Danish Pharmacovigilance Update

#10
Year 4
28 November
2013

Contents

News from the EU

News from the Danish Health and Medicines Authority

Short news

News from the EU

Acipimox (Olbetam®) should only be used to lower triglycerides when other treatments of dyslipidaemia are not sufficient

The European Pharmacovigilance Risk Assessment Committee (PRAC) has reviewed data on the efficacy and safety of the nicotinic acid analogue acipimox, which is used for the treatment of dyslipidaemia.

The withdrawal of a combination product containing nicotinic acid formed the basis for a new assessment of acipimox

The reason for the review is the withdrawal of the medicine Tredaptive® at the beginning of 2013. Tredaptive® contained a combination of nicotinic acid and laropiprant and was withdrawn when a large study[1] into the effect of supplementing statins with nicotinic acid/laropiprant indicated that the adjunctive treatment did not lead to an additional reduction of the risk of serious vascular events as compared with statins alone, but did result in an increased risk of serious adverse reactions.

Recent assessment does not give cause to suspension of acipimox

According to the assessment, the results of the study cannot be directly extrapolated to acipimox, partly because the study concerned combination treatment so that it is not possible to distinguish between the efficacy of the two substances, partly because of potential differences between nicotinic acid and the analogue acipimox. However, the overall data for acipimox are very limited as compared with data on other available treatment options, and acipimox has only shown effect on lipid changes (primarily triglycerides) and not on changes in cardiovascular morbidity or mortality.

On this basis, the PRAC concluded that acipimox may stay on the market as an adjunctive or alternative treatment for lowering triglycerides. However, acipimox should only be used when changes in lifestyle and treatment with other medicines such as statins and fibrates alone have not been sufficient.

For further information, please read the EMA's press release.
PRAC recommends using acipimox only as additional or alternative treatment to lower high triglyceride levels.

1 HPS2-THRIVE: Heart Protection Study 2 – Treatment of HDL (high density lipoprotein) to Reduce the Incidence of Vascular Events.

News from the EU

Risk of blood clots from the use of the cancer medicine ponatinib (Iclusig®)

The committees of the European Medicines Agency, EMA, are currently reviewing new information about the risk of blood clot related events associated with the tyrosine kinase inhibitor ponatinib (Iclusig®).

Approved indication
Ponatinib is approved for the treatment of chronic myeloid leukaemia (CML) and for patients with particular types of acute lymphoblastic leukaemia (ALL). The risk of blood clots has been known and described in the product information since the approval of ponatinib in July 2013. Since its approval, ponatinib has been limited to use in patients who could not be treated with other tyrosine kinase inhibitors.

Need for a new assessment of benefits and risks of the medicine
However, the new data show that the risk of cardiovascular events, including blood clots, may be higher than assessed earlier. Therefore, a thorough assessment of the benefits and risks of the medicine is necessary.

Until further notice, ponatinib may be used within the approved indication provided the following is observed:

- Ponatinib may not be used in patients with a history of myocardial infarction or stroke, unless the potential benefits of treatment are assessed to outweigh the risk.
- The cardiovascular treatment should be optimised before starting treatment with ponatinib, and the cardiovascular status should be monitored and optimised continuously during treatment.
- Hypertension should be well-controlled during treatment with ponatinib and discontinuation of the treatment should be considered if the hypertension cannot be controlled.
- Patients should be monitored closely for symptoms of blood clot related events, and the treatment should be interrupted immediately if such symptoms occur.

For further information, please read the EMA's press release.
European Medicines Agency recommends changes in use of leukaemia medicine Iclusig (ponatinib) in order to minimise risk of blood clots.

Indication for Iclusig®

Iclusig® is indicated for the treatment of adult patients with:

- Chronic phase, accelerated phase, or blast phase chronic myeloid leukaemia (CML), who are resistant to dasatinib or nilotinib, who are intolerant to dasatinib or nilotinib and for whom subsequent treatment with imatinib is not clinically appropriate, or who have the T315I mutation.
- Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL), who are resistant to dasatinib, who are intolerant to dasatinib and for whom subsequent treatment with imatinib is not clinically appropriate, or who have the T315I mutation.

News from the EU

All patients should be screened for hepatitis B virus (HBV) before starting treatment with rituximab (Mabthera®)

Based on a recent analysis, the Committee for Medicinal Products for Human Use (CHMP) under the European Medicines Agency, EMA, has decided that all patients – not just those at risk of HBV infection – should be screened for HBV before starting treatment with rituximab.

HBV reactivation has been reported in persons with positive hepatitis B surface antigen (HBsAg) and in persons with positive core antibody (anti-HBc), even when HBsAg was negative – particularly when administering rituximab in combination with steroids or chemotherapy.

There are reports of cases of fulminant hepatitis, some of which were fatal.

New recommendations for doctors:

- All patients (not just those at risk of HBV infection) should be screened for HBV before starting treatment with rituximab within all indications
- Patients with active hepatitis B disease should not be treated with rituximab
- Patients with positive hepatitis B serology should be referred to a liver disease expert before starting treatment with rituximab. These patients should be monitored and managed to prevent HBV reactivation during treatment.

The product information for MabThera® has been updated, and letters with this new recommendation have been issued to relevant doctors. See the letter on the Danish Health and Medicines Authority's website: *List of issued DHPC letters (in Danish only)*.

Indication for MabThera®
Non-Hodgkin's lymphoma, chronic lymphocytic leukaemia, rheumatoid arthritis, granulomatosis with polyangiitis and microscopic polyangiitis.

News from the EU

Preparation error resulting in overdose of cabazitaxel (Jevtana)

In the EU, Jevtana overdose events resulting in serious adverse reactions including bone marrow suppression have been reported. The overdose events resulted from a preparation error due to which the actual dose was 15-20% higher than the prescribed dose.

Also in Denmark, Jevtana overdose events have been reported.

Be aware of the dosage when preparing Jevtana

Cabazitaxel is supplied as a vial of concentrate and a vial of solvent. The concentrate must first be diluted with the solvent supplied to a concentration of 10 mg/ml before adding to the infusion solution.

The vials each contain an overfill to compensate for liquid loss during preparation. This means that the dose in each vial is higher than the dose stated on the vial.

Therefore, it is very important to transfer the entire content of the solvent to the concentrate in order to obtain the correct concentration of cabazitaxel. The entire content of the solvent is more than the content stated on the vial – the content stated is the nominal value (4.5 ml) and not the actual value (5.67 ml).

Risk in case of overdose

The anticipated complications of overdose are exacerbation of adverse reactions such as bone marrow suppression and gastrointestinal disorders.

Special precautions when using an automated software system in the preparation

When using an automated software system in the preparation, it must be ensured that the system is set up to allow withdrawal of the entire content of the solvent vial for adding to the concentrate vial in order to ensure a concentration of 10 mg/ml.

The marketing authorisation holder has informed the Danish Health and Medicines Authority (DHMA) of yet another preparation error where the weight entered into the automated software systems is the value stated on the vial of concentrate (60 mg) and not the actual weight in the vial (73.2 mg).

Letters with the above-mentioned information have been issued to the hospital pharmacies and to relevant doctors. See the letter on the DHMA's website: *List of issued DHPC letters (in Danish only)*.

The summary of product characteristics will be updated to ensure that the guidelines concerning preparation of Jevtana cannot be misunderstood. In addition, initiatives to minimise the risk of future errors are being prepared.

Jevtana is included in the EU list of medicines under additional monitoring.

Indication for Jevtana

Jevtana is indicated in combination with prednisone or prednisolone for the treatment of metastatic hormone-refractory prostate cancer (mHRPC) in patients previously treated with a regimen containing docetaxel.

Ciprofloxacin and the risk of tendon disorders

In September, the Danish Health and Medicines Authority (DHMA) received an adverse reaction report concerning an elderly man who developed pain in one of his Achilles tendons eight days after starting treatment with ciprofloxacin for pneumonia. The tendon turned out to be partially ruptured. The patient is currently in recovery.

Reports of tendon disorders in association with the use of ciprofloxacin

The DHMA has received a total of 33 reports of tendon disorders suspected to be adverse reactions from the use of ciprofloxacin. In the reports, the adverse reactions are described as tendinitis, tendon rupture, tendon pain, tendon injury etc.

Doctors should pay attention to the following:

- Even within the first 48 hours after starting treatment with ciprofloxacin, tendinitis and tendon rupture (in particular involving the Achilles tendon) may occur, sometimes bilaterally. Even several months after completing the treatment with ciprofloxacin, inflammation and tendon ruptures may occur. The risk of tendinopathy is higher in elderly patients and in patients in concomitant treatment with corticosteroids.

- At the first sign of tendinitis (e.g. painful swelling or inflammation), ciprofloxacin should be discontinued.

- In general, ciprofloxacin should not be used in patients with a history of tendon disorders associated with the use of quinolones. However, in very rare cases ciprofloxacin may be prescribed for the treatment of certain serious infections following microbiological documentation of the causal organism and an assessment of the risks and benefits. This mainly applies if the standard treatment has failed or in case of bacterial resistance where the microbiological data justify the use of ciprofloxacin.

- Caution should be used when prescribing ciprofloxacin to patients with myasthenia gravis.

See the indication for ciprofloxacin in Danish at: *www.produktresume.dk*.

Note: The DHMA recommends to limit the consumption of this antibiotic, see the DHMA's *Guidelines on prescribing antibiotics*.

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.

Decrease in the use of medicines for the treatment of anogenital warts in adolescents under the age of 20

In June 2013, a Danish study was published electronically in the journal *"Clinical Infectious Disease"*. The study showed that the vaccine against human papillomavirus (HPV) had a good effect on anogenital warts in girls. Another Danish study published in the ACTA Dermato-Venereologica in October 2013 also showed a reduction in the incidence of anogenital warts in boys, particularly in young boys under the age of 20[1]. Figures from the Statens Serum Institut, National Institute for Health Data and Disease Control, at *www.medstat.dk* support these results when looking at the use of medicines for the treatment of anogenital warts.

	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
14 years	23	30	26	30	34	40	22	14	19	11
15 years	47	78	88	99	112	141	120	49	42	27
16 years	120	169	191	238	308	373	285	129	62	41
17 years	236	293	344	413	519	608	657	395	160	82
18 years	376	400	494	572	723	909	1000	768	409	153
19 years	503	568	722	790	880	1089	1208	1026	840	438
In total	**1305**	**1538**	**1865**	**2142**	**2576**	**3160**	**3292**	**2381**	**1532**	**752**

Table 1. The number of adolescents under the age of 20 who redeemed a prescription for podophyllotoxin.

	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
14 years	8	13	7	9	8	15	19	10	6	6
15 years	11	11	10	15	17	18	19	7	1	3
16 years	5	8	15	13	20	24	22	10	4	3
17 years	12	12	21	24	27	27	32	28	9	14
18 years	23	17	27	36	61	39	45	44	22	11
19 years	15	20	40	44	46	74	74	51	48	24
In total	**74**	**81**	**120**	**141**	**179**	**197**	**211**	**150**	**90**	**61**

Table 2. The number of adolescents under the age of 20 who redeemed a prescription for imiquimod.

Antiviral medicines containing podophyllotoxin (Condyline® and Wartec® (dereg. Sept. 2012)) or imiquimod (Aldara®) are used for medical treatment of anogenital warts. The medical treatment must be initiated with podophyllotoxin, which is also used more frequently than the other active substance on the market.
The consumption of podophyllotoxin in adolescents under the age of 20 increased significantly until 2009, after which the trend reversed. Table 1 shows that the number of adolescents under the age of 20 who redeemed a prescription for this medicine was 3,292 in 2009, and in just three years the number decreased to 752. Accordingly, the number of users of this antiviral medicine in this population was reduced by 77%. There is a temporal association between the significant drop in the consumption and the introduction of the HPV vaccine, which was included in the Danish childhood immunisation programme as of 1 January 2009.

In adolescents under the age of 20 there is also a significant drop in the consumption of the less frequently used medicine Aldara (imiquimod) (Table 2).

The significant drop in the consumption of podophyllotoxin is seen in both boys and girls with figures of 71% and 81%, respectively, during the period 2009 to 2012 (Figure 1). Only approx. 1% of the boys aged 12-26 years were vaccinated[2], so the large drop in the consumption in boys may indicate that the risk of infection decreased.

The significant drop in the consumption of the antiviral medicines for the treatment of anogenital warts may be explained by other factors including the more frequent use, in recent years, of alternative treatment methods such as freezing, surgery or laser therapy. However, when looking at the consumption of the antiviral medicines

1 Sandø N, Kofoed K, Zachariae C, Fouchard J. A Reduced National Incidence of Anogenital Warts in Young Danish men and Women after Introduction of a National Qaudrivalent Human Papillomavirus Vaccination Programme for Young Women – An Ecological Study.

2 http://www.ssi.dk/Aktuelt/Nyheder/2013/2013_11_HPV-vaccinerede%20drenge.aspx (in Danish only)

in other age groups, the drop is much less significant than in the young adolescents under the age of 20, see Figure 2. Data on the participation in vaccination for the HPV vaccine show that approx. 80-90% of all girls born during the years 1993 to 1999 have received all three doses of the vaccine[3]. For girls and women who are to pay for the vaccine themselves, the coverage is much lower (<30% for at least 1 dose)[4].

Published studies and consumption figures already indicate that the introduction of the HPV vaccine in the Danish childhood immunisation programme has had a good effect on the prevention of anogenital warts. The effect of the vaccine is detectable this early, because the incubation time for anogenital warts is 3 months on average.

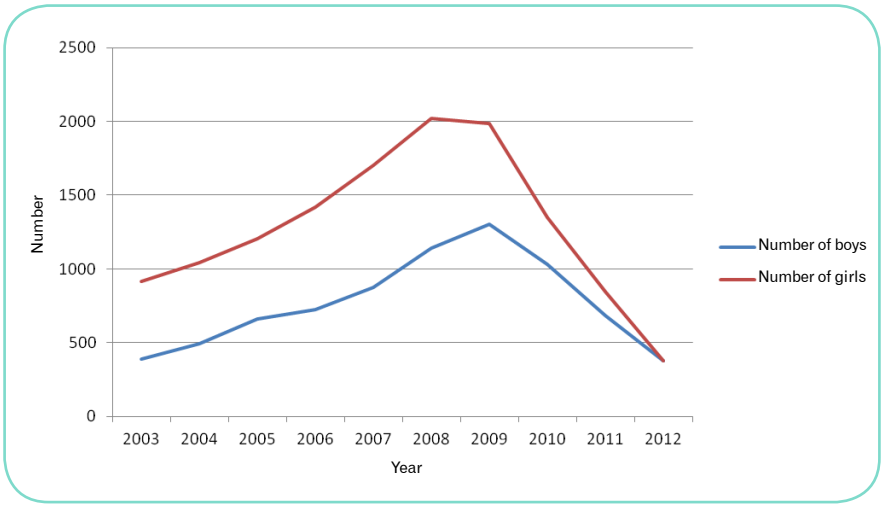


Figure 1. The number of girls and boys under the age of 20 who redeemed a prescription for podophyllotoxin.

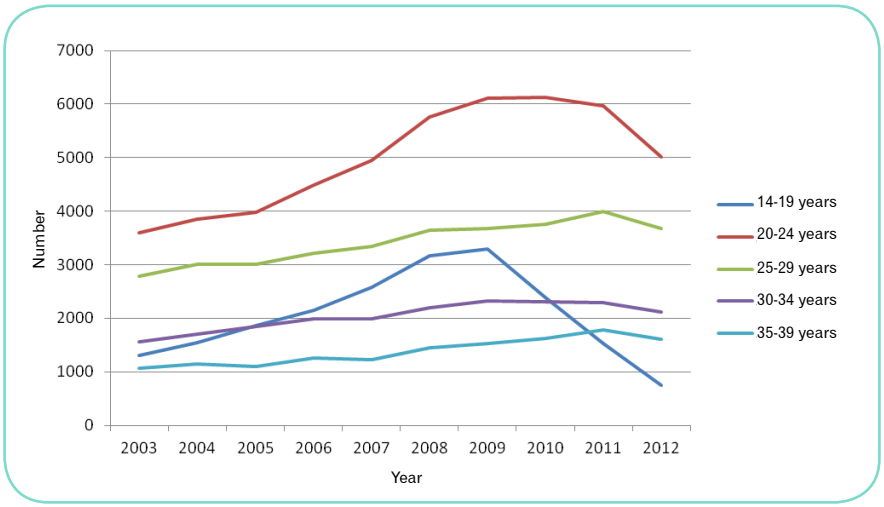


Figure 2. The number of persons in the age groups under the age of 20, 20-24 years, 25-29 years, 30-34 years, respectively, who redeemed a prescription for podophyllotoxin.

3 http://www.ssi.dk/Smitteberedskab/Sygdomsovervaagning.aspx (in Danish only)

4 Maria Blomberg, Christian Dehlendorff, Christian Munk and Susanne K. Kjaer. Strongly Decreased Risk of Genital Warts After Vaccination Against Human Papillomavirus: Nationwide Follow-up of Vaccinated and Unvaccinated Girls in Denmark. Clinical Infectious Disease 2013; 57 (7): 929-34.

Bisphosphonates/denosumab and the risk of osteonecrosis of the jaw

Osteonecrosis of the jaw (ONJ) is a serious bone disease associated with pain and inflammation and, potentially, infection and fistula formation secondary to exposure of the bone tissue.

Recently, the Danish Health and Medicines Authority (DHMA) has received several adverse reaction reports concerning osteonecrosis of the jaw in association with the use of bisphophonates.
The topic has been described earlier in *Danish Pharmacovigilance Update 18 February 2010*. However, due to a high number of new reports and an increasing consumption of bisphosphonates and denosumab, the DHMA has once again reviewed risk factors and preventive measures.

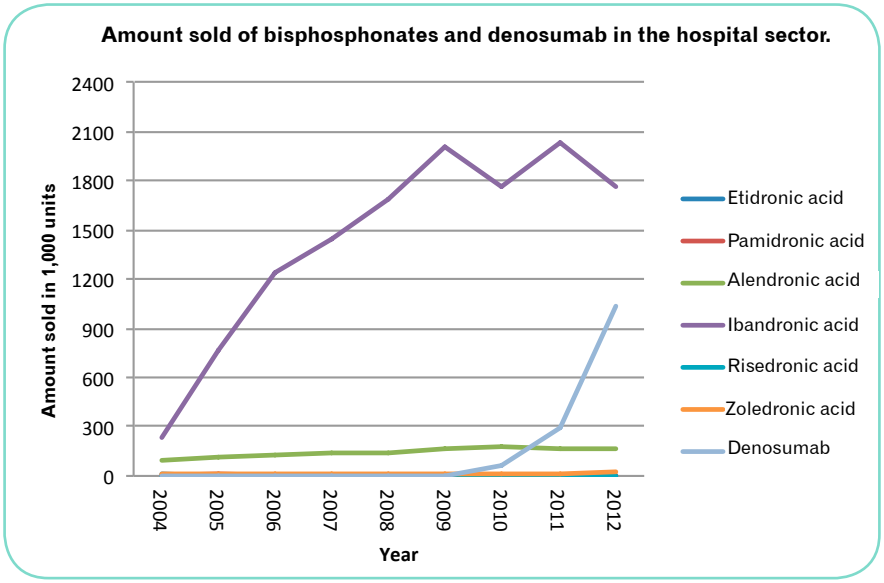


Figure 1. Bisphoshonates and denosumab sold, in DDD, in the hospital sector during the period 2004 through 2012. Source: The Danish Register of Medicinal Product Statistics, at the Statens Serum Institut, National Institute for Health Data and Disease Control.

Danish adverse reaction reports concerning ONJ

During the period January 2004 to July 2013, the DHMA received 95 reports concerning ONJ in association with the use of bisphophonates or denosumab. The majority of the reports concern cancer patients, but a few reports concern patients with osteoporosis.

Consumption of bisphosphonates and denosumab[1] in the hospital and primary care sectors

Figure 1 shows that the sale of ibandronic acid increased from 234,000 units in 2004 to 1.7-2 million units in 2009, after which the sale did not increase any further. This makes ibandronic acid the best selling bisphosphonate in the hospital sector, even though the sale of denosumab, which was approved in 2010, also increased considerably over the past year. Ibandronic acid and denosumab are used in the hospital sector for the treatment of osteoporosis and prevention of skeletal-related

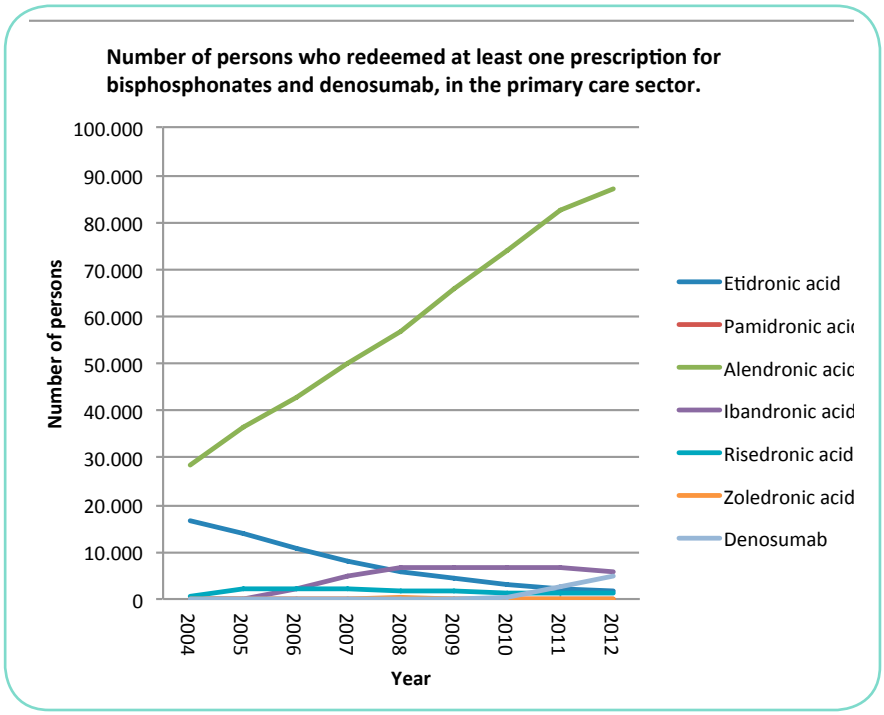


Figure 2. Number of persons who redeemed at least one prescription for biphoshonates or denosumab in the primary care sector during the period 2004 through 2012. Source: The Danish Register of Medicinal Product Statistics, the Statens Serum Institut, National Institute for Health Data and Disease Control.

1 The list of bisphosphonates and products containing denosumab, marketed in Denmark, is shown in the box.

events in cancer patients. Furthermore, ibandronic acid, clodronate and pamidronate are used in the treatment of hypercalcaemia caused by tumours. Zoledronic acid is indicated for Paget's disease of the bones.
In Denmark, ibandronic acid and zoledronic acid are marketed as solutions for infusion that are mainly used in the hospital sector. Ibandronic acid is also marketed as tablets, which explains the use in the primary care sector for the treatment of osteoporosis.

Figure 2 shows the sale pattern for the primary care sector which, as expected, differs from the pattern for the hospital sector. In the primary care sector, the sale share for denusomab is very small with 4,650 redeemed prescriptions in 2012 vs. 87,272 prescriptions redeemed for alendronic acid/ alendronate.
The number of prescriptions redeemed for alendronate increased throughout the period from 2004 up until 2013, whereas a decrease was observed in the number of prescriptions redeemed for etidronic acid/ etidronate.
Ibandronic acid/ ibandronate, which dominate the sale in the hospital sector, only comprise a small part of the sale in the primary care sector with just below 6,000 redeemed prescriptions in 2012 – a consumption which has been fairly stable since 2008. Ibandronate is marketed as both tablets and solution for infusion. This explains the use in the primary care sector for the treatment of osteoporosis. Denosumab is marketed exclusively as solution for infusion.

The sale of zoledronic acid/ zoledronate, risedronic acid/ risedronate and pamidronic acid/ pamidronate is small in both sectors.

Bisphosphonates marketed in Denmark:

Treatment of osteoporosis:	
Aclasta® (zoledronic acid)(also indicated for the treatment of Paget's disease of the bones)	Solution for infusion
Alendronate, Bonasol® (alendronate)	Tablets
Fosama® (alendronate)	Weekly tablet
Fosavanc® (alendronate, cholecalciferol)	Tablets
Bonviva® (ibandronic acid)	Tablets
Ibamyl, Ibandronat, Ibandrostad (ibandronic acid)	Tablets
Didronel (etidronate)	Tablets
Optinate® Septimum, Risedronate sodium, Risostad (risedronate)	Tablets
Treatment of hypercalcaemia:	
Zoledronic acid (zoledronic acid)	Solution for infusion
Bondronat®, Iasibon (ibandronic acid)	Solution for infusion
Bonefos (clodronate)	Tablets
Pamidronate disodium (pamidronate)	Solution for infusion

Products containing the active substance denosumab, marketed in Denmark:

Treatment of osteoporosis and prevention of skeletal-related events in adults with bone metastases from solid tumours:	
Prolia (denosumab)	Injection fluid
Treatment of osteoporosis and bone loss caused by hormone ablation or bilateral orchiectomy in case of prostate cancer:	
Xgeva (denosumab)	Injection fluid

Risk factors for the development of ONJ

A recent meta-analysis has shown that the risk of developing ONJ is equally high when treating cancer patients with either bisphosphonates or denosumab[2].

Other known risk factors for ONJ are:

- Cancer with bone lesions.
- Treatment with the most potent bisphosphonates (e.g. zoledronate).
- Intravenous administration of bisphosphonates.
- Concomitant or previous treatment with corticosteroids, chemotherapy, antiangiogenic treatment or head and neck radiotherapy.
- Local dentoalveolar surgery.

Preventive measures to minimise the risk of ONJ described in the summary of product characteristics

All the summaries of product characteristics for bisphophonates

2 Prashanth Peddi et al 2013

3 CHMP assessment report on bisphosphonates and osteonecrosis of the jaw 2009.

and denosumab specify the risk of developing ONJ and possible preventive measures. Retrospective studies have shown that the risk of ONJ is decreased, if the patients, prior to initiation of treatment with bisphosphonates or denosumab, get a dental check-up and complete any dental treatments and if the administration intervals for intravenous treatments are increased[3].

Prescribing doctors should provide the following instructions to the patient:

- The importance of being particularly careful about oral hygiene
- The patient must contact his or her dentist as soon as possible to prepare a plan for preventive examinations and treatment, for example including scheduling more frequent examinations or regular fluoride treatment, if deemed necessarily
- The patient must inform the dentist about any medical treatment – including use of bisphosphonates or denosumab, so that the dentists can take possible precautions against ONJ
- The patient should, whenever possible, complete major dental treatments prior to initiating treatment with bisphosphonates or denosumab, and the patient should direct the dentist's attention to the ongoing treatment with these medicines, in case major dental treatments become necessary during such ongoing treatment.
- Discontinuation of the treatment with bisphosphonates or denosumab prior to a dental treatment will not reduce the risk of ONJ.

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.

Danish Pharmacovigilance Update here brings an article from the Danish weekly newspaper Weekendavisen of 25-31 October 2013.

Lately, the HPV vaccine Gardasil® has been debated in various media, and the Danish Health and Medicines Authority's (DHMA's) work of monitoring the vaccine and the status of the adverse reaction reports have been described in Danish Pharmacovigilance Update. Most recently, the newspaper Weekendavisen featured a front page article entitled 'The tugboats of preventive health' that puts the entire debate on the HPV vaccine and vaccination in general into perspective. Therefore, we have chosen to include the article in this issue of Danish Pharmacovigilance Update.

The tugboats of preventive health

By Lone Frank

There is no shortage of online warnings for young girls. 'Remember that we will start a new round of stories about Gardasil and Cervarix next week' is a statement shared with the Facebook group 'HPV Vaccine' by a man who calls himself Chandler Marrs. And continues: 'When you share your story, it makes others hesitate to get the vaccine. Thank you.' While you are waiting for the personal stories, a furious woman shares a new scientific study from British Medical Journal. Based on data from a million Scandinavian adolescents, the article rejects that the vaccine, which is aimed at protecting against infection with the HPV virus responsible for 70 percent of all cases of cervical cancer, causes serious adverse reactions. The comment on Facebook is as follows: 'Bullshit!'

Vaccines constitute an interesting field. Their position as one of the greatest health advances of mankind cannot be rejected, and they have saved unnumbered millions from diseases, their complications and, ultimately, death. The American epidemiologist and strategist behind the eradication of the smallpox virus, William Foege, has referred to the vaccines as 'the tugboats of preventive health'. Still, they continue to be a controversal topic. One can hardly imagine a movement fighting persistently against the use of cholesterol-lowering medicines or psychotropics, whereas many countries harbour an actual anti-vaccination lobby.

'And it really is of practical importance', says David Hawkes, Molecular Virologist and vaccine researcher at Melbourne's Florey Institute.

For instance, vaccine opposition has resulted in the return of diseases such as measles and pertussis in certain Western countries and the current spread of the life-threatening polio in several developing countries.

'The reasons for the vaccine opposition are numerous and complex. But it seems as if we are dealing with a sort of scapegoat in the healthcare area. The general dissatisfaction has increased and has been directed towards vaccines to a degree that triggered a protest'. says Hawkes and counts on his fingers: 'There is dissatisfaction with the pharmaceutical industry, uncertainty as regards the role of the medical establishment vs. the industry and, in some places, a basic aversion to anything emanating from the authorities.'

Symptoms and cause

Hawkes spent most of his summer on debating the HPV vaccine. He went into action when a discussion about potential serious adverse reactions rekindled in several countries following the withdrawal of the Japanese health authorities' official recommendation of the vaccine.

'We were in the middle of a paradox', says Hawkes. 'The attacks on the vaccine came at a time when the Americans presented impressive new data on its efficacy.'

In June, a group from the American Centers for Disease Control published a study which shows that the vaccine halved the number of HPV infections in young girls in the USA between 2006 and 2010. This decrease occurred even though only a third of the American teenage girls receive the full vaccine dose of three injections and exceeds the researchers' expectations. In the wake of the publication, the New York Times features a series of articles about the HPV vaccine and its assumed ability to prevent not only cervical cancer, but also virus related neck cancer in both men and women. In a leading article, the newspaper even concludes that: 'Doctors should recommend and parents should accept a vaccine which can save thousands of lives.'

So why do the Japanese withdraw their recommendation?

'Traditionally, they are extremely careful when it comes to vaccinations', says Hawkes. 'The vaccine is still available, and the authorities consider it safe. However, due to an ongoing detailed review of potential adverse reactions they refrain from recommending actively.'

The fact of the matter is that 1,968 potential serious adverse reactions have been reported in Japan, a country

in which 3.3 million women have received HPV vaccination. Various symptoms ranging from heart palpitations and fainting to severe chronic pain. So far, 43 cases have been investigated by a task force in the Japanese Ministry of Health, but it hasn't found any evidence of a correlation with the vaccine.
The same pattern applies in the USA, as pointed out by Hawkes and two colleagues in a thorough review of the available data in the most recent issue of the journal *Infectious Agents and Cancer*. In the USA, among the 111 million doses given, potential serious adverse reactions have been reported in 0.03 percent, i.e. three in ten thousand. However, as emphasised by Hawkes: 'A causal relationship has not been shown in any cases.'

This does not quieten critical organisations such as the Danish VaccinationForum.

'They are just doing an estimate of the likelihood of causality and not a clinical examination of the injured persons', says Chairman, Nurse Else Jensen. She threw herself into the Danish discussion of the HPV vaccine which was launched in the middle of the summer silly season. Two young girls with tears in their eyes as they were seen on TV describing their chronic suffering which, according to the girls, most definitely was caused by the vaccine. The symptoms are general – muscle and joint pain, dizziness, fatigue – and even though no doctor has been able to identify any disease at this point, the media quickly went into overdrive. As claimed by the Danish newspaper BT in a headline: '400,000 girls in danger: The HPV vaccine may cause serious adverse reactions.'

Following the press coverage, the Danish VaccinationForum was flooded with communications, and so far 25 women have reported similar diffuse symptoms to the DHMA. Here, all reports are assessed. However, as described by the DHMA in the most recent issue of Danish Pharmacovigilance Update, it is impossible to determine a possible causal relationship without a diagnosis.

'I have no doubts that this is a specific HPV syndrome', says Else Jensen who is now focusing on having the vaccine withdrawn. 'And my judgement is based on some patterns I see. The women have reactions from three major areas – the immune system, the hormonal system and the nervous system – and I do not at all believe that the symptoms could be randomly occurring.'

Put off with talk

Jan Pravsgaard Christensen, Professor of Immunology at the University of Copenhagen, refer to the specific criticism of the HPV vaccine as 'unscientific'. And at the same time, he calls attention to a general issue in the vaccine debate. 'Every time you ask for documentation from various vaccine critical organisations, you are put off with talk. The media allow them to deliver anecdotes and cast a general suspicion, whereas I, as a researcher, have to provide solid documentation. I'm typically asked to guarantee that a given vaccine is not the cause of symptoms in a given patient.'

Obviously, that kind of guarantees are impossible to give. As stressed by Kåre Mølbak, Consultant Doctor and Head of Department at the Statens Serum Institut, National Institute for Health Data and Disease Control, no vaccines are free of risks or adverse reactions. 'The purpose is to stimulate the immune system, and people are not physiologically alike. There will always be individuals who develop an unfortunate and inappropriate immune reaction.'

And the reason for monitoring vaccines continuously is to detect potential effects that may appear in connection with widespread use or unforeseen local circumstances.
The latter was seen with the vaccine against H1N1 influenza, Pandemrix, which was used globally in 2009, but is under suspicion for causing the rare neurological disorder narcolepsy in approximately 300 children in Finland and Sweden.

'These are the only countries with an increased incidence of the disorder among vaccinees, and Finnish immunologists are working on shedding light on the mechanism. The theory is that another virus circulated at the time of the vaccination and impacted on the children's immune system', says Mølbak and stresses that 'there should certainly be room for an open debate on vaccines'.

There are indications that an actual debate with the organised vaccine criticism may be difficult. Mainly because the Internet and the social media provide opportunities to both come together and to isolate oneself. This is seen already in the earliest study of the phenomenon published in the *Journal of Medical Internet Research* in 2005, where researchers from the Pittsburgh School of Medicine analysed hundreds of websites and found clear patterns. First, 'serious accusations' are put forward, typically referring to a vaccine as a trigger of a disease. Examples are autism, sclerosis and cot death. The next step is to blacken the reputation of vaccine advocates in general and, finally, the websites are linked to each other to an extreme degree thereby creating an echo chamber where people can move in peace and confirm each other.

'There are several types of underlying motivations in the vaccine criticism', says anthropologist Ayo Wahlberg. As associate professor at the University of Copenhagen, he participates in a major mapping of scientific controversies, where, among other things, the HPV vaccine will be scrutinised. 'We are looking at a group of people who have chosen a critical approach to mainstream medicines and swear by alternatives. They typically consider vaccination another example of 'harmful chemistry' that we put into our bodies."

However, as soon as an actual debate rekindles, it becomes clear, according to Wahlberg, that something more is at stake.

'The essence is uncertainty in the professional debate. Discussions that used to be held behind the closed doors of medical conferences, are now conducted in the media and are apparent to all of us. The uncertainty with regard to vaccines emanates from always facing a number of potential adverse reactions, but never really being able to identify a causality. Also, our risk tolerance is generally very low. You need to act on every risk. Otherwise you are disengaged. So you search out a dissident in the scientific environment and make that person's statements the main focus of your criticism and opposition.'

The vaccine against measles

A good example is the most 'successful' anti-vaccine campaign to date, which has been conducted against the so-called MMR vaccine for a good ten years. Given to young children to protect against measles, mumps and rubella, the vaccine was correlated to autism by the British doctor Andrew Wakefield. He did so in 1998 with a study published in the Lancet, and even though it was based on just 12 children, the British media succeeded in creating an atmosphere of uncertainty that spread internationally. Major studies on, for example, Scandinavian data contradicted the statements very clearly, but did not permeate through the often personal and emotional noise.

In the USA, science, among other things, was up against the model and mother of an autistic son, Jenny McCarthy, and the organisation Generation Rescue, both keen on pushing parents towards refraining from having their children vaccinated then and now. They and other activists have typically pointed out that the vaccine contained the mercury-based additive thimerosal.

'Actually, the content of mercury in a dose of MMR vaccine was lower than that in a tuna sandwich', states David Hawkes. 'And when thimerosal was removed from the vaccine there was no subsequent decrease in the number of autistic children. But the myth lives on.'

Despite the fact that Andrew Wakefield has been deprived of the right to practise and that his results have become thoroughly discredited following the Lancet's withdrawal of the original article, as it turned out to comprise highly selective and even fabricated data. Those steps were taken in 2010, and the following year an article in the Annals of Pharmacotherapy termed the entire MMR case: 'The most harmful medical swindle of the past hundred years.' Harmful, since it resulted in a decrease in the vaccination coverage among young children in several Western countries. The greatest impact occurred in the UK, where a drop from 92 to 73 per cent, and in certain parts of London to only 50 per cent, was observed around the turn of the millennium. Since then, the UK as well as the USA and the Netherlands have experienced epidemics of particularly measles with associated complications and a few deaths.

In Norway and Sweden the vaccination coverage is still above 95 per cent, whereas it has decreased to 90 per cent in Denmark. And that is actually too low for us to expect flock immunity to measles virus. This means that the number of vaccinees is not sufficient to prevent spreading of infection among the non-vaccinees, in case it should occur.

'People should realise that they opt *for* a risk for their children by opting out of vaccination', as emphasised by Jan Pravsgaard Christensen. 'If they get ill from childhood diseases, they may also suffer from complications, and perhaps they will contract these diseases in adulthood where the complications are particularly serious.'
Rubella in pregnant women will result in abortion, and mumps in adult men can make them sterile.

Pravsgaard Christensen continues: 'I believe that the opposition has much to do with the fact that we do not experience the effect of a vaccine. You won't notice that you *avoided* a disease, and today entire generations are thoroughly vaccinated and have grown up without childhood diseases.'

And Mølbak adds: 'When a vaccine works so well that a given disease disappears, people only see the adverse reactions of the vaccine. That way the success of vaccines is almost their own worst enemy.'

HOWEVER, only almost, since there are worse enemies out there. There are indications that the deadly polio virus, which causes infantile paralysis, may spread again due to political and religious opposition to vaccination.

In Nigeria, where the virus is endemic, conservative Muslim leaders started encouraging a boycott of polio vaccination of children in 2001, since they believe that it is a Western plot aimed at sterilising Muslims. The state Kano suspended vaccination for months, and the disease spread to neighbouring countries where it had previously been eradicated. Also, since that time, Nigeria itself has experienced several outbreaks with considerable numbers of deaths. As recently as February, healthcare workers who tried to dispense vaccine were shot in Kano.

Currently, the situation is the same in the northern part of Pakistan where the tribal regions of Waziristan are experiencing an outbreak of polio. Based on the same grounds as in Nigeria, the local Taliban is making an energetic attempt to prevent vaccination of children, and both healthcare professionals and the police, who are charged with protecting them, have been killed. So far, the Taliban action is believed to have cost dozens of children their mobility, and sewage water tests in several major cities in Pakistan have shown that the virus has started spreading in regions that used to be free of it.

Batches of the NovoMix®30 FlexPen® recalled

A manufacturing fault in batches of the insulin medicine NovoMix®30 FlexPen®, which contain too much or too little insulin, may lead to an increased risk of hypoglycaemia or hyperglycaemia.

Therefore, the marketing authorisation holder, Novo Nordisk, has recalled specific batches of NovoMix®30 FlexPen® from wholesalers, pharmacies and patients.

Only a few faulty batches

Information from Novo Nordisk shows that only 0.14% of the cartridges contain an incorrect amount of insulin. However, in the pens affected, the content of insulin may vary from 50% to 150% of the number of insulin units specified.

Advice for doctors:

- As soon as possible, patients using the batches of NovoMix®30 FlexPen® affected should be switched to batches that are not affected by the recall, or – if not possible – to another treatment.

  Patients should be encouraged to check the batch number / lot number of their NovoMix®30 FlexPen®.

NovoMix®30 FlexPen® – faulty batches:

Product number: 006024

Batch no.	expiry:
CP51098	10/2014
CP50915	10/2014
CP50412	07/2014

Product number: 500814

Batch no.	expiry:
CP50904	10/2014
CP50650	07/2014
CP51097	10/2014
CP50641	07/2014

Product number: 016361

Batch no.	expiry:
CP5109500	10/2014
CP5090400	10/2014
CP5090401	10/2014
CP5090402	10/2014
CP5090403	10/2014
CP5065000	07/2014
CP5065001	07/2014
CP5064100	07/2014

NovoMix® is an insulin product used for the treatment of diabetes. The active substance in NovoMix® is insulin aspart. NovoMix® is available in pre-filled pens (FlexPen®) and cartridges (Penfill®).

NovoMix®30 contains 30% rapid-acting insulin aspart and 70% intermediate-acting insulin aspart.

In Denmark, an estimated number of approx. 15,000 patients receive treatment with NovoMix®30 FlexPen®.

The other strengths of NovoMix® are not affected by the manufacturing fault.

Short news

Reporting of adverse reactions to the Danish Health and Medicines Authority

According to Danish executive order no. 826, doctors have an obligation to report all serious[1] adverse reactions to the Danish Health and Medicines Authority within 15 days from suspecting their existence. Furthermore, doctors have an obligation to report all unexpected adverse reactions and all adverse reactions caused by new medicines, i.e., medicines that have been on the market for less than two years.

The obligation to report within 15 days for serious adverse reactions thus applies from the time when the doctor suspects the existence of the adverse reaction and not from the time of onset of the adverse reaction in the patient. In some cases, suspicion of an adverse reaction in a patient will be somewhat delayed – and sometimes it may arise several years after the patient's experience of the adverse reaction. These adverse reactions must also be reported to the DHMA.

It is important to report all adverse reactions to the DHMA.
The DHMA receives and records all reports of suspected adverse reactions. This also applies to reports of any suspected serious adverse reactions submitted later than 15 days from the doctor's suspicion of them.

The DHMA is aware that systematised retrospective reviews of medical records are conducted from time to time to identify particular diagnoses emerged in association with a given treatment. Also in such cases is it important to submit a report, even if a correlation between the diagnosis and the medicine used for treating the patient is only suspected.

The best possible patient safety
The deadline of 15 days was established in the Danish executive order to ensure that the DHMA is informed about suspected serious adverse reactions as soon as possible and that the DHMA this way is provided with the best possible basis for reacting quickly to new and important knowledge of potential adverse reactions.

1 An adverse reaction is serious, if it:
- is fatal
- is life-threatening
- causes or prolongs hospitalisation
- causes persistent or significant disability or incapacity
- causes foetal defects or congenital anomaly.

Short news

Danish Pharmacovigilance Update celebrates its 4th anniversary

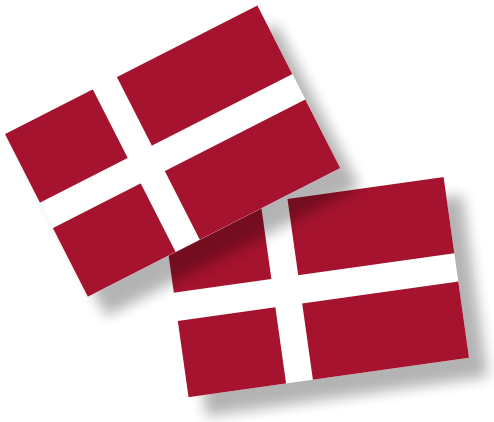
In November 2009, the first issue of Danish Pharmacovigilance Update was released. This means that this year we are celebrating the 4th anniversary of the newsletter with our approx. 2,700 subscribers.

Over the past four years, the DHMA has dealt with many different topics in the newsletter articles, ranging from updates of summaries of product characteristics and new potential signals to suspension of medicines.

In 2013, we have featured articles on topics such as the HPV vaccine Gardasil® against cervical cancer in *Danish Pharmacovigilance Update, 27 June 2013*, *Danish Pharmacovigilance Update, 29 August 2013*, *Danish Pharmacovigilance Update, 26 September 2013*, valproic acid and the safety of use during pregnancy in *Danish Pharmacovigilance Update, 25 April 2013*, and a status of the study mapping the consumption and the safety profile of the anticoagulant Pradaxa® – a study carried out by the DHMA in collaboration with the Thrombosis Centre in Aalborg in *Danish Pharmacovigilance Update, 17 January 2013*.

We are very pleased that the newsletter continues to attract strong interest and positive response, and we hope that it will attract even more interest in future.

Subscribe to *Danish Pharmacovigilance Update*.



Danish Pharmacovigilance Update is published by:
Danish Health and Medicines Authority
http://www.sundhedsstyrelsen.dk/English.aspx
Editor-in-Chief:
Henrik G. Jensen (HGJ)
Editor:
Nina Vucina Pedersen (NVP)
ISSN 1904-2086