

# ANNUAL REPORT

**The Danish Medicines Agency's  
annual pharmacovigilance  
report 2010**



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## 2010 – development and renewal in the pharmacovigilance area

*By Henrik G. Jensen, Director of the Consumer Safety Division, Danish Medicines Agency*

The work in the pharmacovigilance area in 2010 was particularly characterised by development and renewal. This development and renewal was very much attributable to the implementation of the Danish Minister for the Interior and Health's action plan for side effects (Action Plan I) which was introduced in January 2009 in collaboration with the Council for Adverse Drug Reactions\*. However, the passing of new EU pharmacovigilance legislation to be implemented in 2012, as well as targeted establishment of the Danish Medicines Agency's new IT system for the handling of side effect reports, have also contributed to the development and renewal in the area.

The Minister's action plan for side effects designed to improve the pharmacovigilance system was launched in order to augment the assessment and utilisation of side effect data and to increase side effect reporting through simpler reporting systems and strengthened competencies. The outcome of the initiatives taken in connection with the implementation of the action plan became apparent in 2010, and the results have generally given the pharmacovigilance work a tremendous boost and provided a solid foundation for further development and renewal in the pharmacovigilance area.

The new EU legislation on pharmacovigilance, passed by the EU Council of Ministers and the European Parliament in 2010, is a significant step forward for medicine users as well as pharmaceutical companies and authorities. Focus is directed towards more risk-based pharmacovigilance work, more collaboration and work sharing between the competent authorities in the EU, which will contribute to enhancing patient safety. Furthermore, changed procedures will provide both companies and authorities with an opportunity to simplify work processes, freeing up resources that can be spent more efficiently on safety and avoiding unnecessary red tape.

The purpose of the new rules is to ensure, among other things, that the member states make uniform decisions in matters relating to safety, and that this takes place on the basis of recommendations from European experts. Another important thing is that a new common web portal on European medicines and safety must be established and managed by the European Medicines Agency (EMA). The individual member states must create national web portals linking to the European web portal. The web portal must contribute to ensuring as much transparency as possible about medicine safety.

In 2010, the work of the Council for Adverse Drug Reactions also focused on implementing Action Plan I. However, other subjects were also discussed at the Council's four meetings in 2010, including: Safety when using paracetamol during pregnancy, discussion of the Danish Medicines Agency's focus reports and information activities, and the Danish Medicines Agency's planning of the work on risk-based monitoring was also scrutinised. Finally, the status of the Danish Medicines Agency's pharmacovigilance work on the influenza vaccination A (H1N1) was reviewed.

\*The Council for Adverse Drug Reactions provides general consultancy to the Danish Medicines Agency on pharmacovigilance issues and makes recommendations and solution proposals on how to improve the prevention and monitoring of side effects from medicine. Read more about the Council for Adverse Drug Reactions [here](#).



Whereas the pharmacovigilance work in 2009 was heavily influenced by the many side effect reports concerning Pandemrix®, Gardasil® and Eltroxin®, accounting alone for close to 1,000 reports, the pharmacovigilance work in 2010 has in many ways been focused on communication, involving several targeted information campaigns, monthly newsletters and a focus project on the safety of treatment with methylphenidate – an issue which received much media attention. The focus project on the safety of treatment with methylphenidate was the first specific result of a more risk-based approach to the work with side effect reporting as well as with more transparency in the Danish Medicines Agency's pharmacovigilance work.

In 2010, following discussions with the Council for Adverse Drug Reactions, the Danish Medicines Agency completed two information campaigns – one with the object of getting more side effect reports from hospital doctors, and one targeted at making medicine users aware of the possibility of reporting side effects to the Agency themselves.

The campaign aimed at hospital doctors was planned after thorough preliminary analysis. The campaign used the chief medical officers responsible for training at the hospitals to issue information about the pharmacovigilance system and the pharmacovigilance work. Already, there is an increase in the number of reports from the hospitals. A solid foundation has thus been created for further reports from the hospitals – but the work to increase the number of hospital reports continues.

'Danish Pharmacovigilance Update', the Danish Medicines Agency's electronic newsletter on medicine and side effects, continued publishing in 2010 and now has nearly 1,700 subscribers. A survey conducted among subscribers in 2010 indicated a high level of satisfaction with the newsletter. We also received a number of suggestions for changes, which we will incorporate in the coming work.

The work focusing on development within the pharmacovigilance area will continue in 2011. During spring 2011, a new action plan (Action Plan II) will be planned, focusing further on information, collaboration and analysis. The new action plan, which will also be executed in collaboration with the Council for Adverse Drug Reactions, will continue to focus on the fact that efficient and thorough pharmacovigilance work requires close collaboration between all involved parties. We are looking forward to working together with medicine users, doctors and other healthcare professionals, the Danish regions, the organisations and the pharmaceutical companies in order to continue our fruitful collaboration to the benefit and promotion of patient safety.



## Development in the number of reported side effects from 2008 to 2010 by reporter type

### Development in the number of reported side effects from 2008 to 2010 by reporter type

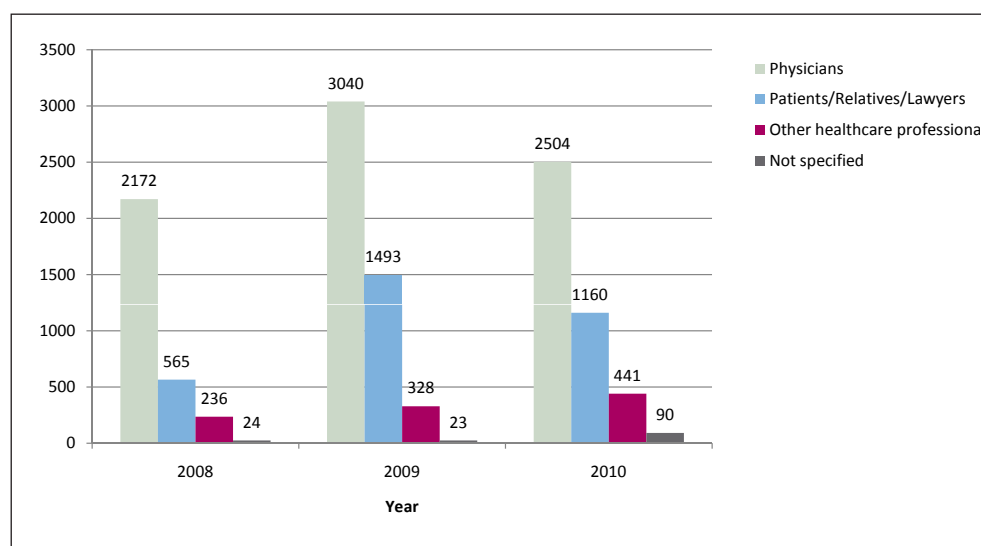


Figure A. Development of the number of side effect reports from 2008 to 2010 according to the function of the person who submitted the report.

The past two years have seen a significant increase in the number of side effect reports received by the Danish Medicines Agency. Overall, the increase was 20% in 2010 compared to 2008 – from 2,997 reports in 2008 to 4,195 reports in 2010. In particular the number of reports from patients and relatives has increased dramatically.

In 2010, almost twice as many patients and relatives reported side effects as in 2008. However, among other healthcare professionals – nurses, pharmacy staff, social and healthcare assistants etc. – the number of reports has also almost doubled since 2008. The number of reports from doctors, patients and relatives was particularly high in 2009, which saw almost 1,000 more reports from doctors than in 2008 and more than double the number of reports from patients and relatives – from 565 in 2008 to 1,493 in 2009.

Seen from a Danish viewpoint, 2009 was a very special year with unusually many side effect 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 annual report on monitoring of side effects 2009 [here](#).



Seen in this light, the total number of side effect reports in 2010 has fallen back to a more normal and steadily inclining curve compared to 2009, once the individual media cases from 2009 have been taken out of the equation. Side effect issues with intense media focus often appear in the report statistics, and 2009 was a fine example of this.

The upward curve for side effect reports in 2010 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 side effects in order for medical treatment to become as safe as possible. And as we saw in 2009, a massive focus on medicine and side effects can considerably stimulate reporting.

### **Who filed reports in 2010?**

In 2010, doctors again filed the most side effect reports with the Danish Medicines Agency. Doctors accounted for a total of 2,504 reports in 2010, medicine users and their relatives for 1,160 reports and other healthcare professionals for 441 reports.

Not surprisingly, doctors generally report the majority of side effects. In addition to the fact that doctors, due to the nature of their work, have a professional interest in reporting side effects, doctors also, in accordance with Danish pharmaceutical legislation\*, have an obligation to report all serious side effects from all medicines as well as unexpected suspected side effects – i.e. side effects not stated in the summary of product characteristics for the medicine. Furthermore, doctors have an obligation to report all suspected side effects observed within the first two years following placement on the market.

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

Side effects can be reported via the Danish Medicines Agency's website [www.meldenbivirkning.dk](http://www.meldenbivirkning.dk).



# Top 10 of the most frequently reported active substances and consumption figures in 2010

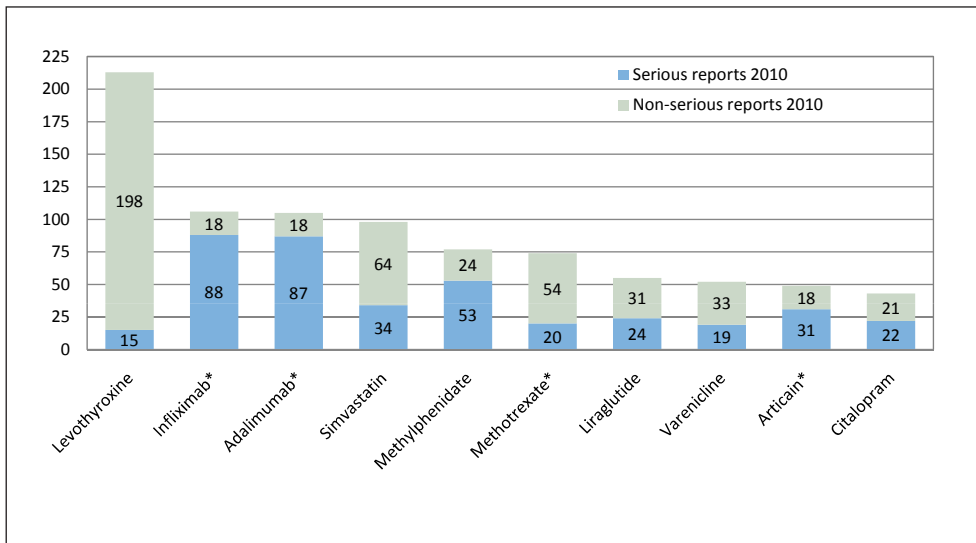


Figure B. Top 10 of the most frequently reported active substances with side effects in 2010.

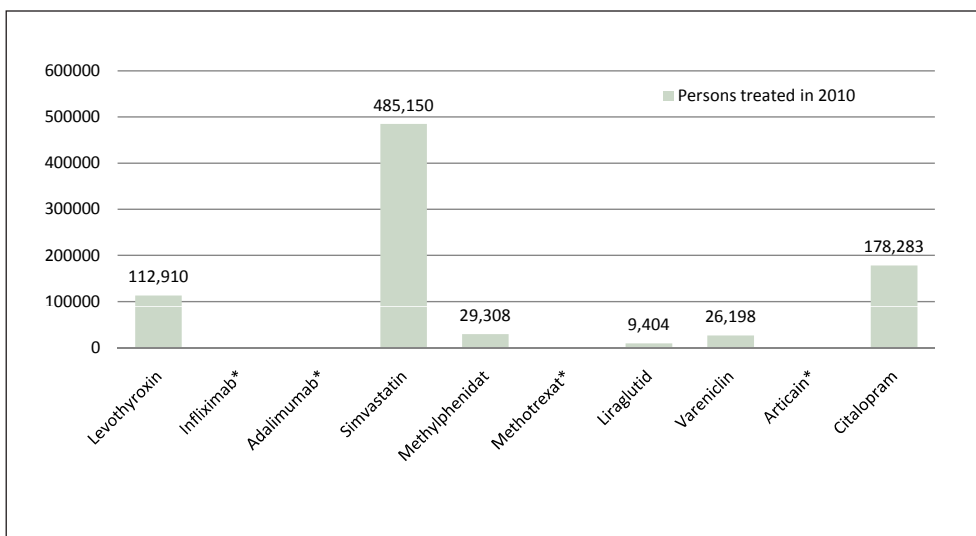


Figure C. Number of persons in treatment with active substances on the top 10 of the most frequently reported in 2010.

Figure B shows the ten active substances for which most side effects were reported in 2010. The number of side effect reports for a specific type of medicine should be seen



in relation to the consumption of that medicine. Figure C shows the consumption of the ten active substances. The number of persons undergoing treatment is calculated as the number of persons having submitted at least one prescription for the active substance in question in 2010.

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

### **Several explanations why an active substance is among the top 10 most reported**

Several factors may influence whether many or few side effects are reported for a specific type of medicine. The most obvious factor is the scope of medicine consumption, which is the case for e.g. medicine containing simvastatin or citalopram, which has wide-spread consumption, but the age of the medicine is also important. As mentioned, stricter reporting requirements apply to doctors concerning medicine that has been on the market for less than two years. For instance this applies to medicine containing liraglutide. However, the number of reports may also reflect that there are actually more side effects than for other drugs. Among others, this applies to the group of biological medicines, which may entail more serious side effects, and which are therefore only used to a limited extent for the treatment of serious diseases.

Last, but not least, specific incidents as well as increased focus in the media as well as in clinical circles may cause periodic changes in the reporting pattern for specific types of medicine.

### **Levothyroxine (Eltroxin® and Euthyrox®)**

The highest number of reports in 2010 concerned the active substance levothyroxine, used for the treatment of low metabolism. The Danish Medicines Agency received a total of 213 reports in 2010 concerning levothyroxine. This was also the most frequently reported active substance in 2009, but in comparison, there were 998 reports in 2009.

The number of reports concerning levothyroxine thus saw a considerable decrease compared to 2009, even though the number of people undergoing treatment has been almost constant – close to 113,000 in 2010 and 107,000 in 2009.

The frequent reports concerning levothyroxine in 2009 and 2010 were caused by a switch to a new Eltroxin® formulation in 2009, which may have caused changed reactions to use of the medicine. The vast majority of reports in 2010 concerning levothyroxine were submitted at the beginning of the year. Since then, the number of reports has stabilised at the same level as before the switch to the new formulation.

For many years, Eltroxin® has been the only marketed levothyroxine product in Denmark, but towards the end of 2009, another product, Euthyrox®, was also marketed. For more details on Eltroxin®, see the annual report on monitoring of side effects 2009 [here](#).





Fatigue, headache, dizziness, concentration difficulties and weight increase were the primary side effects reported for levothyroxine in 2010 – symptoms which may indicate medicine overdosing or underdosing. The vast majority of reports concerning levothyroxine in 2010 were thus not serious.

### **Simvastatin (Zocor® etc.)**

Simvastatin is one of eight active substances in a group of so-called statins used in the treatment of high blood cholesterol levels. As shown in Figure C, more than 485,000 people underwent treatment with simvastatin in 2010. Given the high consumption of this type of medicine, it is consequently not surprising that relatively many side effect reports concern simvastatin. 65% of the total of 98 side effect reports in 2010 were well-known and not serious. Among the most frequently reported side effects were muscle and joint pain, muscle spasms and fatigue.

### **Citalopram (Cipramil® etc.)**

In 2010, a total of 44 side effect reports concerned antidepressants containing citalopram. Also in this case, the number of reports should be considered in relation to the fact that treatment with citalopram is widespread. Close to 180,000 people underwent treatment with medicine containing citalopram in 2010. Half of the side effects reported were serious. The most frequently reported side effects – dizziness, headache and nausea – are common and known side effects from this medicine. There have also been cases reported of suicidal thoughts in patients being treated with citalopram, which may be a side effect from the medicine, but which is also a known element of the symptoms of severe depression.

### **Methylphenidate (Ritalin® etc.)**

Methylphenidate is used in the treatment of ADHD and narcolepsy. In recent years, there has been much focus on treatment with methylphenidate. This may have stimulated reporting of side effects for this specific type of medicine and may have contributed to methylphenidate being on the list of the most frequently reported active substances. In 2010, the Danish Medicines Agency also focused on medicine containing methylphenidate, when we performed a thorough assessment of the safety of using methylphenidate in the treatment of ADHD. See the Danish Medicines Agency's focus report on the safety in treatment with methylphenidate [here](#). An English summary is available [here](#).

A considerable part of the side effect reports concerning methylphenidate in 2010 were categorised as serious – almost 70 per cent. These were primarily known psychiatric side effects described in the product information for medicine containing methylphenidate, e.g. anxiety, sadness, sleeping problems, aggression and depression.

The Danish Medicines Agency continues to focus strongly on medicine containing methylphenidate and possible signs of changes in the side effect profile.

### **Varenicline (Champix®)**

In 2010, the Danish Medicines Agency received 52 side effect reports concerning the use of varenicline, which has been approved for the treatment of tobacco addiction. Most of the reports submitted in 2010 did not concern serious side effects. They concerned e.g.



sadness, nausea and headache, which are known side effects described in the product information for Champix®.

In connection with renewal of the marketing authorisation for Champix®, the Danish Medicines Agency recently concluded a thorough assessment, in collaboration with the other EU countries, of the safety profile for varenicline. The conclusion was that the benefits still outweigh the potential risks associated with the medicine.

### **Biological medicines containing infliximab (Remicade®) and adalimumab (Humira®)**

The biological medicines Remicade® and Humira®, so-called 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 medicines are only prescribed if other medicines have had insufficient effect.

In 2010, more than 80% of the side effects reported for these medicines were categorised as serious, and they concerned well-known symptoms such as infection and allergic reactions. The relatively large proportion of serious side effects reported for these medicines should be seen in the light of the severity of the diseases being treated. In the opinion of the Danish Medicines Agency, there is still an acceptable balance between the benefits of the availability of biological medicines for patient treatment and the disadvantages in the form of risk of serious side effects.

### **Methotrexate (Metex® etc.)**

In 2010, the Danish Medicines Agency received a total of 74 reports of suspected side effects concerning methotrexate. Methotrexate is used for the treatment of different types of cancer and for the treatment of diseases such as arthritic diseases and psoriasis.

The most frequently reported side effects in 2010 were well-known symptoms such as nausea, diarrhoea, vomiting, fatigue and headache. The vast majority of reports were not serious. A considerable part of the side effects reported concerned the product Ebetrex®, which was marketed in Denmark in December 2009 for the treatment of arthritic diseases. Shortly after marketing of the new product, the Danish Medicines Agency received an increasing number of reports about changes in effect when switching from other methotrexate products to Ebetrex®.

Subsequently, the Danish Medicines Agency investigated the potential cause of the many reports and found no differences in formulations between the different methotrexate products that could immediately explain the side effects reported. Furthermore, new medicine often receives particular attention from doctors and patients and is also subject to stricter reporting requirements for the first two years on the market. The stricter reporting requirements for Ebetrex® may also help explain the large number of reports.



**Liraglutide (Victoza®)**

Last year, the Danish Medicines Agency received 55 reports concerning side effects 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.

The most frequently reported side effects in 2010 from liraglutide were nausea, constipation and vomiting. The most likely reason why this medicine is on the top 10 of the most frequently reported in 2010 is the stricter reporting requirements.

**Articain (Septanest® etc.)**

Articain is used as an anaesthetic in dental treatments. The Danish Medicines Agency received 49 reports concerning the use of articain in 2010. The vast majority of the side effects reported concerned nerve damage and loss of or changed mouth sensitivity after treatment.

During 2010, the Danish Medicines Agency reviewed articain in regard to suspected nerve damage, and in this connection a number of cases have been reported of which a large proportion concern side effects occurring before 2010. Having discussed the overall international experience, the European Pharmacovigilance Working Party has concluded that there is no basis for adding further warnings to the summary of product characteristics, and the balance between benefits and risks is still assessed to be positive.



# Top 10 of the most frequently reported vaccines and consumption figures in 2010

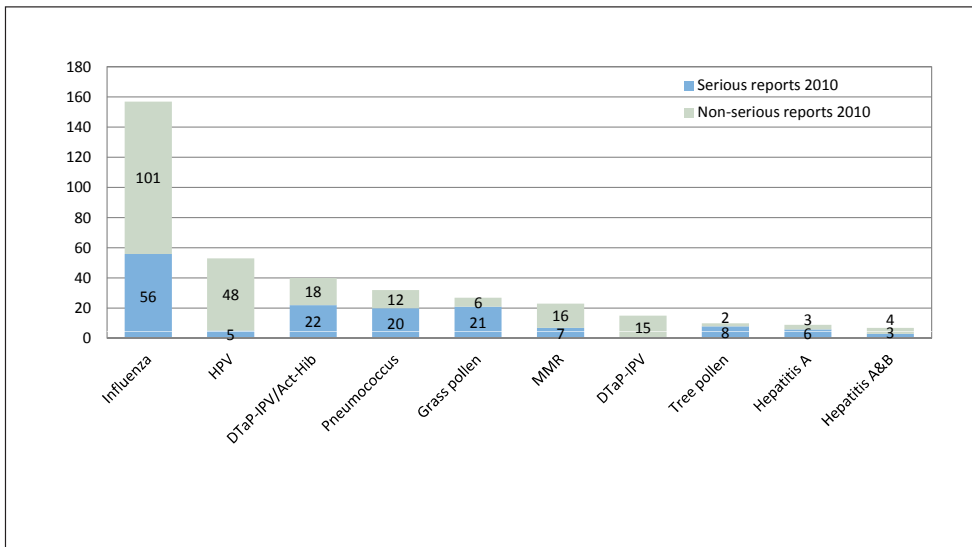


Figure D. Top 10 of the most frequently reported vaccines with side effects in 2010.

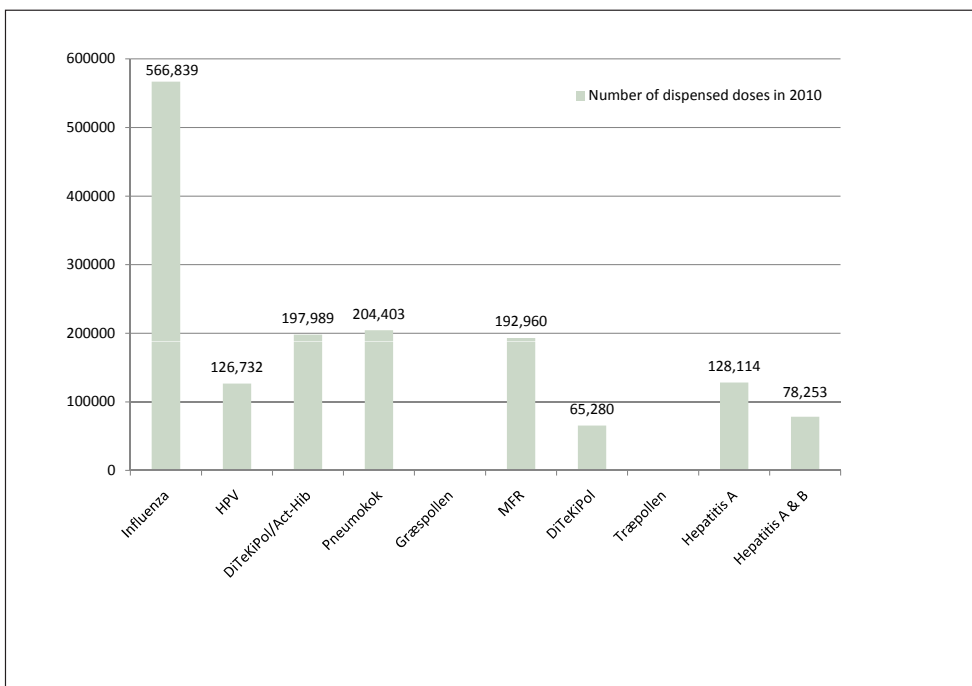


Figure E. Number of doses dispensed of vaccines on the top 10 of the most frequently reported in 2010.



The ten most frequently reported vaccines in 2010 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 side effects 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 State Serum Institute has stated the number of doses dispensed. Figure E shows the figures from the Danish State Serum Institute. It has not been possible to obtain the number of allergy vaccines against grass pollen and tree pollen. 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.

### **Pandemrix® and seasonal influenza vaccines**

Mass vaccination of persons in special risk groups in connection with the influenza A (H1N1) pandemic dominated the side effect reports for vaccines in 2010. Normally, there are only very few reports concerning vaccination against seasonal influenza, but the heavy focus on the pandemic vaccine Pandemrix®, combined with the rule on stricter reporting requirements for doctors, caused an increase in the number of reports submitted in 2010. The majority of the side effect reports concerned Pandemrix®, a total of 111, and they were predominantly submitted by doctors. Of these, 32% were categorised as serious in the form of e.g. joint pain, pain in the vaccination area and allergic reactions. By far the most reports concerned known side effects such as reactions at the injection site and influenza-like symptoms. Together with other authorities, the Danish Medicines Agency continues strict monitoring of reports concerning Pandemrix®.

Pandemrix® has attracted particular attention after several instances of narcolepsy were reported as a side effect from the vaccine in Sweden, Finland and, most recently, in France. This also gave rise to several investigations into the possible connection between narcolepsy and vaccination with Pandemrix®.

The EU continues the work on mapping any correlation between Pandemrix® and narcolepsy. In autumn 2010, a collaboration between the European Centre for Disease Prevention and Control (ECDC), research institutes and the company that produces the vaccine launched a project, VAESCO, involving epidemiologic studies of Pandemrix® in nine countries, including Denmark. The results of these studies will be available during summer 2011. The matter will also be assessed by the European Pharmacovigilance Working Party and the Committee for Medicinal Products for Human Use (CHMP). New Swedish study results will, combined with the results from a Finnish study and the results from the rest of the world, form part of these discussions.

In Denmark we have not received any reports on narcolepsy following vaccination with Pandemrix®. Although Pandemrix® is no longer used in Denmark, pharmacovigilance continues in 2011.



### Allergy vaccines

Allergy vaccines (grass pollen and tree pollen) and vaccines often given in connection with travel abroad (hepatitis A and hepatitis A and B) were also on the top 10 of vaccines for which the most side effects were reported in 2010. However, there were only very few reports compared to the large number of persons vaccinated. As is the case for the other vaccines, the side effects were almost exclusively reported by doctors and other healthcare professionals, the vast majority being non-serious side effects. The side effects reported are already known: allergic reactions as well as shortness of breath and malaise.

### Vaccines included in the childhood immunisation programme

In 2010, the Danish Medicines Agency received a total of 168 side effect reports concerning side effects in connection with the Danish childhood immunisation programme. 55 of these were classified as serious, e.g. seizures and high fever. The most side effects were reported in girls following vaccination with Gardasil® – the HPV vaccine against cervical cancer. Primarily girls are vaccinated with Gardasil®, so if reports concerning Gardasil® are excluded, there is no gender difference in the number of reports submitted.

The Danish Medicines Agency does not know the exact number of children vaccinated in 2010, but approx. 60,000 children were born in 2010, and the Danish State Serum Institute estimates that there was a coverage of 80-90%, depending on vaccine, just like the previous years. The vast majority of reports were submitted by doctors, 87%, which has also been the general trend in previous years. Other healthcare professionals represented 10% of these reports in 2010.

In April 2010, Prevenar (7-valent) was replaced with the 13-valent pneumococcal vaccine, Prevenar13, otherwise the programme is unchanged compared to 2009.

In 2009, focus was on the newly introduced HPV vaccine, Gardasil®, which is probably one of the explanations of the many reports specifically concerning this vaccine. In 2010, there were thus considerably fewer reports compared to 2009. In particular reports on atopic dermatitis, which were subject to much attention in 2009, dropped significantly in 2010.

Primarily well-known non-serious side effects were reported for Gardasil® in 2010, such as local reactions at the injection site, headache, fever and nausea.



## Side effect reports from hospitals in 2010 by region

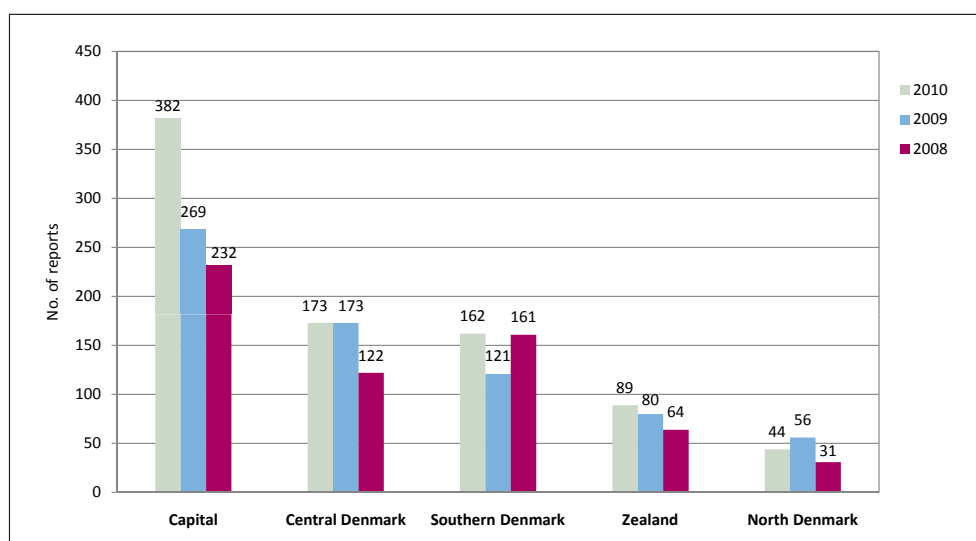


Figure F. Side effect reports from Danish hospitals in 2010 by region.

### Increase in the number of side effect reports

In 2010, the Danish Medicines Agency received 850 side effect reports associated with a hospital. This was an increase of more than 22% compared to 2009, where we received a total of 699 reports, an increase of 39% over 2008.

2008 is the most relevant year for comparison because 2009, as mentioned previously, was an unusual year. This was particularly due to the three specific issues which received much media attention and resulted in extraordinarily many reports: Eltroxin®, Pandemrix® and the contrast medium Omniscan®.

To increase the number of side effect reports from hospitals, the Danish Medicines Agency launched a nationwide side effect campaign in September 2010 specifically aimed at hospital doctors. The campaign focused on side effect reporting in hospitals and was designed to give doctors more insight into the pharmacovigilance system and the rules in the pharmacovigilance area. Read more about the hospital campaign [here](#). Even though we cannot measure definitively whether the campaign had an effect on the number of reports submitted in the long term, things still seem to be going in the right direction.

However, the total number of reports should be seen in the light of the large consumption of medicine at hospitals, including the large consumption of new medicines, the side



effects from which doctors have a duty to report. So even though positive results have been achieved, there is still some way to go before the number of reports submitted reaches the level where the Danish Medicines Agency believes it should be, i.e. more than a doubling.

We will therefore initiate dialogue with the Danish regions and the regional medicinal products committees\* during 2011, and we will also continue our collaboration with the Danish Medical Association and the Council for Adverse Drug Reactions on the further work to get doctors to report more side effects from medicines.

\*The regional medicinal products committees must 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.





## Campaigns 2010 – focus on side effect reporting

In 2010, we launched two side effect campaigns – one consumer campaign and one hospital campaign – and we started a third – a campaign targeted at healthcare professionals in the care sector. Common to the campaigns was that they focused on reporting side effects to the Danish Medicines Agency. The campaigns formed part of the Minister's action plan for improved pharmacovigilance.

### Report a side effect – a consumer campaign

#### The campaign in brief

In May 2010, we launched a 2-week campaign in pharmacies in order to make medicine users aware of the possibility of reporting side effects to the Danish Medicines Agency. The campaign focused particularly on serious and unexpected side effects.

The campaign involved various material for the pharmacies, help for patient organisation phone counselling in order to handle questions on side effects, and input for the organisations for articles in member magazines and on websites.

#### The result – an efficient model for the work ahead

The campaign helped establish a very efficient collaboration model which we can use in the work ahead with patient organisations and pharmacies, which are in direct contact with the medicine users, regarding their medicine and any side effects.

The campaign confirmed an assumption that pharmacies can assist in identifying serious and unexpected side effects of which the Danish Medicines Agency particularly wants to receive reports. On average, each pharmacy was in dialogue with customers about 5-6 side effects experienced during the 2-week campaign period. Of these, one or two were relevant to report. This corresponds to each pharmacy potentially being able to identify 35 side effects in a year.

A private course is now being offered in side effect reporting at pharmacies, using the experience gathered from the campaign.

In addition, the number of reports submitted from patients and relatives has been steadily increasing since 2008, and there is every indication that this trend will continue in the years ahead.

### Respond to serious and unexpected side effects to increase patient safety – a hospital campaign

#### The campaign in brief

In September 2010, the Danish Medicines Agency launched a nationwide campaign with the message above, targeted at Danish hospital doctors.

The purpose of the campaign was to increase hospital doctors' awareness and knowledge about side effects and the duty to report them to the Danish Medicines Agency.



The campaign was initiated with personal letters to all hospital doctors and a folder on side effect reporting and monitoring. To ensure local rooting, hospital managements appointed a contact person in every hospital who had the task of following up on the efforts locally. The chief medical officers responsible for training also played an important role because an important element of the initiative was a presentation designed to teach the wards about side effects.

### **The result – higher knowledge about side effects and side effect reporting**

If we look at the number of side effect reports from hospitals, there has been progress since 2009, to some extent attributable to the campaign. As it happens, the average number of reports has increased to 90 reports submitted per month during the 6-month campaign period. In comparison, the average number of reports submitted was 55 per month during the six months prior to the start of the campaign.

Furthermore, there was generally widespread knowledge about the information efforts among hospital doctors. The information efforts met an information need and increased the focus on identifying and reporting side effects. A subsequent analysis showed that considerably more people have knowledge about which side effects to report and know the definition of a side effect than was the case in a pre-analysis in 2009.

Our analysis also showed that there is widespread understanding in the hospital sector of the importance of reporting side effects. We have thus created a solid foundation for our activities in 2011 as regards getting more reports from hospital doctors.

## **Respond to side effects – an information effort towards healthcare professionals in the care sector**

### **The campaign in brief**

In November 2010 we started the preparations for a third side effects campaign with the goal of heightening the focus on side effects with healthcare professionals in the care sector. The efforts are especially directed at nurses and social and healthcare assistants as well as social and healthcare helpers.

### **The campaign will be launched in summer 2011**

The campaign involves a folder for the nurses and social and healthcare assistants, a flyer for social and healthcare helpers and training material for use in department meetings at the individual nursing homes and living units.

The campaign material was prepared by the Danish Medicines Agency on the basis of a pre-analysis and continuous sparring with Local Government Denmark (association of municipalities), the union Fag og Arbejde, the Danish Nurses' Organization and the Association of Social and Health Directors in Denmark.

### **The outlook for the campaign is good**

A pre-analysis has shown that the target group generally feels responsible for monitoring whether citizens experience side effects from their medicine, and they are therefore very motivated to acquire more knowledge about side effects and report them to the Danish Medicines Agency.



The pre-analysis also showed that the target group is apparently unaware that they can report side effects to the Danish Medicines Agency themselves, and they are also unfamiliar with the Danish Medicines Agency's website [www.meldenbivirkning.dk](http://www.meldenbivirkning.dk).

There is thus not only a need to make healthcare professionals in the care sector aware of the possibility to also report side effects, there is also a desire to know more about the pharmacovigilance system.



## Focus 2010 – risk-based pharmacovigilance

**The Danish Medicines Agency monitors all medicines authorised in Denmark. Monitoring is particularly intensive for new medicines, but there may also be a need to focus increasingly on medicine which has been on the market for many years – for instance if we receive signals about new side effects or if there are changes in the use of the medicine.**

**In 2010, we therefore started focusing much more than usual on special circumstances within medicine and safety.**

### **Safety of methylphenidate in the treatment of ADHD – a focus project**

Our first focus area was medicine containing methylphenidate for the treatment of ADHD, because our statistics showed an explosive increase in consumption. The number of people who had been given methylphenidate had seen a more than tenfold increase in the period from 2000 to 2009. And the increase turned out to be particularly high for adults above the age of 18. For this group, the number of patients had increased from 839 in 2000 to 11,444 in 2009 – an increase of approx. 1,200 per cent. In 2009, 11,500 children and adolescents (aged 6 -18 years) were given methylphenidate.

Our study did not cause any immediate concern regarding the use of methylphenidate in the treatment of children and adolescents with ADHD. Even though the number of side effect reports concerning methylphenidate has increased over the past ten years, the majority of the side effects are well-known, primarily psychiatric side effects. Furthermore, we have received no new information causing us to change the existing safety information for methylphenidate.

On the other hand, the study showed that there is extensive off-label consumption among adults with ADHD – medicine containing methylphenidate has not been approved for the treatment of adults with ADHD because of insufficient documentation on the safety and efficacy of the medicine in relation to this patient group.

The study also showed that there is no detailed treatment guide for adults in the way that it exists for children. It is thus more difficult to minimise the risks in connection with the treatment of adults with ADHD.

#### **Special risk areas in the treatment of adults**

In the report, we focused on the fact that the risk profile may differ for adults with ADHD because of the insufficient documentation for efficacy and safety in the treatment with methylphenidate. In this context, we identified a number of special risk areas. They involve the risk of developing cardiovascular diseases, the risk of treatment in connection with pregnancy, the risk of abuse of methylphenidate and serious mental disorders. In addition, we found that a basis for consensus in the treatment of adult ADHD patients is



an important prerequisite for increasing patient safety – particularly given the constantly increasing number of adults undergoing treatment.

### **What has happened since the focus report?**

Since we published the focus report, we have received 55 reports concerning methylphenidate. This is a high number of reports compared to the number of reports submitted previously for methylphenidate. Since the Danish Medicines Agency started recording side effects in 1968 and up until 1 June 2010, we have received a total of 186 reports on methylphenidate. The 55 reports submitted since the focus report thus represent a high number over a short period. 36 of these have been submitted by a pharmaceutical company marketing one of the methylphenidate products.

The Danish Medicines Agency is currently in contact with the company regarding the circumstances of these reports.

The latest 55 reports also include two deaths. In one instance, we have assessed that there is a possible link to the treatment with methylphenidate. The case involved a young man, hospitalised with ventricular fibrillation, who subsequently died from a cerebral incarceration after extended resuscitation attempts. ECGs taken during the hospitalisation showed indications of the congenital heart disease WPW (Wolff-Parkinson-White syndrome). The patient had been treated with Ritalin® (methylphenidate) since childhood and was also being treated for asthma. The patient had consulted a doctor specifically because of episodes of heart palpitations. Read more in the Danish Pharmacovigilance Update, December 2010 [here](#).

The other case involved a young man undergoing treatment with Concerta® (methylphenidate) against ADHD, who died suddenly. Within the previous six months, the man had undergone treatment with Concerta® for approx. six weeks. It cannot be ruled out that Concerta® contributed to the death. The Danish Medicines Agency currently awaits a post-mortem report that will bring us closer to discovering whether any causal relationship exists between the death and the treatment with Concerta®. Read more in Danish Pharmacovigilance Update, March 2011 [here](#).

We continue to maintain a heightened focus on reports concerning methylphenidate.

Read the entire focus report [here](#).

## **Long-term treatment of osteoporosis patients with bisphosphonates**

Following the completion of our focus report on the safety related to methylphenidate, we started on a new focus area which will be published during 2011.

Here, we focus on long-term treatment of osteoporosis patients with bisphosphonates and side effects in connection with the treatment. In recent years, we have received reports



on e.g. atypical stress fractures, osteonecrosis of the jaw and oesophageal cancer as possible long-term side effects from treatment with bisphosphonates.

In addition, our knowledge about long-term treatment with bisphosphonates is extremely limited. Only very few studies have investigated the issue, and the study results are not unambiguous.

In spite of the limited knowledge about effect and side effects from long-term treatment, figures from the Danish Medicines Agency's Register of Medicinal Product Statistics show that over 75% of osteoporosis patients undergoing treatment with bisphosphonates continue their treatment for more than five years, and more than half of the them continue their treatment for more than 12 years.

Until further knowledge is available, we will focus on the importance of paying attention to symptoms which may be signs of potential long-term side effects and, not least, reporting them to the Danish Medicines Agency.



# Danish Pharmacovigilance Update – strong interest in the Danish Medicines Agency's newsletter on side effects

**Danish Pharmacovigilance Update addresses issues which are important to the use of medicine both in general practice and in the hospital sector. The newsletter addresses important issues, such as new medicine that is subject to stricter reporting requirements, new potential side effects from medicine that has been on the market for several years, medicine with exceptionally high consumption in the population or just medicine which, for some reason or other, requires special attention.**

**Danish Pharmacovigilance Update also intends to contribute to making it clearer how Danish side effect reports are used in Denmark and forms part of an overall effort through our international collaboration.**

**Danish Pharmacovigilance Update is issued on the third Thursday of every month in Danish, and the English version follows shortly after.**

In November 2010 we celebrated Danish Pharmacovigilance Update's first anniversary. Since the first newsletter was issued, the number of subscribers has increased steadily. Today, we have close to 1,700 subscribers, and new ones are added constantly.

To ensure the continued professional relevance of the newsletter, we conducted an evaluation in November 2010 on the basis of a questionnaire survey among the subscribers.

## **Great satisfaction with the newsletter**

The questionnaire asked, among other things, about the subscribers' attitude to the contents of the newsletter, its form and relevance.

Overall, the survey disclosed great satisfaction with the newsletter. The vast majority of subscribers read all articles, and they are considered to be relevant in everyday practice. For instance, we received the following response:

*"...I think that your topics are good and thought-provoking".*

*"An excellent newsletter with short updates on news in the pharmacovigilance area. Good idea to have links to the individual articles to allow you to seek additional knowledge".*

*"To me, the length is appropriate, and the content is OK and relevant".*

*"It is useful that you can use Danish Pharmacovigilance Update as a reference work, so I don't have to remember where and when a topic was addressed".*

We also received a number of useful suggestions for articles and themes, which we will include in the work ahead with the newsletter.

Subscribe to Danish Pharmacovigilance Update [here](#). You can also subscribe to Danish Pharmacovigilance Update using the e-form for side effect reporting.



## The Omniscan® case 2010

In 2009, the Minister of the Interior and Health decided to launch an independent legal investigation of the Danish Medicines Agency's procedures concerning the MRI contrast medium Omniscan® and the side effect nephrogenic systemic fibrosis. The result of the legal investigation was ready in November 2010. Read the result of the legal investigation published on 12 November 2010 [here](#) (in Danish only).

As a consequence of the Omniscan® case, the Minister launched the national action plan to improve pharmacovigilance in Denmark (Action Plan I) back in 2009. The action plan was the result of thorough preparatory work including all relevant stakeholders. It consisted of a total of seven focus areas with the purpose of ensuring strengthened pharmacovigilance.

Action Plan II, which will be launched during 2011, is one of the measures to further improve the pharmacovigilance system.

In September 2009, the Danish National Board of Health published guidelines for examination of kidney patients using contrast media. At the editor's deadline, the National Board of Health has initiated a revision of the guidelines to take account of amendments passed by the EU. Read the National Board of Health's guidelines from September 2009 [here](#) (in Danish only)

Read more about MR contrast media containing gadolinium, and the side effect nephrogenic systemic fibrosis in the Danish Medicines Agency's description of the contrast medium Omniscan® [here](#) (in Danish only).





# International collaboration in the pharmacovigilance area 2010

**Since the establishment of the European Medicines Agency (EMA) in 1995, the Danish Medicines Agency has participated in meetings in the European Pharmacovigilance Working Party (PHVWP).**

**Here, many important cases concerning side effects are assessed, either at the initiative of the European Committee for Medicinal Products for Human Use (CHMP) or at the initiative of one or more national authorities, e.g. the Danish Medicines Agency.**

**Examples of side effect cases considered by the European Pharmacovigilance Working Party in 2010:**

## **Hormonal preparations used in the genetic treatment in connection with menopause (oestrogen and progesterone)**

Since 2001, a joint European Core Summary of Product Characteristics has existed for oestrogen and progesterone products approved for the treatment of menopausal symptoms. The joint European Summary of Product Characteristics is continuously updated as new knowledge emerges.

In 2010, the Summary of Product Characteristics was updated with new information about the risk of several cancer types, breast cancer, ovarian cancer, uterine cancer and circulatory disorders, blood clots in the heart or brain. See the updated summary of product characteristics [here](#) (in Danish only)

Read more in the PHVWP monthly report, January 2010 [here](#).

## **Fluoxetine and the risk of heart deformities**

The product information for fluoxetine was updated in 2010 with information on the potential slightly elevated risk of heart deformities when using fluoxetine during the first trimester of pregnancy. This update took place on the basis of a meta-analysis of epidemiological studies of the risk of deformities in children born by mothers who, during their pregnancy, took medicine containing fluoxetine to treat severe depression. Read more in the PHVWP monthly report, February 2010 [here](#). You can also read the Danish Medicines Agency's newsletter Danish Pharmacovigilance Update, April [here](#).

## **SSRI products and risk of elevated pulmonary circulation hypertension in newborns**

New studies have shown a slightly elevated risk of persistent pulmonary hypertension in newborn babies whose mothers took an SSRI product during pregnancy because of severe depression.

The summaries of product characteristics for medicines containing the following active substances have been updated with the new information: citalopram, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, paroxetine, sertraline, venlafaxine. Read more in the PHVWP monthly report, March 2010 [here](#). You can also read the Danish Medicines Agency's newsletter Danish Pharmacovigilance Update, April [here](#).



**Antidepressants (SSRI, TCA) and risk of fractures**

Several studies published in literature suggest that there may be a slightly elevated risk of fractures in connection with treatment with SSRI antidepressants and tricyclic antidepressants. Information about this risk has therefore been added to the summary of product characteristics for the SSRIs citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine and sertraline as well as for the tricyclic antidepressants amitriptyline, clomipramine, dosulepine, doxepine, imipramine, lofepramine and nortriptyline. Read more in the PHVWP monthly report, March 2010 [here](#).

**Tamoxifene and risk of reduced therapeutic response**

Studies have shown that patients with oestrogen receptor-positive breast cancer who are undergoing treatment with tamoxifene may have reduced effect of medicine containing tamoxifene when used together with medicine which inhibits CYP2D6. Information about this risk has been added to the summary of product characteristics for medicines containing tamoxifene. Read more in the PHVWP monthly report, November 2010 [here](#).

**Corticosteroids and psychiatric side effects**

It is well-known that systemic treatment with corticosteroids may be accompanied by psychiatric side effects. A review of side effect reports and published epidemiological studies have shown that even corticosteroid treatment administered intranasally or via inhalation may be associated with psychiatric side effects. Information about psychiatric side effects has been added to the summary of product characteristics for corticosteroids. Read more in the PHVWP monthly report, November 2010 [here](#).

**Fluoroquinolones and risk of prolongation of the QT interval**

A review of various data from pre-clinical and clinical studies, side effect reports and studies conducted after marketing of fluoroquinolones began has shown a slightly elevated risk of prolongation of the QT interval and possibly torsades de pointes associated with the treatment. The risk is not the same for all fluoroquinolones. It is considered to be the greatest for the fluoroquinolones gemifloxacin and moxifloxacin. The information has been added to the summary of product characteristics. Read more in the PHVWP monthly report, December 2010 [here](#).



## Pharmacovigilance 2011

The headings for the pharmacovigilance work in 2011 are increased collaboration, further digitalisation and more communication. At the same time, the preparations for the new legislation on pharmacovigilance, which is to enter into force in mid-2012, will be drawing a lot of resources. The 2008 pharmacovigilance action plan (Action Plan I) has been completed, and as follow-up, we will launch a new pharmacovigilance action plan (Action Plan II) in 2011, running from 2011 to 2013. The focus of the new plan will be on strengthening collaboration between all players, further improvement of the various IT tools and solutions, strengthening professional knowledge about and utilisation of side effect data and strengthening development of new knowledge about medicine safety.

Action Plan II must also be developed in collaboration with all players – i.e. doctors and other healthcare professionals, organisations, medicine users via the patient organisations, the Danish regions and the pharmaceutical companies. The action plan will have a tremendous impact on the pharmacovigilance work in the years ahead. It is therefore important that all stakeholders within the area submit comments during the consulting procedure ahead of the final approval of Action Plan II.

The work in the Council for Adverse Drug Reactions will continue in 2011 where it ended in 2010. The implementation of Action Plan II will also be characterising the work for the year, and the Council for Adverse Drug Reactions will be making recommendations and providing inspiration to the Danish Medicines Agency's informational activities and will be discussing initiatives for promoting a safer medicine use.

During 2011, the Danish Medicines Agency will fully benefit from our new IT system in the pharmacovigilance area. We will be able to utilise an improved analytical capacity – an opportunity which we should use to perform a number of new analyses of medicine safety.

In 2011, we will also continue our work on informing about the importance of reporting side effects, and in this connection we will increasingly involve the various players and invite them to participate in dialogue in this area.

Reporting of side effects from hospitals is an important part of the overall monitoring of medicine safety in Denmark. During 2010, we have come far down the road, and we have thus established a solid foundation for our new activities in 2011.

We are looking forward to continuing our work of monitoring of side effects and not least to the collaboration with medicine users, healthcare professionals and the pharmaceutical companies to the benefit of patient safety.

