denmark's ADR Manager

Since the introduction of the ADR Manager at the Department of Clinical Pharmacology at Bispebjerg Hospital in October 2010, and in the entire Capital Region of Denmark in January 2012, there has been a total of 37 reports of hyponatraemia as a suspected ADR from the use of a thiazide diuretic*. The number includes 24 patients treated with bendroflumethiazide 2.5 mg and potassium chloride 573 mg (Centyl with potassium chloride), mainly with 1 tablet daily, and 12 patients treated with a combination product containing hydrochlorothiazide.

Furthermore, one of the patients was treated with hydrochlorothiazide as well as bendroflumethiazide.

The patients' average age was 77 years with an age range of 59-96 years. 73% of the patients were women.

Serious cases

In two of these cases, the ADR was life-threatening: In one of the patients, the ADR caused a fall trauma followed by rhabdomyolysis, and the other patient was hospitalised with generalised convulsions. In the remaining 35 cases, hyponatraemia contributed to hospitalisation or prolonged hospitalisation, which is considered a serious ADR.

*Reported to the Danish Health and Medicines Authority.

ADR reports to the Danish Health and Medicines Authority concerning hyponatraemia from the use of thiazides

The Danish Health and Medicines Authority's (DHMA's) ADR reports of hyponatraemia from the use of thiazides

The DHMA has received a total of 98 reports of hyponatraemia as a suspected ADR from the use of a thiazide diuretic* (the first report of hyponatraemia was received in March 1993, and the most recent report was received in June 2013). Of these, 95 were categorised as serious.

Be aware of medicines that have been on the market for many years

It is important to be aware of ADRs of medicines that have been on the market for many years, are frequently used and (apparently) have a known ADR profile – such as medicines with thiazides. Especially in the case of serious ADRs, it is important to report these to the DHMA.

This way ADR signals may be identified and contribute to a more complete safety profile for the medicine. Prior to approval, a medicine has typically been tested in relatively healthy persons, typically persons below 80 years of age, who do not suffer from other diseases and are not treated concurrently with several different types of medicines.

Therefore, ADR reporting to the DHMA is important for the patient safety and for our knowledge of medicines.

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

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

Acute pancreatitis and hepatitis associated with the use of vildagliptin (Galvus®) and linagliptin (Trajenta®) reported as potential adverse reactions

In April 2013, the Danish Health and Medicines Authority (DHMA) received an adverse reaction (ADR) report concerning an elderly patient treated with Galvus® and Trajenta®, who developed acute pancreatitis and hepatitis*. Both products are DPP-4 inhibitors. The patient had been using the products for approx. a month prior to onset of the symptoms. The patient is currently in recovery.

The DHMA has previously received two reports of possible development of pancreatitis in association with the use of vildagliptin and one report in association with the use of linagliptin. There are no previous reports of hepatitis for these two drugs.

As a doctor you should be aware of the following:

- Development of pancreatitis is described in the summaries of product characteristics for both vildagliptin and linagliptin. Patients should be informed of the characteristic symptoms of acute pancreatitis – persistent, severe abdominal pain. If pancreatitis is suspected, suspect drugs should be discontinued.

- Hepatic dysfunction (including hepatitis) in association with the use of vildagliptin is described in the summary of product characteristics for this drug. Patients are generally asymptomatic without clinical sequelae, and hepatic function tests are normalised following discontinuation of treatment. Hepatic function tests must be performed prior to initiating treatment in order to identify the patient's baseline values, and the hepatic function must be monitored during treatment every three months during the first year and regularly thereafter. Patients developing elevated levels of transaminases must be monitored with a secondary assessment of the hepatic function to confirm the result. After that, they must be followed with frequent hepatic function tests, until the values are normalised. In the event of an increase in AST or ALT of 3 x the upper limit of normal persists, discontinuation of the product is recommended. The treatment should not be re-initiated.

The European medicines regulatory agencies are currently performing an investigation

The European medicines regulatory agencies are currently performing a detailed investigation of the risk of ADRs related to pancreas from the use of medicines affecting the GLP-1 system (such as vildagliptin and linagliptin). For further information, please read the EMA's press release: *European Medicines Agency investigates findings on pancreatic risks with GLP-1-based therapies for type-2 diabetes*.

Indication for vildagliptin and linagliptin
Used in the treatment of type 2 diabetes mellitus in adults.

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

Reports of adverse reactions from the use of Gardasil® during the period 2009-2012

Since the HPV vaccine Gardasil® was included in the Danish childhood immunisation programme in 2009, the Danish Health and Medicines Authority (DHMA) has monitored and assessed reports of potential adverse reactions (ADRs) from the use of the vaccine on a continuous basis. In parallel, the benefit/risk ratio for the vaccine has been under discussion. Therefore, the reports of potential ADRs from Gardasil® received by the DHMA within the past four years are stated herein.

Gardasil®	2009	2010	2011	2012	Total
Number of reports	287	48	38	95	468
Number of serious reports	25	5	6	17	53
Number of ADRs	524	140	107	251	1022
Number of doses sold	347,200	151,300	162,700	347,100	1,008,300

Table 1 *Shows the total number of reports of ADRs following a Gardasil vaccination, the number of reports comprising serious ADRs, the total number of ADRs and, finally, the number of doses sold per year in Denmark. (Note! Be aware of the fact that when the DHMA receives additional information, it may cause changes of the codes and number of ADRs. This means that there may be minor differences in accumulated numbers between previous publications and the above-mentioned).*

In outline, the listing shows:

- That the ADRs reported for Gardasil® so far in Denmark are comparable with international experience. There are no signs of increased incidence or deviation in the types of serious ADRs in Denmark for Gardasil® during the period 2009-2012.
- That the DHMA received a total of 468 ADR reports, 53 of which were classified as serious, during the 4-year period in question.
- That the ADRs most frequently reported were fainting/dizziness, general malaise and anaphylaxis.

Introduction to the Danish childhood immunisation programme

On 1 January 2009, the vaccine was included in the Danish childhood immunisation programme. This means that all 12-year-old girls have been offered the vaccine 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 2008/2009.

Additionally, HPV vaccination became available free of charge as of 27 August 2012 for all young women born between 1985 and 1992 (the offer ended on 31 December 2013).

Since the introduction of the vaccine, potential ADRs have been monitored by the DHMA. This listing summarises the ADR reports received by the DHMA during the period 1 January 2009 - 31 December 2012. The listing includes adults vaccinees. The average age for vaccinees in 2012, for whom one serious ADR was reported, was 18 years (the age distribution was 11 to 30 years).

Number of reports, ADRs and doses sold

The number of reports, ADRs and doses sold in Denmark are shown in Table 1.

As appears from Table 1, the highest number of reports was received in 2009 – the first year following introduction of the vaccine. This is probably due to the stricter reporting requirements during the first two years. However, the frequency of serious reports remained fairly unchanged over time as compared to the number of vaccines sold.

Also, it appears from the table that each report often comprised several ADRs. The total sale during the period amounted to more than a million vaccine doses (three doses per vaccinee).

Serious ADRs reported to the DHMA 1 January 2009 - 31 December 2012

During the 4-year period, the DHMA received 53 ADR reports that were classified as serious according to the common European guidelines[1]. To date (1 June 2013), no reports of death have been sent to the Danish ADR database in association with Gardasil vaccination.

All serious reports have been described previously in Danish Pharmacovigilance Update[2]. Therefore, the detailed assessment of every report is not repeated below.

Table 2 lists the serious ADRs reported. Also, it appears from Table 2 whether the ADRs are known ADRs from Gardasil® and therefore mentioned in the *Summary of product characteristics for Gardasil®* (in Danish only).

Approximately half of the reports described unexpected ADRs from Gardasil®

Approximately half (27) of the serious ADRs reported are unexpected, i.e., not described in the summary of product characteristics for Gardasil®. In cases where the ADRs are known, it doesn't necessarily mean that the ADRs were caused by the vaccine. Likewise, some unexpected ADRs may have been assessed as potential ADRs caused by the vaccine.

The last column of Table 2 states the DHMA's result of the causality assessments. A correlation between the vaccine and the ADR may here be assessed as either possible, less likely or "not possible to assess" based on the available information.

In addition to fainting/dizziness and general malaise, anaphylaxis was the serious ADR most frequently reported with a total of five reports. This ADR is mentioned in the summary of product characteristics for Gardasil® with the frequency "not known". There were four reports of idiopathic thrombocytopenic purpura (ITP). Normally, this disorder occurs in seven out of 100,000 persons every year in Denmark (according to *www.sundhed.dk*). There were three cases of facial paresis. However, since this is a relatively frequent disorder (approx. 15-30 per 100,000 according to *www.sundhed.dk*), three cases per 1,000,000 doses sold are not considered a high number.

There was no accumulation of other disorders. Some of the unexpected ADRs reported are rare disorders that were probably isolated cases with no clear correlation with the vaccinations (such as rhabdomyosarcoma – a cancer type typically seen in children). There were reports of various neurological disorders and autoimmune conditions, but with no clear pattern among them.

Non-serious ADRs

The most frequent non-serious ADRs were general malaise, dizziness, redness and irritation at the injection site. These are all known ADRs described in the summary of product characteristics for Gardasil®.

Summary

During the 4-year period, symptoms were interpreted as anaphylaxis in five reports classified as serious (in one case,

Organ system	Potential ADR(s)	Number	Described as a potential ADR in the SPC	Result of causality assessment Possible/less likely correlation
Cancer	Rhabdomyosarcom	1	No	Less likely
Haematological disorders	Idiopathic thrombocytopenic purpura	4	Yes	1 less likely/3 possible
	Aplastic anaemia	1	No	Less likely
Allergic reactions	Anafylaksi, (tolket som anafylaksi)	5	Yes	Possible

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Table 2

1 A report is serious, if one or more of the ADRs are serious. 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.

2 See listings of childhood vaccinations and ADRs in the following issues of Danish Pharmacovigilance Update: *March 2013, October 2012, June 2012, March 2012, December 2011, October 2011 and April 2011.*

	An allergic reaction within the first hours after-vaccination given concurrently with another vaccine	1	Yes	Possible
	Exacerbation of hives following the 2nd and 3rd vaccinations	1	Yes	Possible
General symptoms	Hyperventilation	1	Yes	Possible
	Fainting	1	Yes	Possible
	Hyperventilation/nausea/ presyncope/fever	1	Yes	Possible
	Fainting/dizziness/ nausea/fever	1	Yes	Possible
	Fainting after 15 minutes (2nd vaccination). Subsequently, Subsequently, headache and temporary paralysis of one leg.	1	Yes for fainting/ No for paralysis of leg	Possible
	Swollen glands	1	Yes	Possible
	Dizziness	1	Yes	Possible
	Vasovagal reaction following vaccination with Gardasil and Priorix, headache, nausea, dizziness	1	Yes	Possible
	Dizziness, muscle and joint pain, muscle spasms and weakness	1	Yes for dizziness/ No for weakness	Less likely
	12-year-old girl vaccinated with Priorix and Gardasil. Fainted the following day, developed morbilliform rash 3 days after vaccination, and glands were swollen.	1	Yes	Possible; however, rash probably caused by Priorix
	Dizziness, marked fatigue, headache and a slight-temperature elevation	1	Yes	Possible
Primarily neurological symptoms	Twitching arms and legs, trembling, impairment of speech, difficulties with fine motor control, headache	1	No	Less likely
	• Prickling sensation in hands and feet	1	No	Possible – due to hyperventilation
	Sensory disturbances in hands and feet following the 1st vaccination (2nd vaccination received without problems)	1	No	Less likely
	Facial paresis 3 months after the 2nd vaccination	1	No	Less likely
	Facial paresis 2-3 days after vaccination; the paresis returned twice spontaneously at a later date.	1	No	Less likely

	Facial paresis in a 12-year-old girl, occurring on the same night that the first Gardasil® and Priorix® vaccine were administered	1	No	Less likely
	12-year-old girl vaccinated with Gardasil® developed tonic-clonic seizures 73 and 83 days after vaccination. EEG is compatible with idiopathic generalised epilepsy.	1	No	Less likely
	Grand mal seizures minutes after vaccination	1	Yes	Possible
	Monosymptomatic Chorea Minor 35 days after vaccination	1	No	Less likely
	Spinal cord inflammation affecting muscle strength and sense of touch 1 month after the first vaccination	1	No	Less likely
	Optic neuritis 3 weeks after the third Gardasil® vaccination	1	No	Less likely
	Guillain-Barré syndrome	1	Yes	Possible, as individual cases have been described
Respiratory illness	Asthma	1	No for asthma (but acute bronchospasm mentioned)	Less likely
	Cough and narrowing of airways a while after vaccination	1	Acute bronchospasm mentioned, not cough	Less likely
Presumed autoimmune diseases	Henoch-Schönlein purpura	1	No	Less likely
	Intermittent periods of arthritis	1	Yes (arthalgia)	Possible
	Pregnant woman vaccinated and developed ulcerative colitis 1 month after the final-Gardasil© vaccination. Alopecia areata developed 5 months later. The child was born with a branchial fistula (see below)	1	No	Less likely
	Erythema nodosum (patient suffers from juvenile idiopathic arthritis) approx. a month after the second vaccination	1	No	Less likely
Infection	Meningitis	1	No	Less likely
	Sense of touch affected in the right-hand side of the face and the upper arm the day after vaccination. Lumbar puncture showed signs of meningitis	1	No	Less likely

	One case of herpes zoster following vaccination with MMR and Gardasil® 28 days after vaccinations	1	No	Less likely
Liver/stomach	An unresolved impact on the liver following the 2nd vaccination	1	No	Less likely
	Diarrhoea and hepatic impact	1	No	Less likely
	Severe stomach ache 2 days after vaccination	1	No	Less likely
Malformation	Vaccinated pregnant woman gives birth to a child with a branchial fistula	1	No	Less likely
Psychiatric diagnoses	Developed psychosis following vaccination with Priorix and Gardasil	1	No	Less likely
	Depression after the 1st vaccination	1	No	Less likely
Abortion	Pregnant woman had a miscarriage in week 6. Vaccinated when around 1 week pregnant	1	No	Less likely
Various	43-year-old woman vaccinated with Gardasil developed voice problems and vocal cord dysfunction the next day	1	No	Less likely

however, vasovagal reaction may be suspected based on the treating doctor's description, but the doctor's interpretation of the symptoms has been retained). All vaccinees were in their habitual state the following day. The cases were spread over time, and they are not suspected to be correlated with particular batches. Anaphylaxis/anaphylactic reactions are mentioned in the summary of product characteristics as a potential ADR of unknown frequency. There were six reports of fainting and several reports of presyncope (near fainting).

There was one report of the rare ADR with fainting followed immediately by tonic-clonic seizure which is mentioned in the summary of product characteristics. The girl was discharged feeling well the following day.

Comparison with reports from the USA

When comparing serious ADRs reported in Denmark with reports from the USA, the pattern is more or less the same (Memorandum: Gardasil: Utilization and Safety Review for the Pediatric Advisory Committee Meeting May 7-8, 2012 by Andrea Sutherland Department of Health and Human Services, USA). In the USA as in Denmark, there are many reports of fainting, relatively more children with seizures and fewer with anaphylaxis.

Study in Swedish and Danish women

The reports of serious ADRs comprise a number of various autoimmune conditions and neurological disorders, but with no pattern. Whether the vaccine is capable of causing such disorders in general, cannot be determined based on the individual reports, but Arnheim-Dahlström L, Pasternak B, Svanström H et al. have presented an abstract, 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 groups were compared with regard to autoimmune conditions, neurological disorders and thromboembolic disorders, and increased incidence among the vaccinees was not observed for any of the conditions and disorders mentioned. Coeliac disease, facial paresis and epilepsy had lower incidences in the vaccinees, perhaps because women at risk of these disorders had opted out of vaccination.

Even though this study rejects a correlation between the vaccine and the above-mentioned conditions and disorders, and there is no signal in the reports, continued monitoring remains important. Especially due to the fact that more adult women are now vaccinated, and there may be other issues of relevance to them.

Important to report potential ADRs
The reports may lead to knowledge of new potential ADR signals. Therefore, it is important that doctors continue to focus attention on reporting potential ADRs, including in adult women.

Furthermore, the Danish reports together with reports from all other countries serve as background for Periodic Safety Update Reports prepared by the company to provide an update of the worldwide ADR monitoring and to identify the more rare ADRs.

The ADRs reported so far in Denmark are comparable with international experience, and there are no signs of increased incidence or deviation in the types of serious ADRs in Denmark for Gardasil® during the period 2009-2012 as compared to previous information.

Report ADRs to the DHMA on *report a side effect or incident*

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.

New report from the Danish Health and Medicines Authority on the consumption of and adverse reactions from immunomodulatory biological drugs

The Danish Health and Medicines Authority (DHMA) has just finished preparing a report on the consumption of and adverse reactions (ADRs) from immunomodulatory biological drugs that are approved for the treatment of rheumatological, gastroenterological and dermatological diseases.

The report contains an analysis of the consumption of the drugs and the suspected ADRs reported to the DHMA through 2011. Furthermore, the report contains a review of the most recent publications in this field.

The main conclusions of the report:

- The consumption of the immunomodulatory biological drugs continues to rise – especially in the field of rheumatology
- Primarily known serious ADRs from the drugs are reported
- The drugs are generally well-tolerated with only a few ADRs
- In particular, attention should be paid to atypical infections
- Thorough screening of the patients prior to initiating treatment may reduce the risk of ADRs.

Read the entire report on the DHMA's website. *Report on the consumption of and adverse reactions from immunomodulatory biological drugs (in Danish only)*

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