swissmedic

Vigilance-News

Edition 17 – Nov. 2016

Report of an adverse drug reaction (ADR):

Swissmedic recommends using the reporting portal.

- **Online reporting portal-ElViS:**
  Direct-insert or by xml.file upload

  Details:
  www.swissmedic.ch/elvis

Contents

Impressum

Editorial team

Martina Schäublin, Eva Eyal, Helena Bill, Joy Diggelmann

Authors

Lorenz Amsler, Beat Damke, Véronique Ditesheim, Cedric Müntener, Thomas Schwartz, Rudolf Stoller, Valeriu Toma

We want to thank all colleagues for their contribution to the realisation of this edition of Vigilance-News.

Contact

Please send your comments, questions or suggestions to the following address:

news.vigilance@swissmedic.ch

Editorial

Dear Reader

Once again, in this edition we have selected a wide variety of topics for you:

Before a medicinal product can be newly authorised, the prospective authorisation holder has to submit documentation on efficacy, quality and drug safety. This applies not only to chemical active substances but also to natural ones, for example plant-based substances. An article on this subject describes the risk-benefit ratio of so-called “phytopharmaceuticals”.

In the annual statistics for 2015 relating to pharmacovigilance, vaccinovigilance, haemovigilance and the monitoring of veterinary medicines, we report on the latest changes in drug safety for human medicines, vaccines, blood products and veterinary medicines.

It is important regularly to review the risk-benefit ratio known at the time of authorisation. In this process, it is crucial to provide information to, and obtain feedback from, the affected patient groups and healthcare professionals. The introduction of a patient card, for example, is one way to avoid accidental overdoses with low-dose methotrexate.

The regional pharmacovigilance centres (RPVC) in Switzerland play an important role in obtaining information about adverse drug reactions (ADR). On the one hand, they are in direct contact with healthcare professionals and patients while, on the other, they communicate with the national pharmacovigilance centre at Swissmedic and offer their expertise in the identification and evaluation of ADR reports that might constitute safety signals. The six RPVC recently published a selection of interesting ADR reports in the Swiss Medical Forum, which are reproduced in this edition (Swiss Med Forum 2016;16(37):757-763).

Please send any suggestions or feedback on this issue of Vigilance-News to news.vigilance@swissmedic.ch.

We wish all our readers a happy festive season and a successful start to 2017.

The Editors

Flash: Drug safety signals

Herbal medicines and pharmacovigilance

Introduction

Phytotherapy, from the Greek *phyton* for plant and *therapeia* for treatment, is the study of plants used in medicine. Phytotherapy, also known as herbal medicine, has been practised through the ages in many countries of the world. It involves complex mixtures of compounds that may have multiple physiological effects and are not without risk. The concentrations of active principles also vary according to the preparation form used, which may be herbal powders or extracts. The use of herbal medicine as an alternative or complement to conventional medicine has led to the use of plant-based medicinal products on a significant scale, particularly in Switzerland. Swissmedic considers that, while the quality and efficacy aspects of these products are obviously important, it is equally vital to review their safety as part of the authorisation process.

Herbal medicinal products authorised by Swissmedic are largely used on the advice of healthcare professionals. It should be noted that the active substances in the plants may cause serious adverse drug reactions and may interact with other medicinal products.

Pharmacovigilance

Pharmacovigilance based primarily on the reporting of adverse drug reactions by healthcare professionals and pharmaceutical companies is therefore of fundamental importance. Consumers, i.e. patients, are equally able to report adverse drug reactions likely to be due to medicinal products in general and, more particularly, to herbal medicinal products.

Adverse drug reactions are harmful and unwanted effects associated with a medicinal product, whether or not it is used in accordance with the conditions of its marketing authorisation. This includes inappropriate or abusive use, overdosage, occupational exposure and medication errors. Reports of such reactions are recorded and investigated by the Regional Pharmacovigilance Centres (RPVC), then evaluated and confirmed by Swissmedic.

Submission, evaluation and communication of adverse drug reactions makes it possible to identify the risks associated with medicinal products. Additional analyses are performed if necessary and, where appropriate, corrective measures are implemented in order to reduce these risks.

It should be noted that this approach also makes it possible to record adverse drug reactions resulting from the following

- Use during pregnancy or breastfeeding
- Drug interactions
- Loss of efficacy
- Lack of quality other than the occurrence of an adverse drug reaction.

Although herbal medicinal products are considered by most people to be “harmless”, this is not necessarily the case. In recent years, a number of articles describing adverse drug reactions due to plants have been published. In some cases, risk minimisation measures, which have even included banning the products concerned, have been adopted, and healthcare professionals and the public have been informed in announcements and/or publications.

Examples:

- **Kava and hepatitis** (1, 2, 3): In April 2003 Swissmedic withdrew the authorisations for medicinal products containing kava-kava as a result of the risk of serious hepatic lesions.
- **Medicinal products based on Petasites (butterbur)** (1): Several cases of hepatic lesions, in particular, led Swissmedic to withdraw the marketing authorisations of products based on Petasites.

Drug interactions

When herbal medicinal products and synthetic products are used together, they may interact, resulting in a modification of the action of one or other of the products.

There are several types of interaction:

- **Pharmacokinetic interactions**

  They may modify the blood concentration of synthetic medicinal products. If the interaction results in an increase in blood concentration, adverse drug reactions may occur. If the interaction results in a decrease in blood concentration, there is a risk of efficacy being reduced, which in turn may result in treatment failure and/or the development of drug resistance.

  Combination with medicinal products with narrow therapeutic ranges requires particular vigilance. Such products include, for example, cardiac glycosides and oral anticoagulants.

- **Pharmacodynamic interactions**

  When taken at the same time, herbal medicinal products and synthetic medicinal products can exert a synergistic or an antagonistic effect on a “target” such as a receptor, an enzyme, a protein or a pathogen.

Example:

- **Medicinal products based on St. John’s wort** (4, 5, 6, 7) are widely known to have clinically relevant interactions with oral anticoagulants, immunosuppressants (cyclosporine, tacrolimus), oral contraceptives, digoxin, certain other antivirals, some cytostatic agents, some antidepressants and methadone. Furthermore, spontaneous reporting of adverse drug reactions played a central role in the identification of interactions involving St. John’s wort. Some of the cases reported in the course of market surveillance have in fact helped to round out the data available on interactions with hormonal contraceptives and antivirals. Moreover, it appears that significant amounts of hyperforin in these products confer on them a greater potential for interaction, although the content of the different compounds can vary depending on the St. John’s wort (Hypericum perforatum) preparation.

Contraindications

Contraindications do not only exist for synthetic medicinal products. In fact, herbal medicinal products are not suitable for everyone. Some phy-siological situations, such as pregnancy, breastfeeding and age (particularly children), represent contraindications not only for numerous synthetic medicinal products but also for herbal medicinal products.

Examples:

- **Allergic reactions** to one or more ingredients or excipients.
- **Products based on Echinacea purpurea** that have a non-specific stimulant effect on the immune system are not recommended for individuals with progressive systemic diseases or autoimmune conditions, immunodeficiency and immunosuppression or white blood cell disorders such as tuberculosis, leukaemia, collagenosis (generalised autoimmune diseases with connective tissue modification such as lupus erythematosus), multiple sclerosis, AIDS or HIV infection.
- **Laxatives containing Sterculia** are contraindicated in patients with ileus and stenosis of the digestive tract, those with abdominal pain of unclear origin and during nausea and vomiting.

Conclusion

Herbal medicinal products are not always considered to be real therapies. However, even though they can be obtained without a prescription, this does not mean that they are free of risk. They can certainly be associated with adverse drug reactions and interactions. Moreover, a number of serious adverse events connected with herbal medicinal products (kava, Petasites, St. John’s wort) have occurred in recent years. The risk of such effects occurring is greater if patients with kidney and/or liver failure take several

medicinal products at the same time. Spontaneous reports of adverse drug reactions naturally play a key role in identifying risks of this type. In order to identify and confirm these risks, we rely in particular on healthcare professionals to report to Swissmedic all adverse drug reactions suspected of being associated with a medicinal product.

Reporting of adverse drug reactions

Swissmedic encourages those concerned to report all adverse drug reactions (ADR) using the reporting tool developed for this purpose. The Electronic Vigilance System ElViS enables reporters to submit an ADR directly. All the necessary information can be found at www.swissmedic.ch → Market surveillance → Human medicines → Pharmacovigilance.

References

1) Swissmedic 2003 Annual Report
2) Stickel F, Baumuller HM, Seitz K, Vasilakis D, Seitz G, Seitz HK, Schuppan D (2003) Hepatitis induced by Kava (Piper methysticum rhizoma). Journal of hepatology 39 (1): 62-67
3) Russmann S, Lauterburg BH, Helbling A (2001) Kava hepatotoxicity. Annals of internal medicine 135 (1): 68-69
4) Swissmedic 2005 Annual Report
5) Schweizerische Ärztezeitung, 2005;86: Nr 47
6) Madabushi et al. Hyperforinin St. John's wort drug interactions. European journal of clinical pharmacology2006, 62:225-33
7) Mai et al. Hyperforin content determines the magnitude of the St John's wort–cyclosporine drug interaction. Clinical pharmacology and therapeutics 2004; 76:330-40

Corrigendum to the article "Progessive multifocal leukoencephalopathy (PML) and medicinal products for treating multiple sclerosis – update" (Vigilance-News Ed. 16, p. 11ff)

Corrections are underlined:

P. 11 bottom left: The JC antibody index has recently been developed for this purpose. In patients <u>being treated with natalizumab</u> who have not been previously treated with immunosuppressants, this index correlates with the risk of contracting PML.

P. 11 bottom right, paragraph on dimethyl fumarate (Tecfidera®): Instead of "A reduction in lymphocyte count occurs in around 30 % of patients who take such preparations", the correct wording should be: <u>During the first months of treatment, lymphocyte count falls by an average of 30 %.</u>

As regards the paragraph on natalizumab (Tysabri®), (at the top right of p. 11), we can inform you that the announced new risk-minimising measures were published on 20 September 2016 (updated medicinal product information and DHPC): <u>DHPC – TYSABRI® (Natalizumab) dated 20.09.2016</u>

Accidental overdoses of low-dose methotrexate due to daily instead of once-weekly administration in patients with rheumatoid arthritis and psoriasis

Despite warnings in the medicinal product information texts and repeatedly in professional publications, cases of severe accidental overdosage with low-dose methotrexate continue to occur as a result of incorrect daily, instead of once-weekly, administration in patients with rheumatoid arthritis or psoriasis. The designated weekly interval conflicts with the normal habit of taking medicines, particularly tablets, on a daily basis.

Together with the 6 marketing authorisation holders Curatis AG, Gebro Pharma AG, Orion Pharma AG, Pfizer AG, Sandoz Pharmaceuticals AG and Teva AG and the Patient Safety Switzerland foundation, Swissmedic has devised measures to ensure that all those concerned are aware of and adhere to the correct once-weekly administration of low-dose methotrexate in daily practice.

A DHPC was sent out on 20.07.2016 and published on the Swissmedic website on 21.07.2016: DHPC – Low-dose methotrexate in rheumatoid arthritis and psoriasis dated 21.07.2016

The risk-minimising measures are:

Sticker/fixed overprint on the pack

(available in German and French)

The following “Boxed Warning” has been affixed to the outer packages as a sticker or fixed overprint: **For rheumatoid arthritis and psoriasis, take/administer only once a week**. The pack also has space for the dispensing outlet to enter the specified day of the week for administration.

“Boxed warning” on the Information for healthcare professionals and Patient information

A prominently highlighted notice in colour and framed in a box in the “Dosage and administration” section stating that the medicinal product may be taken/administered only once a week for non-oncological indications and requesting prescribers to note the specified day of the week for administration on the prescription.

Patient Card

The card is intended to be issued to the patient by the physician/pharmacist, who enters the specified day of the week for administration and the methotrexate preparation. The card provides information on correct administration, possible symptoms of an overdose and the steps to be taken in this situation. The patients should carry the card with them and present it to physicians and medical personnel, particularly on admission to a hospital department or care institution or in the event of a change of the caregivers.

The Patient Card is available in credit card format in the three national languages (see sample). It can be ordered from the company contacts listed below (see table). The content can also be downloaded in a larger font and format from the websites of the companies and Swissmedic: Methotrexate Patient Card

English translation of patient card

Issued on: by: physician/pharmacist (stamp)

PATIENT CARD

Absolutely to be noted on treatment with Methotrexate:
You are being treated with a methotrexate product due to chronic polyarthritis (= rheumatoid arthritis), juvenile arthritis or psoriasis.

Name _____

First name _____

Methotrexate preparation _____

Weekday of administration _____

Show this patient card to your relatives and the healthcare professionals who care for you, or to the treating physician on hospital admission.

Please pay attention to the following points besides the package insert:

- You should take in or administer your methotrexate preparation ONLY ONCE A WEEK. Define a weekday of intake/administration with your physician/pharmacist. He will write down the weekday on the package and on this card.
- In case the following discomforts occur during treatment with methotrexate, contact your physician immediately: fever, sore throat, ulcers of oral mucosa, diarrhea, vomiting, skin rash, bleeding, unusual weakness or tiredness. Such signs can indicate an overdose of methotrexate due to too frequent administration.
- If you suffer from renal function disorder tell your physician.
- If you need anti-inflammatory analgesics (also over-the-counter such as e.g. ibuprofen, diclofenac), inform your physician/pharmacist about the treatment with methotrexate.

Company contacts

Company	Preparation	Tel./Fax	E-Mail
Curatis AG	**Methotrexat Proreo®**	Tel. 061 927 8777 Fax 061 927 8775	info@curatis.com
Gebro Pharma AG	**Metoject®**	Tel. 061 926 88 33 Fax 061 926 88 44	info@gebro.ch
Orion Pharma AG	**Methotrexat Farmos®**	Tel. 041 767 40 90 Fax 041 767 40 99	info.switzerland@orionpharma.com
Pfizer AG	**Methotrexat Pfizer®**	Tel. 043 495 71 11 Fax 043 495 72 80	info.ch@pfizer.com
Sandoz Pharmaceuticals AG	**Methotrexat Sandoz®** **Methrexx®**	Tel. 041 763 74 11 Fax 041 763 74 00	info.switzerland@sandoz.com
Teva Pharma AG	**Methotrexat-Teva®**	Tel. 061 705 43 43 Fax 061 705 46 27	kundendienst@mepha.ch

Further risk minimisation measures, like smaller package sizes (reduction of the total quantity of methotrexate per package) or therapy-appropriate dosages, are currently being implemented.

Drug Safety in Switzerland: Selected cases from the Regional Pharmacovigilance Centres

We are permitted to publish this article courtesy of the SWISS MEDICAL FORUM (Swiss Med Forum 2016;16(37):757-763).

Dr. Stefan Weiler[a], MD, Ph.D.; PD Dr. Anne B. Taegtmeyer[b], MD, Ph.D.; Dr. Sabine Müller[c], MD; Dr. Victoria Rollason[d], pharmacist, Ph.D.; Dr. Françoise Livio[e], MD; PD Dr. Alessandro Ceschi[a,f], MD; Prof. Gerd A. Kullak-Ublick[a], MD; for the Swiss RPVC collaboration

[a] Regionales Pharmacovigilance-Zentrum Zürich, Klinik für Klinische Pharmakologie & Toxikologie, UniversitätsSpital Zürich und Universität Zürich
[b] Regionales Pharmacovigilance-Zentrum, Klinische Pharmakologie & Toxikologie, Universitätsspital Basel
[c] Regionales Pharmacovigilance-Zentrum, Universitätsklinik für Nephrologie, Hypertonie und Klinische Pharmakologie, Inselspital Bern
[d] Centre régional de pharmacovigilance, Service de pharmacologie et toxicologie cliniques, Hôpitaux Universitaires de Genève
[e] Centre régional de pharmacovigilance et Swiss Teratogen Information Service STIS, Division de pharmacologie clinique, Lausanne CHUV
[f] Centro regionale di farmacovigilanza, Servizio di farmacologia e tossicologia clinica EOC, Ospedale Regionale di Lugano

Before marketing authorisation is granted, both the efficacy of a new medicinal product and the safety of the substances it contains are investigated as thoroughly as possible. However, less common adverse drug reactions do not emerge until after marketing authorisation, once medicinal products have been used in a much bigger and unselected population.

Drug Safety in Switzerland

Spontaneous reporting is the most important method of identifying adverse drug reactions (ADR). Pharmacovigilance involves the systematic compilation and recording of ADR. This is a form of continuous market surveillance that aims to minimise risk. Once a safety problem has been identified, a risk-benefit assessment is carried out. As in everyday clinical practice, the desired benefit is weighed against the potential risk associated with drug therapy. Even a small number of well-documented cases can lead to risk-minimising measures and allow fast decisions intended to protect patients.

The Regional Pharmacovigilance Centres (RPVC) are responsible for recording, evaluating and documenting ADR reports and for coding them in the database. Important reports from which signals can be derived are passed on to the Swissmedic National Pharmacovigilance Centre especially rapidly. The RPVC also provide feedback reports, including advice, to primary reporters.

Up to the end of 2015, six RPVC throughout Switzerland were responsible on behalf of Swissmedic for receiving ADR reports from healthcare professionals, patients and consumers and processing them according to the regulations. In April 2015, Swissmedic issued a public WTO call for tenders (in accordance with World Trade Organisation rules) for pharmacovigilance services. All the existing RPVC in Switzerland submitted bids for their pharmacovigilance services and their tenders were considered. The Clinical Pharmacology and Toxicology departments at the university hospitals in Zurich, Basel, Bern, Geneva and Lausanne and the EOC (Ente Ospedaliero Cantonale) hospital network in Ticino were chosen as the successful bidders. This development strengthened the existing Swiss pharmacovigilance system that had evolved over time and had demonstrated its value for the future.

This article presents ADR reports from the different Swiss RPVC that contain relevant potential signals or deal with current topics in pharmacovigilance. These are real reports from the pharmacovigilance centres. They feature clinically relevant, educational, instructive or unusual cases within their pharmacological context.

Basel: rivaroxaban

Gastrointestinal bleeding under rivaroxaban in a patient with renal failure and concomitant administration of amiodarone

The 70-year-old male patient was hospitalised as an emergency following repeated falls. Prodromal symptoms (mild dizziness, ascending sensation of warmth) with presyncope had been present each time. Moreover, the patient had had no appetite and had hardly eaten or drunk anything; he had also noticed blood in his stool for the first time. Laboratory workup showed a creatinine level of 142 mmol/l (eGFR 43 ml/min/1.73 m^2) and haemoglobin at 90 g/l. The lower GI bleeding stopped when Xarelto® was withdrawn; subsequent colonoscopy showed nothing abnormal. Other diagnoses were an arrhythmogenic and coronary cardiopathy with paroxysmal atrial fibrillation and Gold II COPD. Medication on admission: Xarelto® (rivaroxaban) 20 mg/day, amiodarone 200 mg/day, Aldactone® (spironolactone), atorvastatin, Duodart® (tamsulosin/dutasteride), Seroquel® (quetiapine; at night), Seretide® (salmeterol/fluticasone), Spiriva® (tiotropium).

The lower GI bleeding may have been triggered by the potentiated action of rivaroxaban in the context of acute renal failure caused by dehydration. There is an inverse correlation between increasing exposure to rivaroxaban and diminishing kidney function. The Swiss Drug Compendium (www.compendium.ch) states that the AUC is increased 1.5-fold if renal function is moderately impaired (GFR 30–-35 ml/min) and that the pharmacodynamic effects were even more marked (1.9-fold increase in total inhibition of Factor Xa activity in moderately impaired renal function). According to the information for healthcare professionals, the dosage of rivaroxaban for stroke prophylaxis must be reduced to 15 mg/day in patients with a GFR of 30–49 ml/min; however, 20 mg/day is retained for the indication of secondary prophylaxis of deep venous thrombosis or pulmonary embolism.

The medicinal product information mentions known interactions with CYP3A4 and P-gp inhibitors such as azole antifungals or certain HIV medications, and approx. 2.5-fold AUC and approx. 1.6-fold mean C_{max} are observed, resulting in an elevated risk of bleeding and the recommendation that bleeding parameters should be monitored (in the "Precautions" section). The information for healthcare professionals on Xarelto® did not explicitly mention the interaction with amiodarone – an inhibitor of most CYP and also a P-gp inhibitor – at the time the report was made, whereas the potential interaction, particularly if renal function is impaired, is mentioned in the US information for healthcare professionals (Product Information Xarelto® oral tablets, 2011).

The bleeding that occurred under rivaroxaban in a patient with moderately impaired renal function and concomitant administration of amiodarone, leading to anaemia and possibly to syncope, was therefore considered to be a possible ADR using the WHO criteria. The concentration of rivaroxaban was not known in this case.

The subject was recorded and processed as a signal by Swissmedic. The pharmaceutical manufacturer modified the information for healthcare professionals in November 2015, adding the following in the "Warnings and precautions" section: "*Xarelto should be used with caution in patients with moderate impairment of renal function (creatinine clearance 30–49 ml/min) who are concomitantly taking other medicinal products that lead to elevated plasma rivaroxaban concentrations.*"

The following was also added in the "Interactions" section: "*Results of an analysis of data from the ROCKET AF trial showed that concomitant use of rivaroxaban with combined P-gp and either weak or moderate CYP3A4 inhibitors (e.g. amiodarone, diltiazem, verapamil, chloramphenicol, cimetidine and erythromycin) did not show an increase in bleeding in patients with moderately impaired renal function (creatinine clearance 30–49 ml/min). Caution is required in these patients since elevated plasma concentrations of rivaroxaban may occur".*

This amendment is, however, also formulated cautiously. Physicians and pharmacovigilance centres should therefore remain alert with respect to rivaroxaban therapy in patients with impaired renal function and concomitant treatment with amiodarone.

Bern: influenza vaccine

Neuralgic shoulder amyotrophy following influenza vaccination

A 48-year-old woman experienced a burning sensation and muscle hardening in the left deltoid immediately after injection of Mutagrip® (influenza vaccine). Two days later, she experienced shoulder pain rated at NRS 9/10, hypersensitivity of the arm and pain on pressure on the scapula, over the AC joint and over the slightly hardened deltoid muscle. Formication in the region of the left ulnar and radial nerves and a sensation of the upper arm being swollen developed subsequently. There were no signs of inflammation, while duplex sonography of the veins and neurography showed normal results; a diagnosis of neuralgic shoulder amyotrophy following influenza vaccination was made. The effect of non-steroidal analgesics, tizanidine and vitamin B complex was inadequate; ultimately pregabalin and duloxetine led to a regression of the pain and dysaesthesia. The patient was finally free of symptoms three months later. She had sustained a fracture of the left humeral head 8 years before, with arthroscopic lysis of adhesions 5 years later.

Neuralgic shoulder amyotrophy (also known as Parsonage-Turner syndrome or brachial neuritis) is a rare syndrome that may persist for months. It involves neuropathic pain, muscle weakness or atrophy and sensory deficits in the neck, shoulder and upper arm. The symptoms may differ in intensity, and indolent forms have also been described. The suprascapular nerve and the infrascapular and suprascapular muscles are usually involved, with resulting impairment of abduction and external rotation. The syndrome is thought to be due to autoimmune inflammation of the brachial plexus; in isolated cases antimyelin antibodies or evidence of a complement- or T cell-mediated process have been observed. In addition to infections and trauma/surgery, various vaccines have been associated with the syndrome. The WHO pharmacovigilance database lists 91 global cases of neuralgic shoulder amyotrophy occurring several days to weeks after influenza vaccination. There are no known clear risk factors. The causal connection with Mutagrip® was assessed as “probable” in this case in view of the suggestive temporal correlation, the absence of non-pharmacological explanations and the fact that neuritis, neuralgia, muscle and joint pain are mentioned as adverse effects in the information for healthcare professionals for Mutagrip®.

Reports of idiosyncratic ADR of this type also help to identify risk factors. The question arises here as to whether the contralateral side should be preferred for vaccination if the patient has joints damaged by prior trauma. There was no indication of quality problems with the batch concerned in this case.

Geneva: propafenone

Interaction of propafenone with verapamil and slow metaboliser status

A 70-year-old female patient with hypertension following a transient ischaemic attack in the context of atrial fibrillation was treated with verapamil (Isoptin® retard 120) and digoxin. A single dose of 600 mg propafenone (Rytmonorm®) was tolerated well following a new episode of atrial fibrillation and the patient converted back to sinus rhythm after several hours. While heart monitoring was being performed, the ECG again showed atrial fibrillation, and 600 mg Rytmonorm® was administered again at 11.00 a.m. the same day. At approx. 1.30 p.m. the patient developed weakness and vomiting. When the emergency team arrived, the patient was in cardiac arrest; cardio-

pulmonary resuscitation was unsuccessful. Further genotyping of this patient showed that she was a slow metaboliser of cytochrome P450 (CYP) 2D6 (*4/*4).

Propafenone is an anti-arrhythmic drug used to treat ventricular and supraventricular arrhythmias. It is metabolised primarily by cytochrome 2D6 and, to a lesser extent, by CYP1A2 and CYP3A4. It has a plasma elimination half-life of 3.6 hours after a single dose, but this can vary between 12 and 16 hours in slow metabolisers of CYP2D6. Similarly, the mean plasma concentration is 1.1 ng/ml/mg in a regular metabolisation situation compared with 2.5 ng/ml/mg in slow metabolisers. Around 10% of the Caucasian population have slow CYP2D6 activity.

The ADR associated with propafenone also include proarrhythmogenic effects (ventricular tachycardia, atrial fibrillation or flutter, torsades de pointes). Verapamil is a potent inhibitor of CYP3A4. In this patient, metabolisation of propafenone was dependent almost solely on CYP2D6.

The interaction of propafenone with verapamil and the slow metabolisation of CYP2D6 both contributed to a possible increase in the plasma concentration of propafenone and its proarrhythmogenic action. This ADR could have been avoided by checking for pharmacokinetic drug interactions and performing predictive genotyping.

Lausanne: carfilzomib

Respiratory distress syndrome and acute renal failure

A 60-year-old male patient was given two doses of carfilzomib (Kyprolis®) within 24 hours for the first time by the intravenous route to treat recurrent multiple myeloma. The infusions were administered in accordance with the recommended starting dose (20 mg/m^2). 48 hours later, the patient was admitted to hospital with acute respiratory distress, haemoptysis, anuria and hypertension. A chest X-ray showed bilateral ground-glass infiltrates. The bronchoalveolar lavage fluid was bloody and sterile. The following laboratory findings were recorded: platelets 10 G/l; haemoglobin 87 g/l; schistocytes 7‰; haptoglobin 0.16 g/l (0.3-2.0); LDH 2504 UI/l (135-225); creatinine 546 µmol/l; albuminuria 7.8 g/l. The patient was intubated rapidly. Continuous haemofiltration was started. The patient's respiratory symptoms resolved and he was extubated after 5 days. Haemofiltration followed by intermittent haemodialysis was continued for 3 weeks. The patient's kidney function gradually normalised (creatinine approx. 100 µmol/l). The other laboratory findings also returned to baseline approx. 2 weeks after the patient had been admitted to hospital. The final diagnosis was acute respiratory distress syndrome in the context of alveolar haemorrhage and acute renal failure associated with thrombotic microangiopathy as an adverse reaction to carfilzomib.

This patient developed respiratory distress syndrome and acute renal failure 48 hours after the start of treatment with carfilzomib. In the absence of any other evident reason, the temporal sequence is extremely suggestive of this being an ADR. A connection is also suggested by the subsidence of the symptoms once carfilzomib had been discontinued.

Carfilzomib is a second-generation proteasome inhibitor that was approved by Swissmedic in November 2015 for the treatment of recurrent multiple myeloma. Cases of renal thrombotic microangiopathy associated with carfilzomib therapy have been reported in clinical trials and after the product had been brought onto the market. These cases generally occur at the start of treatment (after days or weeks). Changes in laboratory parameters (anaemia, haemolysis, schistocytes) may be more subtle than in thrombotic microangiopathy not associated with medication. Treatment is supportive. As with most other thrombotic microangiopathies of drug origin, plasma exchange appears to be ineffective. The reported cases generally have a favourable

course, with the symptoms improving a few weeks after carfilzomib has been discontinued.

There are no known pathophysiological causes, although the hypothesis has been put forward that there might be a connection with inhibition of vascular endothelial growth factor (VEGF). Carfilzomib does indeed inhibit VEGF transcription. The VEGF produced by podocytes is, however, required to maintain the glomerular filtration barrier.

Carfilzomib has also been associated with cases of acute respiratory distress in the context of alveolar haemorrhage, in some cases with a fatal outcome.

The simultaneous occurrence of renal thrombotic microangiopathy and alveolar haemorrhage in a patient being treated with carfilzomib has not been documented to date. The simultaneous occurrence suggests that there could be a joint pathophysiological basis for both ADR: pulmonary thrombotic microangiopathy? Alveolar haemorrhage hastened by severe thrombocytopenia in the context of thrombotic microangiopathy?

The case was reported to the RPVC by the doctor treating the patient. Reports of this kind play an important role in improving the characterisation of the ADR profile, particularly for medicinal products that, like carfilzomib, are new on the market.

Ticino: mirtazapine

Serotonin syndrome after monotherapy with mirtazapine

Therapy with Remeron® (mirtazapine, 15 mg) was started in a 74-year-old female patient because of depression. Confusion developed after 36 hours, and the patient became increasingly agitated and disorientated. Clinical findings included rigidity, particularly in the neck region, and fever. Further investigation of possible meningitis/encephalitis was negative. A diagnosis of suspected serotonin syndrome was made. Mirtazapine was immediately withdrawn, and the patient was monitored in the intensive care unit. The patient was not taking any other serotoninergic medicinal products and there was no pharmacokinetic interaction with the other medication she was taking. Her condition improved progressively over a period of 24 hours, and she was transferred to a normal ward. This case was reported to the RPVC by the doctor treating the patient.

Mirtazapine is a centrally acting presynaptic alpha-2 antagonist that increases the central transmission of noradrenaline and serotonin. The increased release of serotonin is mediated specifically by 5-HT_1 receptors since mirtazapine blocks the 5-HT_2 and 5-HT_3 receptors.

Serotonin toxicity is a potentially life-threatening syndrome caused by central serotoninergic overstimulation. It is characterised clinically by a classic triad of neuromuscular excitation (seizures, hyperreflexia, rigidity), autonomic instability or excitation (hyperthermia, tachycardia) and an altered state of consciousness (agitation, confusion). Serotonin syndrome can develop if several medicinal products with serotoninergic actions are administered concomitantly or, more rarely, in patients under monotherapy with a serotoninergic active substance. In most severe cases of serotonin syndrome a monoamine oxidase inhibitor (MAOI) that inhibits serotonin metabolism, such as moclobemide, is involved.

In this case, the product information for healthcare professionals for Remeron® did not contain any information about the possibility of serotonin syndrome occurring during monotherapy with Remeron® before this case was reported. The report contributed to the modification of the drug information. The information that serotonin syndrome occurs very rarely in patients treated with Remeron® alone was added during post-marketing surveillance.

In the practical setting, it is important to know which medicinal products have a strong serotoninergic action (e.g. certain antidepressants, antiemetics, analgesics or recreational drugs) so

that such combinations can be avoided as far as possible.

Zurich: phenazone

Medicinal products with the same name may contain different ingredients.

This 39-year-old female patient took the combination product Migraine Kranit®, containing paracetamol, caffeine and chlorphenamine, as needed to relieve migraine-type symptoms. The patient had always tolerated the medication well, with no adverse effects. At some point, the medicinal product was no longer obtainable in Switzerland, and the patient ordered a product with the same name from another country. She then developed angioedema with swelling of the tongue and "inflammation of the oral cavity" on four occasions after taking the product. The active substance in the imported product was the prostaglandin synthetase inhibitor phenazone, and not the paracetamol, caffeine and chlorphenamine combination that the patient had previously been using. The patient reported this case directly to the Regional Pharmacovigilance Centre.

Migraine Kranit® is no longer available in Switzerland. Phenazone is a pyrazolone derivative with analgesic, antipyretic and mild antiphlogistic and spasmolytic properties. It inhibits prostaglandin synthesis and causes reversible inhibition of platelet aggregation. According to the German information for healthcare professionals, rare cases of swelling with water retention, inflammation and swelling of the mucous membranes, particularly in the throat, rashes and even angioneurotic oedema have been observed during therapy with Migraine Kranit® containing the active substance phenazone. However, the product Migraine Kranit® that was formerly available in Switzerland contains completely different active substances: paracetamol, caffeine and chlorphenamine.

There was a plausible temporal connection between the use of phenazone and the development of angioedema with subsequent swelling of the oral cavity, and in fact the same symptoms developed when the product was taken again – a phenomenon that can be described as a positive rechallenge.

In 2015, the customs posts reported 1,134 packages containing suspicious medicinal products, representing illegal imports from 62 different countries. This has led to the use of wrongly declared or undeclared active substances becoming a growing problem. In the case described here, however, two products with the same name contained different active substances.

The advice here must be not to order medicinal products on the internet. At the same time, however, attention is drawn specifically to the risk of products with the same name containing different ingredients. It is also possible for the composition of a product to change over time. The situation is complicated by the fact that product packs in Switzerland often do not declare the active substance. For this reason, it is vital to read the patient information leaflet in the pack. Both healthcare professionals and their patients should pay particular attention to what active substances are actually present in the medicinal product.

Regulatory aspects and relevant clinical information for an ADR

The cases presented here illustrate the broad spectrum covered by pharmacovigilance. They range from dose-dependent (calculable) to dose-independent (idiosyncratic, unexpected) reactions. Risk factors such as pharmacological interaction partners (particularly via cytochrome P450 or P-glycoproteins) or organ failure (mainly impaired renal function) lead to increased exposure to medicinal products and thus to an elevated risk of ADR. Individual genetic factors also play a relevant role in susceptibility to medicinal products. Medication errors of all kinds represent a further possible risk for ADR. Personalised

drug therapy tailored to the individual patient improves the safety of medicinal products and thus patient safety.

Healthcare professionals are required to report serious or previously unknown ADR to Swissmedic.

In Switzerland the mandatory requirement for healthcare professionals to report ADR has been regulated in the Therapeutic Products Act (TPA) since 2002 (Table 1). Healthcare professionals and anyone, who manufactures, professionally administers or dispenses therapeutic products, are obliged to report the occurrence of serious or previously unknown ADR to Swissmedic (Art. 59, (3) TPA). Even a suspicion of an ADR with no clear causality is sufficient to report it. Presumed quality deficiencies must also be reported, preferably stating the batch/lot number.

Since 2002 Swissmedic has been working in the field of pharmacovigilance with the clinical pharmacology units of the university hospitals in Bern, Basel, Zurich, Geneva and Lausanne and with the Ente Ospedaliero Cantonale, which has also had a clinical pharmacology unit since 2015 (Fig. 1).

E-mail addresses of the Regional Pharmacovigilance Centres

Basel: vigilance@usb.ch
Bern: vigilance@insel.ch
Geneva: medvig@hcuge.ch
Vaud (Lausanne): vigil@chuv.ch
Ticino (Lugano): farmacovigilanza@bluewin.ch; farmacovigilanza.EOC@eoc.ch
Zurich: medi.info@usz.ch

Table 1: Serious and medically important adverse drug reactions (ADR).

Serious ADR
Death or life-threatening
Hospitalisation or prolongation of hospitalisation necessary
Permanent damage or causing pronounced, longer-lasting impairment
Congenital damage to the child during pregnancy
Medically important ADR
Patient acutely endangered by it
Intervention necessary to avoid a serious outcome

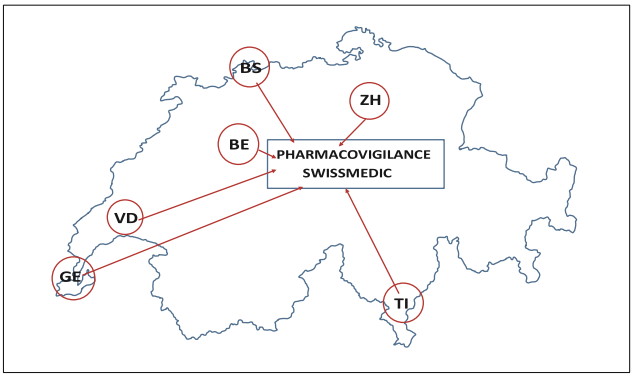


Figure 1: The Regional Pharmacovigilance Centres in Switzerland.

The advantages of the spontaneous reporting system include the monitoring of the entire spectrum of medicinal products in a large population, including special, vulnerable groups such as children, the elderly and pregnant women, the recording of rare events and ongoing observation without affecting prescribing behaviour at a relatively low cost. The disadvantages are the dependency on the quality of reporting, potentially compromised perception, the difficulty of assessing causality when information is so brief and the limited suitability of the data obtained for pharmacoepidemiological studies.

Primary reporters can submit ADR reports to the RPVC using the Swissmedic form or as an electronic report (Electronic Vigilance System, ElViS reporting portal). Both are available at www.swissmedic.ch/market_surveillance. Some

RPVC allow informal reports to be submitted in e-mails, by phone or using the hospital's digital information system. Any additional information required can then be obtained by the RPVC directly from the medical records. This means that the time required by reporters is minimal.

Reports should contain all the available data relevant for an assessment of the ADR. In addition to the temporal relationship between exposure to the medicinal product and the ADR, the course of any dechallenge/rechallenge, the severity of the ADR and its listing in the Swiss medicinal product information, the most important information is the clinical course and outcome (Table 2).

Table 2: Factors for assessing adverse drug reactions (ADR).

Intrinsic factors
Temporal relationship
Dechallenge/rechallenge with the medicinal product (withdrawal or renewed administration of the suspected substance with a reduction of/improvement in the ADR or its recurrence)
Exclusion of other causes
Pathophysiological plausibility
Presence of risk factors
Specific evidence on the basis of diagnostic results
Extrinsic factors
Swiss information for healthcare professionals (www.swissmedicinfo.ch)
Information in pharmacovigilance databases
Other medical databases (PubMed, Micromedex™, Rote Liste, Pharmavista, etc.)

When assessing the causality (imputability) of the drug exposure in the ADR, the RPVC uses extrinsic and intrinsic evidence analogous to the internationally valid WHO criteria. This evidence comprises the chronology of the events, pathophysiology and risk factors, and the description of the ADR in the product information for healthcare professionals and/or scientific literature.

If potential signals are identified, the Agency can adopt a wide variety of measures in line with the legislation (TPA Art. 66) (Table 3).

Table 3: Measures by the Agency if signals relevant for the safety of medicines as defined in Art. 66 TPA are identified.

Issue a letter of deficiency and set an appropriate deadline for rectification
Suspend or withdraw licenses and marketing authorisations
Close establishments
Confiscate, impound or destroy therapeutic products that are harmful to health or not compliant with the law
Forbid the distribution and dispensing of therapeutic products, their import and export and trade in them abroad from Switzerland, and order the immediate recall of therapeutic products from the market or the publication of damage-limiting recommendations for action

Serious, rare or previously unknown or incompletely known ADR, in particular, should be reported to one of the six Regional Pharmacovigilance Centres.

At the centres, reports are assessed on the basis of intrinsic (particularly temporal, pathophysiology, risk factors) and extrinsic (description in the information for healthcare professionals and the scientific literature) criteria and sent to Swissmedic in anonymised form.

Regulatory steps such as documentation and explanation in the information for healthcare professionals (updated version at www.swissmedicinfo.ch) or other risk-minimising measures are initiated by the Agency as necessary.

Public communication of relevant drug safety topics raises the awareness of healthcare professionals and increases patient safety both for the individual and for the population at large in the interests of public health.

Take-home messages

- The established pharmacovigilance system in Switzerland was reaffirmed in a WTO call for tenders in 2015 and has been continued since 1 January 2016 with new responsibilities.
- The identification of adverse drug reactions (ADR) is important in terms of the safety of medicinal products in the individual patient, the benefit-risk assessment of a substance, a therapeutic regimen regarding public health and pharmacoeconomics.
- Previously unknown or serious ADR, and ADR and quality defects of therapeutic products that are described inadequately or not at all in the product information for healthcare professionals must therefore be reported to one of the six Regional Pharmacovigilance Centres in Switzerland in keeping with the current legislation.
- These centres assess the reports and send them in anonymised form to Swissmedic, where a wide variety of measures may be taken to minimise risk.

Acknowledgements

The authors would like to thank the following colleagues at the RPVC: Raffaela Bertoli, Laura Andreocchi, Marco Bissig, Enos Bernasconi, Ursula Winterfeld, Alexandra E. Rätz Bravo, Sarah Hofmann

Disclosure statement

The authors declare that there are no conflicts of interest. Swissmedic was informed about this publication in advance. The aspects described here are the opinions of the authors and not of a regulatory agency.

Correspondence

Dr. Stefan Weiler, MD, PhD, MHBA
Specialist in General Internal Medicine,
Clinical Pharmacology and Toxicology
Department of Clinical Pharmacology and Toxicology
University Hospital Zurich
CH-8091 Zurich
Stefan.Weiler[at]usz.ch

References

- Swissmedic website: Pharmacovigilance www.swissmedic.ch/marktueberwachung/
- Updated information about medicinal products: www.swissmedicinfo.ch
- Uppsala Monitoring Centre. VigiBase™ - WHO individual case safety report (ICSR) database system. Available from: https://vigilyze.who-umc.org/

Additional references on cases 2 and 4

Case 2:

1. Shaikh MF, Baqai TJ, and Tahir H., Acute brachial neuritis following influenza vaccination. BMJ Case Rep, 2012. 2012.
2. Feinberg JH and Radecki J. Parsonage-Turner syndrome. HSS J. 2010;6(2): 199-205.

Case 4:

1. Lendvai N, Hilden P, Devlin S, Landau H, Hassoun H, Lesokhin AM, et al. A phase 2 single-center study of carfilzomib 56 mg/m2 with or without low-dose dexamethasone in relapsed multiple myeloma. Blood. 2014;124(6):899-906.
2. Hobeika L, Self SE, Velez JCQ. Renal thrombotic microangiopathy and podocytopathy associated with the use of carfilzomib in a patient with multiple myeloma. BMC Nephrol. 2014;15:156.
3. Sullivan MR, Danilov AV, Lansigan F, Dunbar NM. Carfilzomib associated thrombotic microangiopathy initially treated with therapeutic plasma exchange. J Clin Apher. 2015;30:308-10.
4. Qaqish I, Schlam IM, Chakkera HA, Fonseca R, Adamski J. Carfilzomib: a cause of drug associated thrombotic microangiopathy. Transfus Apher Sci. 2016.
5. Lodhi A, Kumar A, Saqlain MU, Suneja M. Thrombotic microangiopathy associated with proteasome inhibitors. Clin Kidney J. 2015;8(5):632-6.
6. Lataifeh AR, Nusair A. Fatal pulmonary toxicity due to carfilzomib (Kyprolis™). J Oncol Pharm Pract. 2015.
7. Kwong YL. Fatal pulmonary hemorrhage after carfilzomib treatment in multiple myeloma. Ann Hematol 2015;94:1425-6.

Regulatory

Electronic transfer of pharmacovigilance reports: please note!

We would like to remind that you that, with effect from 1 September 2016, Swissmedic is forwarding all ADR reports from the Regional Pharmacovigilance Centres to the companies concerned exclusively in **electronic form** via Gateway or ElViS. Follow the link below for more information:

News about electronic pharmacovigilance reports dated 18.07.2016

In addition, companies that are already reporting to Swissmedic via Gateway or ElViS should **not send the medical evaluation of the individual cases** by e-mail or as an ElViS attachment. As explained on several previous occasions, the medical evaluation must be entered in the "sender's comment" field (see also Vigilance News Edition 16, May 2016). If the 2,000 characters provided are not sufficient, the evaluation can be continued in the "case narrative" field.

Case follow-up attempts: what should be noted?

The information from adverse drug reactions cases when first received will generally be incomplete. Ideally, comprehensive information would be available on all cases, but in practice efforts are needed to seek additional information on selected reports. This is especially true for spontaneous reports.

Swissmedic assumes that marketing authorisation holders follow the recommendations of the CIOMS V working group, which are summarised below:

1. In any scheme to optimise the value of follow-up, the first consideration is prioritisation of case reports by importance.
2. Highest priority for follow-up are cases which are both serious and unexpected, followed by serious, expected and non-serious, unexpected cases.
3. For non-serious expected cases no follow-up is recommended if all four of the usual minimum criteria for a valid case are present plus country location and source of the report (physician, literature, patient's lawyer, etc.).
4. The extent of follow-up detail needed should be driven primarily by seriousness and expectedness case criteria (for details see pages 129-130 of the CIOMS V report).
5. When the case is serious, especially if also unexpected, and if the ADR has not resolved at the time of the initial report, it is important to continue follow-up until the outcome has been established or the condition has stabilised (e.g., acute renal failure, with the patient still on dialysis). How long to follow-up such cases will require judgment.
6. Every effort should be made to follow up unexpected deaths or life-threatening events within 24 hours.
7. All attempts to obtain follow-up information (whether or not successful) should be documented as part of the case file.
8. If the first written follow-up attempt on a serious case or a non-serious unexpected case fails to generate a satisfactory response, a second follow-up letter should be sent no later than four weeks after the first letter.
9. Acknowledgement letters should be sent to suppliers of follow-up information and they should be given any relevant feedback (e.g.,

that the company is currently updating product information).

10. Consideration should be given to informing regulators, particularly on important cases, if all attempts to obtain follow-up information have failed. This allows them to “close out” the case within their files.

Reference

Current Challenges in Pharmacovigilance: Pragmatic Approaches, Report of CIOMS Working Group V, Geneva 2001

Statistical Review 2015

Vigilance of human medicines

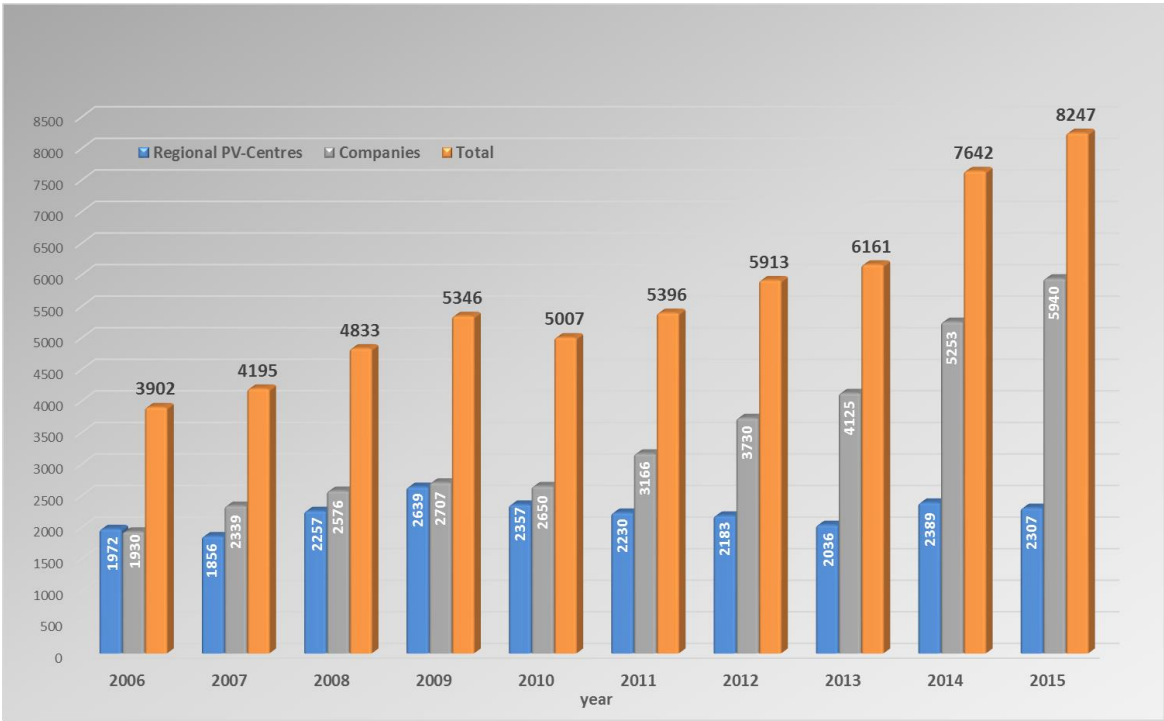
Within the framework of the pharmacovigilance network, the reports on adverse drug reactions are assessed in six regional pharmacovigilance centres (RPVC) on behalf of Swissmedic and recorded in the national database.

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

Activities

- Swissmedic received 8,247 reports of suspected adverse drug reactions (ADR). 2,307 of them were sent by the six regional pharmacovigilance centres (RPVC), 5,940 by the industry. As in previous years, there was again a sharp rise in the number of reports received (7.1%), due mainly to an increase in the volume reported by companies. The number of follow-ups to ADR reports is now also being recorded, as a big increase in the number of reports was observed during the year and they are labour-intensive (2,156 follow-ups).
- A total of 26 signals concerning 87 medicinal products were generated from the ADR reports received from Switzerland, and these were investigated in detail.
- Roughly 70% of the reports from companies were submitted to Swissmedic electronically, using the pharmacovigilance gateway. A further nine companies were given access in 2015. With one more joining in January 2016, there are now 16 companies using the gateway, all with large reporting volumes.
- Healthcare professionals can use the online reporting portal ElViS (Electronic Vigilance System) that was launched in October 2014 to report ADR online to one of the regional pharmacovigilance centres. In 2015 Swissmedic received 115 reports from healthcare professionals via the portal. Pharmaceutical companies without gateway access to the Swissmedic database can also send their reports to Swissmedic electronically via ElViS. As of the end of the year, 62 companies were actively using ElViS.
- All ADR reports received by Swissmedic are collated and processed in the national VigiFlow database. This database no longer meets all the requirements for a modern pharmacovigilance tool. Swissmedic therefore intends to replace VigiFlow with a modern Adverse Event Reporting System (AERS) by the beginning of 2018. A specification for the system was developed and the WTO call for tenders for the new database tool was issued on 8 December 2015.

Figure 1: Swissmedic Pharmacovigilance-Centre: reporting frequency over last 10 years



Vaccinovigilance

Summary of adverse events following immunization reported in Switzerland

During 2015, Swissmedic received 278 case reports of suspected adverse events following immunization (AEFI) from Switzerland. This is nearly on the same level as the number of reported cases during 2014 (296 reports) and a significantly higher number as compared to 2013 (138 reports). Notably, there are no accurate data available regarding the total number of vaccines/doses administered during 2015 and therefore a straightforward conclusion regarding AEFI reporting rates cannot be drawn. Similar to 2014, during 2015 a substantial number of AEFI cases (80 reports in 2015 vs. 106 reports in 2014) occurring in previous years have been submitted retrospectively to Swissmedic and have also been considered in this evaluation. However, no new safety signals have emerged from these older retrospective AEFI-reports received during 2015. As previously, Swissmedic is encouraging spontaneous reporting of AEFIs in high quality, which enables early detection of new safety signals. Since 2010, important safety topics concerning vaccines are being 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.

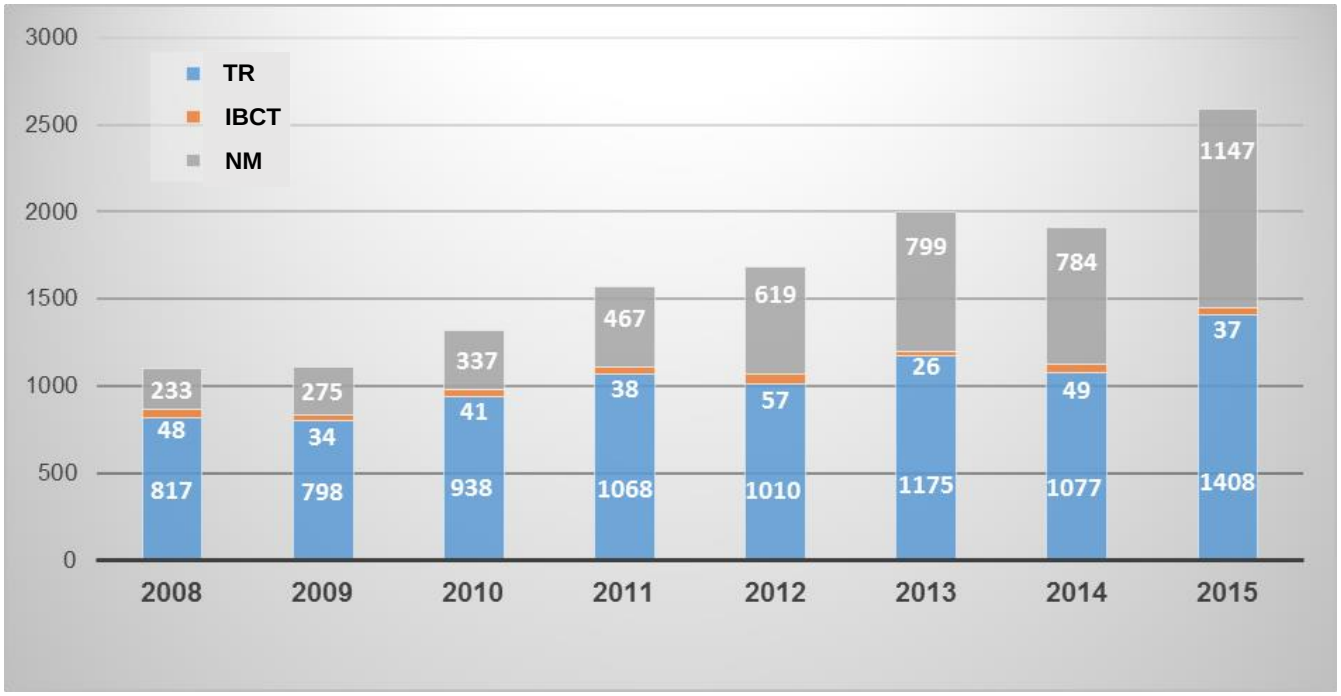
Link: Summary of adverse events following immunization reported in Switzerland 2015

Haemovigilance

Current figures and findings important for transfusion safety in Switzerland

The purpose of the haemovigilance reporting system is to record incidents relating to the manufacture and administration of blood components and serious adverse reactions in donors or recipients of blood components. The data recorded in this way permit the implementation of targeted measures to improve safety in the use of blood and labile blood products. The number of reported transfusion reactions and "near misses" rose sharply in 2015 (Figure 1). This does not indicate lower quality in hospitals, but instead a greater awareness of quality and better reporting behaviour.

Figure 1: Events reported by year (2008–2015)



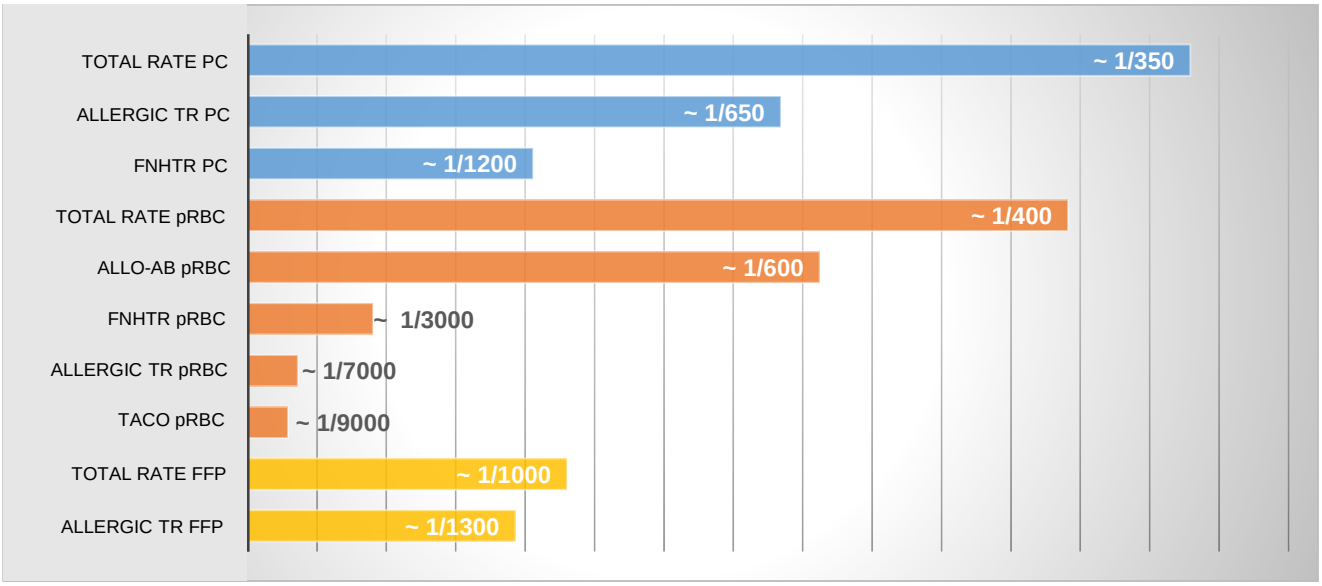
TR = Transfusion reaction
IBCT = Incorrect blood component transfused/transfusion error
NM = Near miss (transfusion error avoided)

Figure 1 shows the number of events reported compared with previous years. The increase is due to increasing reporting compliance and not to an increased risk of transfusion reactions. The increasing number of near misses is also most likely not due to an increased error rate in the transfusion processes, since the number of transfusion errors that have actually occurred has not increased.

Transfusion reactions by product

The three labile blood products of packed red blood cells (pRBC), platelet concentrates (PC) and plasma (FFP= fresh frozen plasma) have differing probabilities of transfusion reactions (Figure 2).

Figure 2: Reporting rates in 2015 by product



pRBC = packed red blood cells, **PC** = platelet concentrates, **FFP** = fresh frozen plasma,
TR = transfusion reaction, **FNHTR** = febrile non-haemolytic transfusion reaction,
TACO = transfusion associated circulatory overload, **Allo-AB** = antibodies resulting from allo-immunisation.

Figure 2 shows the product-specific reporting rate. While allergic reactions account for by far the lion's share of reports involving plasma, they account for only a small proportion of reports involving pRBC. Volume overload, on the other hand, occurs predominantly in connection with pRBC transfusions. A good half of the reactions involving PC is of an allergic nature.

The following additional findings are addressed in the Haemovigilance Annual Report 2015:

- the occasionally underestimated danger of volume overload by red blood cells;
- the internationally recognised evaluation of the country-wide pathogen inactivation of blood platelets in Switzerland, and
- protective measures and developments relating to transfusion-transmitted infections.

Link: Haemovigilance Annual Report 2015

Vigilance of veterinary medicines

Reports on veterinary medicinal products authorised by Swissmedic

292 reports were submitted in 2015, an increase of almost 9 % compared to the 268 submitted in 2014. As in previous years, most of the reports were submitted by the distributors (206 reports, 70.5 % of the total), followed by 40 reports (13.7 %) submitted directly by practising veterinarians. A further 42 reports were recorded during advice given by *Tox Info Suisse* and subsequently sent to Swissmedic (14.4 %); the remaining 4 reports came from government offices or animal owners. The distribution of the reports among the affected target animal species is also comparable to previous years. Adverse reactions were most frequently reported following the treatment of dogs (198 reports) and cats (42 reports). Small animals thus comprise the largest group, accounting for 85 % of reports. Reporting systems in other countries show a similar pattern. In 2014, more than 83 % of a total of 5,592 reports submitted in the United Kingdom involved small animals[1], in Germany the figure was approx. 77 % of 1,062 reports[2]. In decreasing order of frequency, the other reports concerned cattle or calves (31 reports, 10.6 %) and horses (8 reports, 2.7 %). All other target animal species featured in fewer than 5 reports. Finally, 5 reports were submitted about reactions in people who had used veterinary medicinal products to treat animals. 3 of these cases involved allergic reactions in the form of conjunctivitis, asthma or dyspnoea that occurred in people who had treated their animals with antiparasitic agents. One report described staining of the hands after using a spray containing a colouring agent (!), and one animal owner reported bloody nasal discharge after fitting a collar to his dog. No reactions of this type have been described previously and it was not possible to identify a causal connection with the product used.

Table 1 shows the submitted reports sorted by ATCvet code, with a specific breakdown for dogs and cats. Similarly to previous years[3], the most common category of adverse reactions submitted involved antiparasitic agents (161 reports, 55.1 %). This was followed in descending order of frequency by non-steroidal anti-inflammatory drugs (26 reports, 8.9 %) and anti-infectives (24 reports, 8.2 %). There were fewer than 15 reports (5 % of the total) for all the other active substance groups.

In 2015 as a whole, *Tox Info Suisse* handled 38,396 enquiries, 1,786 of which involved animals. 93 cases involving exposure of animals to veterinary medicinal products were passed on to Swissmedic in accordance with a contractual agreement. Antiparasitic agents, anti-inflammatory drugs and anti-infectives were the products most frequently involved. Since the data was incomplete in some cases, only 42 of the reported cases met the minimum criteria for inclusion in the database. 73.8 % (31) of these cases involved accidental ingestion of tablets, most commonly anti-inflammatory drugs swallowed by dogs but also by 4 cats, most of which were overdoses. A dog of unknown breed weighing 22 kg swallowed between 7 and 10 tablets each containing 100 mg of carprofen, equivalent to an 8- to 11-fold overdose. The addition of flavouring agents to the tablets makes accidental ingestion of this kind all the more likely[4]. The medicinal product information supplied with all the products concerned contains a warning to this effect. Most of the animals were asymptomatic at the time *Tox Info Suisse* provided advice, or had already

[1] Davis G, Cooles S, Diesel G, Blenkinsop J. Summary of suspected adverse events, 2014. Vet. Rec. 2016, 178: 187–189.
[2] Von Krüger X., Ibrahim C.: Pharmacovigilance report for veterinary medicinal products 2014. Dtsch Tierärzteblatt. 2015, 2015 (05): 662-669.
[3] Müntener C., Bruckner L., Kupper J., Althaus FR., Schäublin M.: Vigilance for veterinary medicinal products: Adverse reactions reported in 2012. Schweiz. Arch. Tierheilk. 2015, 155: 613–620.
[4] Köppen M.: Nur eine Frage des Geschmacks? Aromatisierte Tierarzneimittel. Dtsch. Tierärzteblatt. 2014, 9: 1242-1248.

vomited the tablets, so in most cases it was not possible to obtain additional information about the further course.

For 62 reports (21.2 % of the total) it was possible to establish a clear link between use of a product and the reported reaction; in 107 cases (40.8 %) at least one possible alternative cause was identified (causality "possible"); and in 12 cases it was possible to unequivocally exclude a connection between the product and the adverse reaction. In the remaining 111 cases (42.4 %) there was too little information to definitively determine causality.

A total of 8 signals were identified during the year. Five were identified from periodic safety update reports (PSUR), one from the reports submitted in Switzerland, and the remaining two as a result of internal reviews. In all cases the medicinal product information was revised.

Table 1

Category of medicines according to ATCvet code		Number of reports (% of total)					
		All Species		Dog		Cat	
QA:	Alimentary tract	9	(3.0%)	2	(1.0%)	1	(2.4%)
QB:	Blood and blood forming organs	4	(1.4%)	0		0	
QC:	Cardiovascular system	10	(3.4%)	7	(3.5%)	3	(7.1%)
QD:	Dermatologicals	4	(1.4%)	3	(1.5%)	0	
QG:	Genito-urinary system and sex. hormones	3	(1.0%)	2	(1.0%)	1	(2.4%)
QH:	Hormonal preparations (except hormones and insulin derivatives)	16	(5.5%)	10	(5.1%)	5	(11.9%)
QJ:	Anti-infectives	24	(8.2%)	5	(2.5%)	3	(7.1%)
QL:	Antineoplastic and immunomodulating agents	8	(2.7%)	6	(3.0%)	2	(4.8%)
QM:	Musculo-skeletal system	26	(8.9%)	21	(10.6%)	3	(7.1%)
QN:	Nervous system	15	(5.1%)	6	(3.0%)	2	(4.8%)
QP:	Antiparasitics	161	(55.1%)	130	(65.7%)	17	(40.5%)
QS:	Sensory organs	4	(1.4%)	4	(2.0%)	0	
QV:	Various	1	(0.3%)	1	(0.5%)	0	
"QZ":	Reconverted products	6	(2.0%)	1	(0.5%)	5	(11.9%)
ALP registered products, animal care products, etc.		1	(0.3%)	0		0	
Total		**292**		**198**		**42**	

Repartition of the reports received during the year 2015, 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).

Information on the Swissmedic website

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

Communications regarding the safety of medicines

- 01.11.2016
  HPC – Hepatitis E bei Transplantatempfängern
  In Europa werden Hepatitis E Virus (HEV) Infektionen durch Nahrungsmittel beobachtet, und in seltenen Fällen auch Übertragungen durch Bluttransfusionen.
- 12.10.2016
  HPC – Valproat (Depakine®, Depakine Chrono®, Valproat Chrono Zentiva®, Orfiril®, Valproat Chrono Desitin®, Valproat Sandoz®, Convulex®)
  Risiken während der Schwangerschaft – Ausgabe einer Patientenkarte
- 23.09.2016
  DHPC – Tarceva® (ERLOTINIB)
  Erstlinien-Erhaltungstherapie bei Patienten mit Tumor ohne EGFR-aktivierende Mutationen ohne Nutzen – Indikationseinschränkung.
- 20.09.2016
  DHPC – TYSABRI® (Natalizumab)
  Risiko von PML (progressive multifokale Leukoencephalopathie). Aktualisierung der Massnahmen
- 16.09.2016
  DHPC – Adempas® (Riociguat)
  Erhöhte Mortalität bei Patienten mit pulmonaler Hypertonie in Verbindung mit idiopathischen interstitiellen Pneumonien (PH-IIP): Neue Kontraindikation
- 31.08.2016
  DHPC – Trasylol® (Aprotinin)
  Einschränkung der Indikation und neue Sicherheitsinformationen zur Aufhebung der Sistierung
- 17.08.2016
  DHPC – BCR ABL Tyrosinkinaseinhibitoren Bosutinib (Bosulif®), Dasatinib (Sprycel®), Imatinib (Glivec®, Glivec® GIST, Imatinib Sandoz, Imatinib-Teva®, Imatinib Zentiva®), Nilotinib (Tasigna®), Ponatinib (Iclusig®)
  Risiko einer Hepatitis-B-Reaktivierung
- 09.08.2016
  DHPC – Erivedge® (Vismodegib)
  Risiko eines vorzeitigen Epiphysenfugenschlusses bei Anwendung von Erivedge® bei nicht abgeschlossener Skelettreife
- 29.07.2016
  DHCP - Trobalt® (Retigabin)
  Weltweite Vertriebseinstellung
- 27.07.2016 see update dated 03.08.2016
  DHPC - Remeron® (Mirtazapin)
  Risiko von Rhabdomyolyse für Mirtazapin-haltige Arzneimittel

- 21.07.2016
  DHPC – Low-dose methotrexate in rheumatoid arthritis and psoriasis
  ADMINISTRATION ONLY ONCE A WEEK
  Measures for preventing accidental overdoses resulting from daily administration
- 18.07.2016
  DHPC – Blincyto® (Blinatumomab)
  Risiko von Pankreatitis
- 29.06.2016
  HPC - Infliximab (Remicade® und Biosimilars von Infliximab: Inflectra®, Remsima®)
  Risiko von Zervixkarzinomen bei Frauen mit rheumatoider Arthritis (RA) unter Behandlung mit Infliximab
- 10.06.2016
  DHCP – Gilenya®: Vereinzelte Fälle von PML bei MS-Patienten
  Information zur Überwachung des grossen Blutbildes

Communications

- 11.10.2016
  International Summit of Heads of Medicines Regulatory Agencies opened in Interlaken: Swissmedic agrees on closer collaboration with UK partner agency
  Federal Councillor Alain Berset opened the International Summit of Heads of Medicines Regulatory Agencies today in Interlaken.
- 21.09.2016
  Haemovigilance Report 2015
  Current figures and findings important for transfusion safety in Switzerland
- 13.09.2016
  Important safety information regarding GlucaGen® Hypo-Kit
  Recall of two batches (FS6X327, FS6X986) of GlucaGen® HypoKit glucagon for injection
- 12.08.2016
  Arzneimittelwerbung: Praxisänderung hinsichtlich Vorkontrolle
  Inkrafttreten: 1. Januar 2017
- 03.08.2016
  Venöse Thromboembolien unter kombinierten oralen Kontrazeptiva – aktualisierte Zahlen
  Die Liste "Spontanmeldungen aus der Schweiz zu hormonalen Kontrazeptiva und venösen Thromboembolien" (Stand 30.06.2016) wurde aktualisiert.
- 20.07.2016
  Ausbau Swissmedic eGovernment Portal
  Registrierte und berechtigte Nutzer von Firmen mit Betriebsbewilligung können künftig einen grossen Teil der Korrespondenz direkt und ohne Papierverkehr elektronisch abwickeln.
- 18.07.2016
  News about electronic pharmacovigilance reports
  Since the start of October 2014, healthcare professionals and pharmaceutical companies have been able to report suspected adverse drug reactions directly via the Internet.

- 08.07.2016 see also updates dated 22.07.2016 and 18.08.2016
  "SINAQUA™ Dermal Glove" disposable washing gloves recalled due to the risk of bacterial infections
- 04.07.2016
  ICH Meeting in Lisbon, Portugal, 11 to 16 June 2016
  The International Council for Harmonisation (ICH) met in Lisbon, Portugal from 11 to 16 June 2016.
- 01.07.2016
  Nachtrag 8.8 der Europäischen Pharmakopöe in Kraft
  Der Institutsrat hat den Nachtrag 8.8 der Europäischen Pharmakopöe auf den 1. Juli 2016 in Kraft gesetzt.
- 28.06.2016
  Action plan to combat illegal fresh cell therapies
  The outcome at the end of the campaign
- 23.06.2016
  Praxisänderung zu kosmetischen Indikationen
- 09.06.2016
  "PANGEA" week of action: Rise in illegal medicinal product imports into Switzerland halted
  Press release
- 03.06.2016
  The new Swissmedic Annual Report has been published
  An entire year's work by 424 individuals summed up in 90 pages: that's the new Swissmedic Annual Report.
- 30.05.2016
  Umfrage zum Revisionsprogramm der Präparate-Monographien der Pharmacopoea Helvetica 11

Please find the complete list at the following web address: www.swissmedic.ch/updates.