Sundhedsstyrelsen
Danish Health and Medicines Authority

ANNUAL REPORT

Danish Health and Medicines Authority's Annual Pharmacovigilance Report 2014

Contents

Preface

In 2014, the Danish database of adverse reactions reached nearly 100,000 ADR reports – reports that the DHMA has received since 1967. The vast majority of the ADR reports come from doctors, but 2014 suggests that the trend may be changing.

The prerequisites for effective pharmacovigilance are good data and optimum data exploitation. While it was therefore essential for us to encourage the submission of more ADR reports in 2014 as part of our pharmacovigilance activities, we particularly devoted efforts to create a basis for receiving ADR reports that are of good enough quality and ensure that we increasingly use the data and tools available to us in our pharmacovigilance work.

We have benefited highly from our analysis tool for analysis of adverse reactions and identification of potential patterns in complex reporting data. Based on the ADR reports received in Denmark, we worked determinedly in 2014 to identify and analyse data therein, and we highlighted several problems.

Media cases impacting pharmacovigilance activities

Like the year before, 2014 was a year with several media cases that shaped our pharmacovigilance activities. Especially the safety of vaccines was in the spotlight – not only the HPV vaccine against cervical cancer, but also the seasonal influenza vaccines and lately the MMR vaccine. It is nothing new that cases in the media's spotlight have a way of growing and also affect ADR reporting statistics – we have seen it before, and we will see it again – the trend is here to stay, and we must relate to it and integrate it in our work.

New web service for easier ADR reporting now available

In 2014, we concluded our work with a new web service that eases the burden of ADR reporting for doctors by extracting data from their medical systems to the electronic reporting form – an activity highlighted as particularly important by the Danish Pharmacovigilance Council. The objectives of the web service are to reuse data, reduce reporting time, eliminate errors and generate better ADR reports. The web service is made available to the companies that deliver medical systems to medical practices, regions, municipalities and pharmacies.

Midwives to report adverse reactions

On 1 April 2014, new rules entered into force making it mandatory for midwives to report adverse reactions on equal terms as doctors. Thus, midwives are now obligated to report suspected adverse reactions – an obligation which enjoyed widespread support. It has been very gratifying to see that the midwives have taken on this task in a constructive manner.

ADR reports in 2014

In 2014, the number of adverse drug reaction (ADR) reports in the Danish adverse reaction database came close to 100,000. The ADR reports go as far back as the late 1960s when the first national system for registration of adverse reactions, as we know it today, was established. Back then, only doctors could report adverse reactions, but in recent years, we have seen an increasing inflow of ADR reports from other healthcare professionals and medicine users. Figure 1 shows the accumulated share of ADR reports distributed between different types of reporters from 1967 to 2014.

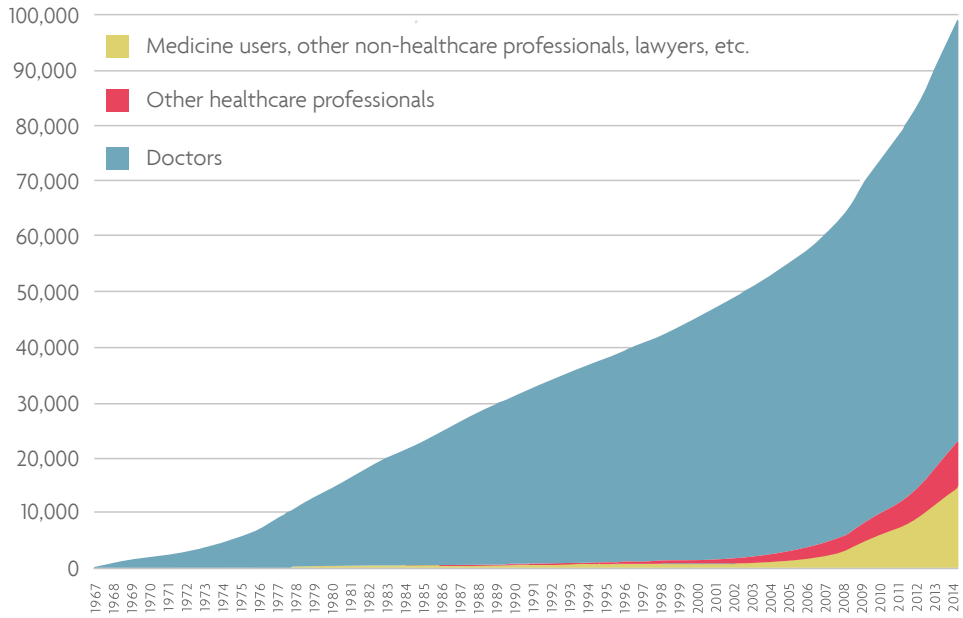

Figure 1: Accumulated share of ADR reports by reporter type (1967-2014)

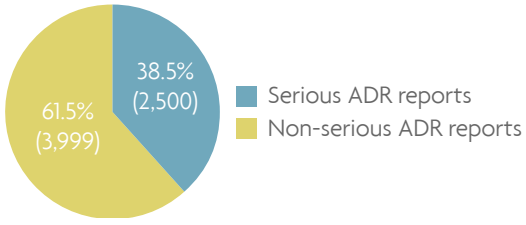

Figure 2: Number of ADR reports in 2014 including duplicates, broken down by serious and non-serious adverse reactions. Duplicates cover ADR reports that have been submitted more than once to the DHMA. This would occur when for example both the doctor and the patient report the adverse reaction. In 2014, the DHMA received 6,499 ADR reports including duplicates, and 6,046 excluding duplicates.

Many reports from medicine users or their representatives

Ever since 2003 when medicine users were given the opportunity to report suspected adverse reactions themselves to the DHMA, the share of ADR reports from medicine users, their representatives and other non-healthcare professionals has grown. In 2014, this group accounted for 28 % of all ADR reports received in 2014 and 15 % of the total volume of ADR reports in the database.

ADR reports from medicine users or their representatives contribute significantly in quantity as well as quality to the total number of ADR reports received, and they are are generally well-documented, providing valuable information. Yet, reports from medicine users are not an alternative to reports from doctors and other healthcare professionals, but the ADR reports from the two segments complement each other. Read more in the DHMA's report from 2012: *Adverse drug reaction reports (ADRs) from consumers may improve patient safety (in Danish only)*.

2014 also saw an increase in ADR reports from other healthcare professionals (e.g. dentists, nurses, pharmacists and midwives). They accounted for more than 20 % of ADR reports in 2014. However, reports from this segment only make up a small proportion of all reports in the Danish adverse reaction database.

Decline in reports from doctors

The share of ADR reports from doctors has decreased steadily, and although doctors are still behind most of the reports overall, they only accounted for 44 % of all ADR reports in 2014. This is the lowest level ever, and the fall cannot only be explained by the fact that other segments are now submitting more reports because there is also a fall in absolute numbers – there were 300 fewer ADR reports from doctors in 2014 compared to 2013. ADR reports from doctors have special qualities and are important in the DHMA's activities of monitoring medicine safety.

We know from surveys that doctors do want to report suspected adverse reactions, but time is a limiting factor. In acknowledgement thereof, we have developed a web service that can ease the burden of reporting adverse reactions for doctors. Read more about the web service on *page 10*.

DHMA stays focused on encouraging doctors to report more adverse reactions

At the DHMA, we continually focus on furthering the incentives and possibilities for doctors to report adverse reactions. In 2014, we completed a campaign targeting doctors in mental health centres across Denmark. Read more about the campaign on *page 9*.

ADR reports from Danish hospitals in 2014 by region

In 2014, the DHMA received altogether 1,330 ADR reports from hospitals across Denmark[1] – including reports from mental health centres in the five regions. The distribution of ADR reports between the individual regions is shown in Figure 3. Two reports came from hospitals in Greenland and the Faroe Islands and do not appear in the figure.

The total number of ADR reports from hospitals was higher in 2014 compared to 2013. Especially the Capital Region of Denmark and Region Zealand saw large increases in the number of ADR reports.

ADR manager role makes a difference

One reason why the number of ADR reports has increased from the Capital Region of Denmark and Region Zealand is that these specific regions have an ADR manager[2]. Ever since the Capital Region of Denmark got an ADR manager in 2013, ADR reports have increased steadily from this region. It is likely that we are seeing the same trend from Region Zealand, which implemented an ADR manager role in February 2014.

The DHMA has entered into a formal collaboration with the ADR managers in the Capital Region of Denmark and Region Zealand. As part of this collaboration, we supply monthly overviews of the ADR reports we receive from the ADR managers. The two regions then use these overviews to evaluate the ADR manager role and to continually enhance patient safety.

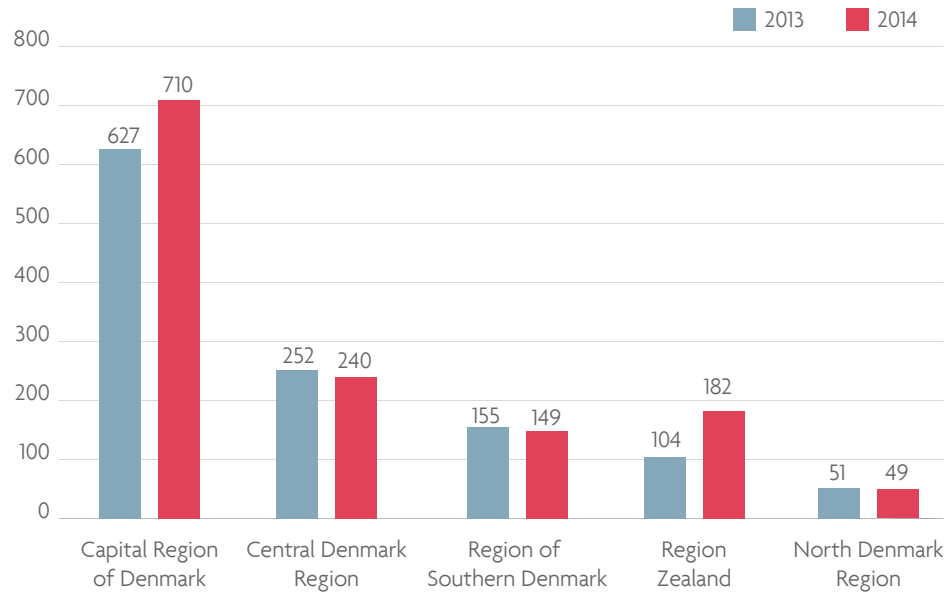

Figure 3: ADR reports from Danish hospitals in 2013 and 2014 by region. Two reports were received from two different regions and are therefore included in both regions. Adjustments have not been made for the population size of the respective five regions.

1 Only reports received directly from the hospitals are included in this report.
2 A regional ADR manager assists doctors in the region with reporting suspected adverse reactions to the Danish Health and Medicines Authority. The doctor has merely to state the patient's name and civil registration number, suspected adverse reaction as well as the suspected medicine, and then the ADR manager takes care of submitting the ADR report to the DHMA.

Overall increase in ADR reports across the regions' mental health centres

In 2014, we received twice as many reports from the regions' mental health centres than we did in 2013 – which could be a result of the DHMA's national campaign targeting regional mental health centres, which was launched in March 2014. The campaign objective was to encourage regional mental health centres to submit more ADR reports.

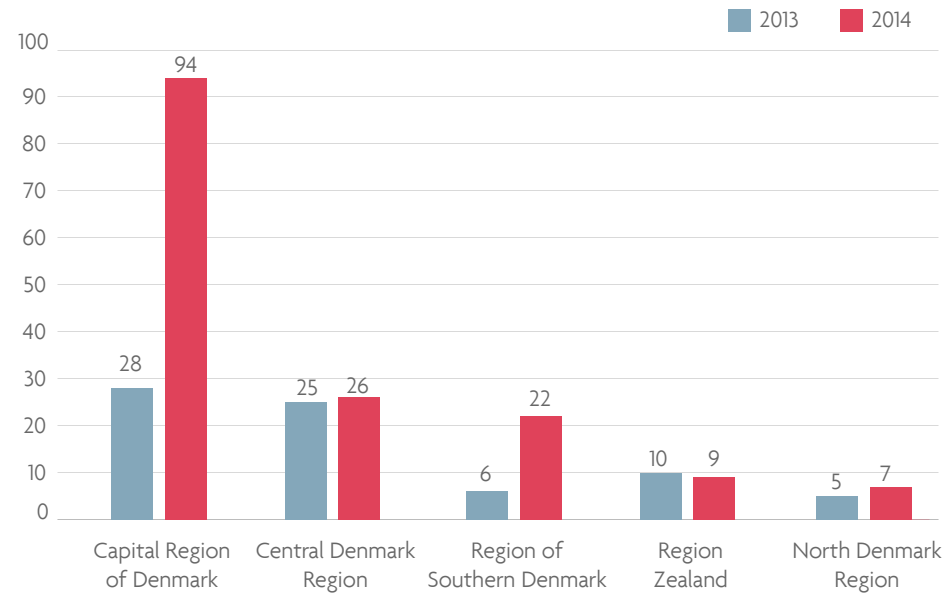

Figure 4: ADR reports from mental health centres in 2013 and 2014

Preparing and implementing Action Plan III (2014-2015)

Action Plan III entered into force in 2014 and carries on the experience and initiatives from the Action Plan for Strengthened Pharmacovigilance 2011-2013, which pursued Pharmacovigilance Action Plan 2008. These action plans aim to increase the number of ADR reports, facilitate reporting, strengthen the DHMA's professional and communicative work with adverse reactions and strengthen collaboration between all players active in pharmacovigilance work. Action Plan III has two overall objectives, namely more and better ADR reports and optimisation of the actual pharmacovigilance work – nationally and internationally.

ADR report quality in focus

The third action plan has special focus on the quality of ADR reports and not just quantity. Specifically, this has resulted in a focused follow-up procedure for ADR reports, which implies that resources are used on collecting follow-up information on precisely those ADR reports considered to bring most value to the assessment. Moreover the DHMA has formed a Quality Forum for Adverse Reactions which is to work to improve the possibilities of enhancing ADR report quality and detail how quality can be improved. Read more about the new follow-up procedure on *page 11*.

Strengthened education in ADR reporting for doctors and medical students

In order to improve the quality of ADR reports, an initiative has been launched to teach doctors as part of their medical education. Actions have been taken to strengthen training in pharmacovigilance, both as part of the medical education and the post-graduate specialty education. Efforts are being made to integrate training in other healthcare professional educations, e.g. in nursing education.

Collaboration with the National Agency for Patients' Rights and Complaints

In 2014, the DHMA expanded its collaboration with the National Agency for Patients' Rights and Complaints, which receives (anonymous) information about adverse reactions caused by medication errors (adverse events) so that coordinated announcements can be made. In parallel, the DHMA and the National Agency for Patients' Rights and Complaints have strengthened collaboration in the analysis area so that analyses of safety issues will provide a broader perspective.

DHMA national campaign targeting mental health centres across the regions

In 2014, we completed a national campaign targeting regional mental health centres across the regions. The campaign ran from March to October 2014. The objective was to raise awareness of ADR reporting and of doctors' obligation to report suspected unexpected and serious adverse reactions. In addition, the campaign was to inform patients in mental care and their relatives that they too can report adverse reactions to the DHMA.

Campaign background

Generally, the DHMA receives very few ADR reports from doctors and patients or their representatives in the mental healthcare area, and yet, medical treatment of mental disorders frequently causes many adverse reactions – and in certain cases serious adverse reactions. Moreover, a survey conducted by the DHMA in 2013 showed that there is generally not enough knowledge about and focus on adverse reactions in the mental healthcare area.

In 2013, the DHMA received only 78 ADR reports from all mental health centres in the regions, which is the level seen for several years.

Campaign results

In 2014, we received a total of 158 ADR reports from mental health centres (see Figure 4). When the campaign was evaluated, it not surprisingly received both criticism and praise, but overall, the campaign paid off – in some regions more than others. The vast majority of the regions said the campaign had put more focus on the reporting of adverse reactions than before in addition to having made it clearer which adverse reactions are mandatory to report. In the Central Denmark Region, the campaign led to the decision of introducing an ADR manager role specifically to service the region's mental health centres.

Web service can make it easier to report adverse reactions to medicines

In June 2014, we launched a new web service for easier reporting of adverse reactions. The web service gives healthcare professionals the possibility to report adverse reactions to medicines directly from the medical systems they use on a daily basis. The DHMA expects the service will encourage more health professionals to report adverse reactions, thus contributing to a better overview of the safety of medicines marketed in Denmark. Not only will health professionals be able to report directly from e.g. an electronic patient record at the hospital or a medical practice, they will also avoid having to enter a number of basic information about themselves, the patient and the medicine he or she is taking.

Available from the National Service Platform

It is up to the owners and suppliers of IT systems in the healthcare sector whether to integrate the new web service in local systems. The new web service is made available on the National Service Platform (NSP) where a more detailed description and documentation of the web service can also be found.

Read more about the web service: *NSP Service: ADR reporting (in Danish only)*.

New procedure for collecting additional information on received ADR reports

When the DHMA receives an ADR report, it is sometimes necessary to collect further information from the reporter in order for the assessment of the ADR report to be as sufficient as possible.

At the end of 2014, we implemented a new follow-up procedure, which is to ensure a focused and relevant process for collecting additional information on ADR reports. Key to this process is that the additional information must significantly contribute to the scientific assessment of the ADR report.

Before, companies had the opportunity of submitting follow-up questions to any ADR report, but the new procedure introduces a number of well-defined criteria describing when additional information on an ADR report can be collected. This applies to:

- All serious ADR reports[3]
- Serious and non-serious ADR reports related to medicines marketed for less than two years.

In addition, additional information to non-serious cases may be collected when the following criteria are satisfied:

- Medicines on the DHMA's *follow up list*.
- Pregnancy cases
- Mother/child cases, or congenital defects
- Off-label use in children

Follow-up can also be requested if other significant additional information may significantly alter the scientific assessment of the ADR report.

The procedure has been developed in collaboration with the Danish Pharmacovigilance Council and upon discussions with the Danish Medical Association and other relevant health professional organisations as well as the industry's organisations.

The process will be evaluated on an ongoing basis in collaboration with the relevant parties.

Read more about the collection of additional information on ADR reports on the DHMA website: *Follow-up on adverse reaction reports*.

3 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.

Focus areas in 2014

The HPV vaccine is still monitored closely

In 2014, the DHMA once again had focus on the safety of the HPV vaccine.

Overall, the number of reports of suspected adverse reactions to the HPV vaccine fell significantly from 2013 to 2014, but during the same period the share of serious ADR reports increased. All serious ADR reports are evaluated by a doctor, and we continued in 2014 to publish the resulting conclusions in our newsletter *Danish Pharmacovigilance Update*.

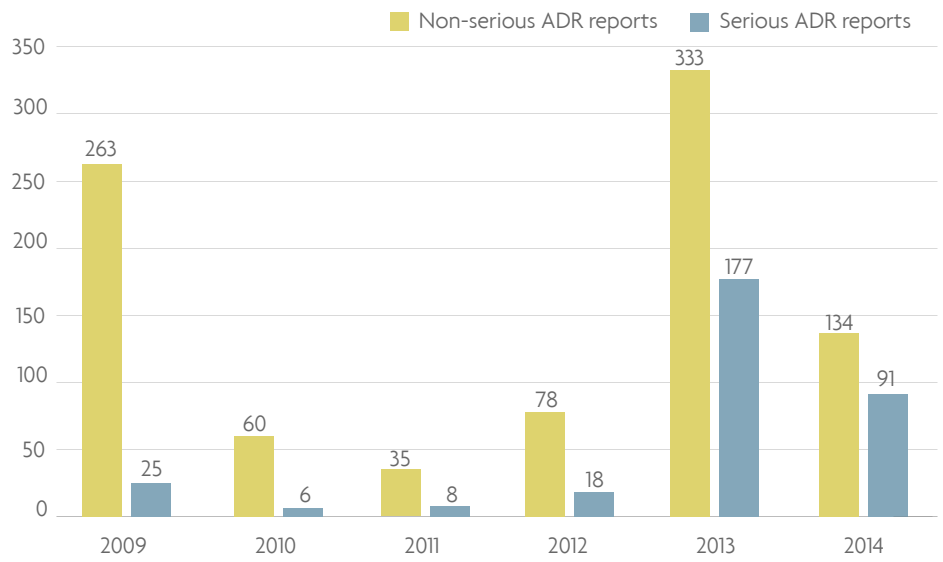

Figure 5: Reports of suspected adverse reactions to the HPV vaccine from 2009-2014, broken down by serious and non-serious ADR reports

POTS as a possible adverse reaction to the HPV vaccine

In 2013, Danish ADR reports prompted us to request the European Medicines Agency, EMA, to investigate POTS (Postural Orthostatic Tachycardia Syndrome) as a possible adverse reaction to the HPV vaccine.

EMA's evaluation progressed in 2014, and the Pharmacovigilance Risk Assessment Committee, PRAC, concluded in December 2014 an annual review of the safety of the HPV vaccine Gardasil®, which included a thorough evaluation of a possible causal link between the HPV vaccine and POTS. The PRAC concluded that at the time it was not possible to confirm or disprove that there is a causal relationship between Gardasil® vaccination and the occurrence of POTS. Therefore, POTS should be monitored closely in future reviews of Gardasil® safety, and a special initiative in the form of a new questionnaire has been launched to ensure appropriate follow-up on ADR reports that describe symptoms suggestive of POTS.

Public funds earmarked for information about the safety of the HPV vaccine

In June 2014, a public funds agreement (a rate adjustment pool) earmarked funds for activities concerning the HPV vaccine in 2014. In this connection, the DHMA prepared informative material for health professionals, which is available on the DHMA website *Adverse reactions from the HPV vaccine*. In addition, the DHMA produced a leaflet that doctors can hand out to girls who are to be vaccinated and their parents to discuss and explain the benefits and risks of the vaccination.

Monitoring continues for suspected adverse reactions to the HPV vaccine

As part of the DHMA's pharmacovigilance activities, we work together with experts to further analyse the Danish reports of possible adverse reactions to the HPV vaccine. Any conclusions from these analyses will be included in the ongoing assessment of the HPV vaccine.

Statements on reported adverse reactions to seasonal influenza vaccines

Vaccines and their safety took up a lot of media space in 2014. In November 2014, the DHMA therefore published a statement on reported adverse reactions to the seasonal influenza vaccines covering the past ten years. In our electronic newsletter Danish Pharmacovigilance Update, we also reviewed the ADR reports of the 2014/2015 influenza season and evaluated all the reported adverse reactions. This review of reports about suspected adverse reactions to the seasonal influenza vaccines has become a permanent feature in our newsletter, which we bring twice during an influenza season.

Reports of adverse reactions related to seasonal influenza vaccines in the past ten years

The statement published in November 2014 showed that during the past ten years, we have received a total of 384 ADR reports related to influenza vaccination. 141 of the reports were classified as serious. Among the serious ADR reports were mostly known adverse reactions such as Guillain-Barré syndrome and thrombocytopenia.

Among the non-serious reports, known adverse reactions were also frequently described, e.g. fever, muscle and joint pain – adverse reactions that often subside during the course of 1-2 days.

During the ten-year period, there have been 13 reports in which the suspected adverse reaction led to a fatal outcome. These cases primarily involved elderly, weakened persons in the risk group. The DHMA assessed that ten of the cases were not connected to the vaccine, whereas a possible causal connection could not be ruled out in the last three cases. These three cases involve neurological adverse reactions that are described in the product information.

DHMA conclusion to the statement

Overall, the conclusion to this statement was that we still assess that the benefits outweigh the possible risks and still recommend influenza vaccination for risk groups based on the overall scientific evidence.

Read the statement on the DHMA website: *Influenza vaccination is still assessed as effective and safe for risk groups (in Danish only)* and our review in *Danish Pharmacovigilance Update, December 2014*.

Antihistamine promethazine (Phenergan® etc.) became prescription only

After a recent review of the safety of promethazine used for the treatment of allergic diseases, motion sickness and insomnia, the DHMA changed the medicine's status from over-the-counter to prescription-only in December 2014. The prescription-only status was affected for both Phenergan®/ Prometazin ERA 25 mg film-coated tablets in units of 100 and Phenergan® 1 mg/ml oral solution for children from two years of age.

This was preceded by long-term concerns about promethazine's potential for abuse, which later on was confirmed in practice. We therefore initiated a large-scale analysis of the use of promethazine, the result of which now means the medicine is available only on prescription.

Increased focus on promethazine safety after enquiry by a proprietor pharmacist

It was a report from a proprietor pharmacist that prompted us to put focus on the use of promethazine. In *Danish Pharmacovigilance Update, December 2012*, we reported that we were monitoring promethazine closely and encouraged the reporting of any suspicion about excessive use or abuse of the medicine. We subsequently received a new report about suspected promethazine abuse, and we were concurrently informed that the Danish Poison Control Hotline had received several calls about inappropriate use of promethazine. The DHMA therefore joined forces with the Danish Poison Control Hotline to identify potential safety problems associated with promethazine.

Why promethazine was made prescription-only

We identified four serious safety problems associated with using Phenergan® and Prometazin ERA 25 mg film-coated tablets in units of 100, which is why the medicine is now available only on prescription:

1. Abuse – use of higher doses than recommended
2. Serious adverse reactions at recommended doses
3. Serious interactions with psychoactive drugs
4. Heavy sedative effect compromising the ability to drive

Read more about promethazine in *Danish Pharmacovigilance Update, December 2014*.

Analysis of reported suspected adverse reactions and reported adverse events associated with using labour-stimulating medicines for induction of labour

The DHMA's *Plan for the monitoring and supervision of the Danish regions' use of labour-inducing medicines (in Danish only)*[4] from August 2013 e.g. provides that cross-cutting analyses of reported suspected adverse reactions and reported adverse events related to medically-induced labour will be implemented in 2014-2016.

The DHMA published the first of these analyses in *Danish Pharmacovigilance Update, December 2014*.

4 The main purpose of the plan is to increase the quality, safety and security of medically-induced labour. The plan was prepared at the request of the Ministry of Health.

The analysis in brief

The analysis was prepared jointly by the DHMA and the National Agency for Patients' Rights and Complaints and covers the medicines dinoprostone, misoprostol and oxytocin.

We analysed ADR reports and adverse events that had been reported in 2013. We identified 30 birth processes for which suspected adverse reactions had been reported to the DHMA and 37 adverse events related to birth processes reported to the Danish Patient Safety Database.

On this basis, we identified five problems

1. Administration of misoprostol at higher doses than recommended
2. Induction of labour in women with previous caesarean sections
3. Temporary discharge after administration of misoprostol in hospital
4. Incorrect oxytocin doses
5. Problems with the oxytocin iv drip.

DHMA continues to monitor medicines for induction of labour

The DHMA will continue monitoring and supervising closely the regions' use of medicines for induction of labour. In 2014, a project was launched jointly by the DHMA, the Danish Society of Obstetrics and Gynaecology, the Danish Association of Midwives and the Danish State Serum Institute (SSI). The project aims to investigate the possibility of implementing a registry study of adverse reactions occurring in the use of medicines for induction of labour. The possibility of implementing such registry study depends on the data quality of the entries in the Medical Birth Registry and the National Patient Registry. At the end of 2014, we started collecting information from delivery centres across Denmark, and this information will be compared to the information in the registers.

Focus on users of antiepileptics and reported ADRs related to these medicines

After a reassessment of reimbursement status for antiepileptics, the DHMA decided in spring 2014 that it would be relevant to analyse users of antiepileptics and reported suspected adverse reactions related to these medicines.

The DHMA prepared a report in this connection. The report includes a literature review with focus on adverse reactions related to antiepileptics, an analysis of the number of users of the different types of antiepileptics from 2003-2012 as well as an analysis of the suspected adverse reactions related to these medicines that were reported to the DHMA in the same period.

Analysis result

The literature review showed, among other things, that most of the serious chronic adverse reactions were related to the older antiepileptics. For the new antiepileptics, no serious chronic irreversible adverse reactions were seen in the period, however, with some exceptions, e.g. pigment changes to the eye and skin in retigabine treatment. It should be noted, however, that many of these new medicines have only been used for a short time, and their profiles of adverse reactions are monitored closely.

Benzodiazepines have the most users

For the period reviewed, the number of adult users was highest for benzodiazepines (clobazam, clonazepam, diazepam and midazolam) and medicines with gabapentin, pregabalin and lamotrigine. The vast majority of users of benzodiazepines as well as gabapentin and pregabalin had been prescribed these medicines for indications other than epilepsy.

The number of users per year had especially increased for gabapentin, lamotrigine and pregabalin. In regard to gabapentin and pregabalin, the increase was primarily due to patients who had been prescribed the medicines for indications other than epilepsy.

ADR reports followed the number of users

By and large, the number of ADR reports related to antiepileptics followed the number of users, i.e. there were most ADR reports about medicines with the most users.

Most of the ADR reports described well-known symptoms appearing from the summaries of product characteristics such as dizziness, rash, nausea and vomiting.

Read the full report on the DHMA website: *Users and adverse reactions of antiepileptics in Denmark (in Danish only)*.

ADR signals 2014

Every week, we monitor the ADR reports in the database of adverse reactions to detect possible new ADR signals. 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. In addition, we focus much on correct use of medicine in clinical practice, i.e. the extent to which medicine is used in compliance with its current guideline and summary of product characteristics.

ADR signals could come from many other sources than ADR reports such as monitoring programmes, scientific literature, various types of studies, drug regulatory authorities in other countries, the media or from citizens and healthcare professionals.

In 2014, the DHMA monitored and detected a number of ADR signals from different sources.

Table 1 briefly describes the ADR signals we processed in 2014.

Medicine	ADR signal	Source	Status and informative action if any
Benzodiazepines	Alzheimer's disease	Literature	Signal closed. Recommendation from PRAC for continued routine monitoring.
Cetirizin	Intense itching after discontinuation.	Routine monitoring	Signal closed. The marketing authorisation holder will update the product information.
Citalopram	QT prolongation in concurrent treatment with methadone.	Routine monitoring	Signal closed. Article in Danish Pharmacovigilance Update, November 2014.
Dentocain (articaine)	Severe allergic reaction. Suspicion of product defect.	Information from health professional	Signal closed.
Docetaxel "Hospira"	Chest pain. Suspicion of product defect.	Information from health professional	Signal closed.
Dopamine agonists	Dopamine agonist withdrawal syndrome.	Literature	Signal awaits assessment.
Epirubicin "Medac" and Sendoxan (cyclophosphamide)	Fever in patients with low neutrophil, white blood cell, count (febrile neutropenia). Suspicion of product defect.	Information from health professional	Signal is being monitored
Fosphenytoin	Dose error due to mix up with another product	Danish Patient Safety Database (DPSD)	Signal closed. Article in Danish Pharmacovigilance Update and bulletin from the National Agency for Patients' Rights and Complaints in June 2014.
Lamotrigine	Hair loss.	Routine monitoring	Signal awaits assessment. Disseminated in the EU network.

Levemir	Lump formation and soreness at the injection site.	Routine monitoring	Signal closed.
Meropenem	Severe allergic reaction Suspicion of product defect.	Information from health professional	Signal is being assessed.
Methylphenidate	Treatment of schizophrenia with mehylphenidate is contraindicated.	Surveillance programme	Signal closed. Article in Danish Pharmacovigilance Update is planned.
Methylphenidate "Sandoz"	Lack of efficacy.	Routine monitoring	Signal closed. Article in Danish Pharmacovigilance Update is planned.
Pregabalin	Abuse.	Surveillance programme	Signal is being assessed.
Warfarin and miconazole oral cavity gel	Increased risk of bleeding (known interaction).	Routine monitoring	Signal closed. Article in Danish Pharmacovigilance Update is planned.

Table 1. List of ADR signals that the DHMA focused on in 2014

Assessment of ADR signals

It is both complicated and time-consuming to detect and assess ADR signals, and all signals are therefore prioritised based on a clinical assessment and likely consequences for patients and public health in general. When a new signal is detected, it first needs to be validated and confirmed before any further measures are taken. A signal can be closed any time during the process if for example no causal relationship can be established between the medicine and the adverse reaction. Sometimes it happens early in the process, sometimes not until the evaluation has finished, and further actions have been decided. The DHMA's signal process is shown in figure 6.

Figure 6: The DHMA signal process

An action could be to close the signal without further measures, to inform Danish health professionals and citizens of the signal, to forward the signal 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 or to continue monitoring the signal through either a surveillance programme or through the DHMA's and the pharmaceutical company's routine monitoring.

Information about ADR signals

On our website *dhma.dk* and in our newsletter *Danish Pharmacovigilance Update*, we routinely keep Danish medicine users and health professionals updated on ADR signals and problems important to patient safety.

The Drug Interaction Database

In 2014, the DHMA completed its close collaboration with the departments of clinical pharmacology at Aarhus University Hospital, Odense University Hospital and Bispebjerg Hospital of expanding the scientific content of the Drug Interaction Database.

The project in brief

The project aim was to expand the Drug Interaction Database with data from the interactions paragraphs in the medicines' summaries of product characteristics (SPCs). Previously, the database was mainly updated based on data from published studies, which, particularly for new medicines, could prove inadequate because at the time of authorisation the SPCs could hold knowledge about interactions not yet published in studies. We improved this in 2014, and now the Drug Interaction Database includes also the newest knowledge from the SPCs that has not yet been published in the scientific literature.

In addition, all interactions advised against in the Drug Interaction Database (red interactions) were reviewed once more to ensure the warnings in the Drug Interaction Database are genuine and clinically meaningful. Read more about the project in *Danish Health and Medicines Authority's annual pharmacovigilance report 2013*.

Drug Interaction Database integrated in doctors' medical systems

In 2014, we also worked on a solution, which makes it possible to integrate data from the Drug Interaction Database in one of the medical systems that doctors use in their daily work, thereby giving them a better overview of the medicine's safety when they prescribe medicines and ultimately enhancing patient safety. It is an important initiative that we will develop further in 2015.

Further information about the Drug Interaction Database is available in Danish at *interaktionsdatabasen.dk*.

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 Danish Health and Medicines Authority 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 also via direct communication to doctors and relevant organisations. The cases reviewed by the PRAC in 2014 included:

- Diacereine for the treatment of osteoarthritis and risk of severe diarrhoea and effects on the liver
- Domperidone for the treatment of nausea and risk of heart arrhythmia
- Zolpidem for the treatment of insomnia and risk of next-morning medicine effect
- Angiotensin-receptor blockers, angiotensin-converting enzyme inhibitors and direct renin inhibitors for the treatment of hypertension, heart disease and proteinuria and risk of hyperkalaemia, hypotension and kidney impairment in combination treatment with any two of these medicines
- Agomelatine for the treatment of depression and risk of effects on the liver
- Valproate for the treatment of epilepsy or bipolar disorder and risk of congenital malformations when used during pregnancy
- Testosterone for the treatment of hypogonadism and effects on the heart
- Ponatinib for the treatment of leukaemia and risk of blood clots
- Ivabradine for the treatment of angina pectoris and risk of bradycardia.

The PRAC's meeting agendas and minutes are published on the EMA website. The minutes are also published on the DHMA website: *The EU Pharmacovigilance Risk Assessment Committee (PRAC)*.

DHMA is active in various international working groups

Throughout 2014, the DHMA also participated actively in the European joint action project SCOPE – Strengthening Collaborations for Operating Pharmacovigilance in Europe.

SCOPE aims to support knowledge and experience sharing between the EU Member States in the area of pharmacovigilance. The project is to give the national authorities an overview, a common understanding and practical tools within a number of areas to enhance medicine safety for patients throughout Europe.

The work in 2014 was particularly focused on creating an overview of the current status of processes and workflows employed by each EU Member State within various defined areas.

Denmark contributes with information in all areas, but is especially active in the area of ADR signal management and communication. The SCOPE project runs until the end of 2016.

Quality and prioritisation – focus areas in 2015

We must continually ensure that we spend our resources in areas that will give us most health value for money. Therefore, as part of the pharmacovigilance action plan for 2014-2015, which has been developed in collaboration with the Danish Pharmacovigilance Council, the DHMA has established a quality forum which is to help us identify areas in which we can simplify and rationalise tasks that yield only a poor health and safety output. Typically, this would be modifications in our work practices with e.g. doctors and the pharmaceutical industry where we can make the pharmacovigilance activities even more relevant and focused through changes and adjustments. We have already rearranged the procedure for requesting additional information on reported suspected adverse reactions.

Still focus on simplifying ADR reporting

Reports from patients or their representatives remain an important element in pharmacovigilance. It is a challenge – not only in Denmark but internationally – to make the ADR form so simple that it can be filled out by everyone without the need for special qualifications. In 2015, we will make special efforts to ease reporting for medicine users – one element will be a short film on how to report an adverse reaction and a practical step-by-step presentation of the special electronic ADR form to be used in reporting.

In the recent years, we have developed the DHMA's way of working with pharmacovigilance in collaboration with the Danish Pharmacovigilance Council. New IT systems have been implemented, new scientific working areas have been prioritised, and communication has been intensified. But it is important that we follow how the other EU Member States are handling the tasks and see if we can learn from them. In 2015, we will therefore be visiting one or more of our sister organisations to discuss specifically selected areas to find out if there are areas in which we can do better at even better quality as permitted by our own framework.

Further involvement of patients and medicine users

It is important to the DHMA that we involve users in our work. And therefore we will continue in 2015 to collaborate with selected patient organisations and discuss both the challenges and possibilities we have together of collaborating on medicine safety.

The number of reported adverse reactions is high in Denmark – this is good as it contributes to enhancing medicine safety. But we must not focus on quantity alone – it is really important that we maintain and develop the quality of ADR reports. To accommodate this, we will continue in 2015 to launch a number of initiatives to enhance the quality of ADR reports. Our approach will be targeted through collaboration with health professionals and designed to reduce bureaucratic burdens. We must give quality and prioritisation even more precedence in 2015.