ANNUAL REPORT

The Danish Medicines Agency's annual pharmacovigilance report 2011

Sundhedsstyrelsen
Danish Health and Medicines Authority

Contents

2011 – rapid renewal of pharmacovigilance in progress

In 2011, pharmacovigilance was characterised by five major activities in particular:

- The initial phase for implementing the new EU legislation on pharmacovigilance
- The establishment of most of our new IT system for the handling of adverse drug reactions and analyses
- Adoption and initiation of a new action plan for pharmacovigilance for 2011-2013
- Evaluation of an information campaign targeted at hospital doctors and launch of an information campaign targeted at municipal nursing staff.
- Establishment of cooperation agreements with Aalborg Hospital Science and Innovation Center, Aalborg Hospital, North Denmark Region and the Statens Serum Institut (SSI).

The international negotiations on the new pharmacovigilance, after prolonged discussions in the EU were finalised in December 2010, and the first preparations towards implementing the provisions were initiated throughout 2011. In February 2012, guidelines targeted at authorities as well as the pharmaceutical industry were submitted for consultation by previously initiated international task forces. International negotiations have been held on, among other things, procedures as regards reporting adverse reactions from the pharmaceutical companies directly to the European pharmacovigilance database EudraVigilance. The outcome of these negotiations is being published. Finally, the Danish Medicines Agency has participated in establishing the Danish legal rules implementing a number of the new EU provisions.

Improved IT system for the handling of adverse drug reactions and analyses
In 2009, the Danish Medicines Agency initiated a cooperation partnership with the UK Medicines and Healthcare products Regulatory Agency (MHRA) on a new IT system for pharmacovigilance and analysis. In 2011, the part of the system handling pharmacovigilance was really brought into use. The part analysing adverse reactions was delivered in December 2011, and in 2012 the agency will output adverse reaction analyses as well as overviews of the adverse reactions in the Danish adverse reaction database to the general public. The result of this partnership was not only a very useful IT system, but also a professional cooperation with our English colleagues from MHRA – one of the largest European medicines agencies. We have benefited a lot from this partnership and share professional experience with our colleagues to a wide extent.

New action plan for the pharmacovigilance area
After a comprehensive consultation, a new action plan for the pharmacovigilance area was issued by the Ministry of Health in the summer of 2011. The action plan covers the period 2011 to 2013, and the main purpose of the plan is to improve patient safety through strengthened pharmacovigilance and cross-sectorial cooperation between all stages of the pharmacovigilance process, and to leverage the experience from the first action plan. The action plan includes four focus areas: Improvement of IT tools, strengthening professional knowledge and data utilisation, strengthening development of new knowledge about drug safety, and strengthening the cooperation between different stakeholders.

A number of initiatives under the new action plan have been completed, including, e.g., a major review of the pharmacovigilance work, organisation and quality assurance within the Danish Medicines Agency. In the action plan, establishment of an Adverse Drug Reaction Manager function in Danish hospitals is a point of particular importance, on which also the Council for Adverse Drug Reactions has placed considerable emphasis. Further work on this proposal will be carried out in cooperation with Danish Regions.

Focus on increased adverse reaction reporting through targeted information
The Agency's nationwide adverse reaction campaign targeted at hospital doctors was evaluated in 2011. The campaign was successful, but the need for repetitions is still present. In 2011, we developed an e-learning program for doctors as a supplement to the campaign, in cooperation with the Danish Medical Association and the Danish Association of the Pharmaceutical Industry to further increase the awareness of adverse reaction reporting. The information work will continue and in 2011 was targeted at the care sector where special material was prepared in cooperation with Local Government Denmark (association of municipalities), the trade union FOA (Fag og Arbejde) and the Danish Nurses' Organization.

Cooperation with research institutions
The improved opportunities for analysing adverse reaction data facilitate more comprehensive analyses of special issues. Therefore, the Danish Medicines Agency, after discussions in the Council for Adverse Drug Reactions, has entered into cooperation with Aalborg Hospital Science and Innovation Center, Aalborg Hospital, North Denmark Region and the Statens Serum Institut (SSI) with focus on registry studies.

The Council for Adverse Drug Reactions – inspiration and sparring in the area of pharmacovigilance
In 2011, the Council for Adverse Drug Reactions met four times. Among other things, the Council discussed the new legislation, finalising the use of the old action plan and preparing the new action plan, generic prescription, adverse reaction issues concerning SSRIs, paracetamol, NSAIDs, and many other aspects. Furthermore, the Council discussed prioritisation of the Agency's major assessment work. Again in 2011, the Council was an active partner inspiring a number of activities.

Development in the number of adverse reaction reports from 2009 to 2011

Development in the number of adverse reaction reports from 2009 to 2011

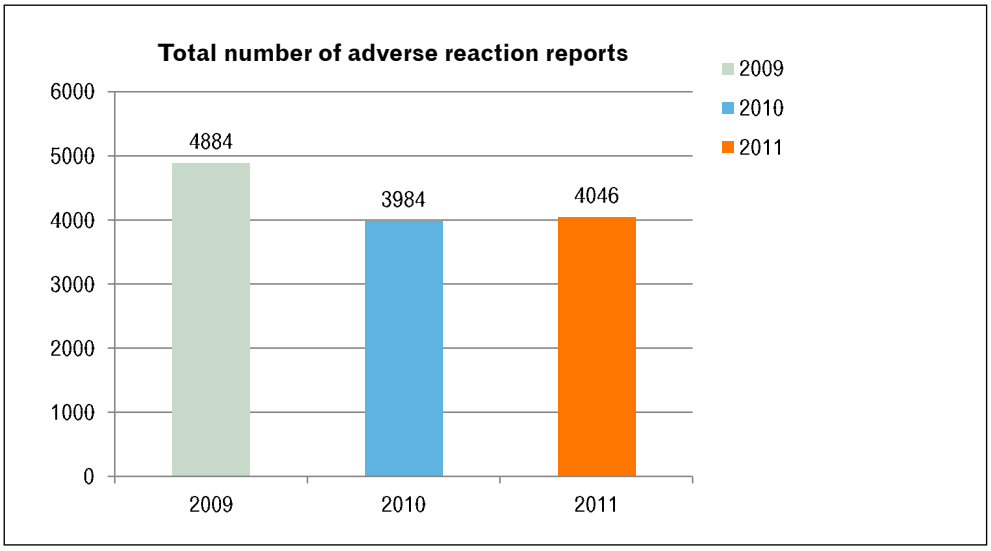

Figure A. Development in the number of adverse reaction reports from 2009 to 2011.

In 2011, we received a total of 4,046 adverse reaction reports. Of these reports, 2,434 – approx. 60% – were classified as serious.

The number of adverse reaction reports in 2011 was more or less identical with that for 2010. Seen from a Danish viewpoint, 2009 was a very special year with unusually many adverse reaction reports. One of the explanations for this can be found in the many reports concerning Pandemrix®, Gardasil® and Eltroxin®, which especially characterised the pharmacovigilance work in 2009. In 2009, these three products alone represented almost 1,000 reports, corresponding to nearly a fifth of the total number of reports.

See *The Danish Medicines Agency's annual pharmacovigilance report 2009*.

The upward curve for adverse reaction reports in recent years indicates that the development is on the right track, but we at the Danish Medicines Agency will continue to focus on the importance of reporting adverse reactions in order to improve the quality of medical treatment on a continuous basis. And as we saw in 2009, a massive focus on medicine and adverse reactions can considerably stimulate reporting.

Adverse reaction reports in 2011 by reporter type

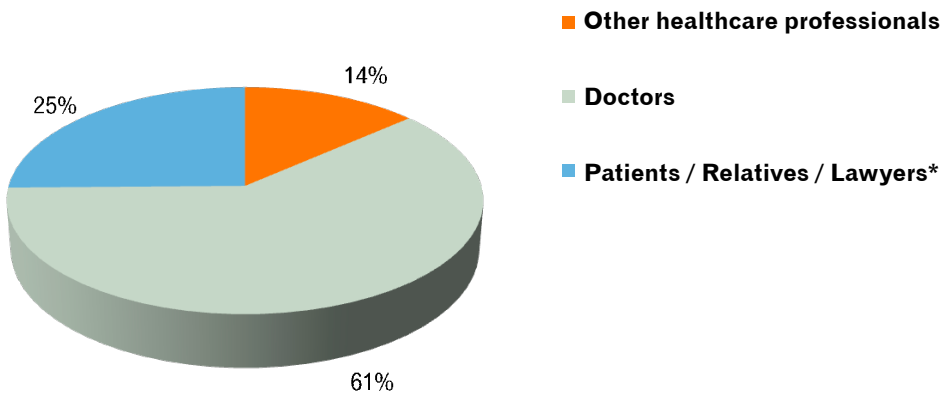

*Figure B. The number of adverse reaction reports in 2011 by reporter type***

In 2011, doctors again filed the most adverse reaction reports with the Agency. Doctors accounted for 61% of the reports, while patients and their relatives accounted for one in four adverse reaction reports. 14% of the reports were filed by other healthcare professionals – primarily nurses, pharmacists and dentists. This distribution is more or less identical with that for 2010.

Doctors are expected to generally report the majority of adverse reactions. In addition to the fact that doctors, due to the nature of their work, have a professional interest in reporting adverse reactions, doctors also, in accordance with Danish medicines legislation, have an obligation to report all serious adverse reactions as well as unexpected suspected adverse reactions*** from all medicines. Furthermore, doctors have an obligation to report all suspected adverse reactions observed within the first two years following placement of a new medicine on the market.

Other healthcare professionals, medicine users and their relatives do not have an obligation to report adverse reactions to the Danish Medicines Agency, but they have an opportunity to do so.

You can report adverse reactions at report a side effect or incident

* We have chosen to include reports from lawyers along with reports from medicine users, since reports in this category are received from the Danish Patient Insurance Association – thereby being cases representing a medicine user.

** Among the reports received, there are several so-called duplicates – a duplicate in the sense that the same report was received from different reporters. Such reports are taken as one, therefore only counting as one report, but both reporters are included in the statement of types of reporters.

*** Unexpected adverse reactions are adverse reactions not included in the summary of product characteristics for the medicine in question.

Top 5 of the most frequently reported active substances and consumption figures in 2011

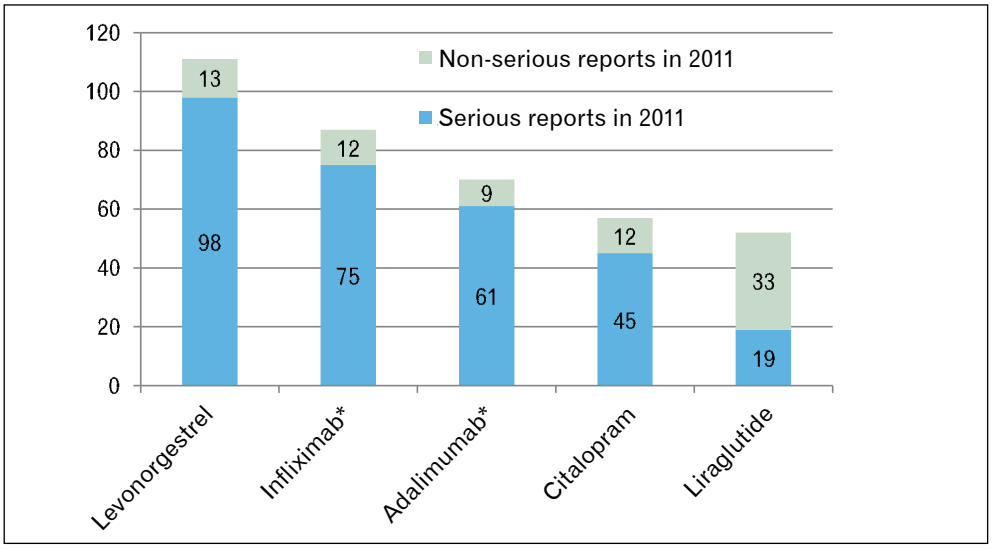

Figure B. Top 5 of the most frequently reported active substances with adverse reactions in 2011

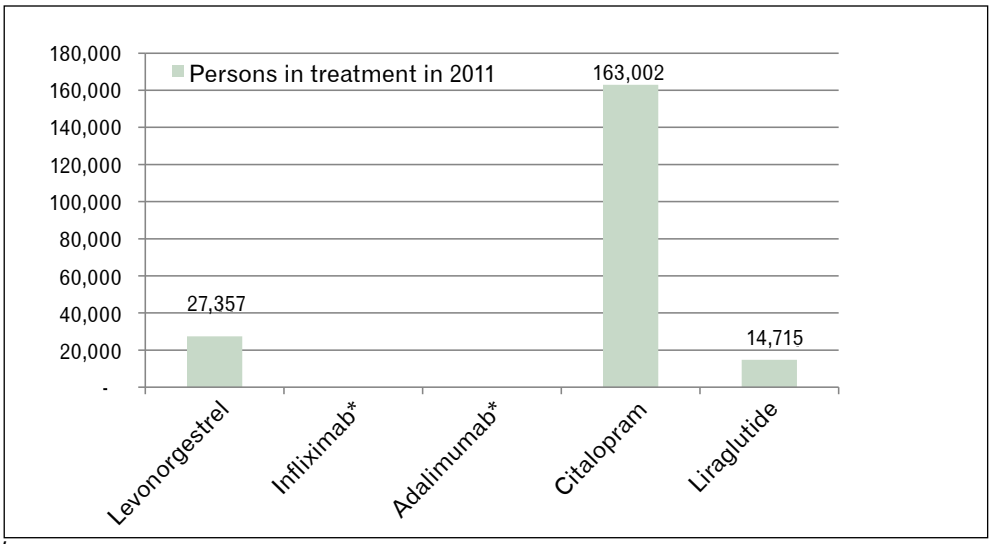

Figure C. Number of persons in treatment with active substances on the top 5 of the most frequently reported in 2011.

The five active substances for which the most adverse reactions were reported in 2011, are shown in Figure B. The number of adverse reaction reports for the active substances should be seen in the light of the consumption of medicine. Figure C shows

the consumption of the five active substances. The number of persons in treatment was calculated as the number of persons having redeemed at least one prescription for the active substance in question in 2011.

The consumption figures are from the Danish Medicines Agency's Register of Medicinal Product Statistics. Some of the active substances (marked with an *, figure p. 8) are primarily given to patients in hospitals or purchased for use in the general practice of doctors or dentists and are therefore not given to patients on prescription. The Agency does not know the exact number of patients undergoing treatment with these medicines.

Levonorgestrel (Mirena®)
The highest number of reports in 2011 concerned the active substance levonorgestrel, for which the Danish Medicines Agency received a total of 111 reports.

Levonorgestrel is a gestagen hormone used either alone or in combination with oestrogen in different types of contraceptives. The statement herein only covers medicinal products containing levonorgestrel as the only active substance, and therefore does not include contraceptive pills. All the adverse reactions reported concern the medicinal product with the trade name Mirena® which is a hormone IUD inserted into the uterus as contraception. Mirena® has been marketed in Denmark since 1993 and thus is not a new medicinal product.

The majority of the reports associated with the active substance levonorgestrel in 2011 concerned known adverse reactions. Out of 111 reports, 98 were categorised as serious. The most frequent adverse reactions include bleeding and IUD dislocation/rejection. By far the most reports have been forwarded to the Danish Medicines Agency by the company marketing Mirena®. To a certain extent, the reporting is stimulated, since the reports have been submitted from doctors to the company via a 'warranty scheme', under which the company covers part of the expense for an IUD, in case it is deemed necessary to remove it based on a medical assessment.

Biological drugs containing infliximab (Remicade®) and adalimumab (Humira®)
The biological drugs Remicade® and Humira® – so-called TNF-alpha inhibitors – are the second-most frequently reported active substances. The TNF-alpha inhibitors are used in the treatment of serious autoimmune diseases affecting joints or bowel, e.g., rheumatoid arthritis, ulcerative colitis, Crohn's disease and psoriatic arthritis. These drugs are only prescribed if other medicines have had insufficient effect.

In 2011, the Danish Medicines Agency received 87 reports concerning infliximab and 70 reports concerning adalimumab. Most of the adverse reactions reported for these drugs were categorised as serious, and they concerned well-known symptoms such as infection and allergic reactions. The relatively large proportion of serious adverse reactions should be seen in the light of the severity of the diseases being treated.

In addition, the relatively large proportion of reports for these drugs may be due to the cooperation between the Danish Medicines Agency and DANBIO, a clinical database that records biological therapy.

In the opinion of the Danish Medicines Agency, there is still an acceptable balance between the benefits of the availability of biological drugs for patient treatment and the disadvantages in the form of risk of serious adverse reactions.

Citalopram (Cipramil® etc.)

In 2011, a total of 57 adverse reaction reports concerned antidepressants containing citalopram. The number of reports should be seen in the context of the total number of patients undergoing treatment with this medicine – in 2011, 163,000 patients were being treated with citalopram, and this number is considerably higher than for the other active substances on the top 5 list.

In 2011, particular focus was on the use of antidepressants in pregnant women, and part of the adverse reactions reported concerned symptoms or congenital disorders in newborns after treating the mother with citalopram during the pregnancy.

There are also reports of cardiac arrhythmias in patients undergoing treatment with citalopram. In 2011, the European Pharmacovigilance Working Party, PhVWP, assessed that citalopram may affect the heart rhythm – especially when given in high doses, and therefore, in October 2011, issued new recommendations reducing the maximum dose of medicines containing citalopram.

The most frequently reported adverse reactions were nausea, abdominal pain and diarrhoea. These are common and known adverse reactions from these medicines. There have also been cases reported of suicidal thoughts and suicide attempts in patients being treated with citalopram, which may be an adverse reaction from these medicines, but which is also a known element of the symptons of major depression.

The Danish Medicines Agency will continue the close monitoring of the use of antidepressants.

Liraglutide (Victoza®)

Last year, the Agency received 52 reports concerning adverse reactions from the use of Victoza®. Liraglutide is approved for the treatment of type 2 diabetes and is a new medicine that has been on the market in Denmark since July 2009. Consequently, liraglutide is still subject to stricter reporting requirements, and an increasing number of patients are undergoing treatment with this medicine. The majority of the reports concerning liraglutide did not concern serious adverse reactions. The most frequently reported adverse reactions in 2011 were nausea, diarrhoea and headache, which are all described in the summary of product characteristics as known and very common adverse reactions from the use of this medicine.

Top 5 of the most frequently reported vaccines and consumption figures in 2011

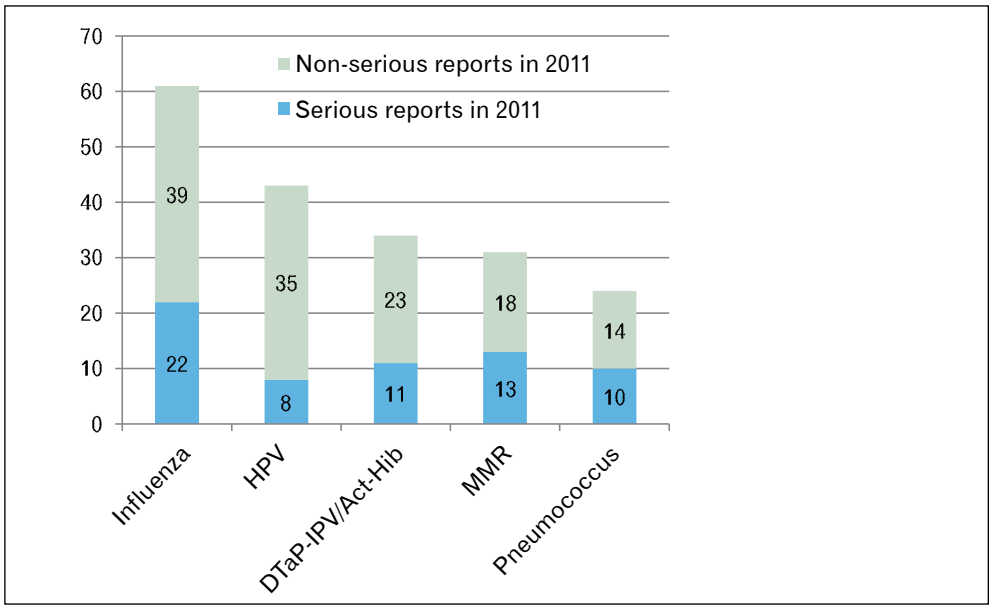

Figure D. Top 5 of the most frequently reported vaccines with adverse reactions in 2011.

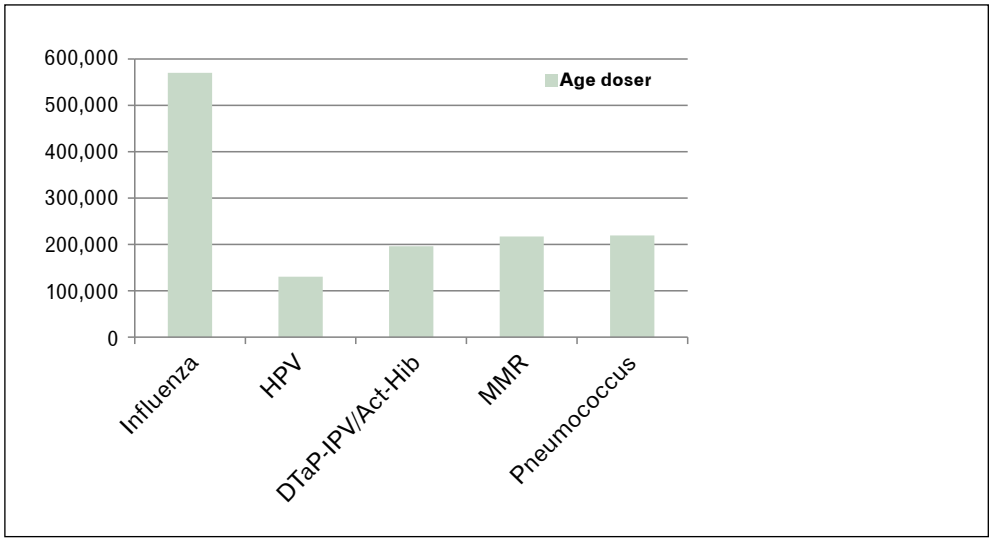

Figure E. Number of doses dispensed of vaccines on the top 5 of the most frequently reported in 2011.

The five most frequently reported vaccines in 2011 are shown in Figure D. In general, there are much fewer vaccines in the market compared to conventional medicines, but on the other hand, many people are vaccinated in connection with different immunisation programmes. In the light of the large exposure, the number of adverse reactions reported for vaccines is low.

Number of persons vaccinated

The Danish Medicines Agency does not have the exact number of persons vaccinated in connection with immunisation programmes, but the Statens Serum Institut (SSI) has stated the number of doses dispensed. Figure E shows the figures from the SSI. The number of vaccines indicates the number of vaccine doses dispensed, and it is thus not necessarily the same as the number of persons vaccinated, as the same person receives several vaccines several times, as is the case, for example, with the vaccines in the childhood immunisation programme.

Influenza vaccines (seasonal influenza and Pandemrix®)

In 2011, the vaccines most frequently reported to the Danish Medicines Agency were influenza vaccines, for which we received a total of 61 reports.

The majority of the adverse reactions reported concerned vaccination against seasonal influenza. The most frequently reported adverse reactions were pain at the injection site and influenza-like symptoms with fever, headache, nausea and muscle pain. All of these are known adverse reactions from the vaccination.

The Danish Medicines Agency also received adverse reaction reports concerning the influenza A H1N1 vaccine Pandemrix® in 2011. Pandemrix® was not used in Denmark in 2011, and the reports concerned all vaccinations carried out in 2009 and 2010. The majority of the adverse reactions reported occurred in 2009/2010, but were not reported until 2011.

Vaccines included in the childhood immunisation programme

Vaccines in the childhood immunisation programme accounted for the other major part of the vaccine reports in 2011. The vaccines concerned included HPV vaccine (Gardasil®), Diphtheria-Tetanus-Pertussis-Polio-Hib(meningitis) vaccine (DTaP-IPV/Act-Hib), vaccine against measles, mumps and rubella (MMR) and pneumococcal vaccine (Prevenar).

The Vaccinationspanelet (Danish medical scientific vaccination panel), represented by the Danish Medicines Agency and the Danish National Board of Health and the Danish State Serum Institute, convenes once a quarter to assess the suspected adverse reactions reported from vaccines – primarily from vaccines involved in the childhood immunisation programme.

The data review in 2011 showed that the majority of the suspected adverse reactions reported were well-known, such as local reactions at the injection site, fever and general malaise – including nausea and fatigue.

The assessment of the adverse reactions reported is described in the newsletter Danish Pharmacovigilance Update from October and December 2011, respectively.
See *Danish Pharmacovigilance Update, October 2011,* and *Danish Pharmacovigilance Update, December 2011*.

Based on the adverse reaction reports received by the Danish Medicines Agency in 2011, the Danish immunisation programme continues to be considered safe.

Steady rise in the number of adverse reaction reports from the hospitals – adverse reaction reports from the Danish hospitals from 2009 to 2011 by region

In 2011, the Danish Medicines Agency received a total of 999 adverse reaction reports associated with a hospital. The number had increased 18% compared with the total of 850 reports received in 2010. See Figure F, page 14.

In autumn 2010, we conducted a nationwide adverse reaction campaign specifically targeted at hospital doctors. The purpose of the campaign was to give hospital doctors more insight into the pharmacovigilance system and the rules in the pharmacovigilance area in order to increase the number of adverse reaction reports from the hospitals.

Already during spring 2011, we saw a rise in the number of reports from the hospitals, and there are indications that this upward trend will continue. See Figure G, page 14.

However, the total number of reports should be seen in the light of the large consumption of medicine in hospitals – including the large consumption of new medicines, the suspected adverse reactions from which doctors have a duty to report. So even though the number of adverse reaction reports from hospitals continues to rise, there is still some way to go before the number reaches a professionally optimal level.

Still a heavy focus on reporting adverse reactions in several hospitals
Several regions have launched initiatives with a particular focus on ensuring that adverse reactions observed in each individual hospital department are reported.

Therefore, in connection with the preparation of this annual report, we offered the five regions to contribute with descriptions of pharmacovigilance initiatives taken in each individual region. Two regions with a particular focus on reporting adverse reaction are the Capital Region of Denmark and Central Denmark Region that both have contributed with a description of their specific initiatives.

The further work to increase the reporting of adverse reactions from hospitals
During 2011, we, the regions and the regional medicinal products committees* have been in a dialogue to uncover the pharmacovigilance-related information need in each individual region, in order to strengthen our cooperation and encourage an increase in the reporting of adverse reactions. In addition, we will continue our cooperation with the Danish Medical Association and the Council for Adverse Drug Reactions on the further work to give doctors an incentive to report more adverse reactions from medicines.

* The regional medicinal products committees' role is to make strategic decisions in the pharmaceutical area with a view to ensuring uniform and optimum use of medicines and at the same time ensuring patient safety in hospitals as well as in general practice.

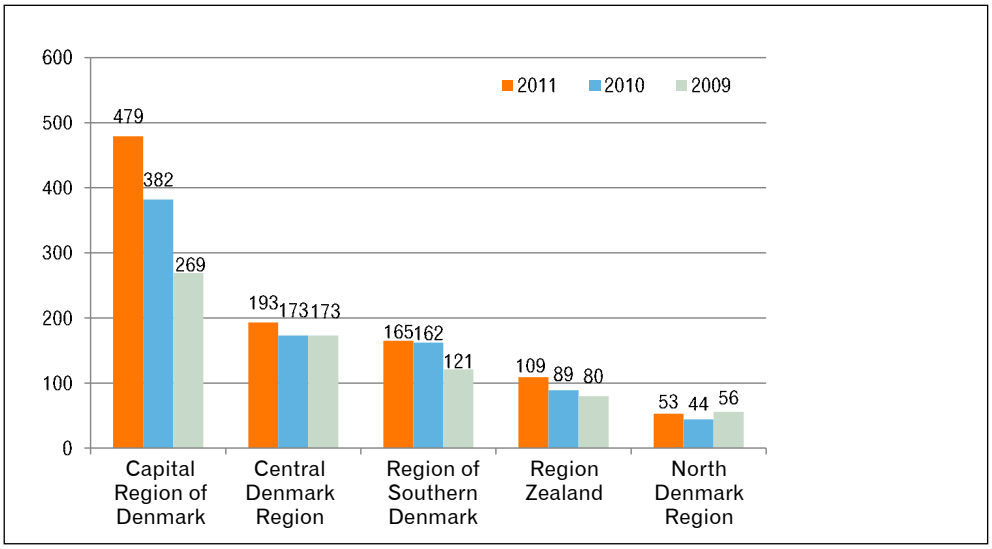

Figure F.

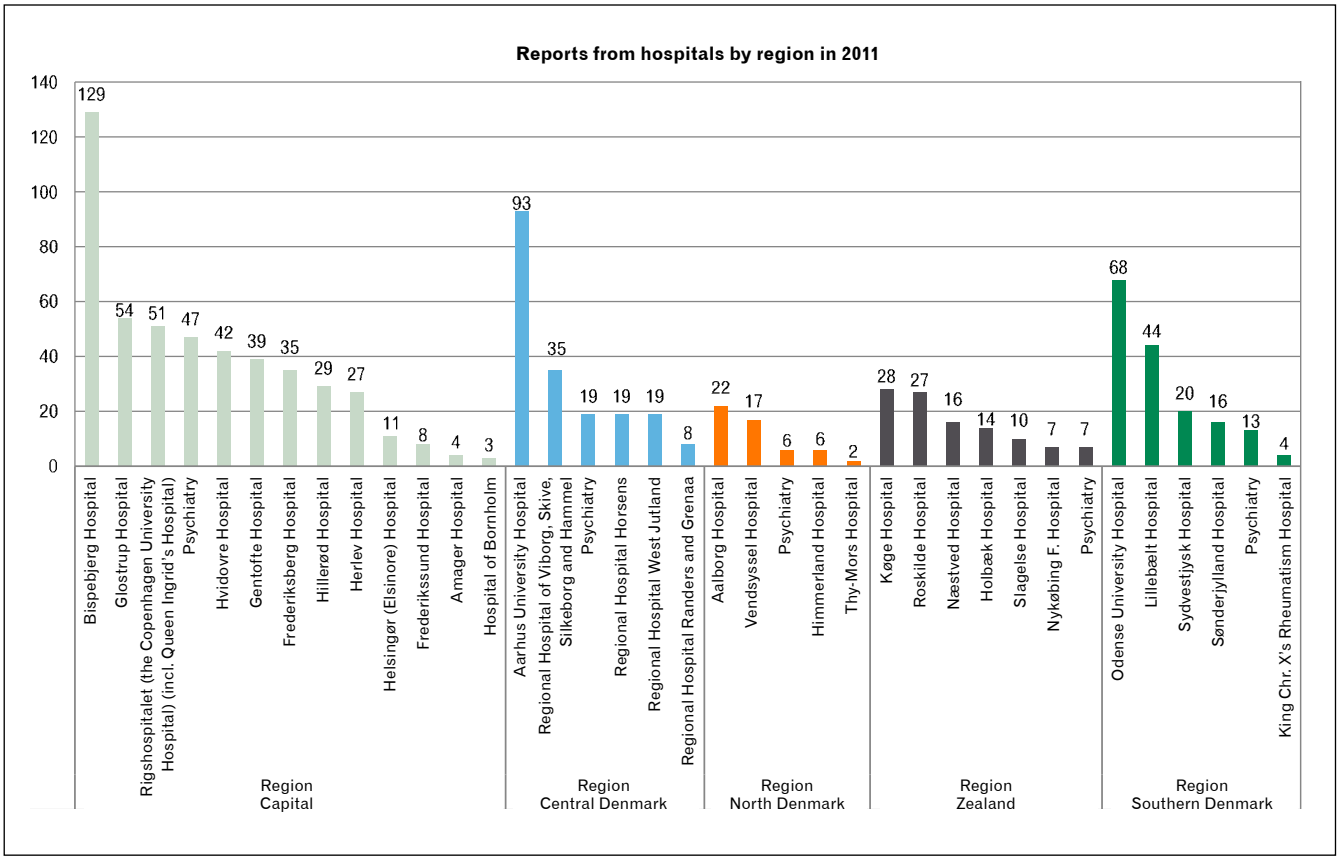

Figure G.

Trial introduction of an Adverse Drug Reaction Manager at Bispebjerg Hospital

Contribution from the medicinal products committee in the Capital Region of Denmark

Adverse drug reactions reported to the Danish Medicines Agency are used in safety monitoring, but it is a well-known fact that under-reporting is substantial.

Based on the national action plan in the pharmacovigilance area, Bispebjerg Hospital introduced an Adverse Drug Reaction Manager (ADR Manager) in their Department of Clinical Pharmacology. The ADR Manager role was handled by doctors in the Department of Clinical Pharmacology, and during the 1-year project period, the ADR Manager handled adverse reaction reporting for five medical departments.

The aim of the project was to facilitate the doctors' work with often lengthy adverse reaction reporting and thereby to step up the number of reports.

In practice, the doctors in the five departments could contact the ADR Manager by telephone or fax, giving information about the patient's civil registration number, medicinal product and adverse reaction. The ADR Manager then took care of submitting the report to the Agency after retrieving information from the electronic data recorded in OPUS, LABKA II, web1000 and EPM.

The ADR Manager was usually contacted by the doctor by telephone, and the conversation lasted for two to three minutes. It took a little less than 30 minutes for the ADR Manager to report an adverse reaction to the Agency (based on 120 reports).

Results showed that the number of adverse reactions reported by Bispebjerg Hospital increased almost fivefold during the project period. See Figure H, page 16.

The Agency was very satisfied with the quality of the reports.

This project shows that a relatively simple reorganisation can step up the number and quality of adverse reaction reports. An ADR Manager function could relatively easy be implemented widely in, e.g., the regions, given that the resources needed are provided.

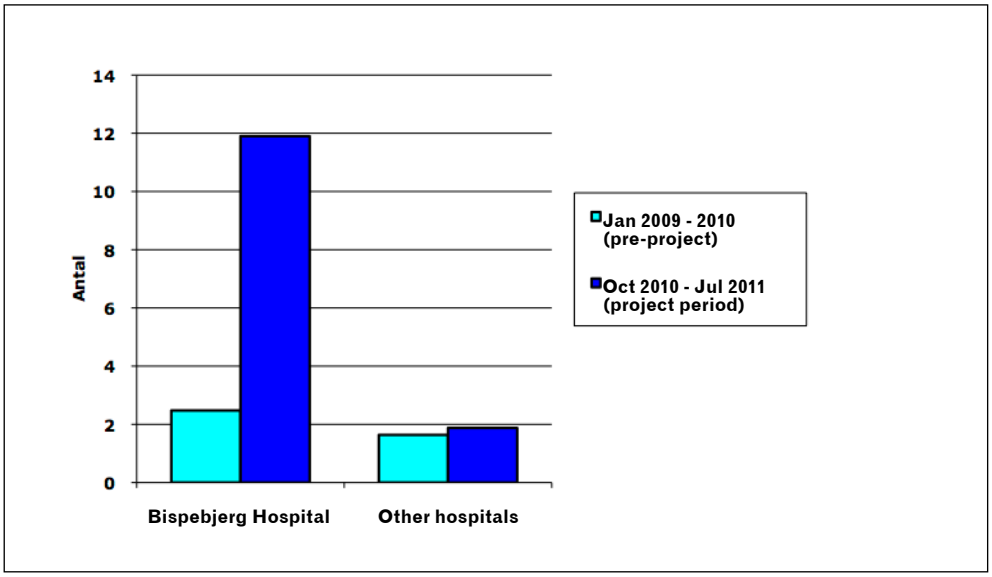

Figure H. Average numbers of monthly adverse reaction reports for Bispebjerg Hospital and other hospitals on average in the Capital Region of Denmark.

Light blue columns show the numbers 21 months prior to intervention.
Dark blue columns show the numbers 10 months after intervention.

Regional guideline for observing and reporting adverse drug reactions

Contribution from the medicinal products committee in Central Denmark Region

Central Denmark Region has issued a regional guideline for observing and reporting adverse drug reactions ("Observation og indberetning af bivirkninger af lægemidler", in Danish only). This guideline serves the purpose of ensuring that adverse reactions are observed and reported correctly when medicating patients.

In hospitals, the clinical pharmacists contribute to adverse reaction reporting, primarily by being alert to new medicinal products as well as being alert when informed about intensified monitoring of older medicinal products. The pharmacists answer questions from the doctors via information from the hospital pharmacy and in the daily clinical contact.

Departments where pharmacists carry out medicine reviews on a regular basis, have a particular focus on adverse reactions. Also, the hospital pharmacy, in connection with EU tender processes, has an extra focus on any new adverse reactions.

The medicinal products committee in Central Denmark Region wishes to simplify the reporting of adverse reactions. We believe it can be accomplished by inserting a shortcut in all EPJ systems to an NSI or RSI service. In this case, the EPJ systems could fill in (nearly) all the fields regarding information known by the medicine systems. Then, all that would be left would be to insert a description of the adverse reaction to be reported. We believe this could increase the number of adverse reaction reports and improve the patient safety.

Medicines subject to stricter reporting requirements, and adverse reaction reports in 2011

When a new medicine is granted a marketing authorisation, it is necessary to follow the safety profile for this new medicine as closely as possible. Therefore, all new medicines are subject to so-called stricter reporting requirements. This means that doctors and dentists, in accordance with Danish pharmaceutical legislation, have an obligation to report all suspected adverse reactions observed within the first two years following placement of a new medicine on the market. Subsequently, doctors and dentists are only obliged to report all serious and/or unexpected adverse reactions.

The Danish Medicines Agency is responsible for updating the list of medicines subject to stricter reporting requirements. The list is updated monthly and is available on the website of the Agency.

Currently, the list concerning stricter reporting requirements includes 51 drugs.

Top 10 of medicines subject to stricter reporting requirements for which the most adverse reactions were reported

The ten drugs on the list for which we have received the most adverse reaction reports during the time they have been subject to stricter reporting requirements, are shown in Table A.

Table A:

	Drug	Company name	Adverse reaction reports (serious)	Users	Prescr. (daily doses)	Hospital (daily doses)
1	Victoza	Novo Nordisk A/S	107 (48)	16318	99%	1%
2	Prolia	Amgen Europe BV	35 (13)	2857	79%	21%
3	Multaq	Sanofi-Aventis	27 (12)	1268	97%	3%
4	Daxas	Nycomed GmbH	26 (8)	748	98%	2%
5	Onbrez Breezhaler	Novartis Europharm Ltd.	22 (9)	9891	99%	1%
6	Simponi	Janssen Biologics B.V.	19 (8)	–	–	–
7	Palexia Depot	Grünenthal GmbH	17 (5)	1470	97%	3%
8	Stelara	Janssen-Cilag International NV	16 (11)	–	–	–
9	Cimzia	UCB S.A. UCB Center	12 (6)	–	–	–
10	Brilique	Astra Zeneca	9 (4)	1797	88%	12%

Drugs that may be prescribed by all doctors.

Medicines that may only be prescribed in hospitals.
The Danish Medicines Agency does not have statements of the number of users for this type of medicines.

Table A. It is important to note the differences in the number of users, daily doses and marketing period, respectively, for the different drugs.

Medicines subject to stricter reporting requirements, and adverse reaction reported in 2011

For 24 out of the 51 drugs that have been subject to stricter reporting requirements in 2011, the Danish Medicines Agency did not receive any adverse reaction reports.

There may be several explanations to this – when a new medicine is marketed it is not necessarily used. And when an adverse reaction is observed, it may not be reported to the Agency. Also, the lack of reports may be due to inadequate knowledge about which medicines are subject to stricter reporting requirements.

Thus, there is an indication that subjecting medicines to stricter reporting requirements does not always have the desired effect. In the opinion of the Danish Medicines Agency there is still every reason to closely monitor adverse reaction reports when new medicines are marketed. Focus is therefore on making it easier for doctors and dentists to stay updated as regards the stricter reporting requirements.

The Agency is using the stricter reporting requirements as a pharmacovigilance tool. The Agency's automated pharmacovigilance system, Empirica, carries out statistical calculations on the entire number of reports received in our adverse reaction database. When evaluating pharmacovigilance results, it will be taken into account whether the medicines are subject to stricter reporting requirements. During our evaluation of signals concerning recently marketed medicines, we pay special attention to new and previously unknown adverse reactions.

On the website of the Danish Medicines Agency, it is possible to see the list of medicines that are subject to stricter reporting requirements. Furthermore, medicines subject to stricter reporting requirements are especially marked on *www.promedicin.dk*.

See the complete *List of medicines with stricter requirements for doctors, dentists and veterinarians to report adverse reactions (in Danish only)*

* An adverse reaction is categorised as serious if it is fatal, life-threatening, causes or prolongs hospitalisation, causes permanent or significant disability, or leads to congenital anomaly or birth defect. An unexpected adverse reaction is an adverse reaction not included in the summary of product characteristics for the medicine in question.

Action Plan I – initiatives during 2011

Respond to adverse reactions – and help making medicine more safe for everyone – a nationwide information campaign targeted at municipal nursing staff

The campaign in brief
At the end of November 2011, the Danish Medicines Agency launched a nationwide information campaign targeted at nursing staff in all Danish municipalities. The purpose of the campaign was to prepare the municipal nursing staff to better respond to adverse reactions and report them to the Agency.

The reason for the campaign was that elderly citizens often have medicine-related difficulties. Difficulties may be caused by too high doses, concomitant use of several types of medicines interacting inappropriately, or adverse reactions in general.

In the beginning of 2012, nursing staff received material from the Danish Medicines Agency concerning how to respond to adverse reactions.

Furthermore, the Authority issued training material for use in nursing staff department meetings – among other things, the aim of the training material was to encourage different professional groups to talk together and to put adverse reactions on the agenda.

The campaign has come off to a good start
The campaign was very well received in all 98 municipalities, all of which have agreed to actively pass on the information about the possibility for nursing staff to report adverse reactions.

The overall campaign results are expected to be ready at the end of April 2012.

Read more about the campaign *Respond to adverse reactions – and help making medicine more safe for everyone* (in Danish only)

Cooperation between the Danish Medicines Agency and professional organisations and networks

At the end of 2010, the Danish Medicines Agency issued a status report on implementation of the Pharmacovigilance Action Plan stating the implementation of Action Plan I. A small number of activities from the action plan continued into 2011. One of these activities concerned preparation of guidelines for use in the cooperation between clinical databases and the Danish Medicines Agency on establishment of IT solutions for adverse reaction reporting, aiming at improving utilisation of existing adverse reaction data in the health care sector systems. These guidelines, resulting from cooperation with the clinical databases Dermbio and DANBIO, were published in autumn 2011 .

Another activity concerned preparation of a new e-learning tool regarding adverse reaction reporting, 'Om at melde bivirkninger' (in Danish only), which is a specific guide for doctors describing how to report adverse reactions from medicines. This tool allows users to test their knowledge of medicines and adverse reactions and find answers to a number of frequently asked questions about adverse reaction reporting. The e-learning tool was launched at the end of 2011, resulting from cooperation between the Danish Health and Medicines Authority, the Danish Medical Association and Danish Regions.

Electronic pharmacovigilance

The Danish Medicines Agency's adverse reaction database comprises more than 76,000 individual reports covering a little less than 4,000 different types of adverse reactions from more than 2,000 different active substances.

Since receiving the first reports in 1968, we have received thousands of adverse reaction reports every year.

The Agency's adverse reaction database has been linked to the analysis programme Empirica. This programme allows for electronic monitoring of combination options in the database.

Increased patient safety

The aim of the electronic monitoring of Danish adverse reaction reports is to increase the safety for medicine users. The new system will point out so-called new signals, i.e., adverse reactions occurring in association with a certain type of medicine more often than expected. Subsequently, the contents of each signal will be assessed based on, among other things, the related reports and biology of relevance for the combination of the medicine and adverse reaction in question.

Cooperation between Denmark and the UK

The UK Medicines and Healthcare products Regulatory Agency (MHRA) has utilised Empirica for signal generation for years. Therefore, a close cooperation between the UK and Denmark is a natural step. This cooperation has great advantages. Firstly, the Danish Medicines Agency may draw upon the vast experience built up by their English colleagues in connection with their use of Empirica. Secondly, the Agency will be given the possibility to compare Danish and English signals.

It is important to activate all the information on patient safety stored in our adverse reaction database. When all the procedures related to signal generation are fully established during the course of 2012, the Danish Medicines Agency's pharmacovigilance will change fundamentally.

New initiatives in 2011 for improved pharmacovigilance

Daily review of serious adverse reaction reports

In 2011, the Agency started to analyse serious adverse reactions reported to the Agency, on a daily basis.

The analyses are reporter-independent. Reports from doctors and other healthcare professionals, companies, lawyers as well as patients and their relatives are all reviewed if we find that a particularly thorough review is needed.

Procedure for daily analyses

The purpose of the daily analyses is to increase patient safety by evaluating whether there is a causal relationship between the medicine in question and the adverse reaction reported.*

Among other things, we look into the temporal correlation between the suspected adverse reaction reported and the medicine, whether the patient is suffering from other diseases or receives treatment with other medicines that may have caused the symptoms, and whether it is an adverse reaction described in the summary of product characteristics for the product in question.

In case of a temporal correlation between the medicine suspected and the adverse reaction, and the latter is not described in the summary of product characteristics for the medicine, the analysis is supplemented with a literature search, among other things, to check whether other similar cases have been described.

In connection with the analyses, we often contact the patient's doctor – general practitioner or hospital doctor – e.g. in order to get medical confirmation of serious adverse reactions reported by a patient. This means that a doctor states that in his/her opinion there may be a correlation between the medicine received by the patient and the adverse reaction in question. The patient's doctor is also contacted if there is a need for further information about the patient’s medical history.

The overall assessment of each individual adverse reaction report is included in the Danish Medicines Agency's safety monitoring of medicines (pharmacovigilance) and, among other things, is compared with other data from the European pharmacovigilance database or Periodic Safety Update Reports (PSURs) for the medicine.

The result of the assessment may be, e.g., that the issue is communicated to the European Medicines Agency, EMA, the European Pharmacovigilance Working Party, PhVWP, and published in the Danish Medicines Agency's newsletter Danish Pharmacovigilance Update.

* A report of a suspected adverse reaction does not imply that a correlation between the adverse reaction and the medicine has been demonstrated. Adverse reaction reports are recorded, even if a correlation between the medicine and an injury is only suspected.

Focus areas in 2011

Safety of antidepressants in pregnant women.

In 2011, another main focus area for the Danish Medicines Agency was antidepressants of the SSRI type, in particular in relation to a potential risk to the foetus and child when the medicine is used for treatment of pregnant women.

Increased consumption of antidepressants

The consumption of antidepressants, especially of the SSRI type, has increased significantly in recent years. This increase in consumption also applies to pregnant women undergoing treatment, which has given cause for concern. In 2010, just below 1,900 pregnant women were undergoing treatment with an SSRI product.

Therefore, in 2011, the Danish Medicines Agency carried out a comprehensive review of safety of the treatment with SSRI products during pregnancy. The review included the scientific literature in this field, Danish consumption and adverse reaction data as well as a review of the current summaries of product characteristics and package leaflets for the products.

Increased risk of malformations in foetuses, if mothers have received treatment with an SSRI product during the pregnancy

Based on literature, we concluded from the review that the use of SSRI products in pregnant women increases the risk of serious conditions in the foetus and the newborn child. There is a risk of malformations – especially including malformations in the cardiovascular system, persistant pulmonary hypertension of the newborn, PPHN, and withdrawal symptoms. However, the scientific studies also show that the risk of serious adverse reactions is low.

Danish adverse reaction reports concerning SSRI products used during pregnancy

Since the market introduction of the first SSRI products at the end of the 1980s and up until the middle of June 2011, the Danish Medicines Agency received 74 Danish reports of adverse reactions in children or foetuses suspected to be associated with use of SSRIs in the mothers. These 74 reports include four cases of infant deaths and 14 cases of foetal death and abortion.

Earlier studies have shown a slightly elevated risk of malformations in the cardiovascular system in newborns, whose mothers have been treated with the SSRI products paroxetine and fluoxetine in the first trimester. As regards the other medicines in the group of SSRI products (sertraline, citalopram, escitalopram and fluvoxamine), the results were not as unambiguous and valid.

The Danish Medicines Agency has received reports of heart malformations in newborns exposed to citalopram or sertraline during pregnancy.

A registry study has outlined the risk of malformations in children, whose mothers have received treatment with other SSRI products during pregnancy

In order to further highlight the risk of malformations after treatment with SSRIs during pregnancy, the Danish Medicines Agency initiated a registry study to investigate if pregnant women's use of other SSRI products may lead to a risk of malformations. The registry study was carried out in cooperation with the Statens Serum Institut (SSI), and the results were published at the beginning of 2012.

Information in summaries of product characteristics for SSRIs

In connection with reparing a report concerning use of SSRIs during pregnancy, we also reviewed summaries of product characteristics and package leaflets for all SSRI products. Based on this review, we concluded that the summaries of product characteristics generally include warnings in relation to pregnancy and lactation; however, the actual wording varies. A few marketed drugs lacked information, and so the Agency initiated a control project in order to ensure that missing warnings are included.

However, potential adverse reactions from medicine must be weighed against studies indicating that an untreated depression in a pregnant woman can cause danger to the woman and foetus. Depression may be associated with increased alcohol and tobacco consumption, unhealthy diet and other unhealthy habits of life. These factors may be harmful to the pregnant woman and foetus.

Overall review conclusions

The Danish Medicines Agency's overall conclusions in the report were in compliance with the Agency's guidelines in the area, according to which medical treatment of depression in pregnant women should be made only in consultation with a specialist in psychiatry and after other non-medical options have been considered. In the individual case, the potential beneficial and harmful effects of treatment should be weighed against the risks involved for the pregnant woman and unborn child if a depression is not treated adequately.

Since the note was published, we have issued regular updates regarding new reports of adverse reactions associated with use of SSRIs in pregnant women, and we will continue close monitoring of medicines in this field.

Read *The Danish Medicines Agency's overview note concerning SSRIs* (in Danish only)

Study on the correlation between urine-derived hormonal preparations and Creutzfeldt-Jakob disease (CJD)

In 2011, information from several national health registers was pooled by the the Danish Medicines Agency in cooperation with the Danish National Board of Health to see whether women who died from Creutzfeldt-Jakob disease in Denmark, at an earlier point in time either had received artificial insemination or redeemed a prescription for a so-called urine-derived hormonal preparation (UHP) for infertility such as Menopur® or Pregnyl®.

The reason for pooling information from the registers was descriptions in foreign reports of prion detection in urine-derived hormonal preparations, and there were speculations as to whether there could be a link to Creutzfeldt-Jakob disease. However, pooling information from Danish registers did not provide a basis for such a conclusion.

The result gave us no reason to take further action, as nothing in the data suggested a possible link, and the data basis at present is not solid enough to indicate such a link at all.

No observed connection

In Denmark, CJD is the cause of death for approximately six persons a year. However, it was only possible to check for a connection for women who had died from CJD in the period 1994-2009, as the Danish registers only began to register fertility treatment and medicine consumption in 1994*.

In this period, 49 women in Denmark died from CJD. In 1994, 44 of these 49 women were older than 45 years, i.e. they were above the age limit for artificial insemination introduced in 1997**. This means that for 90% of the women, we are unable to find information about any previous fertility treatment in the Danish registers.

The remaining five women, who died from CJD in the period 1994-2009, were not registered as having received fertility treatment, including treatment with UHP.

As we have no available data prior to 1994, we could not conclude that the women who died from CJD in the period 1994-2009 had received fertility treatment.

However, based on the study, we can positively say that we have not detected any signals that gave us cause to investigate this matter any further.

The women's age distribution is shown in Figure 1. The women's median age was 68 years.

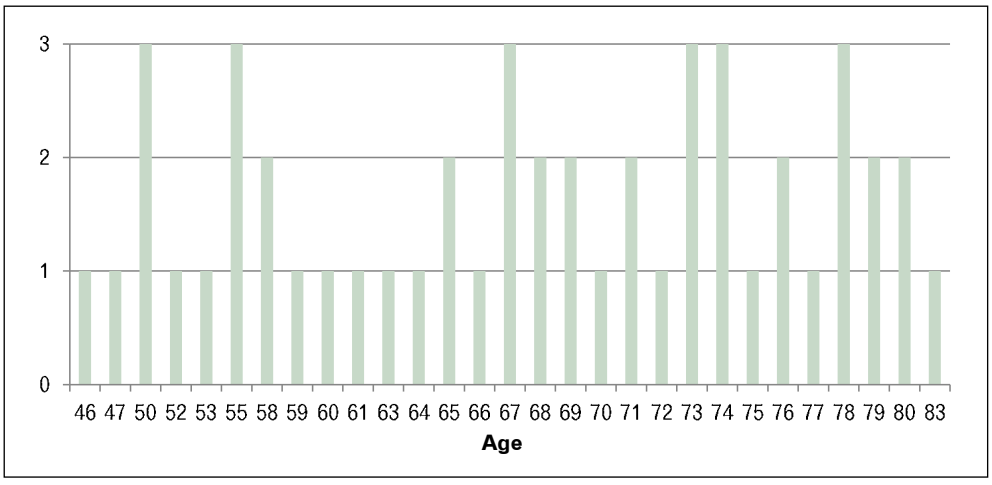

Figure 1. Age distribution of women who died from Creutzfeldt-Jakob disease in the period 1994-2009

The Danish Medicines Agency will continue to monitor the development and regularly update the study results.

* The IVF register, which contains data on artificial insemination in both public and private clinics, was started in 1994 at the same time as the Register of Medicinal Product Statistics. The National Patient Registry began to register data on all types of fertility treatment in the public sector from 1999 and inseminations at private clinics in 2006.

** Following the adoption of Danish Act no. 460 of 10 June 1997 on artificial insemination in connection with medical treatment, diagnostics and research etc. (Lov nr. 460 af 10. juni 1997 om kunstig befrugtning i forbindelse med lægelig behandling, diagnostik og forskning m.v.), women older than 45 years have not been allowed to receive artificial insemination (neither IVF or insemination).

Information from four registers was pooled
The result was obtained by extracting the civil registration numbers of women who have died from CJD from The Causes of Death Registry.

We then tried to find these civil registration numbers in the IVF register (In Vitro Fertilisation), in the Register of Medicinal Product Statistics under redemption of prescriptions for UHP as well as in the National Patient Registry under codes for all kinds of fertility treatment.

Read more about *Detection of prion protein in urine-derived hormonal preparations does not give rise to discourage use*

A new model for proactively monitoring a new medical treatment – the cooperation between the Danish Medicines Agency and Aalborg Hospital Science and Innovation Center, Aalborg Hospital

In August 2011, the Agency initiated a cooperation partnership with North Denmark Region, Aalborg Hospital Science and Innovation Center, Aalborg Hospital – a partnership intended to contribute to improving patient safety for patients who are prescribed the new anticoagulants such as dabigatran (Pradaxa®).

Background for the cooperation
In 2011, 89,410 were undergoing treatment with vitamin K antagonists. Seven out of ten were citizens older than 65 years, and this number will most likely rise due to the age composition of the population. Anticoagulant treatment has always been one of the most risky medical treatments since overtreatment increases the risk of bleeding, while undertreatment increases the risk of blood clots. Compared with older anticoagulants, the new medicines have several benefits such as easier dosing for which reason routine laboratory monitoring is not required. The effect of the new medicines is independent of the diet, and the number of interactions with other medicines is most likely much lower. On the other hand, already at present there are indications that the new medicines increase the risk of bleeding, and there is no specific antidote to inhibit overdose-related bleeding complications effectively. Therefore, it is important to monitor patients undergoing treatment with these medicines closely already from the date of placement on the market. This is when the new potential adverse reactions often appear.

Also, the balance between the efficacy of the medicines and the adverse reactions may change over time, in case the precautions described in the summaries of product characteristics are not followed, or if following placement on the market the patients are from a much wider section of the population than the patients who participated in the studies.

For this reason, the Danish Medicines Agency and Aalborg Hospital Science and Innovation Center in Aalborg entered into cooperation on the new anticoagulant treatment. The work will consist in monitoring the treatment in Denmark and continuously communicating the knowledge gathered on the safety of the medicines.

Data forming the basis for monitoring

Our latest knowledge of safety related to the use of the new anticoagulants comes from literature and the EU collaboration. In coordination with researchers and experts from Aalborg Hospital Science and Innovation Center in Aalborg, the Danish Medicines Agency will keep a close watch on the development in this area in Denmark on a continuous basis based on data from our register of medicinal product statistics and adverse reaction database. We continuously assess the adverse reactions reported and monitor the consumption pattern by looking at the patient population as well as the doctors' prescription pattern.

Furthermore, the researchers from Aalborg Hospital Science and Innovation Center in Aalborg will establish a research database for pooling information from a number of Danish registers such as the Register of Medicinal Product Statistics and the National Patient Registry and for analysing current issues observed in Denmark as well as abroad and including them in scientific research.

The new proactive model involving close cooperation on the latest data will allow us to quickly provide advice to other authorities, doctors and patients in case caution needs to be exercised when prescribing or using the new anticoagulants.

Marketing the new anticoagulants

Dabigatran (Pradaxa®) was marketed in Denmark in August 2011, and rivaroxaban (Xarelto®) was marketed in February 2012. The third active substance, apixaban, is also entering the Danish market. These newer anticoagulants are expected to replace the use of older anticoagulants, the so-called vitamin K antagonists such as warfarin (Marevan®) and phenprocoumon (Marcoumar®), to an increasing extent.

Indication for the new anticoagulants

The new anticoagulants are approved for the prevention of apoplexy and systemic embolism in patients with atrial fibrillation.

Read more about *The first results from a new study on Pradaxa®* (dabigatran etexilate) (in Danish only)

Quality assurance of the Danish Drug Interaction Database

In 2011, the work on quality assurance of the Danish Drug Interaction Database was completed. The project was carried out in cooperation between the Danish Medicines Agency and Denmark's three hospital departments of clinical pharmacology in Aarhus, Odense and Copenhagen.

The quality assurance work was initiated in autumn 2009.

The purpose of the work was to ensure that all data in the Danish Drug Interaction Database are valid and reliable.

Background to the quality assurance

The background to the project was the results of a sampling showing a need for quality assurance of all the existing drug interactions in the database.

The work comprised a revision of the existing texts and recommendations as well as a literature search with the objective of filling any gaps in the documentation of the interactions.

In addition, there has been focused on the class effects – however, only for data for which is was possible to describe a class effect – i.e., descriptions of interactions across substance classes.

In case class effects were missing we assessed whether a class effect could be described based on the existing articles and background knowledge concerning the pharmacokinetics/pharmacodynamics of the substances in the two substance groups.

Cooperation between the departments of clinical pharmacology and the Danish Medicines Agency

The work was done partly by the doctors in the three departments of clinical pharmacology, who were each responsible for quality assuring one-third of the interactions in the database, and partly by the Danish Drug Interaction Database work group in the the Danish Medicines Agency.

Further improvements of the Danish Drug Interaction Database

In addition to quality assuring data, the Danish Drug Interaction Database was improved several times during 2011. The IT system was future-proofed through a technical update, but also improvements affecting internal as well as external database users were made.

Among the improvements for the external users is a general overview of how two different categories of drug groups interact (class effect), the hospital pharmacies' SAD products have been included, and finally, you can search on both active substance and product names for herbal remedies as well as strong vitamins.

The improvements of the Danish website *www.interaktionsdatabasen.dk* have been based on requests from healthcare professionals, and have to some extent also been implemented on the Danish website *www.medicinkombination.dk,* which is aimed at citizens.

International collaboration in the pharmacovigilance area in 2011

The European Pharmacovigilance Working Party, PhVWP, consists of one member from each of the 27 EU countries. The working party convenes 11 times a year in the European Medicines Agency in London. All new signals about serious adverse reactions from the continuous monitoring of medicine safety are discussed in this working party. The working party covers adverse reactions from all medicines and therefore is handling a wide spectrum of cases. The Danish Medicines Agency continuously publishes the results of the assessments on the website of the Agency, in the monthly newsletter Danish Pharmacovigilance Update and as ad hoc announcements on the website. The typical outcome is a revision of the summary of product characteristics and package leaflet, and if necessary issuing a DHPC (Direct Healthcare Professional Communication) letter and initiation of supplementary investigations.

In 2011, the working party among other things looked at:

- The vaccine Pandemrix® for the prevention of H1N1 influenza (swine influenza) and the risk of sleep attack (narcolepsy) and Guillain-Barré syndrome
- The acne product isotretinoin and the risk of psychiatric adverse reactions
- Proton pump inhibitors and the risk of pneumonia, bone fractures and too low magnesium levels
- Antipsychotics and the risk of congenital malformations when using them during pregnancy
- Bisphosphonates for the treatment of osteoporosis and the risk of atypical bone fractures (stress fractures)
- The smoking cessation product Champix® and the risk of cardiac adverse reactions and psychiatric adverse reactions
- Antidepressants (citalopram / escitalopram) and the risk of heart rhythm problems (QT prolongation)
- Statins for the treatment of elevated cholesterol levels and the risk of diabetes
- Tacrolimus (Protopic®) and pimecrolimus (Elidel®) for the treatment of children's eczema (atopic dermatitis) and the risk of cancers
- NSAIDs and the risk of cardiac adverse reactions
- Contraceptive pills and blood clots
- Quality issues with peritoneal dialysis fluids.

In 2011, in addition to looking at specific adverse reactions, the working party was also busy preparing the implementation of the new common European legislation aimed at further strengthening the patient safety. The new legislation enters into force in July 2012. Among other things this implies that the working party in the future will not only be assessing risks of medicines, but also the benefit/risk balance.

Furthermore, the working party is involved in a broad range of development projects concerning, e.g., improvement of the communication of adverse reactions to patients and doctors and optimisation of methods for discovering and monitoring new medicine-related signals.

Pharmacovigilance in 2012

Pharmacovigilance in the year ahead will be influenced by the new European legislation on adverse reactions, which will enter into force in summer 2012. In addition, the communication concerning adverse reactions will be strengthened and changed, and the cooperation with the Statens Serum Institut (SSI) and Aalborg Hospital Science and Innovation Center in Aalborg will be more clearly manifested.

New common European medicines legislation

The new rules on pharmacovigilance which will be harmonised throughout Europe, have two main purposes. One is to strengthen pharmacovigilance. The other is to intensify and rationalise pharmacovigilance through increased work sharing between the medicines regulatory agencies and through easing the administrative burden on the pharmaceutical industry and the regulatory agencies.

The main contents of the changed rules is introduction of a new pharmacovigilance strategy placing greater emphasis on ensuring proportionality between pharmacovigilance and known and potential risks, and a new and broader definition of the concept adverse reactions.

The changes entail increased work sharing between the medicines regulatory agencies of the member countries and new common procedures for assessment of safety data.

New pharmacovigilance committee

A new Pharmacovigilance Risk Assessment Committee (PRAC) will be established under the European Medicines Agency (EMA) with the purpose of providing expertise and resources for monitoring drug safety.

Common European procedures for the assessment of periodic safety update reports

Also, new common procedures for the assessment of periodic safety update reports concerning drug safety will be introduced. Common procedures for the assessment of consequences for the marketing authorisations will be introduced as well. The purpose is to ensure that member states make uniform substantiated decisions based on the overall experience with the drugs.

Overviews of Danish adverse reaction data

For some time, there has been a desire to create more openness with respect to suspected adverse reactions reported to the Danish Medicines Agency by, among others, doctors and other healthcare professionals as well as patients and their relatives. Therefore, overviews of suspected adverse reactions have been made available for the general public by the Authority. This new initiative creates a unique possibility for insight into Danish adverse reaction data. The overviews of adverse reactions are presented in anonymised and systematic form generated in the Danish Medicines Agency's IT business system Sentinel.

Improved utilisation of registers and professional expertise through cooperation with various research institutions

As described, the Danish Medicines Agency entered into professional cooperation with Aalborg Hospital Science and Innovation Center in Aalborg and the Statens Serum Institut (SSI) in 2011. The first concrete results of this cooperation have come in 2012. The professional scientific cooperation is a reinforcement of the Danish Medicines Agency's activities.

Finally, the Danish Parliament will in 2012 discuss a proposal amending the Danish Medicines Act including a proposal to replace the current Council for Adverse Drug Reactions with a new Council for Pharmacovigilance.