LÆGEMIDDELSTYRELSEN
DANISH MEDICINES AGENCY

MARCH 2016

Annual pharmacovigilance report 2015

Danish Medicines Agency
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Keywords
Adverse reaction reports, monitoring.

Language
English

Version
1.0

Version date
March 2016

Published by
The Danish Medicines Agency, 31/03/2016.

ISBN Electronic
ISBN: 978-87-92390-04-2

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1 Preface – openness and dialogue about adverse reactions

The HPV vaccine in focus

Openness and dialogue are keywords in the Danish Medicines Agency's work with adverse reactions. In 2015, this was to become particularly important. Since 2009, almost 2000 girls and young women had reported suspected adverse reactions to the Gardasil® HPV vaccine, and patient organisations and the media wanted us to join the debate.

Several interviews were given in radio, TV and the written press. We have sent out newsletters and established dedicated information spots on our website. We have participated with presentations in patient organisations and expert forums. The Danish Pharmacovigilance Council hosted a dialogue conference with all stakeholders – patients, researchers, physicians and authorities – at which many perspectives were discussed and the complex problem was addressed. It was the first time that all stakeholders met, and it was very fruitful for the work that lay ahead.

Adverse reactions to vaccines are among our focus areas. And this is why, we address the topic every quarter with specific articles in Danish Pharmacovigilance Update. We mention all reported suspected adverse reactions and give our assessment of whether or not there is a link between the vaccine and the reported serious suspected adverse reactions. We firmly believe that openness and factual information can help build a high degree of trust in the vaccines.

Information about biosimilar medicines

Biological medicines have been a step change in the treatment of arthritis and other diseases. But as these medicines are being copied – biosimilar medicines – a need has emerged to take a united approach with patient organisations to prepare information material, e.g. about switches between the original products and their copies. Information and openness about the scientific challenges combined with openness about reported suspected adverse reactions also contribute to building trust in medicines and pharmacovigilance activities.

Openness and dialogue are worth the effort

The occurrence of adverse reactions – especially venous blood clots – to contraceptive pills is a problem which through the years has kept the media and scientific environments busy. In the last few years, we have presented our case for reducing the use of 3rd and 4th generation contraceptive pills in favour of the older 2nd generation pills. At the close of 2015, we had achieved large reductions in the use of 3rd and 4th generation contraceptive pills, and it shows that dialogue and information coupled with an unwavering focus can yield results that are the envy of many countries.

Dialogue and openness will still be our guiding keywords. Sometimes it is easy, sometimes difficult – but whenever dialogue is difficult, there is good reason to start communicating and insist that dialogue promotes understanding, and that it may help improve pharmaceutical safety in Denmark even more.

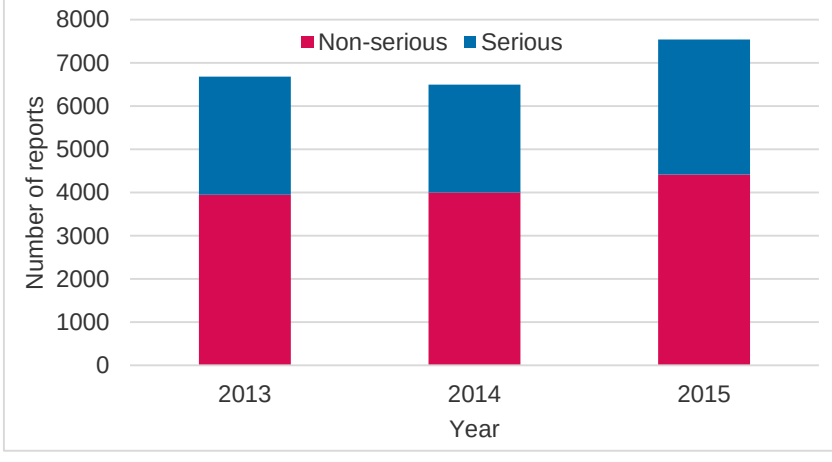
2 ADR reports from 2013-2015

In 2015, the Danish Medicines Agency (DKMA) received altogether 7538[1] adverse drug reaction (ADR) reports, which is 16 per cent more than in 2014 (figure 1).

41 per cent of the total number of ADR reports were classified as serious[2]. The percentage breakdown between serious and non-serious ADR reports was largely the same as the two preceding years.

FIGURE 1

DEVELOPMENT IN THE NUMBER OF ADR REPORTS SUBMITTED TO THE DKMA FROM 2013-2015 BY SEVERITY

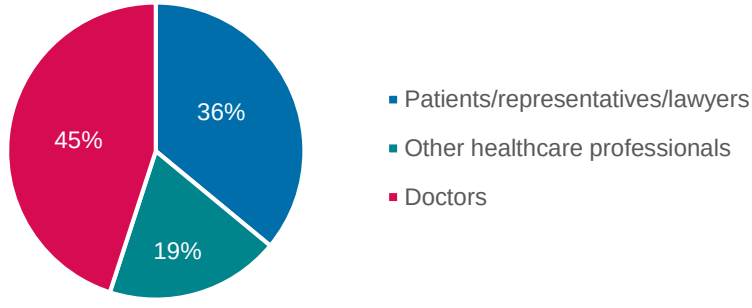


Number of ADR reports in 2015	
Number of ADR reports (including duplicates):	7,538
Number of ADR reports (excluding duplicates):	6,877
Serious ADR reports:	3,120 (41%)
Non-serious ADR reports:	4,418 (59%)

[1] The 7538 ADR reports also include reports submitted to the DKMA more than once, so-called duplicates. Duplicates may occur when, for example, both the doctor and the patient report the adverse reaction. 661 of the ADR reports were duplicates.

[2] An ADR 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.

FIGURE 2
ADR REPORTS BY REPORTER TYPE IN 2015



Still many ADR reports from medicine users or their representatives
As in 2013 and 2014, ADR reports from medicine users and their representatives in 2015 accounted for more than one third of the total number of submitted ADR reports. 36 per cent of the ADR reports received in 2015 were submitted by medicine users or their representatives. The share of ADR reports from medicine users also reached 36 per cent in 2013; In 2014, it was 28 per cent.

ADR reports from doctors still account for the largest share of the total number of ADR reports, which is no surprise since doctors are bound by the Danish Medicines Act to report certain types of adverse reactions.

In 2015, ADR reports from doctors accounted for 45 per cent of all ADR reports, which corresponds to the last years' figures. Unlike doctors, health professionals are not obliged to report suspected adverse reactions, but just as medicine users and their representatives, they can report it if they suspect an adverse reaction has occurred. In 2015, 19 per cent of the total number of ADR reports were submitted by health professionals – including pharmacists, midwives and nurses.

The increase in number of ADR reports in 2015 breaks down evenly on serious and non-serious ADR reports and on the type of reporter.

Small increase in reports from general practitioners
2015 saw a small increase in the number of ADR reports from doctors compared to 2014, which was at an all time low. We especially saw a small increase in the number of ADR reports from general practitioners who in 2015 accounted for 11 per cent of the total number of ADR reports, whereas in 2014 they only accounted for 8 per cent of the total number of ADR reports.

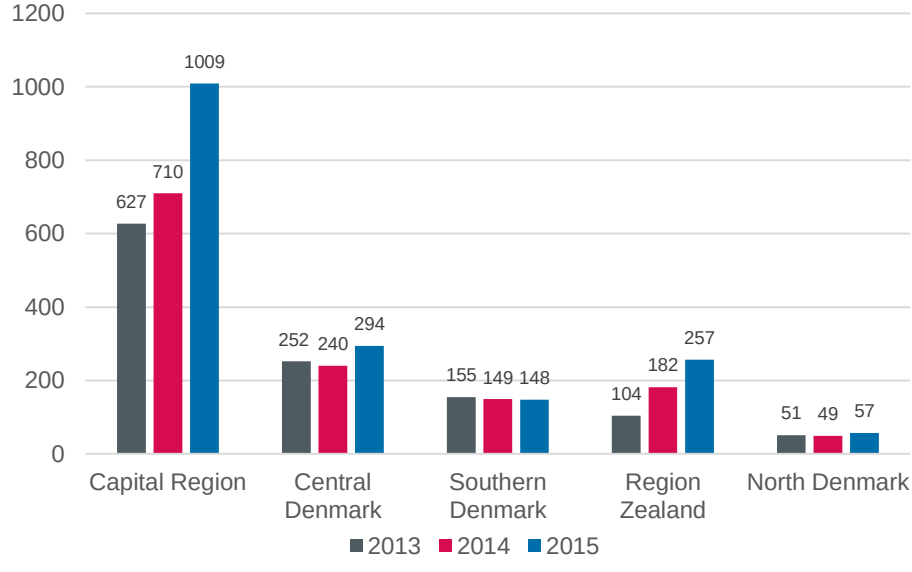
The increase in the number of reports from general practitioners could be the result of a campaign targeting general practitioners and other healthcare professionals launched by the DKMA in 2015. The campaign’s objective was to increase awareness on reporting suspected adverse reactions to the DKMA.

3 ADR reports from Danish hospitals in 2015 by region

In 2015, the DKMA received altogether 1767 ADR reports from hospitals across Denmark[3]. The distribution of ADR reports between the individual regions is shown in figure 3. We received two ADR reports from a hospital on the Faroe Islands – it is not counted in the figure.

Increase in the number of reports from hospitals
The total number of ADR reports from hospitals was higher in 2015 compared to the two preceding years.

FIGURE 3
ADR REORTS FROM DANISH HOSPITALS IN 2013, 2014 AND 2015 BY REGION



Two reports were received from two different regions and are therefore included in both regions. Adjustments have not been made for the population size of the respective five regions.

Large increase in ADR reports from regions using ADR managers
The Capital Region of Denmark and Region Zealand accounted for the largest share of ADR reports in 2015.

The reports from the Capital Region of Denmark accounted for more than half of all ADR reports from hospitals in 2015. For the first time ever, the Capital Region of Denmark submitted more than 1000 ADR reports, 42 per cent more than in 2014.

[3] Only reports received directly from the hospitals are included in this report.

We received 250 ADR reports from Region Zealand, corresponding to an increase of 41 per cent compared to the year before. We also received more ADR reports from the Central Denmark Region in 2015 – 22 per cent more than in 2014.

In 2015, the number of ADR reports from the Region of Southern Denmark and the North Denmark Region more or less levelled the two previous years.

A clear trend has developed over the past few years: The regions with an ADR manager role report many more adverse reactions than the regions with no ADR manager role. The ADR manager, who assists doctors with reporting adverse reactions, has existed since 2013 in the Capital Region of Denmark and since 2014 in Region Zealand.

Easier and faster reporting with an ADR manager
An ADR manager makes it considerably easier and faster for hospital doctors to report suspected adverse reactions. The doctor only has to state the patient's name and civil registration number, the suspected drug, dose and adverse reaction, and the ADR manager then submits the ADR report to the DKMA.

The ADR reports received by the DKMA from ADR managers are far more detailed and complete, which reduces the need for follow-up questions compared to the other ADR reports. ADR managers are experts in filling out the ADR reporting form and ensure that the relevant and important details are submitted to us.

4 Completion of pharmacovigilance action plan III

In 2015, we completed Pharmacovigilance action plan III (Action plan for strengthened pharmacovigilance 2014-2015), which was launched by the Danish Ministry of Health in April 2014. The objective of the action plan was to reinforce the monitoring of adverse reactions, thus improving the patients' safety when using medicines. The action plan had two overall objectives:

1. More and better ADR reports.
2. Optimisation of the concrete pharmacovigilance activities – nationally and internationally.

Main results from Action plan III

Campaign for better and more ADR reports
The number of ADR reports from doctors has been decreasing. We have learned from our experience with the past years' campaigns targeting health professionals – including especially doctors – that a line of barriers make doctors less incited to report adverse reactions to the DKMA despite their obligation. The challenge is basically about facilitating a needed cultural change.

We therefore chose to focus our efforts on reinforcing a culture that would make ADR reporting a natural element in patient care. As part of their specialty training, doctors therefore

now receive mandatory ADR training, which means that tomorrow's doctors will have ADR reporting integrated in their daily routines. In collaboration with the teachers at medical schools, we have also reinforced training in adverse reactions for medical students.

Efforts to improve the quality of ADR reports
The action plan focused heavily on raising the quality of ADR reports to exploit their full potential of contributing to the analysis of adverse reaction issues.

In 2014, the Danish Medicines Agency formed the Quality Forum for Adverse Reactions, which contributes to the work with improving the quality of ADR reports. The Quality Forum has representatives from the Danish Medical Association, the pharmaceutical industry, Danish Regions, the DKMA and the regional ADR managers.

Part of its work was to establish a focused and relevant process for the collection of follow-up information to ADR reports, which led to a set of criteria to ensure a relevant and risk-based follow-up procedure.

Increased involvement in the European collaboration
European pharmacovigilance collaboration is high on the DKMA's agenda. In October 2015, the DKMA entered pharmacoepidemiology experts to the Scientific Advisory Working Party (SAWP), a sub-committee of the Committee for Medicinal Products for Human Use (CHMP) with the objective of giving scientific advice to the pharmaceutical industry. This membership strengthens the DKMA's collaboration with the European Medicines Agency (EMA) and engagement in the international pharmaceutical activities.

5 Focus areas 2015

5.1 The HPV vaccines

In 2015, the DKMA put increased awareness on the safety monitoring of HPV vaccines, which, since 2009, have been offered to girls in the Danish childhood immunisation programme to protect against cervical cancer.

Reports of suspected adverse reactions in 2015
In 2015, we received a total of 822 ADR reports of suspected adverse reactions to HPV vaccines. 475 of them were classified as serious. The reports of suspected adverse reactions to HPV vaccines have been continuously reviewed and described every quarter in our newsletter *Danish Pharmacovigilance Update*. The number of ADR reports received in 2015 was significantly higher than the year before, most likely as a result of the massive public awareness on the vaccines. Our review of ADR reports showed that we received most reports with adverse reaction onset in 2013, followed by 2012 and 2009 corresponding to the years with the highest vaccine dose sales.

New and thorough review of the vaccine's safety
In response to the increasing numbers of ADR reports of long-term reactions, including POTS (postural orthostatic tachycardia syndrome), the DKMA conducted a new review in 2015 of all 363 serious reports of suspected adverse reactions to the HPV vaccine received up until March 2015. Our review showed that 34-43 per cent of the ADR reports described a complex of symptoms with headache, pain, fatigue and circulatory and neurological symptoms. In certain cases, the diagnosis of POTS was made. This complex of symptoms is seen in various conditions and shares similarities with for example chronic fatigue syndrome. Our review also included a comparison of data from other countries prepared by the WHO's collaborating centre, Uppsala Monitoring Centre. The comparison showed that the reported suspected adverse reactions in Denmark were comparable to the reported adverse reactions in other countries. While the review concluded that an association between the reported adverse reactions and the HPV vaccine could not be clarified based on the reported data, it also noted that it was important to investigate the issue in more detail. The report was submitted to the EMA and the members of the Pharmacovigilance Risk Assessment Committee (PRAC) in the beginning of September 2015.

In July 2015, the EMA initiated an additional investigation of HPV vaccines and their risk profile. The investigation, which focused especially on POTS and CRPS (complex regional pain syndrome), was initiated in response to a Danish request to the European Commission. The investigation was based on a thorough review of published research articles, clinical trial data from the companies and reports of suspected adverse reactions submitted by patients and doctors as well as further data delivered by the Member States, including the report from Denmark. The EMA further consulted a group of leading experts in the field of vaccines, POTS and CRPS and took into account information received from a number of patient groups. The final report from the investigation was published in November 2015. Overall, the EMA concluded that the available evidence did not support that CRPS and POTS are caused by HPV vaccines.

Dialogue and openness in our work with adverse reactions
The DKMA has in several connections made efforts to ensure dialogue and knowledge sharing in the area of HPV vaccine safety.

In August 2015, the Danish Pharmacovigilance Council hosted a dialogue conference titled "Greater knowledge about the HPV vaccine". The Danish Pharmacovigilance Council is an external council that offers general advice to the DKMA on adverse reactions and other pharmaceutical risks. The conference was joined by a number of professionals representing different specialties from all five regions in Denmark and also welcomed participants from the Organization of General Practitioners, the Danish Cancer Society, the DKMA, the relatives' group known as HPV Update, and others.

Experience sharing with other countries on suspected adverse reactions to the HPV vaccine
In 2015, the DKMA visited both the Japanese and the Norwegian authorities to exchange experience on reports of suspected adverse reactions in HPV vaccination.

Regional HPV centres
The DKMA also provided knowledge about HPV vaccine safety monitoring to facilitate the regions' efforts to establish "one access" for patients suspected of having adverse reactions to the HPV vaccine.

The safety of the HPV vaccines will still be observed closely, both through participation in the European collaboration and through the evaluation of Danish ADR reports in the DKMA.

5.2 New action plan on biological medicines and biosimilars

Biological medicines also entered the agenda in 2015.

Biological medicines are advancing – new biological medicines are continually being developed with new or improved treatment possibilities, specifically in the areas of hormone treatment, cancer, diabetes and arthritis. It is also expected that more biosimilars will be developed as patents for biological medicines expire in the coming years.

The safety of these medicines therefore became a special pharmacovigilance focus area in 2015, which will continue until the end of 2016.

Information to health professionals and patients
In the autumn of 2015, we sent out invitations to a dialogue conference, which was joined by selected organisations. One of the objectives was to promote dialogue and experience sharing on the use of biological medicines and biosimilars and to uncover the need for information.

To meet the need for information, the DKMA prepared a list of frequently asked questions specific to treatment with biosimilar medicines in the autumn of 2015: *Frequently asked questions about biological medicines and biosimilars*. We subsequently prepared information material for health professionals and continued discussions with the patient organisations in regard to the preparation of patient information.

The information material will be launched in the spring of 2016.

Read more about the action plan on or website: *Action plan on biological medicines, biosimilars and vaccines for 2015-2016 (in Danish only)*.

5.3 Campaign: Make medicine safer – report adverse reactions

In the past few years, the number of ADR reports from general practitioners has declined, despite the fact that these doctors prescribe relatively many medicines for a variety of indications. We therefore launched a campaign in October 2015 with the purpose of raising doctors' awareness on reporting adverse reactions to the DKMA, with the dual purpose of showing them that ADR reporting does make a difference.

The focus was primarily to tell a success story of the work with pharmacovigilance through which to show that reporting does matter. The overall message was that reporting is taking responsibility for patient safety.

Focus on shaping the doctors of tomorrow
We have learned from our experience from the past years' campaigns targeting health professionals – including especially doctors – that a number of barriers mean that doctors do not always get around to reporting adverse reactions to the DKMA despite their obligation. Some of these barriers have to do with lack of time, unfamiliarity with the rules and a need to know what the benefits of reporting are. But a number of myths have also developed among the doctors that ADR reporting is burdensome and far too time-consuming. The challenge therefore mostly concerned the need for a cultural change.

Instead of trying to change the reporting culture among general practitioners, we chose to focus our efforts on upcoming doctors – medical students. We wanted to influence them early in their training course to create a sound reporting culture by teaching them that ADR reporting is a natural element in patient care, so that the future doctors will have ADR reporting integrated in their daily routines.

In order to achieve the greatest effects, we chose a three-tier approach:

1. **General practitioners**

   The efforts aimed at general practitioners ended up being a smaller part of the entire project. We prepared a leaflet and an information card on how to report adverse reactions for the GP's consulting room. In addition, we wrote articles, which were brought in media already used by the target groups.

   The number of ADR reports from general practitioners in 2015 grew slightly compared to the two preceding years, probably on account of the campaign.

2. **Doctors in post-graduate speciality training**

   We entered into a collaboration with the Danish Health Authority's Education & Registration Division, which arranges mandatory courses for post-graduate medical students – courses in organisation and management of health services known as SOL courses (Sundhedsvæsenets Organisation og Ledelse). Since June 2015, the DKMA has been giving lessons in pharmaceutical safety on these courses on a permanent basis. The courses are held twice a month and co-hosted by a staff member from the DKMA's Pharmacovigilance Division and a regional ADR manager/clinical pharmacologist.

   The DKMA's presentation on pharmaceutical safety has been received well by the participants and scores highly in evaluations after each course session.

3. **Medical students**

   The medical students were those we focused on the most as the objective was to prepare the grounds for good collaboration with upcoming doctors.

   In order to strengthen the training in ADR reporting, we developed training material to be used by the teachers in pharmacology at all four universities offering medical education in Denmark. The training material includes the rules governing the reporting requirements of adverse reactions, cases and exercises.

   Once ready, the material was tested in lessons at the University of Copenhagen with the DKMA present. The material was subsequently distributed directly to contact persons at all four universities.

   All universities were contacted prior to preparing the material to collect knowledge about the needs. All four universities declared that educational material in PowerPoint from the DKMA would have the capacity to strengthen their training.

   We also inserted adverts in various professional magazines read by the medical students and on social media platforms. We produced a short film, which explains the rules and ADR reporting in general. The film was, among other things, used as part of a contest in which the medical students could win a voucher for a local medical book store. The purpose of the contest was to encourage the medical students to learn the rules of ADR reporting.

   The contest was a great success, and there was also considerable traffic to pages with our adverts.

5.4 New guideline for pharmaceutical companies

In June 2015, the DKMA published a new guideline for pharmaceutical companies on the electronic exchange of ADR reports between companies and authorities.

The guideline makes a number of recommendations and gives examples of good practice as well as technical and regulatory requirements.

The purpose of the guideline is to ensure good collaboration between the industry and the DKMA and thus continuous high quality and harmonisation of the electronic ADR reports from pharmaceutical companies.

In order to ensure the best possible implementation of the guideline, we presented it at two well-attended after-work sessions for the industry with subsequent dialogue.

Both the guideline and the after-work sessions were received positively and contributed to constructive collaboration.

5.5 Reported suspected adverse reactions and reported adverse events associated with using labour-stimulating medicines for induction of labour (2nd analysis)

Together with the Danish Patient Safety Authority, the DKMA prepared the second cross-cutting analysis of reported suspected adverse reactions and reported adverse events associated with using labour-stimulating medicines for induction of labour: dinoprostone, misoprostol and oxytocin. The analysis investigated ADR reports and reported adverse events from 2014. The second cross-cutting analysis followed up on the first analysis of reported suspected adverse reactions and reported adverse events from 2013.

Results of second cross-cutting analysis
In 2014, the DKMA received reports of suspected adverse reactions after altogether 28 birth processes, which was at the same level as the year before when we received 30 ADR reports about birth processes.

Sixty per cent of the ADR reports were submitted by midwives in 2014, three times as many as in 2013. Most likely it is because midwives in April 2014 were subjected to the same obligation to report adverse reactions on a par with doctors.

Primarily known adverse reactions were reported
The majority of the ADR reports received by the DKMA in 2014 involved known adverse reactions to the medicines such as hyperstimulation, hypertonic uterus/tetanic labour and fast delivery. One fourth of the ADR reports described complications affecting the mother or the child.

Several adverse events were reported
Sixty adverse events were reported in 2014, which was almost twice as many as the year before when 37 events were reported. The increase does not necessarily reflect that more errors occur; It could reflect an improved patient safety culture and increased awareness in this area.

Most of the adverse events reported in 2014 involved induction of labour in women who had previously delivered by caesarean section, induction of labour in twin deliveries using misoprostol instead of dinoprostone as well as events related to the dose/administration of

oxytocin. The vast majority of events had no complications for the mother or the child. One of the reported events had serious consequences for a woman who, after labour was induced, developed frequent contractions affecting the foetus and ending in a caesarean section.

Overall conclusion on the analysis
Based on these data, the DKMA and the Danish Patient Safety Authority still assess that the benefits of using medicines for induction of labour outweigh the possible risks.

The DKMA and the Danish Patient Safety Authority will maintain focus on any problems associated with using medicines for induction of labour, and we will provide information thereon in the DKMA's electronic newsletter Danish Pharmacovigilance Update and on the website of the Danish Patient Safety Authority.

Read the analysis here: *Use of labour-stimulating medicines for induction of labour (in Danish only)*.

5.6 Reports of deaths suspected as adverse reactions to 2nd generation antipsychotic medicines

In the spring of 2015, the DKMA published its first article in a series of five articles in our newsletter Danish Pharmacovigilance Update, putting focus on antipsychotic drugs. We reviewed all deaths reported as suspected adverse drug reactions to the use of 2nd generation antipsychotics.

Publication dates of the five articles brought in Danish Pharmacovigilance Update

Danish Pharmacovigilance Update	Article heading
March 2015	Quetiapine and reports of deaths
April 2015	Clozapine and reports of deaths
May 2015	Olanzapine and ADR reports of deaths
June 2015	Aripiprazole, amisulpride, risperidone and ADR reports of deaths
August 2015	Sertindole, ziprasidone, asenapine and paliperidone and ADR reports of deaths

General analysis conclusions
A large share of the ADR reports described patients younger than 40 years who died suddenly while being treated with 2nd generation antipsychotics. More than 30 per cent of the patients who died in connection with the treatment were treated concomitantly with one or several other antipsychotic medicines. Some patients were also being treated with benzodiazepines at the same time. Antipsychotic polypharmacy is inconsistent with the Danish Health and Medicines Authority's current guideline on antipsychotic treatment in people over 18 years with psychotic disorders (Danish guideline title: *"Behandling med antipsykotiske lægemidler til personer over 18 år med psykotiske lidelser nr.9276 af 6. maj 2014"*).

Polypharmacy using several different antipsychotics is a known problem, which was also addressed in the *Danish Health and Medicines Authority's Danish report about medical treatment of adults diagnosed with schizophrenia of 8 October 2014 (Danish title: Medicinsk*

behandling af voksne diagnosticeret med skizofreni). The report was prepared based on a thorough investigation, which showed that many patients were treated with more than one antipsychotic medicine. The scientific evidence on antipsychotic polypharmacy is limited, and for most combinations, polypharmacy does not provide improved effects compared to monopharmacy. Antipsychotic polypharmacy may be associated with an increased risk of adverse reactions.

After the fifth and final article was published in Danish Pharmacovigilance Update in August 2015, all articles were forwarded to the Danish Patient Safety Authority (then the Danish Health and Medicines Authority), which has the supervisory responsibility.

6 ADR signals 2015

Every week, the DKMA monitors ADR reports to detect possible new ADR signals and other problems specific to adverse reactions and inappropriate use.

An ADR signal reflects a new possible causal relationship between an adverse reaction and a certain type of medicine or a new angle on an already known causality. Signals can originate from ADR reports and a variety of other sources, e.g. monitoring programmes, scientific literature, different types of studies, drug regulatory authorities in other countries, the media or from citizens and healthcare professionals.

Signals about new (not already known) types of adverse reactions are forwarded in the EU system to the Pharmacovigilance Risk Assessment Committee (PRAC) or the EU member state with overall responsibility for authorisation and monitoring of the medicine. Table 1 describes the Danish ADR signals that the DKMA worked with and forwarded in the EU system in 2015.

TABLE 1
LIST OF DANISH ADR SIGNALS FORWARDED BY THE DKMA IN THE EU SYSTEM IN 2015.

Medicine	Signal	Source	Status and informative action
Clozapine	Myocarditis (inflammation of the heart muscle)	Literature	Signal closed. Sent to PRAC in July 2015. Article in Danish Pharmacovigilance Update, August 2015.
HPV vaccine*	Long-term adverse reactions, e.g. POTS, headache, fatigue and neurological symptoms.	ADR reports	New signal evaluation closed, and report sent to EMA. Referral requested by the PRAC in July 2015.
Kinin	Increased risk of deaths in patients with heart failure.	Danish study	Signal closed. Sent to PRAC in October 2015.
Methylphenidate "Sandoz"	Substitution problems and lack of efficacy	ADR reports	Signal closed. Signal was sent to EU signal responsible, but was not confirmed (signal closed). Article in Danish Pharmacovigilance Update, May 2015.
Olanzapine	Myocarditis (inflammation of the heart muscle)	ADR reports	Signal is being assessed. Scientific article prepared, but not yet published.

*See section about adverse reactions in HPV vaccination

The DKMA also pays attention to appropriate use of medicine in clinical practice, and we use ADR reports, and other information, to identify inappropriate use of medicine that could be harmful to patients. For example, we check if a certain type of medicine is prescribed to the right patients, and whether any of its established precautions for use are not complied with exposing patients to discomfort and adverse reactions. ADR reports are often suited to identify problems of this nature, and together with the valuable Danish health registers, we are in a good position to evaluate them and assess the extent of the problem. Table 2 describes the other problems related to adverse reactions and inappropriate pharmaceutical use that the DKMA focused highly on in 2015.

TABLE 2

LIST OF OTHER PROBLEMS RELATED TO ADVERSE REACTIONS AND INAPPROPRIATE PHARMACEUTICAL USE THAT THE DKMA FOCUSED ON IN 2015.

Medicine	Safety issue	Source	Status and informative action
2nd generation antipsychotics	Focus on antipsychotic medicines and review of all reports of deaths.	ADR reports	Five articles in Danish Pharmacovigilance Update, March, April, May, June, August 2015.
Acetylsalicylic acid and inappropriate use	Many reports of severe bleeding.	ADR reports and approaches	Project to analyse problems started in collaboration with Aalborg University.
ADHD drugs	Reports of death and cardiovascular adverse reactions.	ADR reports	Review of all reports of cardiovascular adverse reactions. Article in Danish Pharmacovigilance Update, January 2016.
Desmopressin	Hyponatraemia in desmopressin users over 65 years.	ADR reports	Consumption analysis conducted and brought in Danish Pharmacovigilance Update, August 2015.
Miconazole and warfarin	Bleeding caused by interaction between warfarin and miconazole.	ADR reports and reports of adverse events	Articles on the website and in Danish Pharmacovigilance Update, October 2015. Article in Danish Pharmacovigilance Update, February 2016.
New oral anticoagulants	Risk of major bleeding in treatment with the new oral anticoagulants in elderly patients with renal impairment.	ADR reports and reports of adverse events	Article in Danish Pharmacovigilance Update, February 2015. Bulletin from the Danish Patient Safety Authority, August 2015.
Prescription-only cough suppressants	Concomitant use of prescription-only asthma medicine in asthma and COPD patients, despite concomitant treatment being advised against.	Approaches	Consumption analysis conducted and brought in Danish Pharmacovigilance Update, September 2015.
Warfarin 'Orion'	ADR reports of INR changes after substitution	ADR reports	The product has changed substitution group so that it no longer can be substituted for Marevan. Article on the website and in Danish Pharmacovigilance Update, April 2015.

7 International collaboration

7.1 International pharmacovigilance collaboration

The European Pharmacovigilance Risk Assessment Committee (PRAC) meets every month in the European Medicines Agency (EMA) in London. Every EU Member State has one member and one alternate in the committee. The PRAC also has six experts within pharmacoepidemiology, vaccines and communication as well as representatives of health professionals and patient organisations. The PRAC assesses the safety of all marketed medicines based on all available data, e.g. ADR reports and results of pharmacoepidemiological studies.

The DKMA is an active player in this international collaboration in which we also spearhead the safety reviews of a line of medicinal products.

We regularly communicate the results of the PRAC reviews in our monthly newsletter *Danish Pharmacovigilance Update* (issued in Danish and English) and as needed via direct communication to doctors and relevant organisations.

The cases reviewed by the PRAC in 2015 included:

- Ambroxol and bromhexine for treatment of mucus in the airways and risk of allergic reactions
- Codeine for the treatment of cough and the risk of breathing difficulty in children
- Bisphosphonates for the treatment of bone tissue complications in cancer diseases and risk of osteonecrosis of the jaw
- Ibuprofen for the treatment of musculoskeletal pain and risk of cardiovascular adverse reactions
- Natalizumab for the treatment of multiple sclerosis and risk of progressive multifocal leukoencephalopathy
- Corticosteroids for the treatment of chronic obstructive pulmonary disease and risk of pneumonia
- Diabetic medicines in the SGLT2 inhibitor class and risk of diabetic ketoacidosis
- HPV vaccines for prevention of cervical cancer and risk of Postural Orthostatic Tachycardia Syndrome (POTS) and complex regional pain syndrome (CRPS).

The PRAC's meeting agendas and minutes are published on the EMA website.

The minutes are also published on the DKMA website: *The EU Pharmacovigilance Risk Assessment Committee (PRAC)*

The DKMA joined a new European committee

In October 2015, the DKMA became an active member of the Scientific Advisory Working Party (SAWP) under the European Committee for Medicinal Products for Human Use (CHMP). The SAWP's main remit is to provide scientific advice to the pharmaceutical companies to ensure new medicines are made available to patients.

The objective of scientific advice is to optimise research and development of new medicines to ease the application authorisation process for new medicines thus reducing the medicines' time to market. The aim is orphan medicinal products in particular.

Currently, our Danish experts are taking part in a 12-month pilot with specific focus on advice and assistance in the preparation of trial protocols in the so-called PASS studies (Post-authorisation Safety Studies), which are studies carried out on already marketed medicines with a view to analyse a possible safety risk or to verify the safety profile of medicines.

The Pharmacovigilance Risk Assessment Committee is the entity that formally approves the scientific advice, so the pilot calls for strengthened collaboration between the SAWP and the PRAC.

The SAWP is a multidisciplinary group, which comprises a chairperson, 28 members including three members of the Committee for Orphan Medicinal Products (COMP), one member of the Paediatric Committee (PDCO) and one member of the Committee for Advanced Therapies (CAT).

The SAWP furthermore represents the following areas of expertise:

- Pre-clinical studies
- Pharmacokinetics
- Methodology and statistics
- Therapeutic fields for which there are frequent requests or which are defined in the European legislation such as cardiology, oncology, diabetes, neurodegenerative disorders and infectious diseases.

The SAWP meets 11 times a year at the EMA for a three-to-four-day meeting, and the DKMA is represented by two members.

8 Reinforced international focus in 2016

Ever since the formation of the European Medicines Agency, there has been European and international focus on pharmacovigilance. The DKMA is an active partner in this collaboration – through participation in several working groups and many rapporteurship appointments. The international strategy continues in 2016.

The electronic monitoring of suspected adverse reactions – signal generation and analysis – will be reinforced in 2016. With more than 7500 ADR reports in 2015, this is a natural development – and also in line with the European legislation. This way of working helps ensure that we can prioritise our resources and work in a more risk-based manner, making it possible for us to maintain a high health focus in our subsequent analyses.

In 2016, a new pharmacovigilance action plan will be implemented in Denmark. It will focus on quality and increased IT application as well as concentrate on continued efforts to make ADR reporting increasingly easier for health professionals and patients and their representatives. IT tools have been developed to ease and streamline the doctors' work with reporting suspected adverse reactions – with automated completion of many of the basic details that an ADR report must include.

In 2016, we are going to modernise and expand the lists of ADR reports that patients and their representatives can extract from our website. They will become more interactive so that the search may be adjusted to their needs. We hope it will be received well and look forward to continuing our efforts to strengthen pharmacovigilance in collaboration with doctors and other healthcare staff, patients and the industry.