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## Treatment of hepatitis C with direct-acting antivirals may result in hepatitis B re-activation

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The European Medicines Agency (EMA) has finalised a review of the safety of direct-acting antiviral medicines with the focus on hepatitis B re-activation in patients receiving treatment for hepatitis C.

The risk of hepatitis B re-activation, when hepatitis C is treated with direct-acting antivirals, is caused by the medicines' ability to rapidly reduce the hepatitis C virus, which is known to suppress the hepatitis B virus, and by the lack of activity of direct-acting antivirals against hepatitis B virus.

### **Due to the risk of hepatitis B re-activation in patients receiving treatment for hepatitis C, doctors should follow the recommendations below:**

- All patients should be screened for hepatitis B before starting treatment with direct-acting antivirals for hepatitis C.
- Patients co-infected with hepatitis B and C who are treated with direct-acting antivirals should be monitored and treated according to current clinical guidelines.

The recommendations from the EMA are available here: [Direct-acting antivirals for hepatitis C: EMA confirms recommendation to screen for hepatitis B.](#)

The following direct-acting antivirals have been authorised in the EU: Daklinza, Exviera, Harvoni, Olysio, Sovaldi, Viekirax, Epclusa and Zepatier.

The Danish Medicines Agency (DKMA) has a strong focus on the safety of antipsychotic medicines. As part of our monitoring activities, we and a group of researchers have looked closer at the risk of ketoacidosis in patients treated with antipsychotics. Diabetic ketoacidosis is a known adverse reaction described in the summaries of product characteristics (SmPCs) of several antipsychotics, including olanzapine, clozapine, aripiprazole and risperidone. The result of the review has been published in the *Journal of Psychopharmacology*<sup>1</sup>. Below, we summarise the conclusions of the article.

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## Antipsychotic medicines associated with diabetic ketoacidosis

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### Antipsychotics and development of diabetes

Schizophrenic patients have an increased risk of developing diabetes or experiencing worsening of pre-existing diabetes, which is likely due to a combination of unhealthy lifestyle behaviour, undertreatment of somatic disease and genetic susceptibility to diabetes (1). Antipsychotics are a heterogeneous drug class, which – in addition to being used to treat psychoses – are increasingly being used to treat affective disorders and anxiety disorders. In particular, this is because newer, more atypical antipsychotics have favourable routes of administration and broader therapeutic effect as they not only block dopaminergic receptors (2). However, there is a close association between antipsychotics and the development of diabetes. Especially products posing a high risk of weight gain and metabolic syndrome, such as the high-dose typical antipsychotics clozapine and olanzapine, are associated with reduced glucose tolerance compared to low-risk products, such as the low-dose typical antipsychotics aripiprazole and ziprasidone (3).

### Diabetic ketoacidosis and diabetes

Diabetes presents clinically differently in patients, and especially in psychiatric patients, diabetic ketoacidosis (DKA) may be the first symptom of diabetes onset. The incidence of DKA is 10 times higher in schizophrenic patients compared to the general population (4). DKA is an acute and potentially life-threatening metabolic complication primarily seen in type 1 diabetes (T1D). DKA is not seen that often in patients with type 2 diabetes (T2D), but the incidence of T2D is growing in Denmark and globally, and therefore DKA is increasingly seen in T2D patients. The growing incidence should be compared against the fact that the individual diabetic patient lives longer. DKA is often caused by lack of compliance during acute somatic illness and involves severe hypoglycaemia, metabolic acidosis, dehydration and electrolyte disturbances. Lack of treatment may lead to coma and death within hours (5).

### The underlying mechanism of antipsychotic-associated diabetic ketoacidosis related to type 2 diabetes

The underlying mechanism of antipsychotic-associated DKA is not entirely clear, but the adverse reaction is characterised by early onset (few months) after initiation of antipsychotic treatment and is not exclusively linked to weight gain and acute somatic illness. Furthermore, mortality in antipsychotic-associated DKA is 26.5%, which is markedly higher than the mortality in DKA in patients with T1D, which is lower than 1% (5, 6).

<sup>1</sup> Polcwiartek C et al., Diabetic ketoacidosis in patients exposed to antipsychotics: a systematic literature review and analysis of Danish adverse drug event reports. *Psychopharmacology (Berl)*. 2016 Oct; 233 (21-22):3663-367.

The aetiology of antipsychotic-associated DKA is often considered to be similar to that of T2D patients. Thus, patients first develop DKA, and after the acute phase, they develop regular T2D requiring lifestyle intervention such as physical activity and diet changes or oral antidiabetic treatment, ultimately co-administered with insulin treatment. There is an excess incidence of DKA among male patients over 30 years (7). Elevated long-term blood sugar levels (HbA1c) in the weeks leading to DKA onset, which is an indicator of long-term impact on glucose tolerance mediated by weight gain during antipsychotic treatment, is an important finding compatible with T2D pathophysiology (4). Weight gain as an important risk factor for DKA should therefore not be ignored as the risk related to olanzapine compared to risperidone is 1.7 times higher after more than 30 days' treatment and 3.5 times higher after more than 180 days' treatment (8). Also, weight gain after several months' exposure to olanzapine and risperidone, respectively, is approx. 5 and 2 kg and generally higher in patients not previously treated with antipsychotics (9).

### **The underlying mechanism of antipsychotic-associated diabetic ketoacidosis related to type 1 diabetes**

Aripiprazole, which to a lesser degree causes weight gain and impacts on glucose tolerance, is also associated with DKA, suggesting that the development of DKA could be caused by a more direct effect on the insulin-producing beta cells in pancreas. Several antipsychotics have proven to be immunologically active, and since T2D rarely causes DKA, a different aetiology is suspected. This study identifies 22 case reports in the literature and two ADR reports from the DKMA of antipsychotic-associated DKA with possible T1D aetiology in patients without known diabetes most of whom had schizophrenia. Altogether 37.5% developed confirmed T1D after onset of antipsychotic-associated DKA based on the authors' final diagnosis and T1D autoantibodies such as glutamic acid decarboxylase (GAD) and islet cell autoantibodies (ICA).

### **Conclusions**

Antipsychotic-associated DKA is a rare, severe adverse reaction that could be the first symptom of diabetes onset and could have a fatal outcome in itself. The cause is presumably multifactorial, and other medicines than antipsychotics are also associated with DKA among them glucocorticoids and sympathomimetics.

The article concludes that doctors should be aware of preventing, recognising and managing DKA in patients treated with antipsychotics:

- Psychiatric patients are generally more likely to ignore early diabetes symptoms as well as late diabetic complications and cardiovascular indicators, and close diabetic and psychiatric monitoring is therefore necessary.
- Treatment of DKA in the acute phase is the same regardless of aetiology in the form of rehydration and insulin treatment (DKA regime).
- All patients starting antipsychotic treatment should be given appropriate lifestyle advice, weighed regularly, and HbA1c should be measured at regular intervals (at least once a year).
- The indication for antipsychotic treatment should be reconsidered (and evaluated by a psychiatrist) in case of DKA, but the treatment should not necessarily be stopped in case of DKA.
- The aetiology of antipsychotic-associated DKA is determined in outpatient endocrinology settings (T1D, T2D or LADA) and should take into account the patient's lifestyle history and family predisposition (higher for T2D compared to T1D) and measurement of GAD-autoantibodies and fasting C-peptide.

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## Childhood vaccinations and reported suspected adverse reactions in Q3 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 Q3 2016. The review covers primary vaccines in the childhood immunisation programme as well as booster vaccines (re-vaccination).

### ADR reports related to vaccines in the childhood immunisation programme

Vaccine	Non-serious	Serious	Total
DT booster	3		3
DTaP-IPV Booster	5		5
DTaP-IPV Booster / DTaP-IPV/Act-Hib / Prevenar 13	3		3
DTaP-IPV Booster / MMR vaxpro	1		1
DTaP-IPV /Act-Hib	21	4	25
DTaP-IPV /Act-Hib / Hexyon / Prevenar 13	1		1
DTaP-IPV /Act-Hib / Infanrix Hexa	1		1
DTaP-IPV /Act-Hib / Infanrix Hexa / Prevenar 13	15		15

DTaP-IPV /Act-Hib / Infanrix Hexa / MMR Vaxpro / Prevenar 13	1		1
DTaP-IPV /Act-Hib / MMR Vaxpro / Prevenar 13	7		7
DTaP-IPV /Act-Hib / Pneumococcus	1		1
DTaP-IPV /Act-Hib / Pneumovax / Prevenar 13	1		1
DTaP-IPV /Act-Hib / Prevenar 13	129	1	130
DTaP-IPV /Act-Hib / Prevenar 13 / Priorix	5		5
DTaP-IPV /Act-Hib / Streptococcus Pneumoniae	3		3
Hexaxim / Hexyon / Prevenar 13	1		1
Hexaxim / Prevenar 13	1		1
Hexyon	0	1	1
Hexyon / Prevenar 13	1	1	2
Infanrix Hexa	5		5
Infanrix Hexa / MMR Vaxpro / Prevenar 13	2		2
Infanrix Hexa / Prevenar 13	15		15
MMR	1		1
MMR Vaxpro	3	2	5
Pentavac	1		1
Pneumovax	2		2
Prevenar 13	1	1	2
Priorix	1		1
Gardasil	22	38	60
Cervarix	3	1	4
<b>Total</b>	<b>256</b>	<b>49</b>	<b>305</b>

Table 1. Number of ADR reports by individual vaccines in the third quarter of 2016.

### 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.

## Summary of the Q3 ADR reports

In this quarter, we note the following:

- The DKMA received the same number of reports as in the second quarter of 2016 (305/306). The number of serious ADR reports fell from 94 to 49, driven especially by a drop in the number of ADR reports received about the HPV vaccine (from 78 to 39). For the other vaccines, the number of serious ADR reports received fell slightly as 10 were submitted this quarter against 16 in the last quarter.
- This quarter recorded a rise in the number of reported vaccination granulomas as 206 ADR reports involve granulomas. It is known that granulomas may develop as an adverse reaction to aluminium-containing vaccines. Most of the ADR reports describing granulomas as a suspected adverse reaction concern children who were vaccinated several years ago.
- Granulomas were frequently reported together with aluminium allergy and local reactions such as itching, ulceration and increased hair growth at the location of the granuloma.
- Two cases of vaccine failure and subsequent pertussis were reported. The vaccine does not offer full protection against the disease, but most often it protects against the development of a severe case of infection.



- In addition, there were two cases of febrile seizure occurring after respectively Hexyon and DTaP-IPV /Act-Hib vaccines. This too is a known adverse reaction.
- A 70-year-old woman developed pneumonia three years after vaccination with Prevenar13. This is probably not an indicator of vaccine failure, but rather an indicator of an infection with another pneumococcal strain or other bacteria than those the vaccine protects against.
- Two children, one of whom also had asthmatic bronchitis, were hospitalised with rash after vaccination with MMR Vaxpro. While rash is a known adverse reaction, asthmatic bronchitis is not. Since asthmatic bronchitis is a common disorder in small children and not a known adverse reaction to the vaccine, an association with the vaccine is considered less likely, despite the temporal relationship. The other child developed infantile spasms weeks after receiving DTaP-IPV /Act-Hib. There are no published epidemiological data in support of such association, and since the symptoms occurred at an age when onset of the disease is most likely to occur, an association with the vaccine is considered less likely.
- The two new vaccines in the Danish programme, Hexaxim and Hexyon, still only receive few ADR reports.
- Most of the ADR reports submitted about HPV vaccines describe cases where the vaccines were given several years ago.
- As in our previous reviews, the ADR reports about the HPV vaccine are split evenly on girls over 18 years and under 18 years at the time of vaccination (30 over, 29 under, 2 age unknown).
- For about half of the ADR reports about the HPV vaccine classified as serious, it is assessed that an association with the vaccine is less likely – either because there is no temporal association or because there is another more likely explanation of the symptoms.
- The vast majority of the remaining HPV vaccine ADR reports are unclassifiable since they lack information about a temporal association or examinations performed. Four reports are assessed to lack the documentation needed to assess a possible link to the HPV vaccine. These four reports describe symptoms having occurred in temporal association with the vaccine, but either there is no diagnosis or the diagnosis described has not been linked to the vaccine in the literature.
- The HPV vaccine ADR reports include one case of fibromyalgia, one case of myalgic encephalopathy (chronic fatigue syndrome), one case of POTS and one case of IgA nephritis. No association with the vaccine is considered likely in any of these reports. The causality assessment about the patient with fibromyalgia is classified as unclassifiable due to lack of information in the ADR report. For the remaining ADR reports, there is nothing in the scientific literature describing an association.
- In the 25 non-serious ADR reports about HPV vaccines, the most frequently reported symptoms are fatigue, headache/migraine, dizziness and myalgia – all known from the product information.

## Conclusion

In the third quarter of 2016, the DKMA received a total of 305 reports of suspected adverse reactions to vaccines in the childhood immunisation programme. Most of the ADR reports describe granulomas to aluminium-containing vaccines in cases where the vaccines were given and the granulomas developed several years ago. The ADR reports related to the HPV vaccine also describe cases in which the vaccines were given and the adverse reactions developed several years ago.

This period recorded a drop in the number of ADR reports about suspected adverse reactions to the HPV vaccine and an increase in ADR reports about granulomas after vaccination with the other aluminium-containing vaccines included in the childhood immunisation programme.

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

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## Interactive Adverse Drug Reaction overviews

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Interactive Adverse Drug Reaction (ADR) overviews are a new web-based tool that offers researchers and anyone interested better possibilities of searching for reported suspected adverse reactions.

For several years, the DKMA has facilitated access to data on reported adverse reactions in the form of PDF documents, but now we have launched an interactive version that makes it possible to filter by age, year, gender, severity, etc. It is also possible to filter by reporter, e.g. by healthcare professional or patients or their representatives.

### **Adverse Drug Reaction overviews cannot be used to draw conclusions about drug safety**

Reports about suspected adverse reactions constitute an important information source helping to identify possible medicine safety issues. At the DKMA, we use the reports about suspected adverse reactions as part of our basis to continually assess and analyse the safety of medicines on the market.

However, it is important to keep in mind that no final conclusions can be made about the safety of medicines based on ADR reports alone. The evidence-based knowledge about the adverse reactions of a medicine is described in the package leaflet and the summary of product characteristics.

The new web-based tool is accessible from the DKMA website via the page [Interactive Adverse Drug Reaction overviews](#).

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## Correction to the article "Allopurinol and serious adverse reactions" in Danish Pharmacovigilance Update, August 2016

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In the article "Allopurinol and serious adverse reactions", we reported, among other things, that doctors should be aware of the following:

- Allopurinol is contraindicated in patients with severe renal impairment with creatinine clearance < 0.33 ml/s (20 ml/min).

This contraindication is only described for Allopurinol DAK and not for the entire drug class. Work is currently ongoing to harmonise the SmPCs so that this contraindication will also be removed from the SmPC of Allopurinol DAK and thus no longer applies to allopurinol-containing medicines.

Precautions for patients with renal impairment are, however, described under dosing recommendations in section 4.2 of the SmPCs of the different allopurinol-products.

## 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 24-27 October 2016 concern the following products:

- **Cobicistat-containing medicines** – drug interaction with corticosteroids leading to adrenal suppression
- **Flucloxacillin** – acute generalized exanthematous pustulosis
- **Olanzapine** – restless legs syndrome

See EU's list of recommendations on safety signals: [PRAC recommendations on signals adopted 24-27 October 2016](#) as well as the [Danish translations of the product information](#).

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