

## Report of a suspected adverse drug reaction (ADR):

- **via online reporting portal EIViS:**

directly or by downloading a xml-file. Details see:

[www.swissmedic.ch/elvis](http://www.swissmedic.ch/elvis)

- **via link:** The ADR reporting form can be filled in electronically as before:

[Meldung einer vermuteten unerwünschten Arzneimittelwirkung \(UAW\) \(German\)](#)

[Annonce d'effets indésirables suspectés d'un médicament \(EI\) \(French\)](#)

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## Editorial

Dear Reader

Recently there has been increasing discussion of Swissmedic's interaction with its stakeholders, i.e. patients, healthcare professionals and pharmaceutical companies, as well as the media and government.

Pharmacovigilance is a classic example of how important sharing and interpreting data is to the risk-benefit profile of a medicinal product. Here adverse drug reactions (ADR) that have been known for many years are monitored and re-evaluated based on

the latest findings. In connection with this, it is very important to familiarise healthcare professionals and patients with this new information so that they are able to carefully weigh up the benefits and disadvantages of using the medicinal product in question.

In this edition of Vigilance-News, we publish articles on medicinal products that have been authorised for many years, but which now require certain measures to avoid ADR in response to current data. These ADR include the risk of agranulocytosis after the administration of metamizole, systemic hypersensitivity reactions associated with lamotrigine, the risks to women of childbearing age posed by valproate, or the respiratory symptoms that may occur during the use of codeine-containing cough and cold remedies in children under 12 and in other risk groups.

Apart from specific ADR associated with certain medicinal products, Vigilance News also provides a general report on the therapeutic product groups in the form of an annual statistical analysis. The 2014 figures for pharmacovigilance, vaccine vigilance, haemovigilance and vigilance concerning veterinary medicinal products are now available and are briefly examined.

In addition to sharing information about spontaneous ADR reports and evaluating scientific data from clinical trials, the literature, PSUR / PBRER (Periodic Safety Update Reports / Periodic Benefit-Risk Evaluation Reports), authorisation documents or evaluations by foreign authorities, quality management of authorisation holders' pharmacovigilance systems plays a key role for Swissmedic. In order to obtain an overview of this subject, an increasing number of pharmacovigilance inspections to verify compliance with GVP (Good Vigilance Practice) have been conducted in recent years. Our article on this subject aims to answer a few questions on the subject.

We naturally also welcome suggestions from our readers, and look forward to receiving your feedback at [news.vigilance@swissmedic.ch](mailto:news.vigilance@swissmedic.ch).

We hope you find this edition an interesting read.

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## Flash: Drug safety signals

Serious adverse reactions following metamizole administration – Update based on data available in Switzerland on 31 December 2014

Since the end of the 1980s, the onset of serious adverse reactions (particularly agranulocytosis and anaphylaxis) after the administration of metamizole has resulted in the product being withdrawn from the market in certain countries (USA, Sweden). In Switzerland, however, it remained authorised as rescue medication subject to certain restrictions (supplied only on medical prescription). In practice, its combined analgesic, antispasmodic and antipyretic properties mean that it is still frequently prescribed in an off-label, first-line scenario.

A review of haematological adverse drug reactions following the administration of metamizole has recently been published by a Basel-based team (Divisions of Clinical Pharmacology, Clinical Pharmacy and the Regional Pharmacovigilance Centre). This review includes statistics updated to the end of 2012 and recommendations for use [1].

We present here an update based on the data available at 31 December 2014, which may help us determine whether practice has changed and establish the efficacy of the measures recommended in the Information for healthcare professionals.

Between 1991 and December 2014, Swissmedic received 293 reports of adverse reactions in which involvement of metamizole was suspected. The majority of them concerned women (177 women and 109 men), and most patients were aged over 65. Agranulocytosis was reported in 65 cases (22.2 %). In 52 cases the symptoms improved when the product was discontinued. The outcome was fatal in the other 13 cases.

We also noticed that the number of reports of agranulocytosis has increased and has remained at a high level since 2010, rising from an average of 0 to 4 per year to 14 to 16 (see Figures 1 and 2), including 2 to 4 fatalities. Since the number of products prescribed is not available, a more detailed interpretation of the data is not possible as yet.

Nevertheless, in view of this increase in the number of reports of agranulocytosis, some of which proved fatal, we believe that it is worth reminding prescribers once again that metamizole should only be used for the indications officially approved by Swissmedic in the Information for healthcare professionals (severe pain and high fever that fail to respond to other measures).

Figure 1

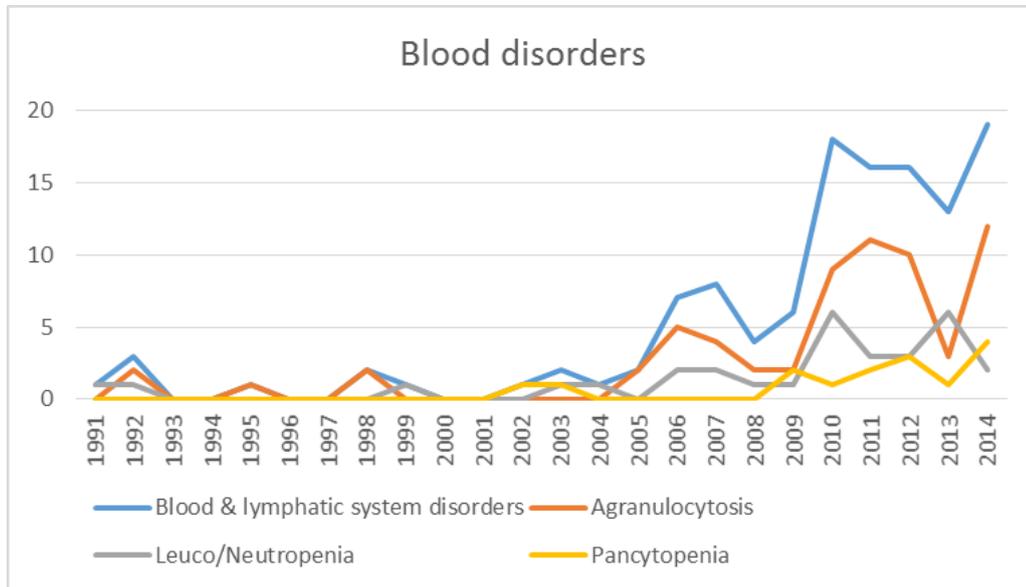
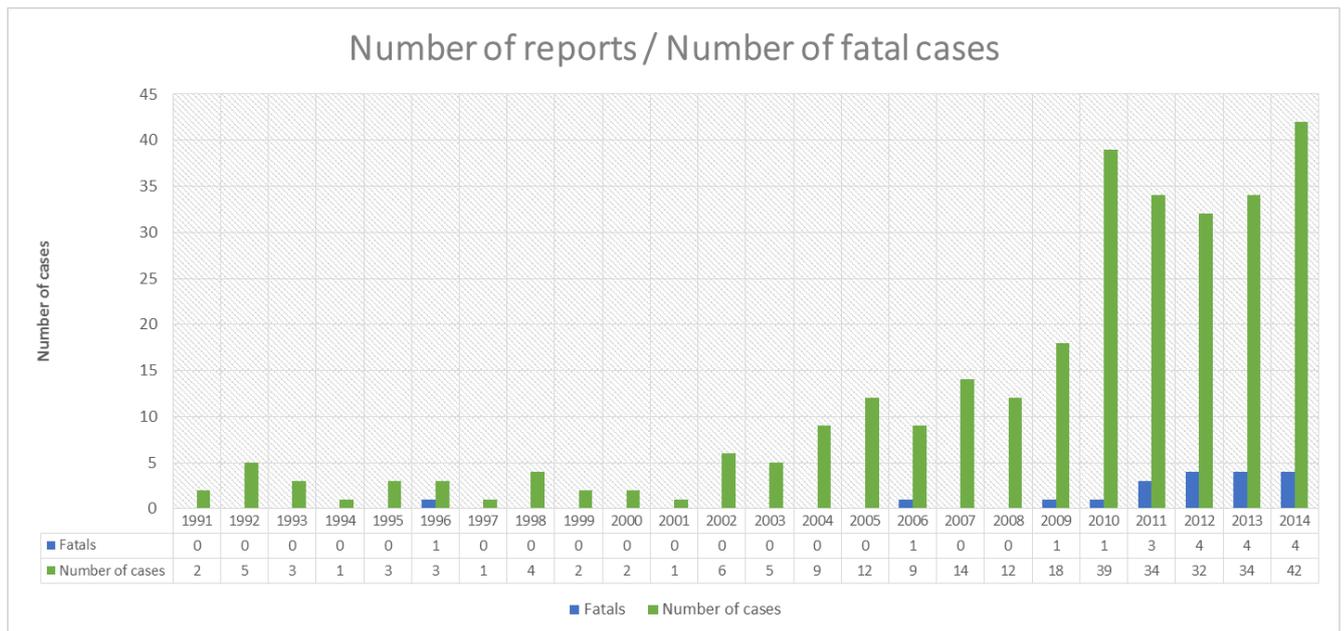


Figure 2



Reference

[1] [Hematological safety of metamizole: retrospective analysis of WHO and Swiss spontaneous safety reports.](#)

Blaser LS, Tramonti A, Egger P, Haschke M, Krähenbühl S, Rätz Bravo AE  
 Eur J Clin Pharmacol. 2015 Feb;71(2):209-17. doi: 10.1007/s00228-014-1781

## Systemic hypersensitivity reactions – Considerations and precautions using the example of lamotrigine

### Background

Hypersensitivity reactions of the skin and mucous membranes such as toxic epidermal necrolysis (TEN) and Stevens-Johnson syndrome (SJS, *erythema exsudativum multiforme*), as well as a wide range of systemic hypersensitivity reactions involving other organs, are rare, but serious and potentially life-threatening risks of medicinal products. Among the causative drugs, antiepileptics play an important role, and for this reason, the term «antiepileptic hypersensitivity syndrome» used to be applied. However, it has now rightly been replaced by terms such as DIHS (drug-induced hypersensitivity syndrome), DRESS (drug-related rash with eosinophilia and systemic symptoms), etc., since these complications are by no means restricted to antiepileptics. A review of the spontaneous reports submitted to Swissmedic confirms the importance of antiepileptics as causative agents. Of the total of 123 reports of TEN, carbamazepine, phenytoin and lamotrigine are reported as the suspected substance in just over 20% of cases – in addition to beta-lactam antibiotics, sulfonamides, certain NSAIDs, allopurinol etc. These figures take no account of the differing frequencies of prescription. Drawing on reports relating to the active substance lamotrigine, which has been authorised in Switzerland since 1992, some important aspects of the risks are discussed below.

### Reports relating to lamotrigine

Our pharmacovigilance database contains a total of 417 reports submitted in Switzerland between 1992 and the end of June 2015 and relating to ADR in which lamotrigine was registered as one of the suspected drugs (Lamictal® and generics). Their number peaked at 51 reports in 2008, since when the number has remained at around 20 a year. Two thirds were classed as

«medically important», while a further third resulted in hospitalisation or serious consequences. A considerable proportion involved younger patients under the age of 50. Permanent damage, e.g. after a serious skin reaction, has particularly significant consequences for such individuals.

### Skin reactions – TEN and SJS

Ten reports concern TEN, with a fatal outcome in one patient and permanent damage in at least two others. One patient became blind as a consequence of scar formation, which regularly also affects the conjunctiva and cornea; a corneal transplant had to be performed by an experimental technique in order to restore – at least partially – his sight. In this patient, and two others in this group of 10 with TEN, Lamotrigine was used for the psychiatric indication (suspected bipolar disorder, respectively prevention of mania), while the rest suffered from epilepsy.

SJS was diagnosed in 14 cases.

### Systemic hypersensitivity reactions

Over 30 reports involved symptoms of a systemic hypersensitivity syndrome in which a skin reaction was not the predominant factor or, in some cases, not present at all. The organ manifestations varied and included, for example, renal and hepatic effects, polyserositis, regularly accompanied by eosinophilia, lymphadenopathy and high fever. Two reports of disseminated intravascular coagulation could not definitely be classed as part of a hypersensitivity syndrome.

Haematological complications are also relevant (4 cases of pancytopenia, as well as reports of bicytopenia, thrombocytopenia etc.).

This analysis does not include reports in which severe liver damage was the determinant ADR and the predominant manifestation.

## Consequences

A classical type B reaction involves immunologically-related or «idiosyncratic» ADR which, in contrast with «pharmacological» type A reactions, are considered to be dose-independent, unforeseeable and unavoidable. This is not correct, however. There are identifiable risk groups and a whole range of primary and secondary preventive measures. These were not properly considered in several cases, although the medicinal product information texts describe them in great detail – e.g. excessively high initial dose, excessively rapid increase in dosage, inadequate dose adjustment in combination with valproate, failure to recognise warning symptoms and too late discontinuation.

## Conclusion

- Already during the clinical trials, skin reactions were observed in 5-10% of subjects receiving lamotrigine. According to the medicinal product information, the frequency of serious skin reactions (SJS) in adults is approx. 1/1000. The risk is higher in children (1/300 to 1/100 for skin manifestations leading to hospitalisation).
- These are systemic hypersensitivity reactions with a wide range of organ manifestations. In most, but not all, cases, the skin and mucous membranes are also affected.
- In view of the significant incidence and severity, the risk should be taken into account when deciding whether lamotrigine is indicated. This applies particularly to children, and also to psychiatric use, since the therapeutic alternatives in this indication are much less likely to trigger hypersensitivity.
- Before treatment is started, patients should be asked about previous symptoms they have experienced while taking the drug. Evidence of hypersensitivity to lamotrigine in the patient's history constitutes a contraindication.
- The risk for lamotrigine has been shown to be dose-dependent. Starting with a low initial dose, the dosage is increased in increments. In neurological practice, this often proceeds at a slower pace than suggested in the medicinal

product information and involves bridging by adding another antiepileptic agent if necessary (but use valproate with caution).

- In combination with valproate, lamotrigine should be given at a lower dose. Valproate inhibits the breakdown of lamotrigine by uridine diphosphate glucuronyltransferase (UDPGT); if both substances are administered at the same time, the half-life of lamotrigine is more than doubled.
- Patients should be made aware of the possibility of serious hypersensitivity reactions and corresponding warning symptoms (painful skin lesions, blister formation, propagation, mucosal involvement) and must follow specific instructions on the action to take.

Valproate (Depakine® and other preparations containing valproate) – Risk of congenital malformations and developmental disorders following exposure during pregnancy

## Update on medicinal product information and information materials used by patients and healthcare professionals

Congenital malformations, particularly neural tube defects, are well known complications of valproate following exposure of the foetus during pregnancy. Recent data from pregnancy registries published over the past few years have enabled us to clarify this risk and identify more clearly the serious risks of developmental disorders in exposed children.

As a result of these studies, changes were made in 2013 to the medicinal product information texts (Information for healthcare professionals and Patient information) in Switzerland. These have since been updated following an in-depth European evaluation, accompanied in March 2015 by

a DHPC (Dear Healthcare Professional Communication). Information materials for healthcare professionals and patients have also been published on the websites of Swissmedic (in Italian, French and German) and pharmaceutical companies that hold marketing authorisation for medicinal products containing valproate. The information for healthcare professionals and the distribution of the documentation have been actively coordinated by the marketing authorisation holder of the original medicinal product, Sanofi-Aventis, in consultation with the authorisation holders of «generic» preparations and with the support of Swissmedic.

<https://www.swissmedic.ch/marktueberwachung/00135/00157/02689/index.html?lang=de>

<https://www.swissmedic.ch/marktueberwachung/00135/00157/02689/index.html?lang=fr>

<https://www.swissmedic.ch/marktueberwachung/00135/00157/02689/index.html?lang=it>

The new information and resulting recommendations are summarised below:

## Results

- The risk of congenital malformations is increased (about 10%): neural tube defect, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (particularly bilateral aplasia of the radius) and multiple anomalies involving various body systems.
- Children exposed to valproate in utero have an increased risk of serious developmental disorders (up to 30 to 40% of cases): delayed acquisition of speech and/or walking, limited intellectual and verbal abilities, memory problems.
- In a study conducted in children aged 6 with a history of valproate exposure in utero, the intelligence quotient was an average of 7 to 10 points lower than that of children exposed to other antiepileptics in utero.

- Available data show that compared to control populations, children exposed to valproate in utero are at increased risk of autistic spectrum disorder (approximately three times more common) and childhood autism (approximately five times more common).
- Limited data suggest that children exposed to valproate in utero are more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD).

## Recommendations

In Switzerland, the indications for valproate include various forms of epilepsy and the prevention and treatment of manic episodes associated with bipolar disorder when lithium is contraindicated or not tolerated. It is also occasionally used off-label as an alternative preparation for the prevention of migraine attacks, but this practice should be strictly prohibited in women of childbearing age in view of the risk of accidental pregnancy and the major risks for the unborn child in these conditions.

In the indications authorised in Switzerland, the following precautions should be observed:

- Valproate should not be prescribed to young girls, female adolescents, women of childbearing age or pregnant women, unless alternative treatments are ineffective or not tolerated.
- Treatment with valproate should be initiated and supervised by a healthcare professional who is experienced in the management of epilepsy or bipolar disorder.
- The benefit-risk balance of treatment with valproate should be carefully assessed before valproate is first prescribed. The need to continue the treatment should be assessed regularly at each consultation, when a girl reaches puberty and when a woman of childbearing age wishes to become pregnant or starts a pregnancy.
- Healthcare professionals should ensure that all female patients are properly informed and understand:

- The risks associated with valproate during pregnancy
- The need to use effective contraception during the treatment
- The importance of regular follow-up in order to reassess the treatment
- The need to consult their healthcare professional promptly if they wish to become pregnant or start a pregnancy.

## Information materials

The information materials have been designed as a consultation support tool to promote transparent information and facilitate an adequate understanding of the risks associated with the treatment and shared decision-making by the patient and her healthcare professional concerning the selected treatment. It aims to improve the safety of use of the medicinal product and avoid, insofar as possible, unborn children being exposed to valproate in utero. These educational materials comprise:

- a brochure intended for female patients (Information brochure for patients – Medicines containing valproate and related substances)
- a brochure intended for HCP (Guide for healthcare professionals – Medicines containing valproate and related substances)
- a care consent form – Treatment of female patients with valproate.

The brochures present the risks encountered during specific clinical situations and the associated particular recommendations: first prescription to a female child, women of childbearing age who do not wish to become pregnant, women of childbearing age who wish to become pregnant, unplanned pregnancies. The care consent form, in the form of a checklist of key points to be checked by the prescriber and key points to be checked by the patient (or her representative), completes the package and aims to promote the adoption of a systematic and transparent approach before medicinal products containing valproate are either prescribed or used.

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## Risks of preparations containing codeine intended for the treatment of coughs and colds

Swissmedic recommends new restrictions on use and plans to amend medicinal product information texts accordingly. These measures were prompted by a recent decision by the European Medicines Agency (EMA).

The European Medicines Agency has reviewed codeine-containing medicinal products for the treatment of coughs or colds and, in April this year, approved the following restrictions on their use (Decision EMA/CMDh/206590/2015).

Codeine-containing medicines can lead to respiratory problems in sensitive patients. At risk are children under 12 years of age and babies of

breastfeeding mothers who take codeine, as well as people who convert codeine into morphine at a faster rate than normal («ultra-rapid metabolisers»). Swissmedic therefore recommends treating coughs and colds in these patient groups with preparations that do not contain codeine. Caution is indicated in adolescents over 12 years with breathing problems.

The EMA's decision and corresponding changes to the medicinal product information texts are currently being implemented in the EU countries. Swissmedic has asked companies that distribute authorised codeine-containing cough and cold preparations in Switzerland to incorporate the same restrictions in their medicinal product information texts. Swissmedic is reviewing the possibility of excluding any use in the above-mentioned risk groups (contraindication).

## Regulatory

### FAQ Pharmacovigilance-Inspections (GVP, Good Vigilance Practice)

*Since when has Swissmedic been conducting GVP inspections and what is the primary objective of inspections?*

Swissmedic has been conducting GVP inspections in Switzerland since the start of 2013. Before then, PV systems were reviewed in the course of GCP inspections.

The main objective is to verify whether the PV systems of pharmaceutical companies (or contract research organisations/research institutes) conform to legal requirements and GVP recommendations for both authorised medicinal products and clinical trials.

Inspections are usually routine in nature, but can also be triggered by the inadequate quality of Individual Case Safety Reports or relevant findings from earlier inspections, for example.

*How is the Swissmedic inspection team structured and what does the inspection involve?*

GVP inspections are usually carried out by two inspectors from the CT (Clinical Trials) department, unit GCP/GVP inspectorate, plus two experts from the Safety of Medicines department. The inspection process is divided into three phases:

**Preparation:** Notification of the inspection 4-6 weeks in advance, request for documents, drafting of the provisional agenda, which is then finalised in consultation with the institution to be inspected.

**Implementation:** The inspection lasts two days: Opening – presentations, interviews, document review – conclusion, with an explanation of the key findings (without classification).

**Inspection report:** The inspection report is sent after about four weeks, after which the inspected institution prepares its CAPA plan.

Inspections are conducted in German, French or English.

*What key aspects are examined during a GVP inspection?*

The inspection team looks at the following systems, processes and documents in particular:

- Organisation and responsibilities of the medical/PV department
- Management of the quality system
- Interfaces with other departments
- PV database and reporting systems (including reporting time limits)
- Individual Case Safety Reports from spontaneous reports and clinical trials
- Signal detection and risk management incl. risk-minimising measures
- Training documents for Health Care Professionals and patients
- Operating procedures
- Contracts with investigators, research institutes and other business partners
- Personal folders and training documents for the company's employees.

*How are findings classified in the inspection report?*

In accordance with EMA standards, findings are classified as critical, major or minor depending on the seriousness in each case. The findings are referenced on the basis of laws and recognised guidelines and directives. The report also includes comments, which usually contain notes for the inspected institution.

## *Can you name a few examples of common inspection findings?*

The findings primarily concern inspected institution's organisation, quality system, Individual Case Safety Reports and risk management:

- No clear description of functions and responsibilities
- Curricula vitae and job descriptions missing, not personalised or updated
- Training courses not taken or not documented
- Unclear or contradictory process descriptions, out-of-date operating procedures
- Individual Case Safety Reports of inadequate quality, late reporting to Swissmedic
- Medical assessment in ICSRs missing or inadequate (information on awareness – causality – need for risk-minimising measures)
- Follow-up information on ICSRs not collected or collection delayed
- Information on signals and safety-related measures in other countries not proactively forwarded to Swissmedic
- Risk-minimising measures promised in the RMP not implemented in Switzerland.

## *What is your assessment to date and what about the future for GVP inspections?*

After some two and a half years, the overall assessment is all around positive. GVP inspections have established themselves as an important tool for improving quality, a conclusion that is also supported by the inspected institutions themselves. They also improve communication and mutual understanding when differing viewpoints and procedures arise. They make a material contribution to the identification of existing shortcomings and provide the inspected companies/institutions with arguments to persuade decision makers of the need to implement the necessary changes.

Swissmedic will continue the successful course it has adopted by conducting approx. 8–10 GVP inspections a year in future.

## Abbreviations

|      |                                   |
|------|-----------------------------------|
| CAPA | Corrective And Preventive Actions |
| EMA  | European Medicines Agency         |
| GCP  | Good Clinical Practice            |
| GVP  | Good Pharmacovigilance Practice   |
| ICSR | Individual Case Safety Reports    |
| PV   | Pharmacovigilance                 |
| RMP  | Risk Management Plan              |

## Health risks of illegal medicinal products – a call to action

Medicinal products manufactured or distributed outside the legal distribution chain can be very detrimental to health. Examples include potency preparations obtained on the Internet, anabolic drugs from gyms, benzodiazepines smuggled across the border or illegal slimming preparations containing the active ingredient sibutramine. The latter was withdrawn from the market several years ago because of the adverse drug reactions it causes. Amazingly, no side effect reports relating to these products have been submitted. This is paradoxical – are these illegal preparations apparently safer than authorised medicinal products?

Laboratory tests on such products repeatedly document their poor quality and undeclared ingredients. There is worldwide unanimity that such illegal medicinal products are harmful and must be controlled. But no-one is recording the resulting damage or is aware of their nature or extent. Cases only come to light in extremely rare instances, for example the death a year ago of a 23-year-old man in the canton of Jura, who wanted to build up his muscles with anabolic steroids obtained online. His mother contacted the press and publicised his death in order to warn other young people about the risks.

We are therefore asking you to question patients who experience «sudden health problems» after taking additional preparations – including herbal products – and to report suspicious cases to Swissmedic.

The Council of Europe has drawn up the «Medicrime Convention», which is designed to combat criminality associated with medicinal products. Switzerland has signed this convention and is currently working towards its ratification. An expert committee of the Council of Europe (*CMED, Committee of experts on minimising public health risks posed by counterfeiting of medical products and similar crimes*) has been tackling the subject of the health risks of illegal medicinal products. Four years ago several European countries joined forces to investigate the health damage caused by illegal medicinal products. A pilot study conducted in Switzerland as part of a master's thesis brought to light the serious adverse effects of illegal potency drugs [1]. A multinational study was then carried out to identify therapeutic classes and highlight influencing factors [2]. A public-health approach was developed to identify at-risk patients during consultations. A decision-making tool consisting of a list of symptoms and a checklist with scores has undergone practical testing in six countries over the past two years.

The experience accumulated in various countries was presented at a workshop of the Council of Europe in Strasbourg on 23/24 June 2015, and further steps were discussed on the basis of this experience. Now it is important to explore the health risks systematically and on a broader basis. Hospitals, medical practices, pharmacovigilance centres and other institutions are called on to assist with future studies. This international cooperation is now entering a very interesting phase, and contributions from Switzerland are welcome. Organisations or practices interested in taking part are asked to contact [market-surveillance@swissmedic.ch](mailto:market-surveillance@swissmedic.ch). Further details can also be obtained from Ruth Mosimann, Head of Market Monitoring of Illegal Medicines (058 462 04 72).

## References

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[2] Identification of health damage caused by Medicrime products in Europe: An exploratory study. Authors: Venhuis BJ, Mosimann R, Scammell L, Di Giorgio D, Van Cauwenberghe R, Moester MGAM, Arieli M, Walser S. RIVM Report 040003001. In: <http://www.rivm.nl> – [Medicrime](#)

## Statistical Review 2014

### Vigilance of Human medicines

Within the framework of the pharmacovigilance network, the reports on adverse drug reactions are assessed in six regional pharmacovigilance centres (RPVC) on behalf of Swissmedic and recorded in the national database.

The professionals who submit the reports receive appropriate feedback. Reports on adverse reactions from within Switzerland are also sent to Swissmedic by the pharmaceutical companies.

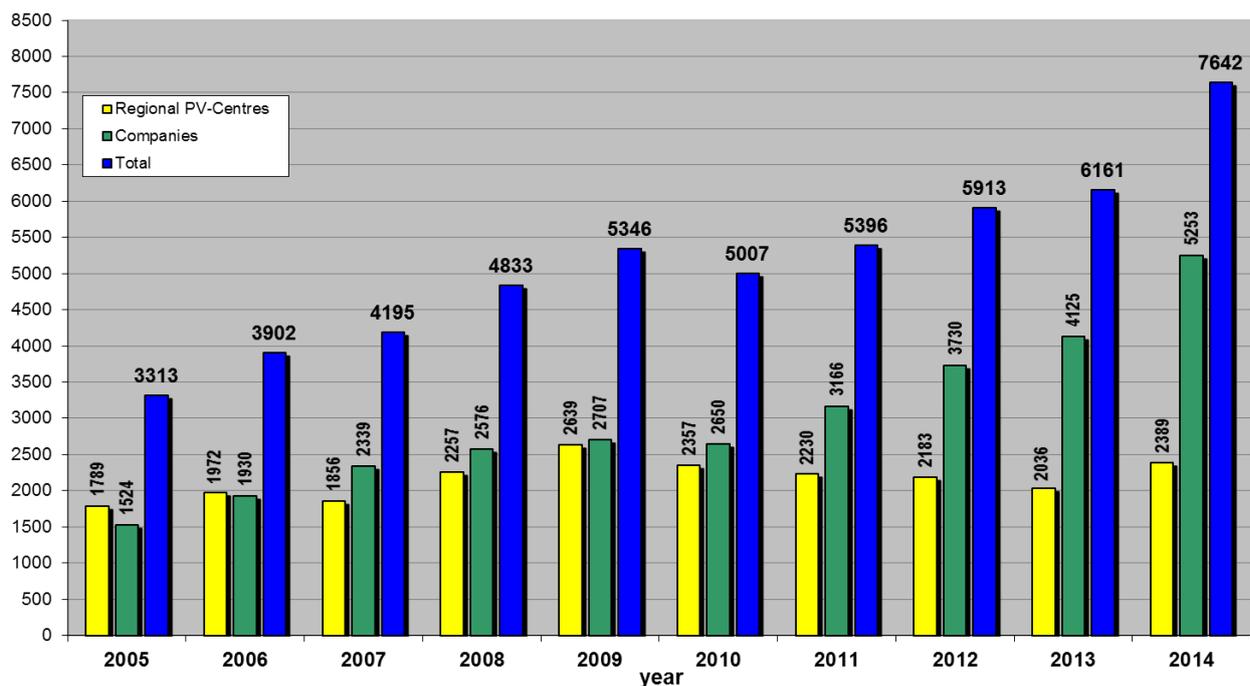
#### Activities

- In 2014, Swissmedic entered 7,642 reports of suspected adverse reactions to medicinal products in the database. These were sent by the six RPVC (2,398) and the industry (5,253). The marked increase compared with the previous

year is primarily the result of a greater reporting volume both from companies and from the RPVC.

- Roughly 25% of the reports from companies were submitted to Swissmedic electronically, using the pharmacovigilance gateway launched in December 2012. In 2014, two more major companies started using the gateway, with two more about to join in the near future.
- After nearly two years of project activities, the online reporting portal EIViS (Electronic Vigilance System) became operational in early October. HCP who have hitherto been using reporting forms to notify the RPVC of suspected cases can now do so online, while pharmaceutical companies without gateway access to the Swissmedic database can also send their reports electronically to Swissmedic. By the end of the year, 16 companies had been given access after receiving the appropriate training.

Swissmedic Pharmacovigilance-Centre: Reporting Frequency



## Vaccinovigilance

### Summary of adverse events following immunization reported in Switzerland

During 2014, Swissmedic received 296 case reports of suspected adverse events following immunization (AEFI) from Switzerland. This is a much higher number of reported cases as compared to 2013 (138 reports), which might reflect an increased incidence of adverse reactions following vaccinations or an increased reporting rate of AEFIs. However, since there are no accurate data available regarding the total number of vaccines/doses administered during 2014, a straightforward conclusion cannot be drawn. Notably, during 2014 a significant number of AEFI cases (106 reports) occurring in previous years have been retrospectively submitted to Swissmedic and have also been considered in this evaluation. No new safety signals have emerged from these older retrospective AEFI-reports. As previously, Swissmedic continues to encourage spontaneous reporting of AEFIs in high quality, which enables early detection of new safety signals. Since 2010, important safety topics concerning vaccines are discussed and evaluated by experts of the Swissmedic Human Medicines Expert Committee (HMEC). An increased AEFI reporting rate followed by a scientific evaluation of relevant cases can lead to risk minimisation measures in order to ensure vaccines safety, if necessary.

Link: [Summary of adverse events following immunization reported in Switzerland during 2014](#)

## Haemovigilance

The haemovigilance system records not only the occurrence of transfusion reactions, but also reports of transfusion errors and so-called near-misses, i.e. mistakes that were discovered before the start of a transfusion, thereby preventing a transfusion error. A total of 1,935 reports were evaluated in 2014, and these are broken down as follows (Table 1):

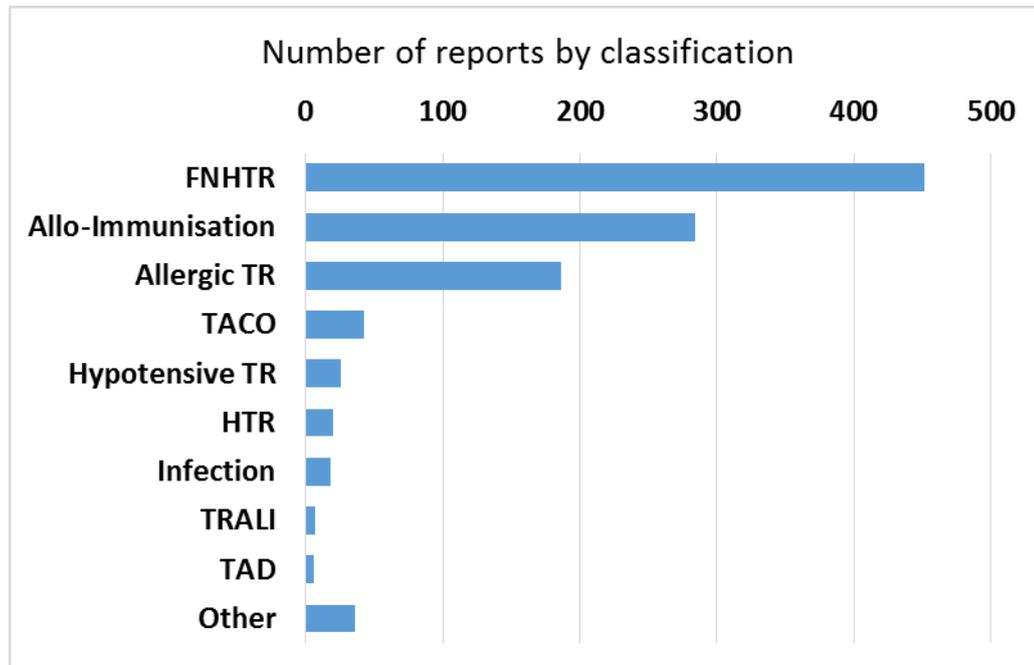
**Table 1: Number of haemovigilance reports in 2014**

| Type  | Number      |
|---|-------------|
| Transfusion reactions                                   | 1077        |
| Transfusion errors / incorrect blood product transfused | 49          |
| Near misses   | 784         |
| Donor reactions   | 13          |
| Quality defects   | 12          |
| <b>Total number of reports evaluated</b>                | <b>1935</b> |

In recent years, the annual requirement for packed red blood cell (pRBC) units and plasma for transfusion in Switzerland has declined steadily. In 2014, approx. 260,000 pRBC units and 38,000 units of plasma were transfused. By contrast, and following an increase in recent years, the number of transfused platelet concentrates (PC) has stagnated. In 2014, approx. 35,000 PC units were administered. The reporting rate calculated from these consumption figures (total of approx. 335,000 delivered blood products) and the number of reports (1,935) works out at 5.8 reports per 1,000 transfusions in 2014. The reporting rate has therefore continued to increase compared to previous years.

The 1,077 reported transfusion reactions can be divided up as follows (Figure 1):

**Figure 1: Transfusion reactions (TR) reported in 2014 by category, N=1,077**



FNHTR = Febrile non-haemolytic transfusion reaction, TACO = Transfusion-associated circulatory overload, HTR = Haemolytic transfusion reaction, TRALI = Transfusion-associated acute lung injury, TAD = Transfusion-associated dyspnoea

As shown in [Table 1](#), FNHTR and alloantibodies accounted for the majority of transfusion reactions. Both occur predominantly in connection with pRBC. Allergic reactions are ranked third in terms of frequency and are more typical of transfusions with PC and especially with fresh frozen plasma (FFP).

The analysis of transfusion reactions with a fatal outcome shows that other reactions are mainly involved. Since 2008 there have been 6 transfusion-related fatalities (link with the transfusion «probable» or «certain»):

- 2008 one TACO after FFP and one TRALI after PC,
- 2009 one acute haemolytic transfusion reaction after pRBC and one bacterial infection after PC,
- 2012 one TACO after pRBC,
- 2014 one acute haemolytic transfusion reaction after pRBC.

Over half of all non-fatal but life-threatening transfusion reactions are allergic reactions. In second place is TACO, which is essentially an avoidable reaction that could often be prevented by a slower transfusion rate in at-risk patients.

The «Preventive measures and conclusions» section of the 2014 Annual Haemovigilance Report deals with pathogen inactivation of PC. The report also presents the alloantibodies occurring in Switzerland that can lead to problems in relation to both transfusions and pregnancies.

The complete 2014 Annual Haemovigilance Report and further information on haemovigilance can be found at [www.swissmedic.ch](http://www.swissmedic.ch) → [Market surveillance](#) → [Blood components](#)

## Abbreviations

|       |   |
|-------|---|
| FFP   | fresh frozen plasma                         |
| FNHTR | febrile non-haemolytic transfusion reaction |
| HTR   | haemolytic transfusion reaction             |
| PC    | platelet concentrate                        |
| pRBC  | packed red blood cells                      |
| TACO  | transfusion-associated circulatory overload |
| TAD   | transfusions-associated dyspnoea            |
| TR    | transfusion reaction                        |
| TRALI | transfusion-associated acute lung injury    |

## Vigilance of Veterinary medicines

### Reports on veterinary medicines authorised by Swissmedic

268 reports were submitted in 2014, an increase of approx. 7% on 2013. The distribution by sources remains comparable with all previous years, with 69% (185) of reports originating from industry, 16% (43) received directly from practising veterinarians and approx. 12% (33) submitted by the Swiss Toxicological Information Centre (STIZ). The remaining 7 reports were contributed by cantonal veterinary offices (5 reports) and by animal owners (2 reports). Also comparable with previous years is the distribution of the target animal species concerned: Over 89% of reports involved small animals (182 reports of adverse reactions in dogs, 58 in cats), while approximately 6% (16 reports) involved administration to cattle and calves. Reports of adverse reactions in other target animal species were rare: there were three reports concerning sheep, two concerning pigs and two concerning horses. There was only a single report for each of the other animal species. No adverse reactions in a user or veterinarian were reported in 2014.

**Table 1** presents the 268 submitted reports sorted by ATCvet code, with a specific breakdown for dogs and cats. The trend (Müntener et al., 2013a) under which most reports describe adverse reactions following the administration of the most common preparation groups such as antiparasitics (128 reports, 47.8%), anti-inflammatory drugs (25 reports, 9.3%) and anti-infectives (23 reports, 8.6%) has continued in 2014. As in 2013, we once again received several reports (14) involving a combined antiparasitic for dogs containing the active ingredients fipronil, S-methoprene and amitraz. The reported symptoms included apathy, fatigue, lethargy, ataxia and, in rare cases, vomiting. As a result of these adverse reactions, which are based on the

known residual effect of amitraz on the presynaptic alpha-2 receptors, the medicinal product information for this preparation was already modified in 2013. While the symptoms are usually self-limiting, the pharmacological action can be antagonised with atipamezole if necessary. The causality for all these reports was rated as «possible». Hormone preparations are particularly worthy of mention since they represented the second commonest group in 2014, with 29 reports (10.8%). Inadequate or excessively short action of a preparation designed to produce temporary infertility in male dogs was most frequently reported. In five of the reported cases, this observation was clearly proven by an excessively high testosterone level. The reported lack of efficacy in these cases was rated as «probable». In 2014, we received 11 reports relating to reconverted preparations, 9 of which involved cats. Although this represents a halving of the number of such reports compared to 2013, the nature of a spontaneous reporting system does not allow any conclusions to be drawn about a possible trend in the incidence of adverse reactions following reconversions, and particularly in cats.

For 59 reports (22% of the total number), a causal link was clearly established between administration and reaction («probable»), in 102 (38.1%; «possible») further cases, at least one alternative cause was identified, and in 92 cases (34.3%), insufficient information was available to enable a definitive rating to be issued. A connection was ruled out in 15 cases (5.6%) due to sufficient data.

Repartition of the reports received during the year 2014, sorted by ATCvet code with specific presentation of dogs and cats. The QZ code is fictitious and allows the specific grouping of reports to reconverted products (i.e. not used for the authorised animal species and / or indication).

**Table 1**

| Category of medicines according to ATCvet code                      | Number of reports<br>(% of total) |            |            |
|---|-----------------------------------|------------|------------|
|   | All Species                       | Dog        | Cat        |
| QA: Alimentary tract  | 5 (1.9%)                          | 5 (2.7%)   | 0          |
| QB: Blood and blood forming organs                                  | 2 (0.7%)                          | 0          | 0          |
| QC: Cardiovascular system   | 7 (2.6%)                          | 4 (2.2%)   | 3 (5.2%)   |
| QD: Dermatologicals   | 1 (0.4%)                          | 1 (0.5%)   | 0          |
| QG: Genito-urinary system and sex. hormones                         | 8 (3.0%)                          | 7 (3.8%)   | 0          |
| QH: Hormonal preparations (except hormones and insulin derivatives) | 29 (10.8%)                        | 21 (11.5%) | 8 (13.8%)  |
| QJ: Anti-infectives   | 23 (8.6%)                         | 7 (3.8%)   | 5 (8.6%)   |
| QL: Antineoplastic and immunomodulating agents                      | 14 (5.2%)                         | 11 (6.0%)  | 3 (5.2%)   |
| QM: Musculo-skeletal system   | 25 (9.3%)                         | 19 (10.4%) | 5 (8.6%)   |
| QN: Nervous system  | 11 (4.1%)                         | 3 (1.6%)   | 6 (10.3%)  |
| QP: Antiparasitics  | 128 (47.8%)                       | 99 (54.4%) | 19 (32.8%) |
| QS: Sensory organs  | 2 (0.7%)                          | 2 (1.1%)   | 0          |
| «QZ»: Reconverted products  | 11 (4.1%)                         | 2 (1.1%)   | 9 (15.5%)  |
| ALP registered products, animal care products, etc.                 | 2 (0.7%)                          | 1 (0.5%)   | 0          |
| <b>Total</b>  | <b>268</b>                        | <b>182</b> | <b>58</b>  |

## Information on the Swissmedic website

*(Most of the links are available in German/French only)*

### Communications regarding the safety of medicines

- 03.08.2015  
Botulinumtoxin vom Typ A  
Zugelassene Arzneimittel und Indikationen, korrekte Anwendung, Risiken und Vorsichtsmassnahmen
- 27.07.2015  
Risks of preparations containing codeine intended for the treatment of coughs and colds  
Swissmedic recommends new restrictions on use and plans to amend medicinal product information texts accordingly. These measures were prompted by a recent decision by the European Medicines Agency (EMA).
- 16.07.2015  
DHPC – Invokana® (Canagliflozin), Vokanamet® (Canagliflozin/Metformin Hydrochlorid), Forxiga® (Dapagliflozin), Jardiance® (Empagliflozin)  
Risiko diabetischer Ketoazidose (DKA) unter Behandlung mit SGLT2-Inhibitoren
- 07.07.2015  
DHPC – Stelara® (Ustekinumab)  
Risiko von exfoliativer Dermatitis und Exfoliation der Haut
- 19.05.2015  
DHPC - Xofigo, Injektionslösung
- 13.05.2015  
DHPC – Risiko klinisch signifikanter Bradyarrhythmien als mögliche Wechselwirkung bei gleichzeitiger Gabe von Harvoni® (Sofosbuvir+Ledispavir) zusammen mit Amiodaron oder Sovaldi® (Sofosbuvir) mit Daclatasvir zusammen mit Amiodaron
- 13.03.2015  
DHPC - Valproat (Depakine®, Depakine Chrono®, Valproate Chrono Zentiva®, Orfiril®, Valproat Chrono Desitin®, Valproat Sandoz®, Convulex®)  
Risiko kongenitaler Missbildungen und von Entwicklungsstörungen bei der Exposition während der Schwangerschaft
- 02.03.2015  
DHPC - Dantrolen i.v., Injektionslösung  
Verwendung einer Filternadel zum Aufziehen rekonstituierter Lösung aus neuer Ware bis auf Widerruf
- 24.02.2015  
DHPC - Procoralan® (Ivabradin)  
Neue Kontraindikation und Empfehlungen zur Risikominimierung für kardiovaskuläre Ereignisse und schwere Bradykardie
- 10.02.2015  
HPC – Celestone® Chronodose® sowie Diprophos®  
Seltene schwerwiegende neurologische Komplikationen nach nicht zugelassener epiduraler Anwendung: Anpassung der Arzneimittelinformation

## New on this website

- 29.07.2015  
European Medicines Agency withdraws 700 medicines from circulation – Swiss market not affected  
Swissmedic has concluded its checks on Swiss medicinal product authorisations
- 23.07.2015  
ICH Steering Committee Meeting in Fukuoka, Japan, 5 to 11 June 2015
- 22.07.2015  
EU and Swiss regulators sign confidentiality arrangement  
Arrangements will improve oversight of medicines for better protection of public and animal health
- 18.06.2015  
Successful operation against illegal drug imports  
This year's "PANGEA VIII" week of action to combat illegal trading in medicines online
- 27.05.2015  
Der neue Swissmedic-Geschäftsbericht ist da
- 05.05.2015  
Dangerous slimming products  
Swissmedic has analysed 61 illegally imported slimming products to establish their contents. The outcome is perturbing.
- 22.04.2015  
Anpassung der Arzneimittelinformation an das Referenzpräparat  
Für Zulassungsinhaberinnen besteht unverändert die Verpflichtung, die Arzneimittelfach- und Patienteninformationen von Arzneimitteln mit bekannten Wirkstoffen an das Referenzpräparat resp. an den aktuellen Stand von Wissenschaft und Technik anzupassen.
- 01.04.2015  
Patientensicherheit bei Medizinprodukten wird erhöht  
Press release
- 26.03.2015  
Confederation and cantons take action against providers of illegal fresh cell therapy  
Press release
- 09.03.2015  
Öffentliche Ausschreibung von Dienstleistungen in der Pharmacovigilance
- 06.02.2015  
Manipulated bioequivalence studies by GVK Biosciences – no affected preparations on the Swiss market  
Swissmedic has concluded its checks on Swiss medicinal product authorisations
- 05.02.2015  
Increase in illegal imports of medicinal products in 2014: The risks are underestimated  
Last year, more illegal medicinal products were again confiscated at the Swiss border than in the previous year.

Please find the complete list at the following web address: [www.swissmedic.ch/updates](http://www.swissmedic.ch/updates).