Danish Pharmacovigilance Update Year 3 #9
18 October 2012

Risk of developing hepatotoxicity in patients undergoing treatment with agomelatine (Valdoxan®)

Based on reported cases of hepatic injury, including hepatic failure, elevations of hepatic enzymes, hepatitis and jaundice in patients treated with Valdoxan®, the EMA's Committee for Medicinal Products for Human Use (CHMP) has reviewed all available data on elevated transaminases in association with the use of agomelatine. The risk of elevated transaminases in patients taking agomelatine has been known since the granting of the marketing authorisation in 2009, but the CHMP has concluded that the product information should be strengthened in order to emphasise the importance of monitoring the hepatic function in patients treated with agomelatine.

Advice for doctors

- Agomelatine is contraindicated in patients with hepatic impairment, i.e. cirrhosis or other active liver disease

- Doctors are reminded to carry out hepatic function tests in all patients receiving agomelatine with the following time intervals:
  - when initiating treatment
  - periodically at 3 weeks, 6 weeks (end of acute phase), 12 weeks, 24 weeks (end of maintenance phase) and thereafter
  - when increasing the dose of agomelatine at the same time intervals that apply to initiation
  - whenever clinically indicated

- Any patient who develops elevated serum transaminases should have the hepatic function test repeated within 48 hours

- Agomelatine should be discontinued immediately if an increase in serum transaminases exceeds three times the upper limit of normal, or if patients present with symptoms or signs of potential hepatic injury, such as: dark urine, light coloured stools, jaundice/yellowing of the eyes, abdominal pain, sustained and unexplained fatigue

- Patients must be informed about the symptoms of potential hepatic injury and advised to stop taking agomelatine immediately and contact the doctor right away if these symptoms appear

- Doctors should exercise caution when prescribing agomelatine to patients with pre-treatment elevated transaminases levels or risk factors for hepatic injury such as obesity/overweight/non-alcoholic fatty liver disease, substantial alcohol intake or concomitant use of drugs associated with a risk of hepatic injury and diabetes.

A letter with the above information was recently sent to healthcare professionals.

Indication for agomelatine (Valdoxan®)
Agomelatine is approved for the treatment of major depression (moderate to severe depression) 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.

Cases of lactic acidosis in patients undergoing treatment with metformin for the treatment of type 2 diabetes

Danish Pharmacovigilance Update from December 2011 described two serious cases of lactic acidosis in patients treated with metformin.
In 2011, the Danish Health and Medicines Authority received a total of ten reports of lactic acidosis, and in 2012 the Authority has so far received 13 reports of lactic acidosis in association with the use of metformin (cf. Figure 1). Of the 11 reports from 2012, six were prepared based on three articles published in the Journal of the Danish Medical Association[1]. Two of the 11 patients diagnosed in 2012 died from lactic acidosis. Therefore, it is important to draw attention to the very rare, but serious risk of lactic acidosis in diabetics.

As a doctor you should be aware of the following:
Metformin is well-documented and has shown effect on all types of diabetes-related complications, including diabetes-related mortality and total mortality in overweight patients following failure of dietary measures alone. In very rare cases, lactic acidosis is seen in patients undergoing treatment with metformin. Lactic acidosis is a serious metabolic complication (high mortality if not treated immediately) which can occur due to metformin build-up.
Reports of lactic acidosis in patients undergoing treatment with metformin have primarily involved diabetics with significant renal impairment. Therefore, the metformin treatment should be paused in case of acute renal failure or renal insufficiency when the creatinine clearance is below 60 ml/min, and in acute conditions that may affect the renal function such as:

- Dehydration
- Severe infection
- Shock
- Intravascular administration of iodine-containing contrast agents.

Accordingly, special caution should be exercised in situations where the renal function may be impaired, such as when initiating antihypertensives, diuretics or NSAIDs.

The lactic acidosis incidence rate can and should be kept low by also assessing other associated risk factors such as:

- Poorly controlled diabetes with ketosis
- Long-term fast
- Excessive alcohol use
- Hepatic insufficiency

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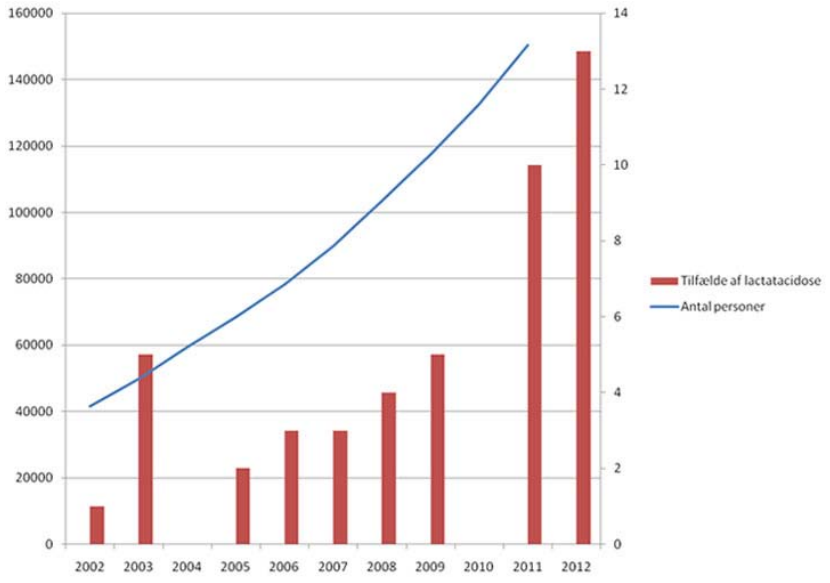
Figure 1: Number of reports of lactic acidosis and number of people treated with metformin broken down by year



1 Helle Holst, Ebbe Eldrup, Nana Harriet Guldstad, Hans Henrik Bülow & Hanne Rolighed Christensen. Laktatacidose ved behandling af type 2–diabetes med metformin. Ugeskr. Læger 174;23:1599-1602 (Lactic acidosis in association with the treatment of type 2 diabetes with metformin. Journal of the Danish Medical Association 174;23:1599-1602) Karin Schousboe, Daniel El Fassi, Erik Liljer Secher, Hanne Elming, Knud Rasmussen & Mads Hornum. Behandling af metforminassocieret laktatacidose med hæmodialyse. Ugeskr. Læger 174;23:1604-1606 (Treatment of metformin-associated lactic acidosis with haemodialysis. Journal of the Danish Medical Association 174;23:1604-1606) Helene Korvenius Jørgensen, Jane Stab Nielsen & Torben Gilsaa. Metforminassocieret laktatacidose kan behandles med kontinuerlig venovenøs hæmofiltration. Ugeskr. Læger 174;23:1602-1603 (Metformin-associated lactic acidosis can be treated using continuous venovenous haemofiltration. Journal of the Danish Medical Association 174;23:1602-1603)

- Conditions related to hypoxia such as heart or respiratory failure, recent myocardial infarction and shock.

Advice for doctors

The risk of lactic acidosis must be considered in case of nonspecific symptoms such as muscle spasms in association with digestive problems (e.g. abdominal pain) and severe asthenia.

Symptoms of lactic acidosis are hyperventilation, abdominal pain and hypothermia followed by coma. Diagnostic laboratory findings are decreased blood pH, plasma lactate levels above 5 mmol/l and an increased anion gap and lactate/pyruvate ratio. If metabolic acidosis is suspected, metformin should be discontinued and the patient hospitalised immediately. The most effective method for removing lactate and metformin is haemodialysis.

Since metformin is excreted by the kidneys, the creatinine clearance should be examined prior to initiating treatment and regularly thereafter:

- at least once annually in patients with normal renal function
- at least two to four times annually in patients with serum creatinine levels at the upper limit of normal and in elderly patients.

Indication for metformin

Metformin is indicated in the treatment of type 2 diabetes mellitus, primarily in overweight patients, when sufficient glycaemic control is not achieved with a dietary change and exercise.

In adults, metformin can be used as monotherapy or in combination with other oral antidiabetics or with insulin.

In children and adolescents aged ten years and older, metformin can be used as monotherapy or in combination with insulin.

Use of MAOIs (monoamino oxidase inhibitors) and other antidepressants

In June 2012, the Danish Health and Medicines Authority received a consumer report on a serious adverse reaction concerning fainting and unconsciousness during treatment with Marplan® (isocarboxazide). The product is an MAOI for the treatment of depressive disorders, when the patient does not respond to other antidepressants. It appeared from the report that the patient was using the product together with two other drugs, of which one was another antidepressant, mianserin.

The Danish Health and Medicines Authority's adverse reaction database contains records of four reports on syncope (loss of consciousness) associated with the use of an MAOI.

Combination treatment may result in serotonin syndrome

According to the summaries of product characteristics for the irreversible, non-selective MAOI, Marplan® (isocarboxazide), as well as the reversible, selective MAO-A inhibitors (RIMA) Aurorix® and Moclostad® (both moclobemide), concomitant use with other antidepressants is contraindicated. Combination treatment with MAOIs and other antidepressants may result in serotonin syndrome, which may be fatal.

Treatment with MAOIs is rather limited in Denmark due to, among other things, the risk of interactions. There is a total of approx. 7-800 users. Data from the Danish Register of Medicinal Product Statistics, Statens Serum Institut, National Institute for Health Data and Disease Control (SSI), indicate that more than one of five users are prescribed this medicine concomitantly with another antidepressant. This concerns approx. 150 people. Concomitant treatment is defined as using a prescription for an MAOI and another antidepressant within a period of 30 days and that this has occurred at least twice within a year (365 days).

Advice for doctors

The Danish Health and Medicines Authority points out that:

- Concomitant treatment with MAOIs and other antidepressants is contraindicated
- When switching between an MAOI and other antidepressants, the treatment should be stopped temporarily. The duration of the pause depends on the product type.

Read more in the summaries of product characteristics (in Danish only) *here*.

Restricted indications for trimetazidine (Vastarel®)

The EMA's Committee for Medicinal Products for Human Use (CHMP) has recently completed a review of all available data on trimetazidine-containing products. The CHMP concluded that the benefits of these products only outweigh the risks for a limited patient population, i.e. patients with stable angina pectoris who are inadequately controlled by – or intolerant to – first-line anti-anginal therapies.

For all other indications the ratio between benefits and risks is no longer positive, since the effect is not considered sufficiently documented according to applicable guidelines and methodology. The CHMP therefore concluded that all other indications are to be withdrawn from the marketing authorisations for these drugs.

Therefore, trimetazidine-containing products are NO LONGER indicated for:

- Symptomatic treatment of morbus Menière
- Vertigo and tinnitus
- Symptomatic treatment of reduced visual acuity or vision field disturbances that are probably of vascular origin.

In Denmark, Vastarel® is the only approved trimetazidine-containing drug.

Advice for doctors

- Trimetazidine should only be prescribed as an add-on therapy for the symptomatic treatment of stable angina pectoris in adults who are inadequately controlled by – or intolerant to – first-line anti-anginal therapies.

- Patients taking trimetazidine for one of the no longer approved indications should discuss alternatives at their next routine visit.

- Trimetazidine may cause or worsen Parkinsonian symptoms (tremor, akinesia and hypertonia) and accordingly is contraindicated in patients with Parkinson's disease, Parkinsonian symptoms, restless legs syndrome and other related motor disorders. In case of the occurrence of motor disorders such as Parkinsonian symptoms, restless legs syndrome and gait instability, trimetazidine must be permanently discontinued.

- Trimetazidine should be avoided in patients with severe renal impairment, as it may result in elevated levels of trimetazidine. The dose should be reduced in patients with moderate renal impairment and in elderly patients.

A letter was recently sent to doctors informing them about the changed indications for trimetazidine. At the earliest possible opportunity, the summary of product characteristics for Vastarel® (trimetazidine) will be updated with the new changes.

The indication for Vastarel® (trimetazidine) is now limited to:
Add-on therapy for the symptomatic treatment of stable angina pectoris in adults who are inadequately controlled by – or intolerant to – first-line anti-anginal therapies.

At present, the following indications are still included in the summary of product characteristics. They will be deleted when updating the summary with the new changes:
– *Symptomatic treatment of morbus Menière*
– *Vertigo and tinnitus*
– *Symptomatic treatment of reduced visual acuity or vision field disturbances that are probably of vascular origin.*

Report of development of jaundice following initiation of treatment with medicines containing amoxicillin plus clavulanic acid

In July 2012, the Danish Health and Medicines Authority received an adverse reaction report on a patient who developed jaundice a week after initiation of treatment with Bioclavid®. At the time of this report the adverse reaction was abating. Bioclavid® contains amoxicillin broad-spectrum penicillin combined with the ß-lactamase inhibitor clavulanic acid. A number of other products with the same ingredients are available on the market.

The Danish Health and Medicines Authority's adverse reaction database contains records of a total of eight reports of hepatic impact associated with the administration of amoxicillin plus clavulanic acid. According to the literature, the risk of hepatic impact is increased five to nine times for products containing amoxicillin plus clavulanic acid as compared to products in which amoxicillin is without clavulanic acid[1].

Hepatic impact is mainly seen in men and elderly patients undergoing long-term treatment

According to the summary of product characteristics, hepatic adverse reactions such as increases in AST and/or ALT, hepatitis or cholestatic jaundice are mainly seen in men and elderly patients undergoing long-term treatment. These adverse reactions are very rarely seen in children. In all populations, symptoms and signs typically appear during treatment or shortly after discontinuation of treatment. However, in a few cases, they may appear up to several weeks after completion of treatment. The symptoms are usually reversible. The hepatic impact may be serious, and there have been very rare reports of deaths. Almost all of these reports concern patients with serious underlying diseases or patients with concomitant use of other drugs known to affect the liver.

Advice for doctors

In case of long-term treatment with amoxicillin plus clavulanic acid, doctors should at least assess the patient's renal, hepatic and haematopoietic functions regularly. Additionally, caution should be exercised when administering in patients with hepatic impairment, and the hepatic function should be monitored regularly. Drugs containing amoxicillin plus clavulanic acid are contraindicated in patients with a previous history of jaundice/hepatic impairment in association with the use of amoxicillin plus clavulanic acid.

Ref 1: J Antimicrobl Cemother 2011;66;1431-1446: Raul J. Andrade and Paul M Tulkens: Hepatic safety of antibiotic used in primary care.

Indication for Bioclavid®

Bioclavid® is indicated in adults and children for the treatment of the following infections:

Acute bacterial sinusitis (adequately diagnosed)
Acute otitis media
Acute exacerbations of chronic bronchitis (adequately diagnosed)
Community-acquired pneumonia
Cystitis
Pyelonephritis
Skin and soft tissue infections, especially cellulitis, animal bites, severe dental abscess with spreading cellulitis
Bone and joint infections, especially osteomyelitis

Childhood vaccinations and adverse reactions in the second 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.

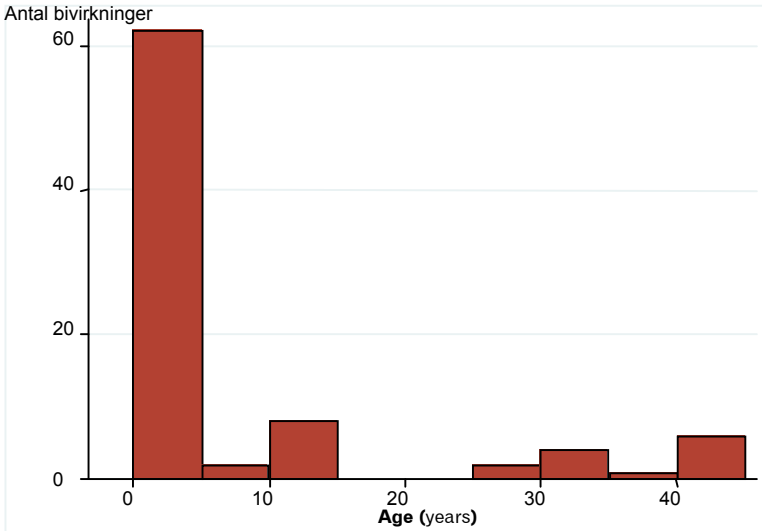
As of 1 April and the rest of 2012, vaccination against measles is available free of charge in Denmark as a special offer. The offer applies to adults born in 1974 or later and comprises persons above 18 years of age who have not had measles and have not previously been vaccinated against measles. This is the only change to the immunisation programme as compared to the last quarter. Estimated coverage in Denmark of each individual vaccine[1]:

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%

Participation in the PCV (pneumococcal vaccination), HPV (human papilloma virus) vaccination, DTaP-IPV/Hib vaccination and MMR vaccination, respectively[2]:

a. During the period 2007-2010, the participation was 92% for the first PCV, 81-92% for the second PCV and 79-90% for the third PCV.
b. For HPV, the participation for girls born in 1996,1997 and 1998 was 88-90%, 83-86% and 76-82% for the first, second and third vaccinations, respectively.
c. For DTaP-IPV/Hib, the coverage for the years of birth 2002-2010 has been calculated to be 89-94%, 88-93% and 87-91% for the first, second and third vaccinations, respectively.
d. For the first MMR vaccination, the participation for the years of birth 2007-2009 is 88%, whereas the participation for the second MMR vaccination is lower. However, since the immunisation programme has been changed to offer the second MMR vaccination at the age of 12 instead of the age of four, the participation per year of birth varies from 69-88%. This is below the target of 95%.

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



At present, there are no data on the number of persons receiving vaccines from the immunisation programme later in life.

Adverse reaction reports for the second quarter of 2012

In the second quarter, the Danish Health and Medicines Authority received a total of 36 reports comprising a total of 100 adverse reactions, which is fairly unchanged compared to previous periods.

37 adverse reactions in a total of ten patients (reports) were classified as serious.[3] .

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1 The Statens Serum Institut, National Institute for Health Data and Disease Control, EPI-NEWS, No. 20, 2012.

2 The Statens Serum Institut, National Institute for Health Data and Disease Control, EPI-NEWS, No. 21, 22, 23a and 23b, 2012.

3 A serious adverse reaction is defined as an adverse reaction 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. This means that any person who has, e.g., 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.

> 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, pain, local irritation, rash and temporary changes of the skin accounted for 59% of the adverse reactions reported.

The vaccines were given to persons aged 0-45 years, and seven of the reports concerned persons over the age of 18 (see Figure 1). The adults had received Gardasil or Td booster. Excluding the Gardasil vaccine (11 reports), 18 reports concerning girls/women and nine concerning boys/men remained.

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

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

Unexpected adverse reactions, for which the reports were classified as non-serious, comprised a case of aphthous stomatitis.

Reports classified as serious:

1. A boy develops fever the day following vaccination with DTaP-IPV/Act-Hib and Prevenar13. He develops fever cramps, a known adverse reaction, and due to the temporal association between the cramps and the vaccination, a correlation is deemed possible.

2. A boy vaccinated with Priorix develops asthmatic bronchitis a day later. Asthmatic bronchitis is a very common disorder in young children, but the literature does not support a correlation between MMR vaccine and asthma/asthmatic bronchitis. Therefore, a correlation is deemed less likely.

3. A girl develops an afebrile tonic-clonic seizure on the same day as her vaccination with Priorix. The seizure lasts for 45 minutes. She has no history of convulsions. There is a family predisposition for epilepsy. All blood samples are normal, and she is discharged feeling well the following day. According to the summary of product characteristics, afebrile cramps may be a rare to very rare adverse reaction. Due to the temporal association between the seizure and the vaccination, a correlation is deemed possible.

4. DTaP-IPV/Act-Hib and Prevenar13 are given to a girl who develops fever, drowsiness and jerking eye movements on the same night. The girl is hospitalised for observation and discharged without examination on the next day. The symptoms are most likely secondary to the affected general condition, and a correlation is deemed possible.

5. A girl develops fever, malaise, affected general condition >

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

Vaccine	Total number of adverse reactions per vaccine*	Number of adverse reactions per vaccine, where the report is classified as serious	Number of reports per vaccine classified as serious	
DiTeKiPol	5	0	0	
DiTeKiPol booster	4	0	0	
DiTeBooster	9	9	1	
DiTeKiPol/Act-Hib	29	12	4	
Prevenar13	16	8	3	(1 concomitantly w. DTaP-IPV/Act-Hib)
Prevenar	1	0	0	
Gardasil	17	5	3	(2 concomitantly w. Priorix)
Priorix	19	6	4	(2 concomitantly w. Gardasil)
Total	**100**	**40**	**10**	

> and a temporary "setback" in development decline following vaccinations with DTaP-IPV/Act-Hib and Prevenar13. The symptoms start immediately after the vaccinations and disappear within a week or so. The symptoms are most likely secondary to the affected general condition, and a correlation is deemed possible.

6. A man develops bilateral brachial plexopathy, fatigue and fever subsequently to his vaccination with Havrix and Td booster. He is found to have a CMV infection in his spinal fluid. The fever and fatigue are attributed to the CMV infection by the Statens Serum Institut, National Institute for Health Data and Disease Control (SSI) and the Danish Patient Insurance Association, whereas it cannot be ruled out that the brachial plexopathy is correlated with the vaccinations. According to the literature, CMV may also trigger brachial plexopathy.

7. A girl vaccinated with Gardasil develops anaphylaxis immediately after the vaccination and is hospitalised. The girl has recovered. There is no information on subsequent assessment or known allergies. A correlation is deemed overwhelmingly likely.

8. A girl develops idiopathic thrombocytopenia approx. five weeks after the second vaccination with Gardasil. According to the summary of product characteristics, thrombocytopenia is a known adverse reaction of unknown incidence, and due to the temporal relationship, a correlation with Gardasil is deemed possible.

9. A girl is vaccinated with Gardasil, and after the third vaccination (not detailed as regards time) she starts coughing and experiences episodes of narrowing of her airways. This is not a known adverse reaction from Gardasil. She is not examined any further, and since cough is a very common symptom in the population, a correlation is deemed less likely.

10. A boy vaccinated with DTaP-IPV/Act-Hib and Prevenar13 subsequently develops a facial rash, fever, and his general condition is affected. Approx. a month later, HiB is detected in his blood after culturing. The boy is now fine. A correlation is deemed likely as regards the first-mentioned adverse reactions, but since the boy had not completed his vaccinations, full protection against HiB infections was not to be expected.

Reports eight and nine mention Priorix. However, due to the lack of a temporal correlation, Gardasil is suspected to be the vaccine that triggered the adverse reactions.

Overall conclusion for the second quarter of 2012

Throughout 2011, the Danish Health and Medicines Authority received 435 reports of adverse reactions from vaccines in the immunisation programme, and thus, the number of reports for the second quarter of 2012 appears to be stable compared to 2011.

There is no clear pattern among the serious adverse reactions. Six of the ten reports assessed as serious concern children under 12 years of age, and only one adult has experienced a serious adverse reaction. As of 1 April 2012, free vaccination with MMR vaccine is offered to young adults, and by the end of the second quarter there were so far no reports of adverse reactions for this group of patients. For the period 1 April through 20 June, the Authority has records of delivery of approx. 700 doses to adult women with rubella.

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

Information on the safety of HPV vaccines

Vaccination against cervical cancer (HPV) has been offered to girls at the age of 12 since 2009 as part of the Danish childhood immunisation programme.

Since 27 August 2012, HPV vaccination has also been offered free of charge to all women born in 1985-1992. All free HPV vaccinations must be given before the end of 2013.

Two HPV vaccines are approved for use in Denmark: Gardasil® and Cervarix®. Gardasil is used in the childhood immunisation programme. There is information on the safety of the two vaccines in the summaries of product characteristics and package leaflets (in Danish only): *Gardasil*, *Cervarix*.

The safety of the two HPV vaccines has been thoroughly examined in both age groups. Since the use in Denmark is becoming more widespread, the Danish Health and Medicines Authority still encourages reporting of all suspected adverse reactions possibly related to the HPV vaccines.

Report adverse reactions from these vaccines to the Danish Health and Medicines Authority

The most common adverse reactions from HPV vaccines are redness, swelling and soreness at the injection site, headache, malaise, fatigue and fever.

If you experience or become aware of suspected adverse reactions from the vaccines, you can report these and other adverse reactions from medicines to the *Danish Health and Medicines Authority*. Listings of adverse reaction reports concerning vaccines (in Danish only) can be obtained by sending an email to dap-box@dkma.dk

You can read more about HPV vaccination (in Danish only) at *the Danish Health and Medicines Authority's website*.

Doctors in Denmark follow new recommendations for contraceptive pills

In early 2012, the Danish Health and Medicines Authority recommended doctors to generally prescribe the older types of contraceptive pills (2nd generation pills), because these pills pose a lower risk of thromboembolism.

In a follow-up report, the Authority has now reviewed the latest scientific articles as well as the consumption trends and reported adverse reactions. The report is in Danish only. The follow-up shows that doctors and patients follow the recommendations.

You can read more at *the Danish Health and Medicines Authority's website*.

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