# Danish Pharmacovigilance Update # 8

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## Contents

### News from the EU



### News from the DHMA



### Short news

News from the EU

# Denosumab (Prolia and Xgeva) and risk of osteonecrosis of the jaw and hypocalcaemia

After marketing of the biological medicinal products Prolia and Xgeva, both of which contain denosumab, cases of osteonecrosis of the jaw and hypocalcaemia have been reported. As part of routine safety updating of these medicines' product information, the warnings about these adverse reactions have now been updated and made clearer.

## Osteonecrosis of the jaw (ONJ)

ONJ occurs when the jaw bone is exposed, becomes necrotic and does not heal within eight weeks. The aetiology of ONJ is not clear, but it may be associated with impaired remodelling of bone. ONJ was reported rarely in the clinical studies based on which the authorisation was granted, and post-marketing cases of ONJ were also reported in osteoporosis patients treated with Prolia (denosumab at a dose of 60 mg every six months). ONJ is common in patients with advanced cancer that is treated with denosumab at the monthly dose of 120 mg.

The known risk factors for ONJ include prior treatment with bisphosphonates, advanced age, poor oral hygiene, invasive dental treatment (e.g. dental extractions, dental implants, oral surgery) and co-morbid disorders (e.g. pre-existing dental disease, anaemia, coagulopathy, infection), smoking, cancer with bone lesions, other concomitant treatment (e.g. chemotherapy, antiangiogenic biological treatment, corticosteroids or radiation therapy to the head and neck).

## Doctors should be aware of the following:

- A dental examination with relevant preventive dental treatment is recommended prior to treatment with denosumab.
- All patients should be evaluated for ONJ risk factors before treatment with denosumab is initiated. Treatment with denosumab should neither be initiated in patients with an active dental disease or jaw disorder requiring surgery nor in patients who have not recovered from oral surgery.
- Patients should be advised to maintain good oral hygiene and appear for routine dental examinations, and to immediately report any oral symptoms such as tooth mobility, pain or swelling during treatment with denosumab.

## Hypocalcaemia

Denosumab inhibits osteoclast formation thereby decreasing the release of calcium from the bone into the blood stream.

There are reports of severe symptomatic hypocalcaemia from treatment with denosumab. Cases of renal insufficiency were described in the majority of these reports. Most of the hypocalcaemia cases occurred within the first weeks after initiation of denosumab treatment. However, hypocalcaemia may develop later.

Examples of the clinical manifestations of severe symptomatic hypocalcaemia include QT interval prolongation, tetany, seizures and altered mental status. Symptoms of hypocalcaemia in denosumab clinical studies included paresthesias or muscle stiffness, twitching, spasms and muscle cramps.

The risk of developing hypocalcaemia during denosumab treatment increases with the degree of renal impairment. The risk also varies with the dose, indication and duration of treatment.

News from the EU

## The following recommendations apply to the risk of hypocalcaemia:

- Pre-existing hypocalcaemia should be corrected before treatment with denosumab is initiated.
- An adequate intake of calcium and vitamin D is important for all patients (unless the patient has hypercalcaemia), particularly in cases of severe renal impairment.
- Patients should be instructed to tell their doctor if they develop symptoms suggestive of hypocalcaemia.

## Calcium levels should be monitored according to the guidelines below depending on indication as the dose and interval between treatments vary:

**Xgeva** (120 mg monthly):
- before the first dose of Xgeva
- within the first two weeks after the first dose
- whenever symptoms suggestive of hypocalcaemia are suspected
- It is advised to consider more frequent monitoring of calcium levels in patients at greater risk of developing hypocalcaemia (e.g. patients with severe renal impairment, creatinine clearance < 30 ml/min), or if, for other reasons, it has been indicated based on the patient's clinical condition.

**Prolia** (60 mg every six months):
- before each dose of Prolia
- within two weeks after the first dose in patients predisposed to hypocalcaemia (e.g. patients with severe renal impairment, creatinine clearance < 30 ml/min)
- whenever symptoms suggestive of hypocalcaemia are suspected, or if, for other reasons, it has been indicated based on the patient's clinical condition.

**Letters have been sent out to prescribers describing the problems. They can also be found in Danish on the DHMA website:** List of circulated DHPCs.

Indication for Prolia
Treatment of osteoporosis and bone loss associated with hormone ablation or bilateral orchiectomy for prostate cancer.

Indication for Xgeva:
Prevention of skeletal related events in adults with bone metastases from solid tumours.



## Interferon beta and risk of serious adverse reactions

There have been reports of cases of thrombotic microangiopathy (TMA) and nephrotic syndrome in treatment of multiple sclerosis with medicines containing interferon beta (Avonex, Rebif, Betaferon, Extavia, Plegridy). A DHPC has been sent out to doctors to raise awareness about the risk.

Most of the reported cases of TMA presented as thrombotic thrombocytopenic purpura or haemolytic uraemic syndrome – in some cases with fatal outcomes. Cases of nephrotic syndrome with varying underlying pathology have also been reported as a possible adverse reaction to treatment with interferon beta.

TMA and nephrotic syndrome may develop weeks or years after the patient started treatment.

### Doctors should be aware of the following:

- Clinical symptoms suggestive of TMA include thrombocytopenia, new onset hypertension, fever, central nervous system symptoms, e.g. confusion or paresis and affected renal function.
- Doctors who observe any of these symptoms in patients should measure blood platelet levels, serum lactate dehydrogenase levels and renal function. In addition, a peripheral blood smear test should be made to detect the presence of any schistocytes.
- If a TMA diagnosis is made, treatment must be initiated promptly. Plasmapheresis should be considered. It is recommended to stop beta interferon treatment immediately.
- Patients, particularly patients at increased risk of kidney problems, should be monitored regularly for any signs of nephrotic syndrome (oedema, proteinuria and affected renal function).
- If a diagnosis of nephrotic syndrome is made, treatment must be initiated promptly, and it should be considered to stop treatment with interferon beta.
- The summaries of product characteristics for interferon beta-containing products have been updated with information on TMA and nephrotic syndrome, and the following frequencies have been inserted in the adverse reactions table: TMA (rare), nephrotic syndrome (rare: Avonex, Plegridy and Rebif/Uncommon: Betaferon and Extavia).

**The letter has been sent out to relevant doctors and can also be found on the DHMA website:**
List of circulated DHPCs.

**Indication for interferon beta-containing products**
Treatment with interferon beta is indicated in patients with relapsing multiple sclerosis (MS).

# Scopoderm® transdermal patches and visual disturbances

In July, the DHMA received an ADR report about a boy younger than 10 years of age onto whom a Scopoderm® transdermal patch had been affixed to prevent motion sickness.

15 hours after the patch had been affixed, the boy developed visual hallucinations and had trouble focusing clearly. The boy was admitted to hospital later that day. The following morning, his condition had improved clearly, but he still had trouble focusing.

## Reports of visual disturbances in connection with Scopoderm® treatment

The DHMA has received a total of 17 reports describing possible effects on the vision (e.g. mydriasis, glaucoma and double vision) suspected to be adverse reactions to Scopoderm® transdermal patches, and nine of the reports were coded with the term hallucinations, of which two specifically described visual hallucinations.

## Doctors should be aware of the following:

- Confusion and/or visual hallucinations are known adverse reactions described in the medicine's summary of product characteristics. If they occur, the patch should be removed immediately. If the symptoms persist, the patient should be admitted to hospital, e.g. for slow intravenous administration of physostigmine, 1-4 mg (in children 0.02 mg/kg, but maximum 0.5 mg).

- Disturbances of visual accommodation (cycloplegia) including blurred vision, myopia and mydriasis (sometimes unilateral) are known adverse reactions described in the summary of product characteristics (frequency: very common (>1/10)).

**Indications and dose:**
Motion sickness. Adults and children over 10 years of age: One transdermal patch every 72 hours. Safety and efficacy have not been studied in children younger than 10 years of age.

(In Denmark, Scopoderm® transdermal patches are available over-the-counter at pharmacies.)

All cases referred to in this article originate from the Danish Health and Medicines Authority's database of adverse drug reactions. 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.

# Childhood vaccinations and reported suspected adverse reactions in Q2 of 2014

Every three months, the reports of suspected adverse reactions to vaccines in the Danish childhood immunisation programme are reviewed and assessed by the DHMA and a vaccination panel composed of experts from relevant clinical settings in Denmark.

## Here are the results of the review for Q2 2014

Since adverse reactions to the HPV vaccine attracted a lot of attention in 2013, our review falls into two sections:

1. A review of the ADR reports related to vaccines of the childhood immunisation programme – excluding the HPV vaccine.

2. A review of the ADR reports related to the HPV vaccine.

The review covers primary vaccines in the childhood immunisation programme as well as booster vaccines (re-vaccination).

## Reports of adverse reactions to vaccines in the childhood immunisation programme (excluding the HPV vaccine) Q2 of 2014.

In the second quarter of 2014, we received a total of 53 reports[1] that concerned vaccines in the childhood immunisation programme (excluding the HPV vaccine), of which 25 were classified as serious[2].

Table 1a shows how many of the reports were classified as serious and how many were classified as non-serious.

| Vaccine | Serious | Non-serious | Total |
|---|---|---|---|
| ACT-HIB | 0 | 1 | 1 |
| DT booster (one given together with Havrix and Stamaril) | 3 | 1 | 4 |
| DTaP-IPV Booster | 0 | 2 | 2 |
| DTaP-IPV / Act-Hib | 10 | 9 | 19 |
| DTaP-IPV / Act-Hib / MMR vaxpro / Prevenar13 | 1 | 0 | 1 |
| DTaP-IPV /Act-Hib / Prevenar | 0 | 1 | 1 |
| DTaP-IPV /Act-Hib / Prevenar 13 | 7 | 0 | 7 |

[1] One report may cover several suspected adverse reactions.
[2] A report is serious when one or more of the adverse reactions are serious. A serious adverse reaction caused by a medicine for human use is a reaction that results in death, is life-threatening, requires hospitalisation or prolongation of hospitalisation, or which results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect.

| | | | |
|---|---|---|---|
| DTaP-IPV / Act-Hib / Priorix | 1 | 0 | 1 |
| Infanrix Hexa | 0 | 2 | 2 |
| Infanrix Hexa / Prevenar 13 | 1 | 1 | 2 |
| MMR vaxpro | 1 | 7 | 8 |
| Pneumovax | 1 | 0 | 1 |
| Prevenar | 0 | 0 | 0 |
| Prevenar 13 | 0 | 2 | 2 |
| Prevenar 13 / Priorix | 0 | 1 | 1 |
| Priorix | 0 | 1 | 1 |
| Total | 25 | 28 | 53 |

Table 1a. Reports broken down by severity

## Review and assessment of the serious reports

When we assess the serious ADR reports, we investigate whether it is likely that there is a causal connection to the vaccine.

The result of our causality assessment is split into three categories:

- Possible
- Less likely
- Not possible to assess based on the available information

| Vaccine | ADR description | Assessment and causality justification |
|---|---|---|
| Pneumovax | Overall reaction with muscle soreness, headache, elevated CRP, lymph node swelling, etc. | Possible – most of the adverse reactions are known, and there is a temporal relationship. |
| Infanrix Hexa, Prevenar13 | Generalised urticaria | Possible – known adverse reaction and temporal relationship. |
| DT booster | Myocarditis | Less likely – an intercurrent infection was described as possible cause. Myocarditis is not a known adverse reaction. |
| DT booster, Stamaril, Havrix | CNS effects, etc. with increased cell counts, but normal protein in spinal fluid | A connection to Stamaril is considered likely due to the temporal relationship. CNS inflammation – with modest increase in spinal protein – is described in the literature after administration of the vaccine. A connection to DT booster is considered less likely. |
| DT booster | Pain in right upper arm. | Could be caused by other factors, but because of the temporal relationship, a causality is considered likely. |

| | | |
|---|---|---|
| DTaP-IPV-Act-Hib and Priorix | Granuloma and aluminium allergy | Possible connection to DTaP-IPV-Act-Hib (Priorix does not contain aluminium) |
| DTaP-IPV-Act-Hib, Prevenar 13 and MMR vaxpro | Granuloma and aluminium allergy | Possible – allergy verified – but not due to MMR vaxpro |
| 9 DTaP-IPV-Act-Hib ** | Granuloma, aluminium allergy | Possible – verified allergy |
| 5 DTaP-IPV-Act-Hib, Prevenar13/ Prevenar | Granuloma, aluminium allergy | Possible – verified allergy |
| Prevenar13, DTaP-IPV-Act-Hib, | Fever, restlessness, obs cramps | Possible – temporal relationship, known adverse reactions |
| Prevenar13 DTaP-IPV-Act-Hib | Irritability, crying, fever | Possible – known adverse reactions – temporal relationship |
| DTaP-IPV-Act-Hib | Hib meningitis | Vaccine failure, possible (had not received all vaccine doses at the time of illness) |
| MMR Vaxpro | Short-term seizure | Possible – occurred a few minutes after vaccination – described previously |

Table 1b: Description of the adverse reactions described in the serious ADR reports and subsequent causality assessment.
** In two of the cases Prevanar13 was given concomitantly, but this vaccine is not described as suspected to have caused the adverse reaction.

## Review of the non-serious ADR reports

The reports classified as non-serious primarily describe known adverse reactions such as local irritations and fever, but some of them also described the formation of granuloma (10 reports).

One case of facial palsy after vaccination with MMR Vaxpro was reported as an unknown, non-serious adverse reaction.

## Conclusion

In the second quarter of 2014, we received a total of 53 reports that concerned vaccines in the childhood immunisation programme (excluding the HPV vaccine). 25 reports were classified as serious. 16 of the reports described aluminium allergy and the formation of granuloma.

In the first quarter, the DHMA received 46 reports of which 12 were serious. 10 of these 12 reports described aluminium allergy and the formation of granuloma.

In both quarters, we note that there were many reports of aluminium allergy and granuloma as suspected adverse reactions to the vaccines. Presumably, this reflects raised awareness on this particular adverse reaction.

Three reports describe elderly people who received the DT booster vaccine – one of whom also received the travel vaccinations Havrix and Stamaril at the same time. He/she developed neurological symptoms. Most likely, these were not caused by the DT booster vaccine, but by the vaccine against yellow fever (Stamaril).

In addition, a case of myocarditis was seen. The report also describes an intercurrent infection, which better explains the condition. There is one case of Hib meningitis in a child who was not fully vaccinated, and since protection can only be considered sufficient after three vaccine doses, this is an expected scenario.

Most of the other serious ADR reports describe known adverse reactions such as fever cramps, irritability and rash.

The Danish Health and Medicines Authority assesses that the benefits of the vaccines still outweigh the possible risks.

## Reports about the HPV vaccine received in Q2 2014

In the second quarter of 2014, the DHMA received a total of 34 reports about the HPV vaccine, of which 14 were classified as serious.

Table 2a shows how many of the ADR reports related to the HPV vaccine were classified as serious and how many were classified as non-serious.

| Vaccine | Serious | Non-serious | Total |
|---|---|---|---|
| HPV vaccine | 14 | 20 | 34 |

Table 2a. Reports broken down by severity

## Number of doses sold and number of ADR reports from 2009-2014

| HPV vaccine | 2009 | 2010 | 2011 | 2012 | 2013 | First half of 2014 * | Total |
|---|---|---|---|---|---|---|---|
| Number of reports | 288 | 66 | 43 | 96 | 511 | 125 (91) | 1129 |
| – of which serious | 25 | 5 | 6 | 18 | 177 | 38 (24) | 269 |
| Number of doses sold | 347,690 | 151,476 | 163,374 | 349,730 | 488,224 | 69,161 (38,640) | 1,569,655 |

*Table 2b. Number of ADR reports related to the HPV vaccine received from 2009 to 30 June 2014, broken down by serious and non-serious reports. The number of doses sold in Denmark is also shown. (Please be aware that when the DHMA receives additional information, this may imply changes. Consequently, there may be small variations between previously published figures and the figures reported here.)*
**Bracketed numbers reflect Q1 2014.*

## Age distribution

The HPV vaccine is the only vaccine included in the Danish childhood immunisation programme that is also offered free of charge to women outside the childhood programme.

From August 2012 until end-2013, the HPV vaccine was offered free of charge to women from the 1985-1992 birth cohorts. Since 1 January 2014, the HPV vaccine has been offered to women from the 1993-1997 birth cohorts. These birth cohorts have previously been offered the HPV vaccine. The offer is available until the end of 2015.

Table 2c shows the age distribution of the girls/women described in the ADR reports we received in Q2.

| Number of reports about persons under 18 | Number of reports about persons aged 18 or over | Number of reports with age unknown |
|---|---|---|
| 14 | 18 | 2 |

Table 2c. Age of the girls/women for whom adverse reactions have been reported

As we have seen it previously, there are relatively more ADR reports categorised as serious among women over 18. It could mean that there are actually more adverse reactions in this population, but an older population will also have a higher underlying morbidity, which could distort the picture.

## Review and assessment of the serious reports about the HPV vaccine

| Vaccine | ADR description | Assessment and causality justification |
|---|---|---|
| Gardasil | POTS with dizziness, etc. | Temporal relationship (2nd vaccine dose). There is no evidence of causality in the literature. However, there are quite many case reports in which symptom onset and the vaccine coincide, which is why a causal relationship is considered **likely** |
| Gardasil | POTS headache, dizziness, etc. | Temporal relationship (after 1st vaccine dose). There is no evidence of causality in the literature. However, there are quite many case reports in which symptom onset and the vaccine coincide, which is why a causal relationship is considered **likely** |
| Gardasil/Silgard | Dizziness, sensory disturbances, etc. | A causal relationship is considered **less likely** as an alternative diagnosis has been mentioned (stress), and there is no obvious temporal relationship |
| Gardasil | Tiredness, visual disturbances, etc. | **Not possible to assess** as the information is very sparse |
| Silgard | Unspecified neurological symptoms | **Not possible to assess** as the information is very sparse |
| Gardasil | Tiredness, dizziness, etc. | Assessed to be **less likely** as there is no obvious temporal relationship, and the symptoms described are relatively common. |

| | | |
|---|---|---|
| Gardasil | Symptoms resembled fatigue syndrome<br>There is intercurrent disease | No conclusive diagnosis is available. However, an increased incidence rate for fatigue syndrome after HPV vaccination has been disproved ( jf. Donegan K et al: Bivalent human papillomavirus vaccine and the risk of fatigue syndromes in girls in the UK . Vaccine 2013 Sep 1). It is therefore considered most likely that it is a a case of coincidence, and a connection to the vaccine is considered **less likely**. |
| Gardasil | Tiredness, tingling sensation, fever episodes, etc. | A causal relationship is considered **less likely**. Symptoms occurred after the first dose of Gardasil, but the symptoms are very unspecific, and a temporal coincidence is considered more likely. |
| Gardasil | Varying discomfort, pain around the heart, dizziness, etc. | There is no diagnosis, but a causal relationship is considered **less likely** because the symptoms started four years after vaccination. |
| Gardasil | Muscle pain, headache, tiredness, etc. | There is no diagnosis, but a causal relationship is considered **less likely** because the symptoms started suddenly 2½ years after vaccination. |
| Gardasil | Orthostatic hypotension, dizziness, nausea, etc. | **Possible**, previously healthy – close temporal relationship between symptom onset and the vaccine – which is why a connection is considered possible. Has been examined for POTS, which is not verified however. |
| Gardasil | Headache and repeated seizures, etc. | **Less likely** since there is no obvious temporal relationship, and no similar adverse reaction has been described in the literature. |
| Gardasil | Extensive swelling and local pain, pericarditis | 9 days after vaccination, the patient developed pericarditis. Prior to this, unusually extensive swelling and pain had developed around the injection site. The patient has been examined for other causes that may possibly explain the condition. There is nothing in the literature about HPV vaccine and pericarditis, but a causal relationship is considered **possible** due to the atypical course of events with pain from the start and temporal relationship. |
| Gardasil | Posterior uveitis | The symptoms began a few days after the first vaccine dose and recurred after the second vaccine dose. There are case reports that describe this condition after vaccination. Even though it is not possible to determine causality conclusively, a connection is considered **likely** due to the temporal events. |

Table 2d. Description of the adverse reactions in the serious ADR reports and subsequent causality assessment.

## Review of the non-serious ADR reports

The most commonly reported adverse reactions classified as non-serious are headache (11%), dizziness (10%) and sensory disturbances (7%). Sensory disturbance is an unknown adverse reaction, which is not described in the medicine's summary of product characteristics.

## Conclusion

We received 32 reports in total concerning the HPV vaccine in the second quarter of 2014. 14 reports were classified as serious. This is a significant drop compared to the first quarter when we received 90 reports, of which 23 were serious. This should be seen in light of how many doses were distributed (see table 2b).

The number of POTS cases (2) is unchanged compared to the first quarter despite increased awareness on this diagnosis. The European Medicines Agency, in which the DHMA is also represented, monitors the reports on POTS continuously. In this quarter there were once again quite many women (10) who reported headache, dizziness, +/- paresthesia, tiredness, etc. Most of the patients have been examined by their own doctor, a hospital or a specialist without a diagnosis having been made.

In addition, we received a report about an adult woman who developed an unusually large local reaction immediately followed by pericarditis. Due to the close temporal relationship, it cannot be ruled out that the reaction was caused by the vaccine. Apparently, the woman is well today.

Another report described an eye disease, uveitis posterior, with symptoms that began after both the first and the second vaccination, which is why a causal relationship is considered likely. We have received no other reports of this disease related to HPV vaccination In Denmark.

The Danish Health and Medicines Authority still assesses that the benefits of the HPV vaccine outweigh the possible risks.

All cases referred to in this article originate from the Danish Health and Medicines Authority's database of adverse drug reactions. 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.

## Most recent Direct Healthcare Professional Communications (DHPCs)

Below is a list of the most recent DHPCs that have been (or soon will be) sent out to relevant doctors and healthcare professionals with safety information and updated recommendations about medicines:

- Antiemetic domperidone (Motilium, etc.) New recommendations to minimise the cardiac risks (also see the article in Danish Pharmacovigilance Update, April 2014
- Osteoclast inhibitor denosumab (Xgeva (120 mg), Prolia (60 mg)): Updated information to minimise the risk of osteonecrosis of the jaw and hypocalcaemia.
- Iimmunosuppressant basiliximab (Simulect®): Warning against off-label use in cardiac transplantation.
- Interferon beta in multiple sclerosis treatment: Risk of thrombotic microangiopathy and nephrotic syndrome (also see article on page 4 in this issue of Danish Pharmacovigilance Update).
- Iron preparation ferumoxytol (Rienso): New important advice to mitigate risk of serious hypersensitivity reactions (also see article in Danish Pharmacovigilance Update, August 2014).
- Ofatumumab (Arzerra) for the treatment of chronic lymphatic leukaemia: Reminder of risk of serious and fatal infusion reactions
- Multiple myeloma product Bortezomib (Velcade): Cracked 3.5 mg vials

The DHPCs are available in Danish at the DHMA website: List of circulated DHPCs.

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