

ANNUAL REPORT

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



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2009 – a busy year for pharmacovigilance

By Ib Valsborg, Chairman of the Council for Adverse Drug Reactions

2009 was in many ways a busy year for pharmacovigilance in Denmark. The Minister of Health launched an action plan to improve the system for the reporting of side effects, and a number of specific cases resulted in a marked increase in the number of side effect reports in relation to previous years – actually an increase of no less than 63% relative to 2008.

For medicine safety, it is important that side effects are reported. At the time of approval, medicine is generally only tested on a few thousand patients, so it is crucial that the side effects are monitored closely to ensure rapid intervention if the benefit/risk balance becomes negative.

The reporting of side effects must be flexible and uncomplicated, but it must, at the same time, contain the information required to register and treat the side effect correctly. A balance needs to be stricken here, and, in my opinion, the Danish Medicines Agency got closer to the goal in 2009.

The electronic reporting forms were made more efficient, and web services are made available free of charge to the IT companies which develop IT for GPs and hospitals.

In 2009, the rules on the reporting of side effects were tightened, so that physicians, dentists and veterinarians must now report serious side effects within 15 days. Follow-up questions to the physicians are now handled by the Danish Medicines Agency and not by the pharmaceutical companies – a large wish from the GPs has now been fulfilled.

The Council for Adverse Drug Reactions has very high expectations for 2010 and the coming years when it comes to the reporting of side effects from hospitals. Together with the Agency, the Council launched an information initiative aimed at hospital physicians in 2009, as a survey shows that hospital physicians do not place special focus on the reporting of side effects and, in some cases, lack information about the pharmacovigilance system. At the same time, under the Danish Healthcare Quality Programme, routines will be incorporated into the hospitals' quality control systems to ensure that pharmacovigilance at hospitals will be structured. Both the information initiative and the quality work were launched in 2009 and will continue in 2010.

The number of side effect reports from patients still see an upward trend. It is very satisfactory that the number of reports from patients is on the increase, as it is an extremely helpful contribution to medicine safety.

In 2009, the Council discussed information activities in relation to day-to-day pharmacovigilance. It has, among other things, resulted in the publication of the Danish Medicines Agency's monthly e-newsletter 'Danish Pharmacovigilance Update' with news about pharmacovigilance in Denmark and, not least, in the EU. The newsletter currently has almost 1,000 subscribers, and the number is rising.



Two major issues dominated this year: the reporting of side effects for the Pandemrix® vaccine against influenza A and of those caused by the changed composition of Eltroxin® (a medicine for low metabolism).

Fast treatment and assessment of the side effects associated with the influenza vaccinations have posed a major challenge, but, in the opinion of the Council, the Agency has solved this task well through quick data entry, weekly newsletters, cooperation with other authorities and, not least, through appearance in the media, which objectively and with focus on both the situation in Denmark and international results has given the right perspective.

The physicians' very active reporting of side effects in connection with the influenza vaccination is commendable. Together with other healthcare professionals, the physicians accounted for 82% of all reports of side effects for the vaccine and thus enabled the Agency to assess whether side effects experienced by the patients correspond with the nature and frequency of the side effects expected. We must maintain and further strengthen this commitment.

In 2009, a change of the composition of the excipients in Eltroxin® resulted in many reported side effects. The Council discussed the issue with the Danish Medicines Agency, and following this discussion, the Agency informed the public of this in many different forums, participated in meetings, provided advice to both patients and physicians as well as made use of more recent social platforms and contributed to special Facebook groups. It turned out to be a good way of maintaining a dialogue on a serious problem experienced by many.

The Gardasil® vaccine was also an area of special focus for the Agency, as the Gardasil® vaccination at the beginning of 2009 became a part of the childhood immunisation programme, and the Council, in collaboration with the Agency, thus decided to continue monitoring the side effects reported for Gardasil®. Three large status reports were prepared and published on the Agency's website.

In 2009, many seeds were sown to drive pharmacovigilance further forward. The Agency's increased focus on digitisation in the area of pharmacovigilance will facilitate reporting and allow for even better monitoring, analysis and communication as well as support the objectives of the action plan. The Council looks very much forward to seeing the results of the information initiative aimed at hospital physicians.

The full impact of the many initiatives of the action plan will not be seen until next year. By the end of 2010, it is important that we review and assess the development. The Council is looking forward to an exciting year for the benefit of the patients.



An insight into the pharmacovigilance work of the Danish Medicines Agency 2009

The following sections will review some overviews of reported side effects to provide an insight into the pharmacovigilance work performed by the Danish Medicines Agency in 2009.

Pharmacovigilance is handled by the Agency's Consumer Safety Division which register and analyse the side effects from medicines reported to us by physicians and other healthcare professionals, pharmaceutical companies, patients and relatives. All the information that we receive about side effects helps us regularly assess the safety of medicines on the market.

The following overviews will be reviewed:

- Development in the number of reported side effects from 2005 to 2009 by reporter type. Go directly to the overview [here](#).
- Top 10 of the most frequently reported active substances and consumption figures. Go directly to the overview [here](#).
- Top 10 of the most frequently reported vaccines with side effects. Go directly to the overview [here](#).
- Side effect reports from hospitals by region. Go directly to the overview [here](#).
- Side effects from Gardasil®. Go directly to the overview [here](#).
- Side effects from Eltroxin®. Go directly to the overview [here](#).
- Side effects from Pandemrix®. Go directly to the overview [here](#).



Development in the number of reported side effects from 2005 to 2009 by reporter type

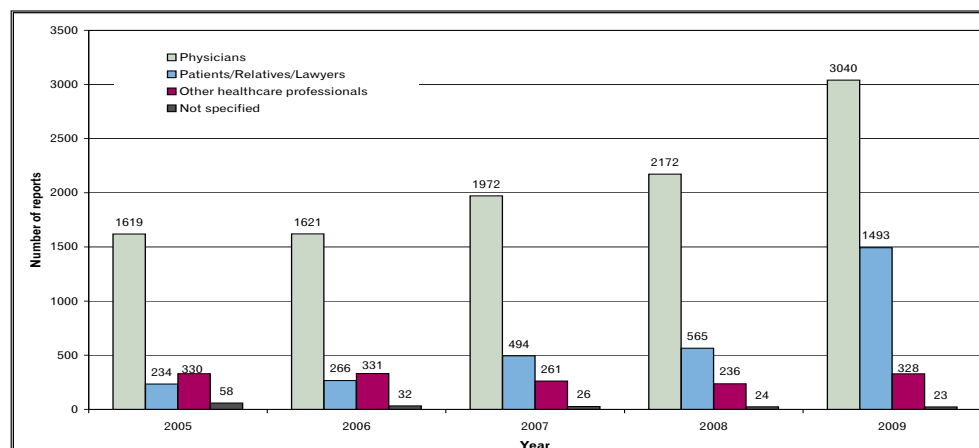


Figure A. Development in number of reported side effects from 2005 to 2009 by reporter type

Since 2005, the overall number of side effect reports have increased dramatically, with more than a doubling from 2005 to 2009. There are several explanations for this development, but a major factor behind the rising number of reports is the overall increased focus on the reporting of side effects.

Side effect campaign aimed at citizens

In spring 2008, the Danish Medicines Agency launched a side effect campaign entitled 'Side effects from your medicine?'. The campaign was aimed at consumers and informed them that they can also report side effects to the Agency. Already in the same year, an increase was noted in the number of side effects reported by the consumers themselves, and the number has seen a steady increase since then.

Media-stimulated reporting

When medicine and side effects receive wide media coverage, it is always reflected in statistics. In the Eltroxin® case, the media coverage is presumed to have contributed to the increase in the number of side effects reported in 2009. See the section on focus areas in 2009 for more information about Eltroxin®. Go directly to the section on Eltroxin® [here](#). The trend towards media-stimulated reporting also confirms the assumption that the area of side effects is generally still characterised by considerable underreporting, and that more suspected side effects would be reported if there is focus on the area.

Another explanation for the large number of reports in 2009 is the many reports associated with the influenza A vaccination, both because a large number of persons were vaccinated, and because it was a new vaccine where physicians were subject to stricter reporting requirements¹.

In 2010, the Danish Medicines Agency will once again focus on the reporting of side effects. In addition to a major side effect campaign aimed at hospitals, the Agency again launches a campaign to remind consumers that they themselves can report side effects from the medicine they take, or if they are relatives of a medicine user experiencing side effects from the medicine.

1) During the first two years that a new medicine is on the market, physicians, dentists and veterinarians have a duty to report all suspected side effects to the Danish Medicines Agency.



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

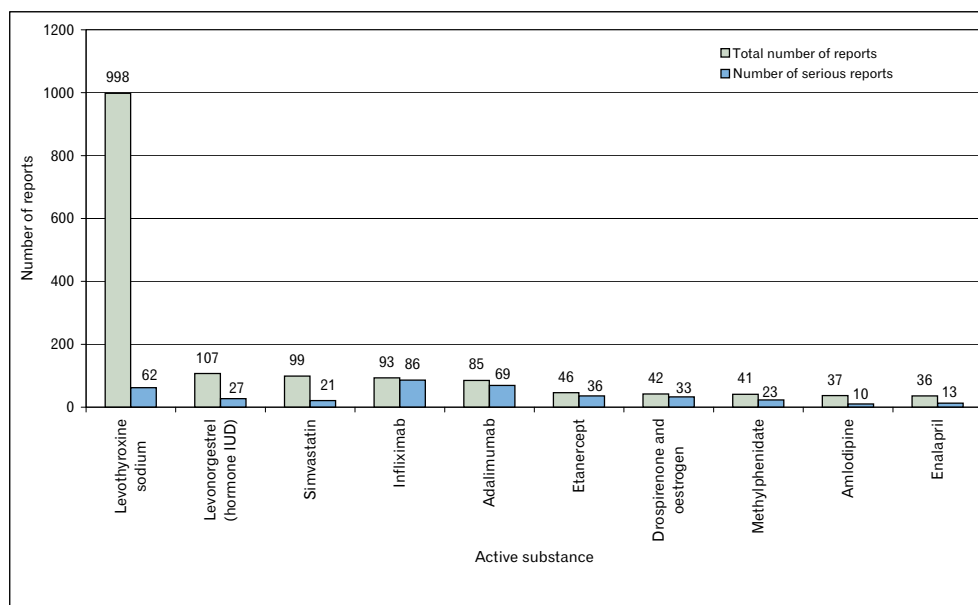


Figure B. Top 10 of the most frequently reported active substances with side effects (2009)

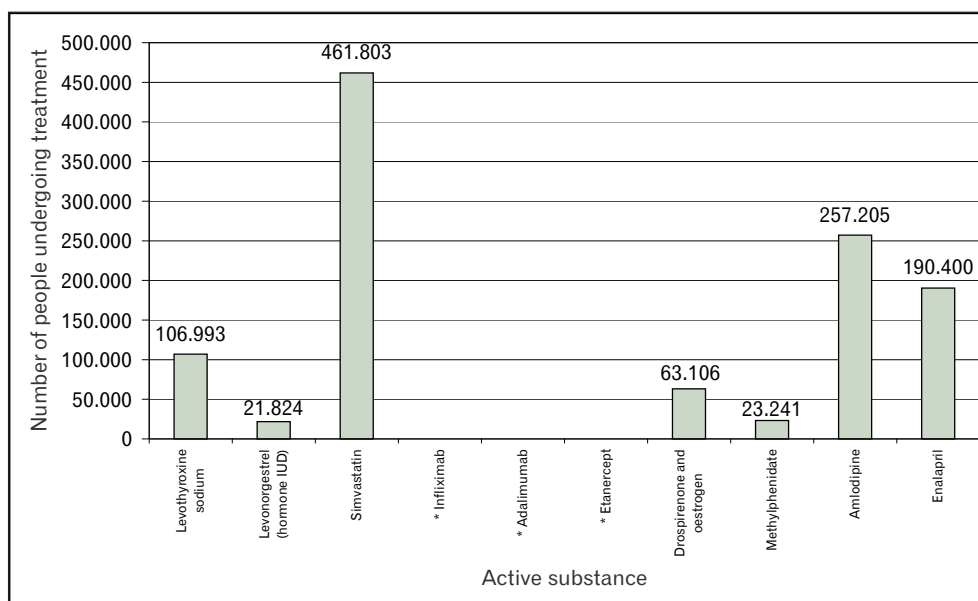


Figure C. Number of persons undergoing treatment with Top 10 medicine (2009)

* These three are so-called biological medicines primarily used at hospitals, and the Register of Medicinal Product Statistics thus does not contain exact figures for the number of persons undergoing treatment.



In 2010, the Danish Medicines Agency will once again focus on the reporting of side effects. In addition to a major side effect campaign aimed at hospitals, the Agency again launches a campaign to remind consumers that they themselves can report side effects from the medicine they take, or if they are relatives of a medicine user experiencing side effects from the medicine.

Figure B shows the ten active substances for which most side effects were reported in 2009. The number of side effects reported for a specific ingredient or medicinal product group (e.g. statins) should always be related to consumption. 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 medicine in question in 2009. In 2009, 4,040,100 persons submitted a prescription for at least one type of medicine. The consumption figures are from the Danish Medicines Agency's Register of Medicinal Product Statistics.

Eltroxin®

As illustrated by the graph in Figure B, in 2009, one in five reports concerned levothyroxine sodium (Eltroxin®²), among other things because the pharmaceutical company GlaxoSmithKline, which held the marketing authorisation for Eltroxin®, changed the excipients in the medicine³. It is unusual for one specific type of medicine to dominate the figures to such extent. As appears from Figure C, almost 107,000 persons underwent treatment with Eltroxin® in 2009, and the patients have reported 80% of the side effects themselves. The vast majority of the reports (93%) concerning Eltroxin® are not serious. See the section on focus areas in 2009 for more information about Eltroxin®, and to see which ten side effects were the most frequently reported for Eltroxin® in 2009. Go directly to the section on Eltroxin® [here](#).

Hormone intrauterine devices (IUDs)

The second-most frequently reported active substance is levonorgestrel hormone IUDs (Mirena® and Levonova®⁴), which are primarily used for birth-control. The hormone IUDs have been on the market for several years and are used by adult women.

As opposed to Eltroxin®, it is primarily physicians (94%) who have reported side effects from hormone IUDs, and 25% of the reports are serious, but known side effects. The most frequent side effects include menstrual irregularity, perforation of uterus, abdominal pain and breast tenderness.

Statins

Simvastatin (Zocor®⁵ etc.) 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, the Danish population has a large simvastatin consumption. In 2009, 460,000 persons underwent treatment, and simvastatin's Top 10 position with 99 reports is thus not surprising. More than half (55%) of the reports were submitted by physicians, and 79% of them were not serious. The most frequent side effects include muscle and joint pain, nausea, headache and hair loss.

2) In 2009, Eltroxin® was the only levothyroxine sodium product on the Danish market. Not until December 2009 did a new levothyroxine sodium product, Euthyrox®, enter the market.

3) Orion Pharma A/S acquired the marketing authorisation for Eltroxin® in November 2009.

4) Mirena® and Levonova® were the only hormone IUDs on the market in 2009; however, Levonova® was deregistered in 2009.

5) Zocor® is the original simvastatin product, but several generics exist. Zocor® is mentioned solely because it is the original product and not because the highest number of side effects are reported for this product.



Biological medicines

The biological medicines Remicade® (infliximab), Humira® (adalimumab) and Enbrel® (etanercept), so-called TNF-alpha inhibitors, are all on the Top 10 list. They are all used in the treatment of serious autoimmune diseases affecting joints or bowel (e.g. rheumatoid arthritis, ulcerative colitis, Crohn's disease, psoriatic arthritis), and they are only prescribed if other medicines have had no adequate effect. The majority (approx. 85%) of the side effects reported from these three medicines are classified as serious. As expected, the side effects reported include, in particular, infections, weakened immune system, neurological symptoms and allergic reactions.

The relatively large number 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.

Consumption of biological medicines

The biological medicines are primarily dispensed from hospitals and only rarely on prescription. The Agency does not know the exact number of patients undergoing treatment with these medicines. The consumption of these medicines is thus stated in defined daily doses (DDD), a unit of measure used in the Agency's Register of Medicinal Product Statistics to compare the consumption of different medicines. The DDD values for infliximab, adalimumab and etanercept are 1,459,645, 953,813 and 710,068, respectively. The DDD value does not directly state how many persons have received the medicines, as the number of DDDs used in the treatment of one patient may vary. The DDD value for a medicine is the assumed average dose per day for a medicine used for its main indication in adults.

Contraceptive pills

In recent years, focus has been on side effects from contraceptive pills, in particular side effects from the new, so-called fourth-generation contraceptive pills (Yasmin®, Yasminelle® and Yaz®)⁶ which contain drospirenone and oestrogen. It has been known for a long time that the use of contraceptive pills is associated with an increased risk of blood clots. Blood clots in connection with contraceptive pills are, however, relatively rare. The side effects reported for fourth-generation contraceptive pills are typically serious and are mainly reported by physicians (88%).

6) Yasmin®, Yasminelle® and Yaz® are the only products on the market.



Methylphenidate (Ritalin® etc.)

The active substance methylphenidate (Ritalin® etc.)⁷ is used in the treatment of ADHD (disorder characterised by inattention, hyperactivity and impulsivity) and the rare disorder narcolepsy. ADHD is seen in 2-4% of children with boys showing a higher incidence than girls. More than 23,000 persons underwent treatment with methylphenidate in 2009, of which almost 70% were men/boys – 60% were boys aged 2-18. Unlike men, more adult women above 19 years undergo treatment. The side effects are mainly reported by physicians and other healthcare professionals, and the number of serious and non-serious suspected side effects is almost equal. Recently, increasing focus has been on Ritalin® treatment, in particular Ritalin® treatment for children, resulting in increased focus on the side effects from the treatment. The Danish Medicines Agency has thus decided to intensify the safety monitoring of Ritalin® in 2010. The most frequently reported side effects include headache, aggression and restlessness.

Amlodipine (Norvasc® etc.) and enalapril (Corodil® etc.)

Amlodipine (Norvasc® etc.) and enalapril (Corodil® etc.)⁸ are both active substances typically used in the treatment of hypertension. Almost 450,000 persons underwent treatment in 2009. Both active substances are one among many similar active substances belonging to each their group, so the actual consumption of this type of active substances is much higher. Against this background, the number of side effects is relatively low, and most of them are not serious. The most frequently reported side effects include nausea, restlessness, cough and peripheral oedema (fluid retention).

8) Norvasc® and Corodil® are the original products within the group of amlodipine and enalapril, respectively, but several generics exist. Norvasc® and Corodil® are mentioned solely because they are the original products within their group of medicines and not because the highest number of side effects are reported for these products.

7) Ritalin® is the original methylphenidate product, but several generics exist. Ritalin® is mentioned solely because it is the original product and not because the highest number of side effects are reported for this product.



Top 10 of the most frequently reported vaccines with side effects

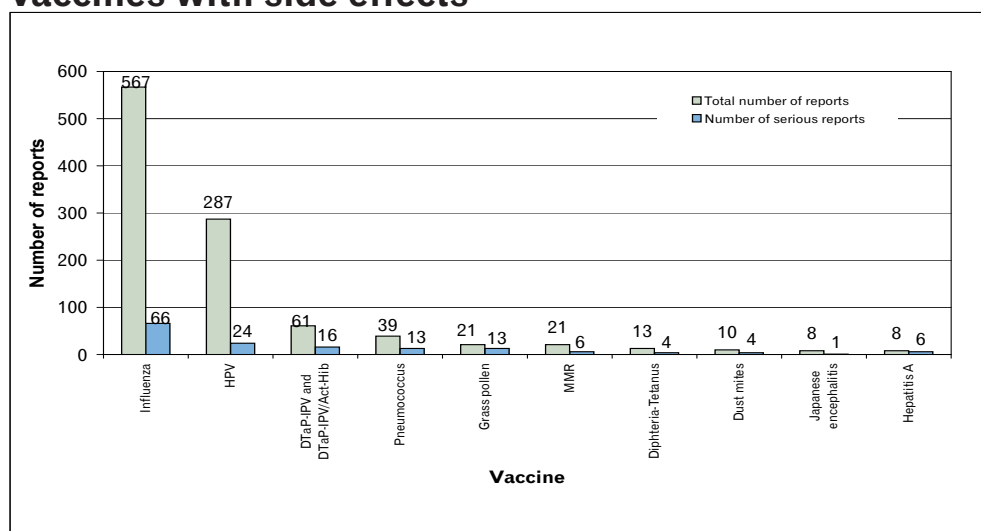


Figure D. Top 10 of the most frequently reported vaccines with side effects (2009)

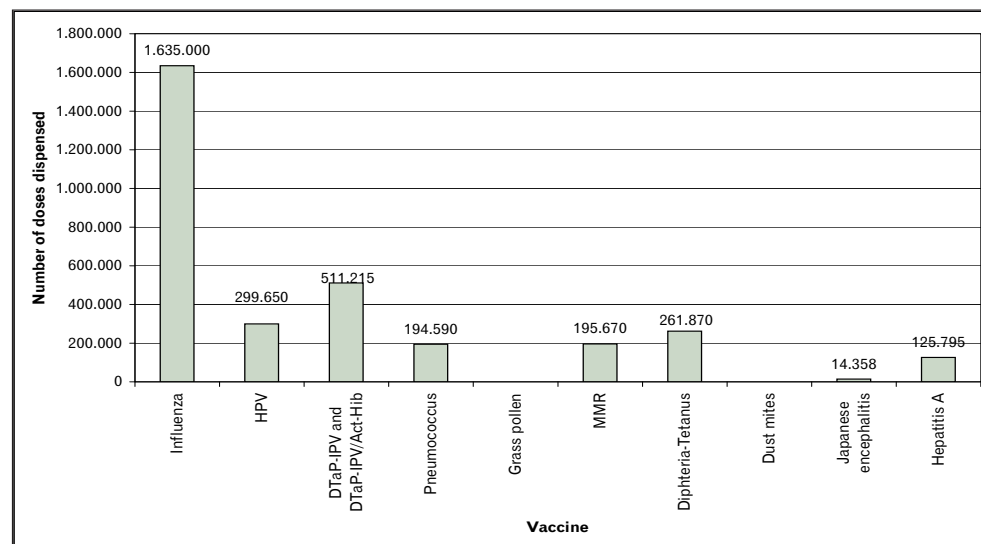


Figure E: Number of doses of Top 10 vaccines dispensed (2009)

Figure D shows the ten most frequently reported vaccines with side effects. Conventional medicines by far outnumber vaccines; on the other hand, many people are vaccinated in connection with the various immunisation programmes. In the light of the large exposure, the number of side effects reported 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 dust mites. 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 patient receives several vaccines several times, as is the case, for example, with the vaccines in the childhood immunisation programme.

Pandemrix®

In 2009, the reporting of side effects from vaccines was dominated by mass vaccination of persons in special risk groups in connection with the influenza A pandemic. Vaccination against seasonal influenza typically only results in very few side effect reports, but the large focus on the pandemic vaccine (Pandemrix®) and stricter reporting requirements for physicians⁹ in connection with new medicine resulted in a large increase in the number of reports. The majority of the influenza reports concern Pandemrix® and are submitted by physicians, with only few serious side effects reported. The monitoring of Pandemrix® will continue in 2010. See the section on focus areas in 2009 for more information about Pandemrix®, and to see which ten side effects were the most frequently reported for Pandemrix® in 2009. Go directly to the section on Pandemrix® [here](#).

Childhood immunisation programme

Vaccines in the childhood immunisation programme account for the other major part of the vaccine reports in 2009, which include HPV vaccine (Gardasil®), Diphtheria-Tetanus-Pertussis-Polio-Hib(meningitis) vaccine (DTaP-IPV/Act-Hib), pneumococcus vaccine (Prevenar) and vaccine against measles, mumps and rubella (MMR). The side effects from these vaccines were almost exclusively reported by physicians and other healthcare professionals, and only very few serious side effects were reported. The vaccines are widely used with well-known side effects, mainly local reactions at the injection site. Gardasil® is the only new vaccine which was included in the childhood immunisation programme in 2009, and this vaccine was thus subject to increased focus and monitoring. The monitoring of Gardasil® will continue in 2010. See the section on focus areas in 2009 for more information about Gardasil®, and to see which ten side effects were the most frequently reported for Gardasil® in 2009. Go directly to the section on Gardasil® [here](#).

Allergy vaccines

Allergy vaccines (grass pollen and dust mites) and vaccines often given in connection with travel abroad (Japanese encephalitis and hepatitis A) as well as tetanus vaccine (diphtheria-tetanus) are also on the Top 10 of the vaccines with most reported side effects in 2009. There are, however, very few reports seen in the light of the large number of vaccinated persons. As is the case for the other vaccines, the side effects were almost exclusively reported by physicians and other healthcare professionals, the vast majority being non-serious side effects. The side effects reported are often known: local allergic reaction at the injection site as well as shortness of breath and malaise.

9) During the first two years that a new medicine is on the market, physicians, dentists and veterinarians **have a duty** to report all suspected side effects to the Danish Medicines Agency.



Side effect reports from hospitals in 2009 by region

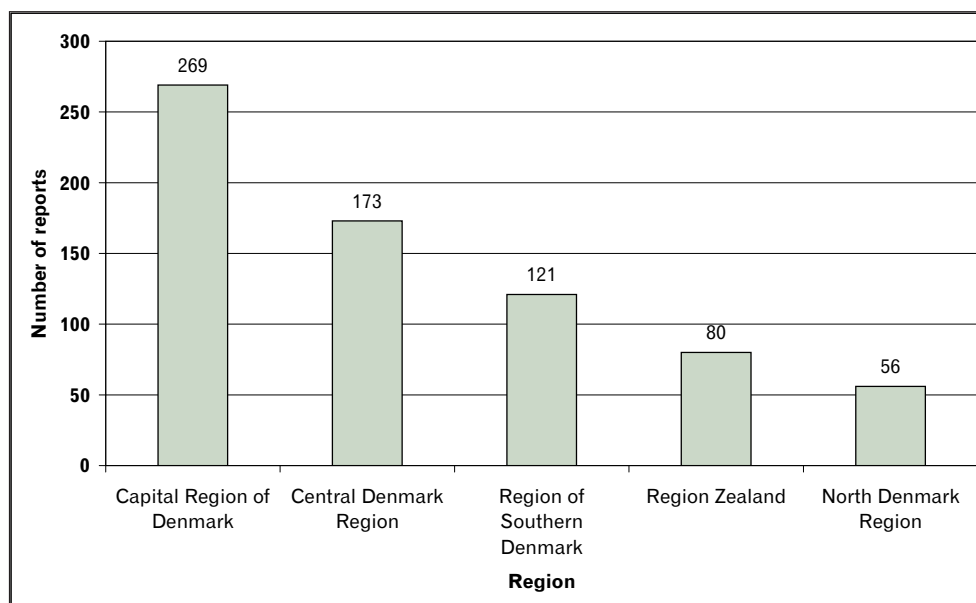


Figure F. Side effect reports from Danish hospitals by region (2009)

In 2009, the Danish Medicines Agency received a total of 699 side effect reports which can be clearly linked to a hospital. There may be reports in the Agency's pharmacovigilance database which are not shown in the overview, e.g. because the hospital is not mentioned in the report.

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 physicians have a duty to report. The number of reports from the hospitals can thus only be explained by underreporting.

To increase the number of side effect reports from hospitals, the Danish Medicines Agency will be launching a nationwide side effect campaign in August 2010 specifically aimed at hospital physicians. The campaign will increase focus on the reporting of side effects by hospitals and provide physicians with more insight into the rules governing the area.



Focus areas 2009

Declining number of side effects reported for Gardasil® in 2009

The Gardasil® vaccine is used to prevent cervical cancer, early stages of cancer in the female genitalia (including the cervix and the external genitalia) as well as genital warts (condyloma acuminata). On 1 January 2009, the vaccine was included in the Danish childhood immunisation programme, which means that all 12-year-old girls have been offered the vaccine since January 2009, and they will also be offered the vaccine in future. However, already in October 2008, GPs started vaccinating girls born in 1993, 1994 and 1995 as part of a pilot programme running until the end of the year.

Side effects reported for Gardasil® in 2009

In the period 1 January to 31 December 2009, the Danish Medicines Agency received 287 new side effect reports for Gardasil®. Most reports were not serious and described side effects already known. 24 reports were classified as serious.

Of the total number of reports, 86% were submitted by physicians and other healthcare professionals, while 14% were submitted by the persons vaccinated or their relatives.

The graph below shows the distribution of side effect reports from 1 January to 31 December 2009.

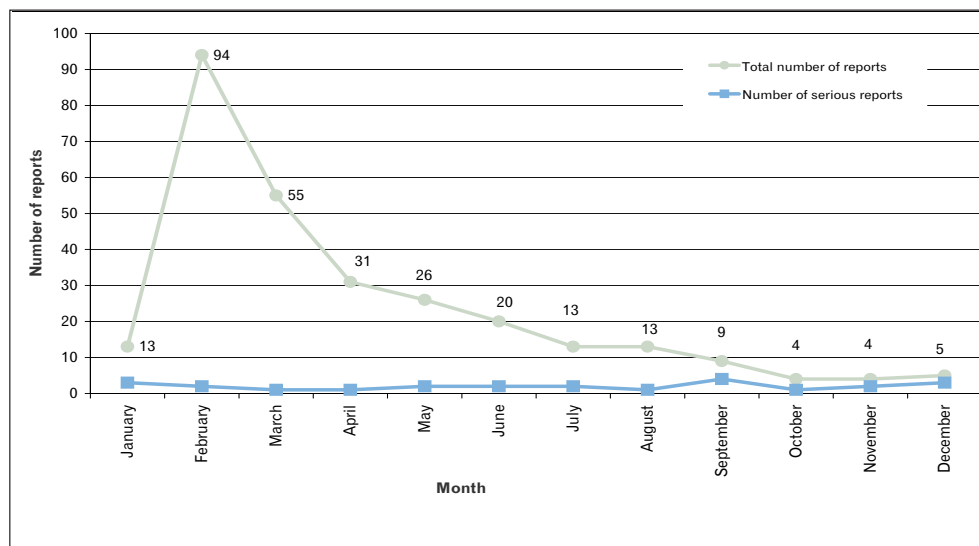


Figure G. Total number of side effects reported for Gardasil® as well as the number of serious side effects reported in 2009.



The table below shows the ten most frequently reported side effects from Gardasil® in 2009.

Side effect	Number
Atopic dermatitis	*62
Dermatitis	38
Urticaria	26
Fever	23
Headache	20
Rash	18
Itchy rash	17
Dizziness	15
Nausea	14
Fatigue	14

*** No indications of correlation between Gardasil® and atopic dermatitis**

In spring 2009, the Danish Medicines Agency received a large number of reports stating atopic dermatitis as the suspected side effect following media coverage of observed cases of atopic dermatitis. Atopic dermatitis is a relatively widespread disease. It is also a disease which frequently flares up around the age when girls are vaccinated. After having reviewed all Danish reports and all European experience, the Agency found no indications of correlation between atopic dermatitis and the Gardasil® vaccination.

The Danish Medicines Agency's overall assessment of the reports for Gardasil® in 2009

Based on Danish and all international experience, the Agency finds the number and nature of the suspected side effects reported to be acceptable seen in relation to the purpose of the vaccine: to prevent a serious potentially fatal disease like cervical cancer.

In some cases, the side effect reports have resulted in further investigations of signals of potential new side effects, e.g. whether there may be a correlation between the Gardasil® vaccination and immune system or nervous system diseases. This is perfectly in line with the purpose of the side effect reports, as they are precisely meant to indicate potential new side effects not seen before a product is launched on the market.

The Danish Medicines Agency will continue to closely monitor the reported side effects from Gardasil®.

Read the most recent status on Gardasil® here: [Adverse reactions from Gardasil® in the period 1 May – 31 August 2009](#)

Read also the summary of product characteristics for Gardasil®: [EMA's summary of product characteristics for Gardasil®](#)



Large increase in the number of side effects reported for Eltroxin® in 2009

Eltroxin® is used in the treatment of low metabolism and has been on the market for many years. So far, only very few side effects from Eltroxin® have been reported to the Danish Medicines Agency, but since the pharmaceutical company GlaxoSmithKline (GSK) changed the excipients in the medicine in 2009, the number of reports grew considerably. It is, however, not possible to see whether the reported suspected side effects were experienced when using the new or the old Eltroxin® formulation, but the majority of the side effects reported probably concerned the new formulation as shown by the graph in Figure H.

Side effects reported for Eltroxin® in 2009

From 1 January to 31 December 2009, the Danish Medicines Agency received a total of 998 side effect reports for Eltroxin®. Most reports were not serious and described side effects already known. 72 reports were classified as serious. 80% of the side effects were reported by the patients themselves, while physicians and other healthcare professionals accounted for 20% of the reports.

The graph below shows the distribution of the number of side effect reports for Eltroxin® during 2009.

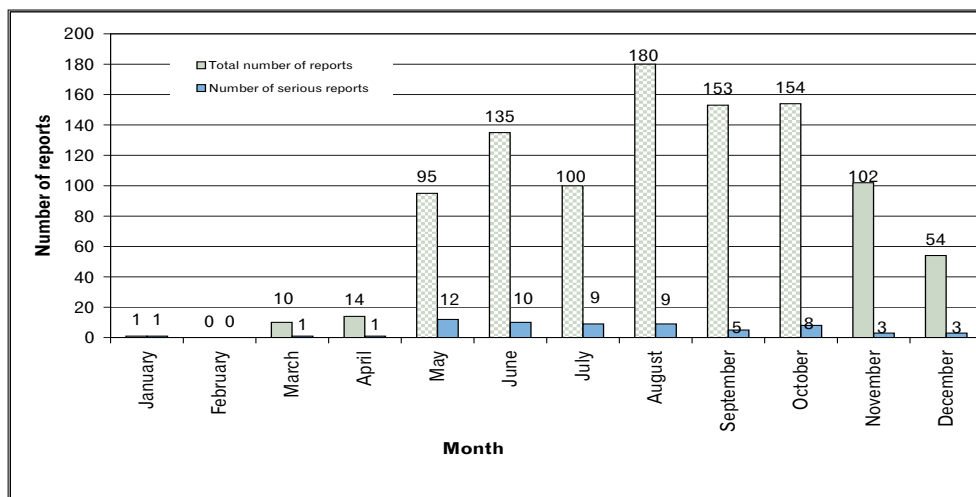


Figure H. Total number of side effects reported for Eltroxin® as well as the number of serious side effects reported in 2009. (Chequered columns = months where Eltroxin® was addressed by the media. See also the table on page 17).



The table below shows the ten most frequently reported side effects. The side effects here are all symptoms which may indicate overdosage or underdosage of Eltroxin®.

Side effect	Number
Fatigue	466
Headache	386
Dizziness	263
Nausea	208
Concentration impairment	184
Weight gain	183
Impaired memory	160
Muscle pain	155
Joint pain	154
Stomach ache	121

Overdosage or underdosage in connection with new Eltroxin® formulation

The majority of the side effects may be explained by the fact that the bioavailability of the active ingredient levothyroxine differs a little for some patients in the new Eltroxin® formulation, which means that some patients either receive too much or too little of the active ingredient levothyroxine and thus experience symptoms compatible with either overdosage or underdosage.

Media-stimulated reporting

The new Eltroxin® formulation is mentioned the first time in May 2009 in the Danish newspaper Ekstra Bladet. After the media coverage, the number of reports saw a considerable increase. In the period from May to October 2009, the new Eltroxin® formulation generally received much media attention.

The large media attention on Eltroxin® presumably also played a significant role for the number of reports submitted to the Danish Medicines Agency in 2009.

The table below shows when the new Eltroxin® formulation was addressed by the media.

2009	Article in
May	Ekstra Bladet
June	Ekstra Bladet
July	Politiken
August	Ekstra Bladet
September	Ekstra Bladet
October	Ekstra Bladet



In addition to the media coverage, from 15 March 2009 and until today, there have also been debates on the Danish version of NetDoctor about the side effects from the new Eltroxin® formulation. A group was also created on Facebook on metabolic side effects from the new Eltroxin® tablet with 450 members (as of 26 February 2010), and the Agency has, on an ongoing basis, written status reports on Eltroxin® on our website, on the Danish Thyroid Association's website and on the Danish Consumer Council's website.

The Danish Medicines Agency's analyses of Eltroxin®

The many suspected side effects reported for Eltroxin® in Denmark also caused the Agency to have a laboratory analysis conducted of Eltroxin® 50 and 100 microgram. The analysis documented that the product complied with the approved quality requirements.

Euthyrox® – new levothyroxine product on the market

In December 2009, a new levothyroxine product was marketed under the trade name Euthyrox® in the strengths of 25, 50 and 100 microgram after many years with Eltroxin® being the only levothyroxine on the Danish market.

The Agency will continue to closely monitor the development in the reported side effects from Eltroxin®.

Read the Danish Medicines Agency's latest status report on Eltroxin® here:

[*Side effects from Eltroxin® – status January 2010*](#)

Read also the Danish summary of product characteristics for Eltroxin®: [*Summary of product characteristics for Eltroxin®*](#)



Side effects reported for Pandemrix®¹⁰ in 2009

In October 2009, the first persons in special risk groups were vaccinated against influenza A (H1N1) in Denmark. Already the following month, in November, the Danish Medicines Agency received the first side effect reports for Pandemrix®.

Since the Agency received the first report concerning Pandemrix® on 4 November and until 31 December 2009, we registered a total of 547 reports. Most of the side effect reports received were not serious and described side effects already known. 53 reports were classified as serious. 85% of the reports were submitted by physicians and other healthcare professionals, while 15% were submitted by the vaccinated persons themselves.

The Danish Serum Institute has dispensed approx. 1,050,000 vaccine doses, and, at present (March 2010), 425,800 vaccinated persons have been registered.

The graph below shows the distribution of the side effect reports from the first report on 4 November 2009 and until the end of the year.

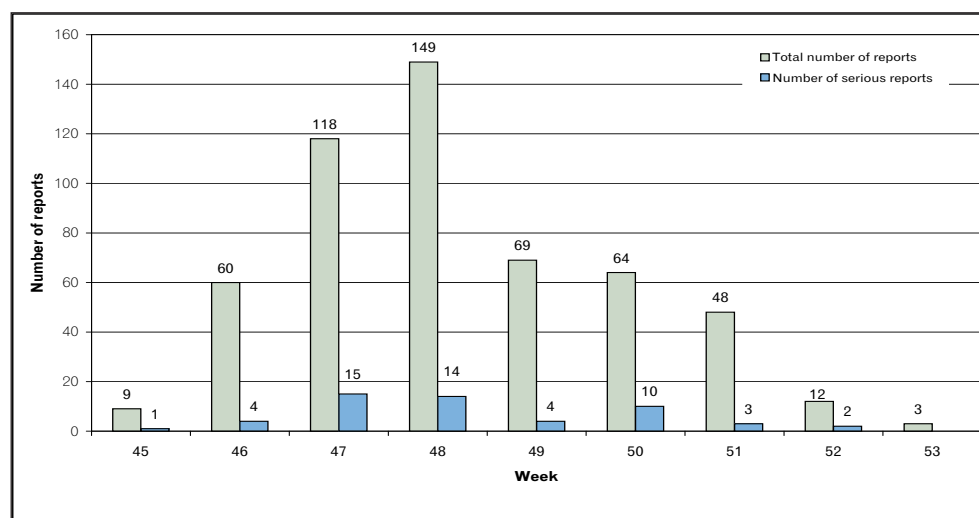


Figure 1. Total number of side effects for Pandemrix® as well as the number of serious side effects reported from 4 November to 31 December 2009.

10) Pandemrix® is the trade name of the vaccine chosen in Denmark to prevent influenza A.



The table below shows the ten most frequently reported side effects from Pandemrix®. All the side effects listed from the vaccine are known.

Side effect	Number
Fever	136
Headache	104
Fatigue	74
Nausea	68
Muscle pain	67
Feeling of uneasiness	66
Dizziness	62
Pain at injection site	59
Arm pain	48
Joint pain	42

The Danish Medicines Agency's overall assessment of the reports for Pandemrix® in 2009

The total number of reports should be seen in the light of the fact that well over 400,000 persons were vaccinated in Denmark. The side effect reports indicate potentially new side effects, e.g. related to the immune system or the nervous system. These indications will now be routinely investigated.

The Danish experience with the side effects from the Pandemrix® vaccination does not only correspond with what was expected in terms of the nature and severity of the reported side effects, it is also in line with all international experience. In the opinion of the Danish Medicines Agency, this means that the Danish material is large enough to be representative. There is reason to assume that the influenza pandemic has made many healthcare professionals and citizens pay more attention to the reporting of side effects, including the importance of their own role in terms of ensuring effective monitoring of side effects.

The Agency will continue to closely monitor the development in the reported side effects from Pandemrix®.

Read the latest status report on Pandemrix® here:

[Side effects from Pandemrix® from 9 to 22 January 2010](#)

Read also the summary of product characteristics for Pandemrix®:

[Product information about Pandemrix®](#)



International collaboration in pharmacovigilance 2009

Since the establishment of the European Medicines Agency (EMA) in 1995, the Danish Medicines Agency has participated in meetings in the European Pharmacovigilance Working Party¹¹. Here, all important cases concerning side effects are assessed, either at the initiative of the European Committee for Medicinal Products for Human Use (CHMP¹²) 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 2009

Influenza A (H1N1) pandemic preparedness plan

In 2009, the European Pharmacovigilance Working Party was part of the pandemic preparedness plan (influenza A) prepared by national authorities in collaboration with the European Medicines Agency (EMA) and the European Center for Disease Prevention and Control (ECDC). For more details, see: [ECDC Forward look risk assessment for the 2009 pandemic influenza A \(H1N1\) and future influenza season](#).

Other cases considered in 2009 include:

- Bisphosphonates and osteonecrosis of the jaw.
- Antipsychotics and blood clots.
- Contraceptive pills and blood clots.
- Gadolinium-containing MR contrast agents and nephrogenic systemic fibrosis.
- Biological medicines and progressive multifocal leukoencephalopathy.
- Insulin and risk of cancer.

Bisphosphonates and osteonecrosis of the jaw

The side effect reports concerning osteonecrosis of the jaw in patients having undergone treatment with bisphosphonates resulted in a thorough investigation headed by the Danish Medicines Agency, which was completed in 2009. Based on the reported side effects and research findings published in the literature, the Pharmacovigilance Working Party assessed pathophysiological mechanisms, risk factors and preventive measures. In addition, proposals were made as to which supplementary investigations are required to further reduce the risk of osteonecrosis of the jaw. For more details, see: [CHMP/606274/2009](#).

Antipsychotics and thromboembolism

Based on the side effect reports concerning blood clots supplemented by a literature review, the Pharmacovigilance Working Party found that the summary of product characteristics for antipsychotics had to be improved. In future, the SPC for all antipsychotics will state that blood clots have occurred in patients undergoing treatment with antipsychotics. The physician should thus take this into account when assessing whether a patient should start treatment with antipsychotics. For more details, see: [Antipsychotics and risk of venous thromboembolism \(VTE\)](#).

11) The European Pharmacovigilance Working Party consists of one member from each of the medicines agencies in the 27 EU countries. It is a (permanent) working group set up by the CHMP. In addition, a number of experts are affiliated to the committee, e.g. specialists in diseases in children and elderly people, specialists within vaccines as well as specialists in pharmacoepidemiology and communication. The committee convenes once a month for a two to three-day session to discuss current pharmacovigilance issues and to prepare guidelines, implement new technology and strengthen the cooperation with patient organisations etc.

12) Among other things, the Committee for Medicinal Products for Human Use (CHMP) assesses registration applications for medicines approved for marketing in the EU via a centralised EU procedure. Read more about the CHMP [here](#).



Contraceptive pills and thromboembolism

It has been known for a long time that the use of contraceptive pills is associated with an increased risk of blood clots. But new research findings are constantly made, and it is thus one of the side effect issues regularly discussed by the Pharmacovigilance Working Party. In August 2009, a major Danish registry study (Øjvind Lidegaard et al, BMJ. August 2009), for example, led to a reassessment of the risk profile of the various contraceptive pills. No conclusion is as yet available (March 2010). The work will continue in 2010.

Gadolinium-containing MR contrast agents and nephrogenic systemic fibrosis

As a result of side effects reported in Denmark, the Danish Medicines Agency placed the correlation between gadolinium-containing MR contrast agents and nephrogenic systemic fibrosis on the agenda at the Pharmacovigilance Working Party in 2006. In 2009, the Agency once again placed the safety of gadolinium-containing MR contrast agents on the agenda of the Pharmacovigilance Working Party, this time to ensure harmonised recommendations in the EU for the use of this type of agents, e.g. for the elderly, newborns and patients undergoing a liver transplant. The case is expected to be concluded in 2010. For more details, see: [CHMP/739818/2009](#).

Biological medicines and progressive leukoencephalopathy

2009 saw an increasing number of side effect reports concerning a rare serious condition, progressive multifocal leukoencephalopathy (PML) following treatment with biological medicines, e.g. the psoriasis drug efalizumab and the sclerosis drug natalizumab. The psoriasis drug efalizumab was withdrawn from the market as the CHMP found that the drug's benefit/risk balance was negative in the light of the risk of PML. The intensive monitoring of the safety of the sclerosis drug natalizumab will continue. For more details, see: [CHMP/20857/2009](#).

Insulin glargine and risk of cancer

The summer of 2009 saw the publication of four registry studies which all looked into the potential correlation between the use of the long-acting insulin analogue insulin glargine and the development of cancer/breast cancer. The four studies included a total of 300,000 patients, but the results are not clear, and supplementary studies are thus required. The topic will be monitored closely in the coming years. For more details, see: [EMA/470632/2009](#).



Pharmacovigilance 2010

Risk-based focus areas

The framework for pharmacovigilance in Denmark is well-defined, but the Danish Medicines Agency will, to an even greater extent, continue to take a risk-based approach to this focus area, i.e. concentrate its efforts where it has the largest health effect. This means that, in 2010, the Agency will work with focus areas and continue to extend digitisation within pharmacovigilance.

In 2010, even more focus will be placed on analyses of the impact of the reported side effects on safety. In this connection, the Agency will benefit from a new pharmacovigilance IT system.

Simplification of the system for the reporting of side effects

The collaboration on the follow-up on side effect reports must be simplified in 2010. The Agency will ensure this by establishing, among other things, electronic communication between the Agency, physicians and pharmaceutical companies. The Minister of Health has proposed an amendment to the Danish Health Act that will allow the Agency to access the Medicine Profile (an electronic register of individual prescriptions in Denmark) when required to consider the side effect reports. If the bill is adopted by the Danish Parliament, the Agency will, in future, be able to obtain important information about medicine dispensed in the Medicine Profile. The bill was read the first time in the Danish Parliament on 25 February 2010 and has been referred to the Health Committee.

More collaboration between patients, physicians and the Danish Medicines Agency

The submission and consideration of side effect reports take place in collaboration between patients, physicians and the Danish Medicines Agency. In 2010, the Agency will focus on this collaboration, including, in particular, the collaboration with hospital physicians, because there is great need for information here to increase the number of side effects reported. This will, among other things, involve an information project on side effect reports aimed at hospital physicians as well as direct dialogue with the regional medicinal products committees.

In 2010, the Agency will continue the implementation of the initiatives listed in the national pharmacovigilance action plan. Simplification of the reporting from physicians to the Agency is one of the main areas, and increased awareness of the reporting of side effects among healthcare professionals and patients is another priority area.



Appendix

The Danish Medicines Agency's pharmacovigilance system

What is a side effect?

A side effect is a harmful and unintended reaction that occurs at a medicine dose normally used for humans or animals for the prophylaxis, diagnosis or treatment of disease or to modify, regenerate, correct or influence a physiological function.

When monitoring side effects, a distinction is made between serious/non-serious and expected/unexpected side effects. A side effect is serious if it:

- Leads to death.
- Is life-threatening.
- Causes or prolongs hospitalisation.
- Causes permanent or significant disability.
- Produces birth defects or congenital anomaly.

An unexpected side effect is a side effect *not* described in the summary of product characteristics (SPC)¹³ for the medicine (an unexpected side effect may be both serious and non-serious).

Physicians, dentists and veterinarians have a duty to report side effects

During the first two years that a new medicine is on the market, physicians, dentists and veterinarians have a duty to report all suspected side effects¹⁴ to the Danish Medicines Agency. After two years, physicians must report all serious and/or unexpected side effects experienced by the patients or animals that they are treating.

For generic medicine, only serious or unexpected, suspected side effects must be reported from the day when it is placed on the market.

All serious side effects must be reported to the Danish Medicines Agency no later than 15 days after the suspected serious side effect has come to the physician's attention.

The Agency has published a list of medicines subject to stricter reporting requirements, i.e. medicines for which all suspected side effects must be reported. The list is updated regularly. See the list [here](#).

The pharmaceutical company holding the marketing authorisation for the medicine must report all suspected serious side effects observed in Denmark and which are reported to the company by a healthcare professional, a patient, a relative or the animal's owner, or which the company can reasonably be expected to know from scientific literature and safety studies. The company must report the suspected serious side effect to the Danish Medicines Agency no later than 15 days after it has come to the company's attention. In addition, the company holding the marketing authorisation must report all suspected serious unexpected side effects observed in countries outside the EU/EEA (third countries) to the Agency within 15 days.

¹³) The SPC contains a description of a the specific characteristics of a medicine and the conditions for its use.

¹⁴) A suspected side effect is a side effect where a clear link does not need to be established between the observed/experienced side effect and the medicine.



Healthcare professionals, patients, relatives and animal owners can also report all suspected side effects to the Agency.**How to report side effects to the Danish Medicines Agency**

At the site [Report a side effect](#), physicians, dentists, patients and relatives can report all suspected side effects using an e-form. Patients and relatives can also contact a pharmacy which can assist them in reporting the side effect. Veterinarians and animal owners can report suspected side effects in animals on a special e-form which can be downloaded from the Danish Medicines Agency's website, www.dkma.dk.

The pharmaceutical company holding the marketing authorisation for the medicine must submit their side effect reports concerning medicine for human use via the European Medicines Agency's Eudravigilance Gateway.

Contents of a side effect report

A side effect report submitted to the Danish Medicines Agency must, as a minimum, contain the following:

- A description of the suspected side effect.
- The trade name of the medicine considered to have caused the side effect or the name of the medicine's active ingredient.
- Information about the person having experienced the side effect: Civil registration number or date of birth, gender, age and initials. Reports submitted by physicians and dentists should, if possible, include the patient's civil registration number.
- Identification of reporter.

The Danish Medicines Agency would like to have precise information about the medicine (including product name) suspected to have caused the side effect as well as information about any other medicine taken by the person having experienced the side effect. We would also like to have information about the patient's weight, height and the medicine dose taken. This is important information for the Agency's ongoing assessment of the safety of the medicine.

Upon request from the Agency, physicians, dentists and veterinarians must also provide information from records, autopsy reports and similar documentation material for the Agency's consideration of the side effect reports. The Agency can thus require supplementary information for its consideration of a side effect report.

The Danish Medicines Agency registers and considers side effect reports

When the Agency receives a side effect report, we enter all suspected side effects into a pharmacovigilance database to register the information about the medicine, its active ingredient(s)¹⁵, dosage as well as a description of the suspected side effect(s) and the patient's gender, age and medical history.

¹⁵ The active ingredient is the ingredient that produces the effect in the medicine, and the same ingredient may appear under various medicine names.



All side effects reported to the Agency will be coded in accordance with an international coding system (MedDRA) which registers the type of side effect, e.g. whether it is a serious side effect. Also information about who has reported the side effect is registered, i.e. whether it was reported by a physician, another healthcare professional or by a patient or his or her relative.

When a side effect is registered in the pharmacovigilance database, it does not always mean that there is a correlation between the side effect and the medicine taken by the patient. All side effects are registered in the database as long as a correlation between the medicine and the side effect is suspected. A side effect report may include information about several suspected side effects.

The Danish Medicines Agency uses the pharmacovigilance database as an internal work of reference and for preparing status reports and statistics on reported side effects from medicine and its active ingredient(s). The side effect reports form part of the Agency's ongoing monitoring of the medicine's safety.

In the database, the Agency also registers side effects observed in connection with clinical trials involving medicine for human use. The reports are subsequently used in the ongoing assessment of approved clinical trials and the safety of the trial subjects. All side effect reports concerning clinical trials involving medicine for human use are forwarded to the European Medicines Agency's common European database.

Ongoing assessment of medicine safety

One of the Danish Medicines Agency's primary tasks is to ensure that the medicine on the market is as effective and safe as possible. Even though the Danish Medicines Agency is obliged to register and monitor side effects, it is the individual pharmaceutical company which has the primary responsibility for the safety and efficacy of the medicine.

A company authorised to market a specific type of medicine must thus regularly submit a periodic safety update report (PSUR)¹⁶ on the medicine to the Danish Medicines Agency. The PSUR must list and review all reported suspected side effects and must also include a scientific evaluation of the benefits and risks associated with the medicine as well as provide an overall assessment of the medicine's safety and proposals for any new safety initiatives.

At the Agency, we subsequently assess whether we concur with the conclusions of the report, and we decide whether it is necessary to implement special safety measures. Furthermore, we also check whether the company concerned follows up on identified safety problems related to the medicine.

The Danish Medicines Agency may change, suspend or withdraw a marketing authorisation for a medicine if we, based on new information about the safety of the medicine, find that the medicine's benefit/risk balance becomes negative. The decision must be in proportion to the safety problem observed.

¹⁶ A periodic safety update report (PSUR) includes a review of all suspected side effects reported worldwide. The report also includes information about sales and consumption figures, any changes to the SPC/package leaflet or marketing status introduced since the most recent safety update report (in one or more countries), presentation of planned, ongoing or completed safety studies. Finally, the safety update also includes the company's own assessment of benefits and risks associated with the medicine and proposals for any new safety initiatives.



The Danish Medicines Agency consults the Council for Adverse Drug Reactions

In connection with general pharmacovigilance issues, the Danish Medicines Agency consults the Council for Adverse Drug Reactions which comprises representatives from the industry and treating physicians as well as patient and consumer representatives¹⁷. In addition to providing general advice to the Agency, the Council for Adverse Drug Reactions also makes recommendations and solution proposals on how to improve the prevention and monitoring of side effects from medicine.

International collaboration on the monitoring of side effects

In the vast majority of cases, common coordinated efforts are required within the EU as well as an assessment from the European Medicines Agency which can form the basis for decisions on safety measures and any consequences for the marketing authorisation for a specific type of medicine. The Danish Medicines Agency thus also contacts collaboration partners in the EU to assess whether the medicine in question should be checked or whether safety measures should be implemented.

The side effect reports are used in a close and formalised international collaboration in the EU. The more reports the Danish Medicines Agency and the European Medicines Agency receive, the more well-founded decisions the national authorities can take. The reports to the Danish Medicines Agency are forwarded to the European pharmacovigilance database and made available for all EU member states. The side effect reports are also sent to the company holding the marketing authorisation and to the WHO. All reports are forwarded in anonymised form.

The Danish Medicines Agency rarely makes decisions on safety measures based on a single report. The decisions will normally be based on periodic safety update reports containing information about side effect reported worldwide and the Agency's existing knowledge of the medicine in question, e.g. supplementary knowledge from safety studies, searches in the Danish and the common European pharmacovigilance databases, scientific literature and information received through our EU collaboration.

17) Members of the Council for Adverse Drug Reactions in the period from 1 July 2007 – 30 June 2011:
Ib Valsborg, Chairman (former State Secretary of the Danish Ministry of the Interior and Health), Jens Peter Balling, Head of Department, Anita Kruse, MSc in Psychology, Lotte Fonnesbæk, Head of the Department of Health, Sine Jensen, Senior Health Adviser, Jørgen Dalsgaard, Anaesthesiologist, Mette Holst, Managing Director, Yves Sales, General Practitioner, Anne Marie Lynge Pedersen, Dentist.

