

Danish Pharmacovigilance Update

Danish Pharmacovigilance Update is an electronic newsletter for doctors intended to ensure easy access to current, updated knowledge about medicines and adverse reactions. It provides quick updates on current medicine safety issues with a practical focus for doctors.

By putting focus on special problems and applicable recommendations, we seek to support medical subscription to reduce the risk of adverse reactions.

The newsletter (in Danish) is sent out to email subscribers on the last Thursday of every month (excluding July) and is available from the website of the DKMA: [Danish Pharmacovigilance Update](#)

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The European Pharmacovigilance Risk Assessment Committee, PRAC, recommends regulatory measures – including suspension of the marketing authorisation for some gadolinium-containing contrast agents

Background

Gadolinium contrast agents are diagnostic products given to patients before or during MRI scans to obtain better images of organs and tissues. After administration, the gadolinium chelate is mostly eliminated via the kidneys. However, gadolinium can accumulate in some organs, such as in the liver, kidneys, muscles, skin and bones, and lately evidence of accumulation in the brain has also been found.

Gadolinium contrast agents are categorised depending on the structure of the chelate in linear and macrocyclic agents. Linear agents have a structure more likely to release gadolinium from the chelate molecule, which means it can accumulate in body tissues. Macrocyclic gadolinium contrast agents are more stable and thus release gadolinium to a much lower degree.

Suspension of four linear gadolinium contrast agents for intravenous use

After reviewing the material in the area, the European Pharmacovigilance Risk Assessment Committee, PRAC, recommended to suspend the marketing authorisations of four linear gadolinium contrast agents because of evidence showing that small amounts of the gadolinium from these products are deposited in the brain of patients having undergone MRI scans.

The PRAC has recommended to suspend the following intravenous linear contrast agents: gadobenic acid (Multihance®)¹, gadodiamide (Omniscan®), gadopentetic acid (Magnevist®) and gadoversetamide (Optimark®). The suspension of the linear products will have a moderate effect in Denmark since we primarily use macrocyclic contrast agents for MRI scans. However, the linear product gadobenic acid (Multihance®) is presently used to a lesser degree in Denmark.

A few linear contrast agents will remain available on the market: The linear contrast agent Gadoxetic acid (Primovist®) is used at low doses for MRI scans of the liver and has an important diagnostic effect in certain patients. Another available product is a formulation of gadopentetic acid (Magnevist®). This product is injected directly into joints at a dose which is 200 times lower than those of intravenous products and is important in MRI evaluations of joints. Both agents should be used at the lowest possible dose and only when it is not sufficient to perform MRI scans without contrast agents. Both formulations are presently used in Denmark.

The PRAC recommends that the macrocyclic contrast agents of gadoteric acid (Dotarem®), gadobutrol (Gadovist®) and gadoteridol (ProHance®) (that remain on the market) be used at the lowest possible dose and only when it is not sufficient to perform MRI scans without contrast agents. These products are used in Denmark.

The result of PRAC's safety review

The PRAC review of gadolinium agents found convincing evidence of accumulation of gadolinium in the brain, partly in studies directly measuring gadolinium in brain tissues, and partly in studies showing increased signal intensity on MRI scans of the brain many months after the last injection of a gadolinium contrast agent. Whereas macrocyclic contrast agents disappear quickly from the brain, the linear contrast agents remain in the brain for up to 12 months or more.

Although, there have so far been no reports of clinical adverse reactions in relation to accumulation of gadolinium in the brain, the PRAC recommends to suspend the marketing authorisation as a precautionary measure, noting that data on the long-term effects of accumulation in the brain are very limited.

Deposition of gadolinium in other organs and tissues has been associated with rare adverse reactions such as skin plaques and nephrogenic systemic fibrosis. These adverse reactions could have serious implications for patients with renal impairment. Pre-clinical studies have furthermore shown that gadolinium is toxic and harmful in tissues.

The DKMA has contributed actively to the review.

Suspension not yet conclusive

The pharmaceutical companies affected by this review can request the PRAC to re-examine the case. If a re-examination is to take place, the decision on whether to suspend the linear products will not be conclusive until after the re-examination.

Read EMA's press release: [PRAC concludes assessment of gadolinium agents used in body scans and recommends regulatory actions, including suspension for some marketing authorisations](#)

¹ This article only mentions the original products. An additional number of generic versions are available on the EU market; they are also covered by the PRAC recommendation.

The DKMA seeks more knowledge about the use of quetiapine in children and adolescents

Antipsychotics have for long been one of the DKMA's focus areas, and it has come to our attention that the consumption of quetiapine, an antipsychotic, has increased markedly among the 15 to 17-year-olds. Quetiapine is not authorised for use in children or adolescents in Denmark.

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In the USA, quetiapine is authorised for the treatment of children and adolescents with bipolar disorders and schizophrenia (aged over 10 and 13 years, respectively), but in Europe it is only authorised for the treatment of adults. In the summaries of product characteristics, one of the main reasons not to authorise quetiapine for children and adolescents in the EU/Denmark is that significant adverse reactions (not seen in the adult population) have been observed in the few short-term studies in paediatric populations and that the occurrence of known adverse reactions is higher among children than among adults. In addition, there is limited evidence of how quetiapine impacts the growth and development of children and adolescents in the long term, including how it impacts cognitive and behavioural development.

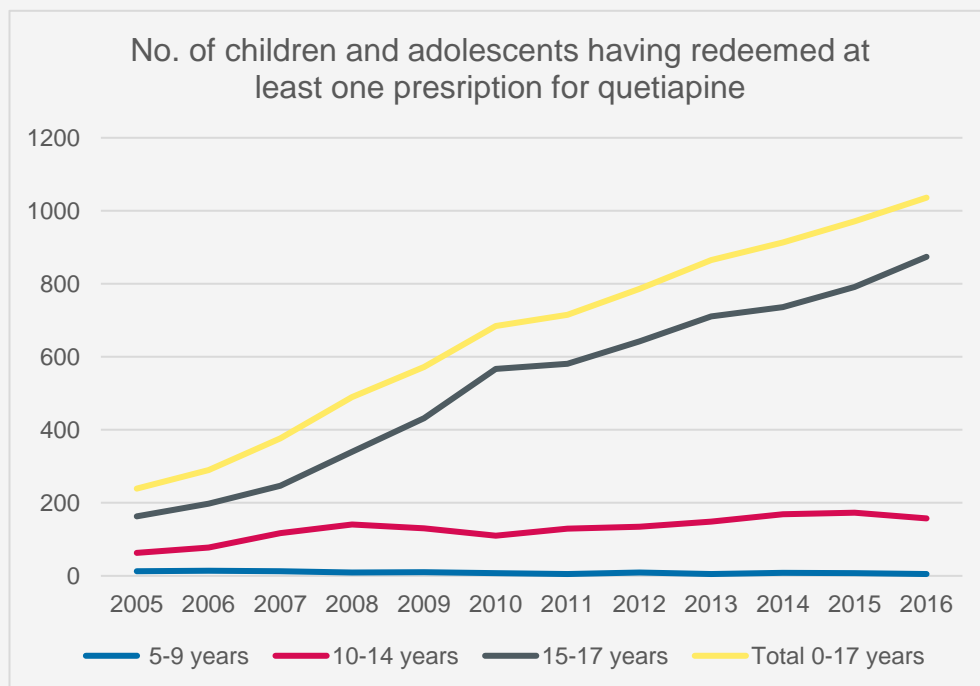


Figure 1: Number of children and adolescents having redeemed at least one prescription for quetiapine from 2005 to 2016 (medstat.dk).

Analysis of reported suspected adverse reactions involving children and adolescents treated with quetiapine

To gain more knowledge about adverse reactions in children and adolescents treated with quetiapine, the DKMA and a group of psychiatrists have reviewed the ADR reports of suspected adverse reactions in children and adolescents treated with quetiapine.

The purpose of the review was to examine the occurrence of suspected adverse reactions among children and adolescents treated with quetiapine and relating them to the adverse reactions described in the Danish product information for quetiapine and to those described in the literature.

The review focused on 15 reports of suspected adverse reactions experienced by boys and girls aged between 15 and 17 years receiving quetiapine. The majority of the ADR reports involve the following suspected adverse reactions:

- Endocrine adverse reactions; hyperprolactinemia (known adverse reaction²) and hyperthyroidism (unknown adverse reaction)
- Cardiovascular adverse reactions; tachycardia and QT prolongation (known adverse reactions)
- Neurological adverse reactions; seizures and cerebral haemorrhage (unknown adverse reactions)
- Psychiatric adverse reactions; hallucinations (unknown adverse reaction).

It has not been possible to assess causality with the medicine for all of the reported suspected adverse reactions.

The study was published in the international journal of Clinical Psychopharmacology: [Adverse events in children and adolescents treated with quetiapine: an analysis of adverse drug reaction reports from the Danish Medicines Agency database.](#)

Review of the DKMA

The DKMA has received an additional seven reports of suspected adverse reactions among children and adolescents that are not described in the published article. Three of them were serious and describe worsening of epilepsy, considerable weight gain and tachycardia.

Compared to the consumption of the medicine, the DKMA has received relatively few reports of suspected adverse reactions in children and adolescents treated with quetiapine. However, the number of ADR reports is not a perfect expression of the occurrence of adverse reactions since not all adverse reactions are reported. This means that it is not possible to conclude anything about the frequency and causality on the basis of the described ADR reports.

Remember to report suspected adverse reactions to the DKMA

The DKMA seeks more knowledge about off-label use of quetiapine in children and adolescents. And we are therefore encouraging doctors to report to us any suspected adverse reactions in children and adolescents treated with quetiapine.

Please report suspected adverse reactions to the DKMA at: www.meldenbivirkning.dk (report a side effect).

Disclaimer

All cases referred to in this article originate from the DKMA's database of adverse drug reactions. The cases have been forwarded to all relevant pharmaceutical companies and to the EudraVigilance database. Therefore, the pharmaceutical companies are not to report these cases to the DKMA.

² When we distinguish between known and unknown adverse reactions, we look at whether the adverse reaction is described in the product information for quetiapine for use in adults and hence is a known adverse reaction.

Childhood vaccinations and reported suspected adverse reactions in Q4 of 2016

Every three months, the reports of suspected adverse reactions to vaccines in the Danish childhood immunisation programme are reviewed and assessed by the Danish Medicines Agency (DKMA) and a vaccination panel composed of a number of experts.

Here are the results of the review for Q4 2016. The review covers primary vaccines in the childhood immunisation programme as well as booster vaccines (re-vaccination).

ADR reports about vaccines in the childhood immunisation programme

Vaccine	Non-serious	Serious	Total
DTaP-IPV Booster	8	0	8
DTaP-IPV Booster / DTaP-IPV/Act-Hib	0	1	1
DTaP-IPV Booster / DTaP-IPV/Act-Hib / MMR Vaxpro / Prevenar	1	0	1
DTaP-IPV /Act-Hib	22	11	33
DTaP-IPV /Act-Hib / Hexaxim	0	1	1
DTaP-IPV /Act-Hib / Infanrix Hexa	2	1	3
DTaP-IPV /Act-Hib / Infanrix Hexa / Prevenar 13	5	0	5
DTaP-IPV /Act-Hib / MMR Vaxpro / Prevenar 13	4	0	4
DTaP-IPV /Act-Hib / Prevenar	5	0	5
DTaP-IPV /Act-Hib / Prevenar 13 / Prevenar	66	0	66
DTaP-IPV /Act-Hib / Prevenar 13 / Priorix	2	0	2
Hexaxim / Prevenar 13	1	0	1
Hexyon	3	1	4
Hexyon / Prevenar 13	5	2	7
Infanrix Hexa	2	0	2
Infanrix Hexa / MMR Vaxpro	1	0	1
Infanrix Hexa / Prevenar 13	5	1	6
MMR Vaxpro	3	0	3
MMR Vaxpro /Prevenar 13	1	0	1
Pneumovax	6	0	6
Pneumovax / Prevenar 13	1	0	1
Prevenar 13	2	0	2
Priorix	1	0	1
Cervarix	1	1	2
Silgaard	1	0	1
Gardasil	12	8	20
Total	160	27	187

Table 1: Number of reports by vaccine.

Fewer ADR reports related to the childhood immunisation programme

The DKMA received fewer ADR reports in the fourth quarter compared to the third quarter of 2016 (187/305). The total number of serious ADR reports fell from 49 to 27. The HPV vaccine alone recorded a fall in the number of serious ADR reports from 39 to 9. The number of serious ADR reports for the remaining vaccines remained unchanged (18 in the last quarter against 16 in the present quarter).

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Few ADR reports about the new childhood vaccines Hexaxim and Hexyon

There are few ADR reports about the new vaccines in the Danish childhood immunisation programme: Hexaxim and Hexyon. These vaccines are subject to stricter reporting requirements, which means that all suspected adverse reactions must be reported.

Fever and seizures

Two serious ADR reports described fever and possible seizures in respectively a 3-month-old baby and a 5-month-old baby after vaccination with Hexyon/Prevenar13. A 2-month-old baby vaccinated with Hexyon/Prevenar13 was suspected to suffer an afebrile seizure.

Serious ADR reports about the HPV vaccine in Q4 concern women vaccinated before 2015

One serious ADR report about the HPV vaccine describes a patient who developed Guillain-Barré syndrome with symptom onset several years after vaccination with Gardasil®, and for that reason causality was considered less likely. The remaining eight serious ADR reports about HPV vaccination describe various symptoms such as fatigue, sensory impairment, pain and dizziness having lasted for a long time with significant impact on work or school attendance. The diagnosis of POTS was also given in these ADR reports. In four of the eight ADR reports, it is considered less likely that the effects are connected to the vaccine as the temporal relationship is inconsistent, or other possible causes may explain the symptoms. The last four reports are impossible to classify due to lack of information.

Fewer ADR reports about granulomas

The number of ADR reports about granulomas nearly halved from the third to the fourth quarter of 2016. There were 119 non-serious ADR reports that described granulomas or nodules. Several of the ADR reports about granulomas also reported aluminium allergy, itching, sores, and increased hair growth, etc. Most of the ADR reports describing granulomas concern children who were vaccinated several years ago. One ADR report describes a vaccination granuloma in a child with subsequent abscess formation. The child had been vaccinated with DTaP-IPV /Act-Hib and Infanrix Hexa. Vaccination granulomas are known adverse reactions of most aluminium-containing vaccines.

Fatigue, headache, etc.

In the 14 non-serious ADR reports about HPV vaccines, the reported symptoms are fatigue, headache/migraine, dizziness and myalgia.

14 ADR reports about vaccine failure after pertussis vaccine

We received 14 ADR reports about vaccine failure and subsequent development of pertussis. Vaccine failure is known for the pertussis vaccine. All children had been fully vaccinated. Ten of them were 12 months old. 12 of them were fully vaccinated with DTaP-IPV/Act-Hib, whereas the remaining two had been vaccinated with DTaP-IPV/Act-Hib and either Hexaxim or Infanrix Hexa.

Conclusion

In the fourth quarter of 2016, the DKMA received a total of 187 reports of suspected adverse reactions to vaccines in the childhood immunisation programme. Most of them (64%) concerned granulomas where the vaccine had been given several years before. The same trend is seen for ADR reports about the HPV vaccine, the majority of which concern women who were vaccinated several years back.

We received fewer reports about granulomas, just as we recorded a fall in the number of ADR reports about HPV vaccines in this quarter. The fall in the number of ADR reports about HPV vaccines should be compared to the recent years' declining HPV vaccination participation rates in the childhood immunisation programme.

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In the fourth quarter of 2016, the DKMA received several ADR reports about vaccine failure and the development of pertussis, which could be related to the pertussis epidemic in 2016 and the generally high occurrence of the disease – the highest occurrence since 2002.

None of the new ADR reports shift the benefit-risk balance of the childhood vaccines.

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EU's list of recommendations on safety signals

As part of routine surveillance of medicines in the EU, the Pharmacovigilance Risk Assessment Committee (PRAC) assesses signals of possible adverse reactions every month to determine whether further measures are needed to improve medicines safety.

The list of signals leading the PRAC to recommend further measures is published on the website of the European Medicines Agency (EMA) every month.

The most important safety signals discussed at the PRAC meeting from 6-9 February 2017 concern the following products:

- **Fluconazole** – Spontaneous abortion and stillbirth
- **Nivolumab** – Pemphigoid

See EU's list of recommendations on safety signals: [PRAC recommendations on signals adopted 6-9 February 2017](#) as well as the [Danish translations of the product information](#)

ADR signals

An ADR signal is a new observation that raises suspicion of a potential association between a medicine and an adverse reaction or a new aspect of a known adverse reaction, e.g. that the adverse reaction is more common than described previously.

ADR signals can come from a multitude of sources, including ADR reports, clinical studies or scientific literature.

The DKMA uses Danish ADR reports to detect possible new ADR signals. Signals about new possible adverse reactions are forwarded in the EU system to the European Pharmacovigilance Risk Assessment Committee (PRAC). The PRAC assesses if there is sufficient documentation to establish causality and, for example, if changes to the medicine's product information are warranted.

Most recent Direct Healthcare Professional Communications (DHPCs)

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

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- **Alutard SQ, Aquagen SQ and Pharmedgen (subcutaneous allergy treatments):**
Supply difficulties for Alutard SQ, Aquagen SQ and Pharmedgen.
Sent out 27 February 2017.
- **DepoCyte (cytarabine):** Notice of expected supply failure – update.
Sent out 28 February 2017.
- **NULOJIX (belatacept):** Temporary limitation in the supply of NULOJIX and consequent restrictions for patients already treated with NULOJIX (from March 2017 to the end of 2017). Sent out March 2017.

The DHPCs are available at the DKMA website – most of them in Danish only:
[Direct Healthcare Professional Communication \(DHPC\) sent to healthcare professionals.](#)