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Vigilance-News

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Report of a suspected adverse drug reaction (ADR):

- **via online reporting portal ElViS:** directly or by downloading a xml-file. Details see: 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)

Content

Editorial

Dear Reader

Every day we are assailed with information from numerous sources, particularly electronic media such as e-mail and the Internet. The staff of the Safety of Medicines division at Swissmedic are tasked with sifting through all these information sources to filter out findings on potential risks associated with medicinal products, subjecting these findings to critical scientific analysis and then introducing appropriate measures.

In the interests of transparency, Swissmedic endeavours to ensure that health care professionals and the public receive safety-related information promptly. It publishes only scientifically verifiable findings, including information obtained through data searches. On this basis, Swissmedic clarifies or reassesses medicinal products' risk-benefit profiles and specific uses. This edition of Vigilance News contains several typical examples of safety signals: the problem of products containing hydroxyethyl starch, the debate on oral anticoagulants or the current status of HPV vaccines.

In addition to these signals, observing risk progression over prolonged periods is a crucially important part of evaluating a medicinal product. This starts even before authorisation by means of clinical trials and a *Risk Management Plan*, and is regularly followed up after authorisation with individual case safety reports (ICSR) and periodic reports, including *PSUR/PBRER*. As part of the continuous improvement of the process, Swissmedic recently published updated information sheets both on submitting PSUR/PBRER and on submitting *RMP/ICH E2E* (Risk Management (PSURs, PV Planning) - Swissmedic -). You can read the Frequently Asked Questions *(FAQ)* on pharmacovigilance in the «Regulatory» section.

You can find more information in the overview of the annual vigilance statistics for human and veterinary medicines, vaccines and blood products.

We would be pleased to receive any feedback or suggestions on this edition of the Vigilance News at our new e-mail address news.vigilance@swissmedic.ch and hope you will find it interesting.

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Impressum

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

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Flash: Drug safety signals

Oral anticoagulants: The risk/benefit profile should be assessed for each patient

The authorisation of a new class of medicinal products, direct oral anticoagulants (DOACs), has fundamentally changed the traditional therapeutic regimens for preventing and/or treating thrombotic and/or embolic events, and has triggered a debate about their benefits and risks. The aim of this article is to review the studies that led to the authorisation of these drugs for the indication of stroke prevention in atrial fibrillation and to present an updated assessment of the adverse reactions reported to Swissmedic as part of its pharmacovigilance system.

Introduction

Oral anticoagulants are authorised for the prevention and treatment of venous and arterial thromboembolic disorders.

For many years, vitamin K antagonists (VKAs) such as acenocoumarol (Sintrom®) and phenprocoumon (Marcoumar®) - indirect anti-coagulants that inhibit the synthesis of clotting factors II, VII, IX and X in the liver - have been used in the absence of any therapeutic alternative. This type of treatment must be monitored closely by regular checking of the INR (*International Normalized Ratio*), which should be maintained between 2 and 3. If it is too low, the preventive effect disappears; if it is too high, the risk of haemorrhage (intracranial and/or gastrointestinal bleeding) increases proportionally. The effect of VKAs can be cancelled out, usually within 24 hours, by administering vitamin K (phytomenadione or Konakion®). If immediate cancellation of the effect is required, clotting factor concentrates (PPSB) can be used in emergencies.

Direct oral anticoagulants (DOACs) have been authorised in Switzerland for several years. This therapeutic class includes an antithrombin or factor-IIa inhibitor (dabigatran) and two factor-Xa inhibitors (rivaroxaban and apixaban). In this article, we shall restrict ourselves to rivaroxaban, since we only have isolated reports relating to apixaban.

Although DOACs are used increasingly nowadays, they require a modification of the criteria for monitoring patients. Their principal practical advantage is that laboratory monitoring of anticoagulant activity is regarded as superfluous. One drawback is the absence of any antidote, although antidotes for all DOACs are currently being developed. The generally short DOAC half-life of 5 – 14 hours means that the effect subsides fairly quickly in bleeding situations. If immediate cancellation of the effect is required, international guidelines recommend - as for VKAs - the administration of clotting factors (PPSB) in emergencies.

Studies comparing DOACs and VKAs

A – ROCKET: Study comparing rivaroxaban and warfarin (1)

This multi-centre, double-blind, placebo-controlled trial with two randomised parallel groups enrolled 14,264 patients over 18 years of age with non-valvular atrial fibrillation or a history of stroke, transient ischaemic attack (TIA) or systemic embolism. The trial compared the efficacy of warfarin at a therapeutic dosage (i.e. a target INR of 2.5) with that of rivaroxaban at a dose of 20 mg/day (15 mg/day in patients with renal impairment). The primary evaluation criterion was the frequency of an ischaemic or haemorrhagic stroke or systemic embolism over a period of two years.

The study showed a 21% relative reduction in the risk of stroke and systemic embolism compared to warfarin (*On Treatment Population*), as well as a reduced risk of haemorrhagic strokes. Moreover, the incidence of all serious or less serious

but significant haemorrhagic events was no higher than for warfarin, although an increase in the risk of serious gastrointestinal bleeds was observed.

Rivaroxaban therefore offers a therapeutic benefit in terms of preventing strokes in patients with non-valvular atrial fibrillation.

B – RE-LY: Study comparing dabigatran and warfarin (2)

This study was conducted with three randomised parallel groups: Dabigatran (110 or 150 mg twice a day) and warfarin at a therapeutic dosage (with a target INR of 2.5). The study enrolled 18,113 patients over 18 years of age with non-valvular atrial fibrillation and one other risk factor for stroke. It compared the respective efficacies of warfarin and dabigatran (at the above-mentioned doses) and the primary evaluation criterion was the frequency of an ischaemic or haemorrhagic stroke or systemic embolism over a period of two years.

Dabigatran was not inferior to warfarin at the two doses used. In the group receiving 150 mg dabigatran twice a day, there was a statistically significant reduction of 35% in the risk of strokes and systemic embolism. Compared to warfarin, dabigatran exhibited an equivalent risk of haemorrhage at a dose of 150 mg twice a day and a reduced risk at a dose of 110 mg twice daily, although the risk of gastrointestinal bleeding was raised at the higher dose.

In recent months, the American FDA conducted an observational real-life study that formed the subject of a *«Safety Communication»* (the detailed results were recently published in the online edition of *Circulation* dated 30 October 2014) (3). It included over 130,000 Medicare patients over 65 years of age with non-valvular atrial fibrillation and compared the respective efficacies of 150 mg dabigatran twice daily and warfarin at a therapeutic dosage (i.e. with a target INR of 2.5). This study confirmed the positive risk/benefit profile of dabigatran: fewer strokes, fewer intracranial haemorrhages, fewer deaths, but an increase in the risk of major gastrointestinal bleeds.

Therapeutic indications and pharmacovigilance

Since pharmacovigilance data have to be considered in connection with the therapeutic indications and exposure (period since authorisation and frequency of use), caution is required in its interpretation. The corresponding reasons are discussed in detail under point D below.

In this context it should be considered that currently Marcoumar® and Xarelto® are sold approx. 20 times more frequently compared to Pradaxa® (4).

A – Xarelto® (rivaroxaban) has been authorised in Switzerland since 18 December 2008.

Therapeutic indications: simultaneous preventive and therapeutic use
Authorised in 2008 for the indication of «Prevention of thromboses after major orthopaedic surgery of the lower limbs, e.g. hip or knee replacement surgery».

Further indications were added **in 2012** (see Information for healthcare professionals at www.swissmedicinfo.ch, version: February 2014) (5):

- Stroke prevention and the prevention of systemic embolism in the presence of non-valvular atrial fibrillation.
- Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and the prevention of recurrent DVT and pulmonary embolism (LE).

Pharmacovigilance

As at 1 September 2014, the Swissmedic pharmacovigilance database had received 569 reports.

63 of these 569 reports were rated as «non-serious», while the ADR were considered to be seri-

ous in 506 cases, i.e. they required hospitalisation in 184 cases and proved fatal in 35 cases (in 16 cases after an intracranial haemorrhage, two of which occurred after trauma, and in 8 cases following gastrointestinal bleeding)

B – Pradaxa® (dabigatran) has been authorised in Switzerland since 29 May 2012.

Therapeutic indications: preventive use (see Information for healthcare professionals at www.swissmedicinfo.ch, version: August 2013) (5)

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and one or more of the following risk factors:

- History of stroke, transient ischaemic attack or systemic embolism
- Left ventricular ejection fraction <40%
- Symptomatic heart failure, ≥ New York Heart Association (NYHA) class 2
- Age ≥75 years
- Age ≥65 years with one of the following illnesses: diabetes mellitus, coronary heart disease or hypertension

The «Information for healthcare professionals» authorised by Swissmedic also mentions the precautions to be taken in the event of an increased risk of haemorrhage, the possibility of laboratory monitoring and the options for stopping or modifying treatment.

Pharmacovigilance

The pharmacovigilance data in Switzerland are still limited.

As at 1 September 2014, the Swissmedic database included 38 reports of suspected ADR (2012: 6 / 2013: 25 / 2014: 7). Of these, 11 were «non-serious». 27 cases were considered to be serious: hospitalisation was required for 13 patients and the outcome was fatal in 7 cases (involving aortic dissection in 2 cases).

C – Marcoumar® (phenprocoumon) has been authorised since 13 August 1953.

Therapeutic indications: also preventive, but primarily therapeutic use

Thromboprophylaxis, thrombosis, embolism, myocardial infarction (see the Information for healthcare professionals at www.swissmedicinfo.ch, version: October 2012) (5)

Pharmacovigilance

As at 1 September 2014, the Swissmedic pharmacovigilance database contained 492 reports that had been submitted since 2008.

Of these 492 reports, 41 were rated as «non-serious». In 451 cases, the consequences were more serious and required hospitalisation in 320 cases. 52 of these 451 reports concerned cases with a fatal outcome, 48 of which occurred following a haemorrhage (37 intracranial haemorrhages and 9 gastrointestinal haemorrhages).

D – Interpretation

The risk of haemorrhage doubtless counts as a significant risk for all oral anticoagulants (direct OACs and VKAs). While the spontaneous reports provide important information about the risks in everyday life, they do not allow a reliable comparison to be made between the various drugs. Such a comparison requires clinical and epidemiological studies. As regards the pharmacovigilance data, Swissmedic would point out the following:

- The data concern spontaneous reports: Swissmedic collates and interprets the spontaneous reports that it receives and then derives corresponding safety signals, i.e. new risks or new aspects of known drug risks. Since Swissmedic receives only a limited number of ADR, it is not possible to calculate an incidence rate, or make a reliable assessment of their frequency.
- The reporting rate is variable: It is higher for newly authorised medicinal products than older ones.

- They only involve a suspected ADR: A report is submitted as soon as a medicinal product is thought to have triggered an ADR.
- Absolute figures for spontaneous reports should be viewed in relation to exposure.
- The date of onset of the ADR: The date mentioned in the report is very often the date of the report rather than the date of onset of the ADR, which has inevitable consequences for the incidence.

Other important parameters also need to be considered when interpreting spontaneous reports:

- Medicinal products are normally prescribed for different indications and for different groups of patients of differing ages and presenting with differing risk factors.
- Other medicinal products or non-drug-related factors may play a triggering role (interaction).
- The severity of the complications/ADR must be placed in the proper perspective in relation to the benefit of the medicinal product (prevention of serious complications, e.g. as in this case strokes).

Consequently, spontaneous reports do not constitute a suitable basis for comparing medicinal products or groups of medicinal products with each other. Comparisons are possible only based on clinical or epidemiological studies.

Conclusions

In view of the regular reports of cases with a fatal outcome in patients with massive and uncontrollable bleeding in the gastrointestinal tract or nervous system and the ever increasing numbers of prescriptions, the discussion about the role of this new therapeutic class (6; 7; 8; 9) continues, focusing on the following points:

- Is the risk of haemorrhage associated with the use of DOACs in real life potentially higher than that reported in the authorisation studies?
  - As regards dabigatran, the American FDA has published a major observational study involving 67,000 patients taking dabigatran and 67,000 receiving a VKA (warfarin). The data confirm the results of the authorisation study (3). Based on this study, the FDA has given a negative reply to this question for dabigatran and confirmed the positive profile for dabigatran in terms of safety and efficacy. The medicinal product reduces the risk of stroke, while the risk of intracranial haemorrhage is lower than that for phenprocoumon.
  - As regards rivaroxaban, the Dresden NOAC Register has published results for the management of bleeding in patients taking rivaroxaban in «real life» (10). This study followed up 1776 patients over 18 years of age during an observation period of more than 2 years, and concluded that the number of serious bleeds with rivaroxaban was lower than that with VKA.
  - The NACORA study compared DOACs and VKAs and was published by the French regulatory authority (*Agence Nationale de Sécurité des Médicaments or ANSM)* (11). This cohort study compared over 10,000 patients aged over 18. One group was newly treated with DOACs (dabigatran 75/110 or 150 mg twice daily and rivaroxaban 10/15/20 mg daily), while the other group was treated with VKAs. In the short observation period (90 days), the study showed no increase in the risk of haemorrhage or arterial thrombosis in the DOAC group.
- Should laboratory monitoring (direct or indirect assay) be carried out in order to better monitor and control the possible adverse reactions? Several types of tests are currently in use in Switzerland for DOACs in the absence of a reference test. Moreover, no generally usable countermeasure or specific antidote is yet available to deal with a massive haemorrhage.
- Finally, the long-term tolerability of these medicinal products is still not fully understood.

Meanwhile, it is the responsibility of the treating doctor to:

- prescribe the appropriate drug class according to the risk-benefit profile for each individual patient, while observing the therapeutic indications, dosage regimens and contraindications/restrictions on use (e.g. renal impairment);
- carefully monitor patients throughout their treatment, paying particular attention to possible interactions with inhibitors of CYP-3A4 (for rivaroxaban) and/or P-gp (for rivaroxaban and dabigatran).

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Hydroxyethyl starch (HES)

Background

Various solutions are available for fluid replacement therapy in patients undergoing anaesthesia and resuscitation. Solutions containing hydroxyethyl starch (HES) have been used for decades for intravenous fluid replacement. Since HES has a high molecular mass, it was hoped that its molecules would be able to maintain the colloid osmotic pressure in the blood, compensate for the loss of fluid and remain in the vascular system longer than crystalloid infusions. Depending on the product, the HES molecules possess differing physical and chemical properties and thus specific pharmacokinetic features. The first generation of HES solutions still had a high molecular mass and major adverse effects, particularly on coagulation. Consequently, HES solutions with ever small molecular masses were used. Whereas the first generation still had an average molecular mass of 450,000 daltons and a substitution grade of 0.7, the corresponding figures for the second generation were 200,000 daltons for molecular mass and 0.5 for the substitution grade and, for the third generation, 130 k daltons and a substitution grade of 0.4 (hence 130/0.4).

Scientific discussion

The complications associated with the use of HES solutions include renal impairment. There are also reports of late-onset renal damage. The choice of whether to opt for a crystalloid, colloidal or saline solution in fluid replacement has been a subject of contention for many years. In 2012, this discussion received fresh impetus with the publication of two studies. In their multicentre, randomised study published in June 2012, Perner et al. investigated 804 ICU patients (Scandinavian Starch for Severe Sepsis / Septic Shock Study; «6S study»[1]) and showed that the use of a 6% HES solution (130/0.42) significantly increased mortality in patients with severe sepsis and septic shock compared to those patients who had received replacement therapy with Ringer's acetate solution.

In another multicentre study involving 7000 randomised ICU patients with sepsis (*The Crystalloid versus Hydroxyethyl Starch Trial; «CHEST study»*[2]), Myburgh et al. found no significant difference in 90-day mortality between patients resuscitated with 6% HES solution (130/0.4) and those treated with saline solution. On the other hand, more patients who were resuscitated with the HES solution required renal-replacement therapy.

It should be noted at this point that Swissmedic had initiated a procedure for reviewing infusion solutions containing HES as early as 2011. This had been triggered by new findings on falsified studies that had only been designed on paper, but never actually performed. In its review procedure, Swissmedic had pointed out significant safety signals such as renal damage, coagulation disorders, pruritus and sepsis-related mortality.

Reaction of the regulatory authorities

As a result of the 6S and CHEST studies, regulatory authorities worldwide introduced various measures. The disparity of these measures was due to the fact they were based on partially conflicting results of scientific studies conducted with differing populations and comparators and drew on additional literature sources, expert bodies and hearings.

In November 2012, Swissmedic announced that, according to the latest publications, the use of HES-containing infusion solutions could lead to increased mortality when used in patients with sepsis and septic shock. Swissmedic also reminded healthcare professionals to exercise par-

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ticular caution when administering HES-containing infusion solutions to patients with a history of renal impairment.

Also in November 2012, the *Pharmacovigilance Risk Assessment Committee (PRAC)* of the *EMA (European Medicines Agency)* announced the start of a European risk assessment procedure on this subject.

Various bulletins were then issued internationally in June 2013 by regulatory authorities:

- The German Federal Institute for Drugs and Medical Devices (BfArM) recommended suspending the use of HES-containing infusion solutions in patients with sepsis until the ongoing procedure had reached its conclusion.
- At this point in time, the UK authority decided not to wait for this conclusion and ordered the withdrawal of HES-containing infusion solutions from the British market.
- The PRAC published the result of its risk assessment procedure on the EMA website and recommended suspending marketing authorisation for HES-containing infusion solutions.
- The *U.S. Food and Drug Administration (FDA)* said it intended to leave HES-containing products on the market but impose enhanced safety conditions. It published a safety warning recommending that HES-containing infusion solutions should not be used for ICU patients with sepsis. HES was also to be avoided in patients with restricted renal function and patients undergoing open-heart surgery.
- Health Canada published a recommendation to the effect that HES-containing infusion solutions should not be used in ICU patients with sepsis, severe liver disease or restricted renal function since patients treated with HES were at greater risk of renal failure or a fatal outcome.
- Until the conclusion of the ongoing review, Swissmedic recommended continued restriction of the use of medicinal products containing HES. Crystalloid solutions should be used as the first-line option in ICU patients with HES-containing products only being used if necessary and always at the lowest effective dose. Furthermore, HES-containing infusion solutions should not be used in patients with sepsis, renal impairment or severe liver disease.

Solution

On 11 October 2013, the PRAC published the key results of its risk assessment procedure on the EMA website, taking account of newly available data focusing on the risk of mortality and renal failure. This procedure included clinical trials, meta-analyses of clinical trials, post-marketing experience, written and oral replies provided by marketing authorisation holders and the submissions of interest groups. The PRAC concluded that the benefit-risk profile for HES-containing medicinal products in the treatment of hypovolaemia for acute blood loss – in cases where crystalloids alone are considered to be inadequate – remains positive, provided the agreed restrictions, contraindications, warnings, other changes to the product information texts and additional risk minimisation measures are observed. In the EMA *HPC (Healthcare Professional Communication)* of 25 October 2013, the higher-ranking EU Coordination Group for Mutual Recognition and Decentralised Procedures, or *CMDh,* endorsed the PRAC recommendation of 11 October 2013. In November 2013, the companies concerned were notified of these new recommendations in a joint communication to healthcare professionals. The final decision of the *European Commission* was published on 19 December 2013.

In Switzerland, agreement was finally reached following a review of all the documents and information that have since become available and extensive discussions with the companies concerned, which had in turn submitted a comprehensive package containing substantial restrictions on use. In August 2014, the review procedure was concluded with an order to modify the Medicinal Product Information and the issuing of a *DHPC (Direct Healthcare Professional*

Communication). Key adaptations to the Medicinal Product Information texts and statements in the DHPC include:

- HES-containing infusion solutions only be used as the second-line option if crystalloid infusion solutions fail to prove sufficiently effective.
- HES-containing infusion solutions should be used only at the lowest effective dose and for a as short duration as possible.

To sum up: HES-containing infusion solutions are **contraindicated**:

- sepsis
- burns
- renal impairment or renal replacement therapy
- intracranial haemorrhage
- critically ill patients (usually in ICUs)
- hyperhydration, including patients with pulmonary oedema
- dehydration
- severe coagulopathy
- severely impaired hepatic function

Conclusion

The administration of HES-containing solutions for fluid replacement was standard practice for many years. Although the idea a colloidal fluid replacement would remain longer in the vascular system than crystalloid solutions, was highly plausible, an intensive debate about the potential risks began at an early stage. The new findings from two major multicentre studies in the New England Journal of Medicine published in 2012 provided additional evidence that the benefit-risk profile was favourable only for a certain proportion of patients. Regulatory authorities worldwide, including Swissmedic, subsequently initiated risk review procedures. As BfArM had already concluded, this example shows «*how multi-faceted and complex these procedures are, not just in scientific respects, but also from the regulatory administrative standpoint*.»[3] This example also shows that it is not just necessary, but also possible to work with the pharmaceutical companies concerned to redefine the justified, correct use of authorised medicinal products on the basis of the latest scientific findings. Since the scientific findings are valid internationally, it is only logical for Switzerland to arrive at comparable conclusions, despite having its own procedures that differ from those in Europe.

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Vaccines against Human Papilloma Virus (HPV): Update

The benefits and risks of HPV vaccines are once again in the focus of public discussions. Currently, two HPV vaccines, Gardasil® and Cervarix®, are authorised for the prevention of cervical cancers, a high percentage of which are caused by certain HPV strains.

Both preparations have been marketed worldwide for years. Swissmedic – responsible for the authorisation and subsequent surveillance of vaccines – and the Federal Office of Public Health (FOPH), together with the Federal Commission for Vaccination (FCV), which is responsible for vaccination recommendations, continue to assess the benefit-risk profile of both HPV vaccines as positive.

HPV infection and its consequences

A large proportion of the population (70–80 % of sexually active men and women) contract an HPV infection in the course of their life, and 16- to 25-year-olds are particularly affected. The infection is predominantly transmitted sexually. While 90 % of cases recover without any complications, the infection can persist in a certain percentage and lead years later to cervical cancer and, more rarely, to other tumours of the genital mucosa.

HPV types 16 and 18 are considered to be responsible for around 70 % of cervical cancers. According to an estimate issued by the Swiss Cancer League, each year some 250 women develop cervical cancer in Switzerland, and about 90 succumb to the disease (figures from the period 2004 to 2008). Further information: Federal Office of Public Health (FOPH) – Human Papilloma Virus (HPV)

Benefit of HPV vaccination

Preparations

The first HPV vaccine to be authorised in Switzerland was Gardasil®, at the end of 2006. The product was authorised internationally during the same period. This acts against the oncogenic HPV types 16 and 18 and also against the types 6 and 11, which cause genital warts. Launched in spring 2010, Cervarix® acts against HPV 16 and 18 and is therefore used prophylactically against tumours only. Vaccination should be completed before sexual activity starts. The FOPH therefore recommends that vaccination take place early, between the ages of 11 and 14. While vaccination does not act against an existing HPV infection, it does afford protection against other HPV types covered by the vaccine.

Clinical trials

The results of major clinical studies conducted in connection with the marketing authorisation procedure have confirmed that the HPV vaccines provide effective protection against infection with the corresponding HPV types and precursors of cervical cancer[1, 2, 3]. Gardasil® has also been shown to protect against genital warts[1].

Post-marketing studies

The results of large-scale population-based studies conducted after the launch of the HPV vaccines are now available. These studies confirm the efficacy of HPV vaccination under everyday conditions, in various countries and continents (Australia, USA, Europe).

One Australian study showed a progressive reduction in high-grade precursors of cervical cancer after the introduction of HPV vaccination, in women under 18 years of age[4]. Long-term observations will show what effect the HPV vaccination has on the incidence of cervical cancer itself.

A large study in Denmark[5] confirms the protective effect of Gardasil® against genital warts: genital warts occurred within 3.5 years in 0.01 % of vaccinated individuals as compared to 1.5 %

in unvaccinated subjects. A series of other studies has shown a decline in the frequency of HPV infections and HPV-related disorders after HPV vaccination[6–12].

Furthermore, the FOPH has launched a study to investigate the effects of HPV vaccines on cervical cancers and their precursors in Switzerland.

Safety of HPV vaccines

The risks associated with HPV vaccines continue to be closely monitored and followed up in Switzerland and abroad, particularly by the World Health Organization (WHO). While extensive experience has been accumulated in the meanwhile worldwide with both preparations, the experience in Switzerland primarily regards Gardasil®. This particular vaccine has been used here for seven years to vaccinate an estimated number of 200,000 people, and over 175 million doses of the vaccine have been administered worldwide[13] so far.

The more common and well-known adverse drug reactions (ADR) are pain and signs of inflammation at the injection site, headache, fever, nausea and flu-like symptoms (e.g. pain in the limbs). Such symptoms usually resolve spontaneously and may be expected to occur with vaccinations generally.

ADR reports from Switzerland

Since 2007 and up to now (status of the database on 11 September 2014), Swissmedic has registered a total of 167 reports of ADR suspected to be associated with HPV vaccines in Switzerland. 164 of these concerned Gardasil®, which may be attributable to its higher market share. Since 2010, the number of reports has been between 10 and 30 per year. The figure peaked at 61 reports in 2009, when milder, non-notifiable events were also systematically recorded and submitted by the Regional Pharmacovigilance Centres (RPVC).

Of the 167 reports, 62 % were assessed as «non-serious» and 27 % as «medically important». Serious consequences such as a hospitalisation occurred in 11 % of cases. None of the reports had a fatal outcome.

The reports suggest a positive ADR profile that reflects the known risks associated with the vaccines, as comprehensively listed in the Medicinal Product Information. Following reports of sudden loss of consciousness immediately after vaccination («vasovagal syncope»), Swissmedic and the FOPH promptly and successfully implemented new precautionary measures: Girls should sit or lie down during and after the vaccination. This adverse reaction might generally occur after injections. It is considered harmless, provided falls and resultant injuries are avoided.

Studies regarding the safety of vaccines after marketing authorisation

Rare ADR reports from post-marketing concern serious events that were carefully assessed and further evaluated as safety signals.

At the international level, these include autoimmune disorders, particularly multiple sclerosis and inflammatory conditions of the central nervous system. Epidemiological studies should be considered to allow further clarification in such signals. A whole series of such epidemiological investigations is now available. One of these is the large-scale study performed in Denmark and Sweden[14], which compared almost 300,000 vaccinated and nearly 700,000 unvaccinated young women. Chao et al[15] investigated the occurrence of autoimmune disorders, while Klein[16] assessed treatments in emergency departments and hospital admissions involving almost 190,000 women who had received at least one dose of HPV vaccine. These studies did not confirm any increased risk of these clinical conditions, particularly autoimmune disorders such as multiple sclerosis, after HPV vaccination. The WHO Global Advisory Committee on Vaccine Safety (GACVS) reached the same conclusion in its 2013[13] and 2014[17] published statements.

Swissmedic – responsible for the authorisation and subsequent safety surveillance of vaccines – and the Federal Office of Public Health (FOPH), together with the Federal Commission for Vaccination (FCV), which is responsible for

vaccination recommendations, continue to assess the benefit-risk profile of both HPV vaccines as positive.

Swissmedic, as authorities in other countries, the WHO and the FOPH, continuously monitor the latest available data on the risks and benefits of HPV vaccines. As part of its review procedure, Swissmedic also consults its external vaccine experts group and makes sure that the Medicinal Product Information texts of these vaccines (see www.swissmedicinfo.ch) are systematically updated.

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[16] Klein NP et al. Safety of quadrivalent human papillomavirus vaccine administered routinely to females. Arch Pediatr Adolesc Med. 2012 Dec;166(12):1140-8

[17] Global Advisory Committee on Vaccine Safety. Safety Update on HPV vaccines Geneva, 12 March 2014

Regulatory

Electronic Vigilance Reporting Portal ElViS

With immediate effect, healthcare professionals and pharmaceutical companies can report suspected adverse drug reactions (ADR) direct on the Internet. Following the successful completion of the pilot phase, Swissmedic launched its *«ElViS» (Electronic Vigilance System)* online reporting portal at the start of October 2014.

Both in Switzerland and internationally, the spontaneous reporting of suspected adverse drug reactions (ADR) remains the most important tool for identifying new medicinal product risks that come to light after market launch and learning more about risks that are already known. This applies particularly in the context of the «WHO Programme for International Drug Monitoring». Health care professionals (HCP) in Switzerland are legally obliged to report ADR to the Regional Pharmacovigilance Centres (RPVC), while pharmaceutical companies have to report them directly to Swissmedic (Figure 1).

The number of reports continues to rise steadily (Figure 2). According to current WHO statistics, Switzerland comes second after Denmark in a European ranking of the number of ADR reports per million inhabitants (Figure 3).

Efficient reporting systems and high-quality reports are particularly important because risks need to be identified as soon as possible in spite of the increasing number of reports. A spontaneous reporting system can only provide a successful risk defence tool if physicians, pharmacists and other HCP use it intensely, since new findings on the safety of medicines are derived primarily from a detailed analysis of carefully documented individual case safety reports [1].

Following the successful conclusion of the pilot phase, Swissmedic launched ElViS (Electronic Vigilance System), its online portal that allows suspected ADR to be reported direct via the Internet, at the start of October 2014.

HCP who have hitherto been using reporting forms to notify the RPVC of such suspected cases are now encouraged to do so online. Moreover, pharmaceutical companies with no direct gateway connection to the Swissmedic database, or who do not send sufficient reports for gateway transmission (usually small and medium-sized companies), are encouraged similarly to submit their reports electronically to Swissmedic.

No special software is required, and only a few minutes are required to complete the one-time self-registration process for HCP. ElViS can also be used to submit case-related documents, such as laboratory reports or hospital letters. Attachments can be in any file format.

Once their report has been successfully sent, users can save the report and acknowledgement of receipt (as pdf or E2B files) on their computer's hard drive for their own records. Data protection and security satisfy the most stringent requirements. The main features of ElViS are summarised in the table below (Table 1).

The user-friendly reporting portal makes it easier for HCP and the pharmaceutical industry to fulfil their statutory reporting obligation and to submit promptly better quality individual case safety reports. The introduction of ElViS by Swissmedic is a further important contribution towards improved drug and patient safety in Switzerland.

Fig. 1

Organisation of Pharmacovigilance in Switzerland

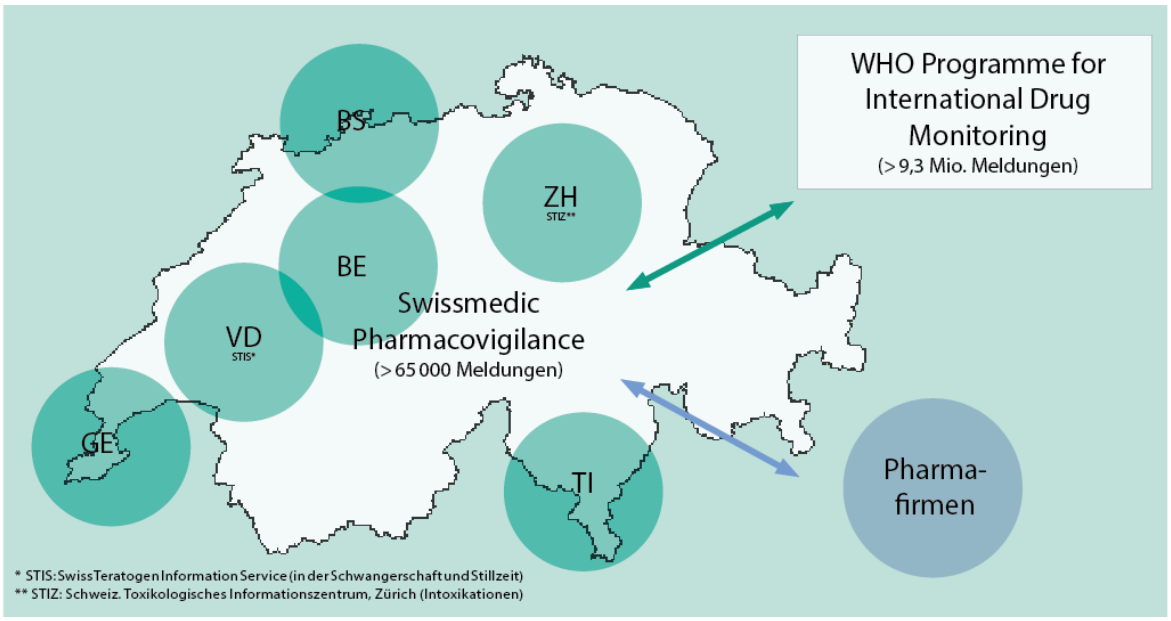


Fig. 2

Number of spontaneous reports in Switzerland

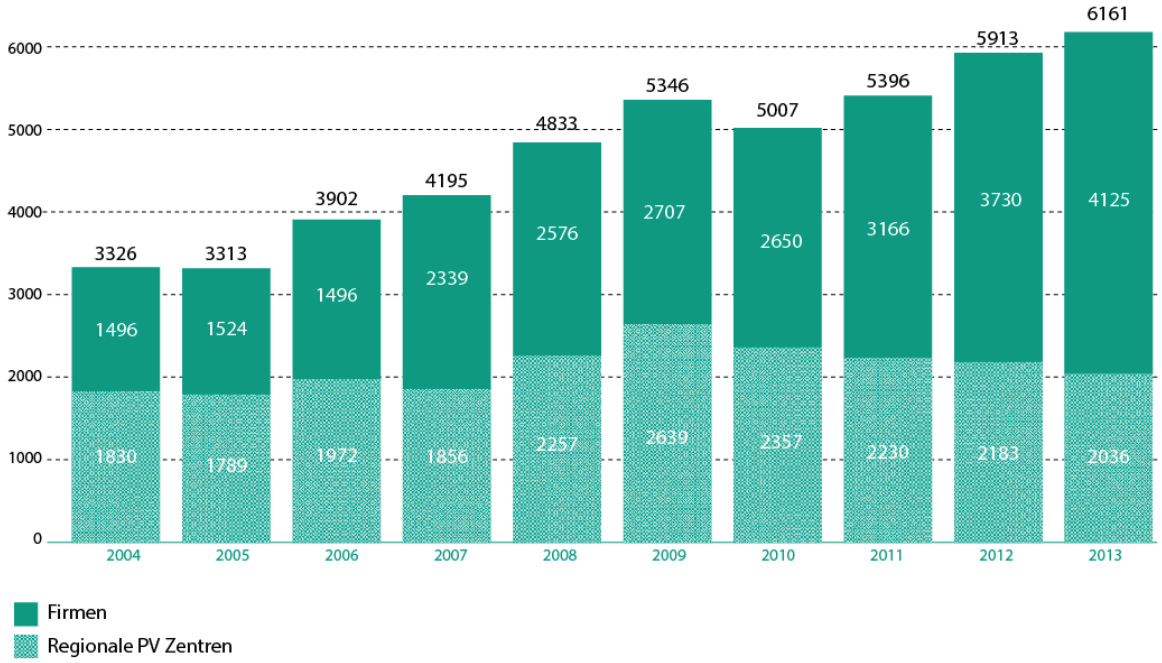


Fig. 3

Number of individual case safety reports in the global WHO database per million inhabitants per year (period 2009–2014)

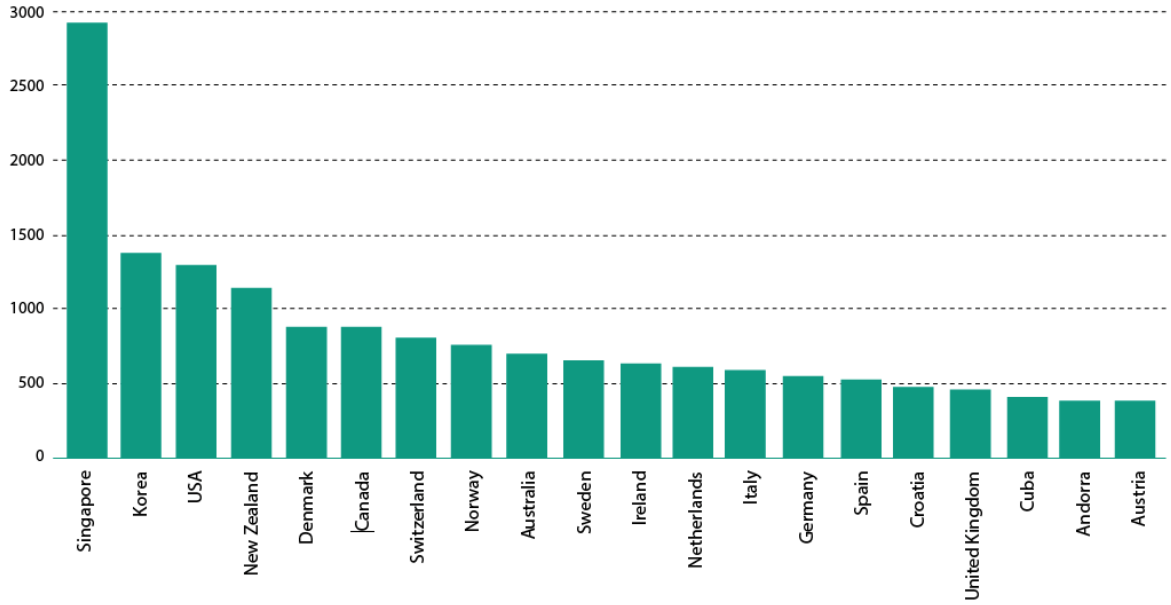


Table 1

Main features of ElViS

	Users: Health care professionals	Users: Pharmaceutical companies
Browser	**Microsoft Explorer (at least vers. 9) or Mozilla Firefox (at least vers. 24)**	
Registration	**Once-only self-registation**	**2 administrators per company**
Reports	**Initial- and follow-up reports, including attachments**	
Data entry	**Direct entry or by uploading E2B files**	
MedDRA-coding	**No**	**Required**
Local archiving	**Required**	**Required**
Languages	**German, French, Italian, English**	**English**
Training by Swissmedic	**No (self-explanatory)**	**Prerequisite**
Information, support	**www.swissmedic.ch/elvis**	**ElViS-hotline**

Reference: [1] Stoller R, Mathys K, Schäublin M, Küng C,
«Was ist eine gute Pharmacovigilance Meldung?» pharmaJournal 20/10.2014 und SÄZ 2014;95: 38

FAQ General Pharmacovigilance

What reporting duties do companies have in Switzerland?

Link: Drug Safety Reporting Duties in Switzerland

The «qualified person responsible for pharmacovigilance» in Switzerland: What conditions apply?

Article 59 of the Therapeutic Products Act (TPA) requires the manufacturer of therapeutic products or the distributor of ready-to-use therapeutic products to ensure that a reporting system is in place. This means, among other things, that the marketing authorisation holder or the manufacturer must designate a qualified person who is responsible for complying with reporting duties with respect to adverse drug effects and must inform Swissmedic of this person's name on request. Qualified means that the person responsible for PV (QPPV) has very good knowledge of pharmacovigilance and can produce the corresponding documentation / certificates on request. This person does not necessarily have to belong to the company, but his or her responsibilities must be set out in writing. The QPPV does not necessarily have to reside in Switzerland, but his or her name and address must be notified to Swissmedic on request.

AMBV Art. 7 para. 3 f; VAM Art. 39 para. 3-

What regulations apply when reporting adverse drug effects from Liechtenstein?

The duty to report ADRs from Liechtenstein is governed by the registration status of a therapeutic product.

The market in Liechtenstein is covered by the Swissmedic monitoring network under the terms of the Customs Treaty. Reports of ADRs involving therapeutic products that are registered in Switzerland and may be marketed in Liechtenstein under the terms of the Customs Treaty must be reported to a regional pharmacovigilance centre (RPVC) in Switzerland (healthcare professionals) or to Swissmedic (companies). Therapeutic products registered in the EEA are covered by the European monitoring system. Adverse drug effects and quality defects involving therapeutic products registered in the territory covered by the Agreement with Austria must be reported to the Ministry of Health in Austria.

http://www.llv.li/#/11134/arzneimitteluberwachung

http://www.ris.bka.gv.at/GeltendeFassung.wxe?Abfrage=Bundesnormen&Gesetzesnummer=20006977

What reporting duties apply to a therapeutic product not registered in Switzerland for which a doctor has obtained special authorisation in individual cases?

Art. 59 TPA requires all ADRs involving therapeutic products not registered in Switzerland and with special authorisation to be reported to the Safety of Medicines Department at Swissmedic. The same criteria apply as for registered therapeutic products: all serious adverse effects and all unknown adverse effects must be reported (Art. 35 VAM). No adverse events should be reported – only adverse drug reactions. This means that the doctor assumes a causal connection between the event and use of the therapeutic product.

The reference document is the SPC or IB (if the product does not yet have marketing authorisation worldwide).

The reporting duty falls on the attending physician (to a regional pharmacovigilance centre, RPVC) and on the company that is made aware of the ADR (to Swissmedic).

When does lack of efficacy / loss of drug effect / drug ineffective have to be reported as a single report?

Lack of efficacy in itself does not have to be reported in Switzerland. However, Swissmedic recommends that all cases of lack of efficacy should be reported, particularly if clinically relevant complications are likely to ensue (e.g. in the case of vaccines, contraceptives, antibiotics or therapeutic products used to treat life-threatening conditions). All reported cases are entered in the national database and subsequently forwarded to the WHO database.

Clusters of cases involving lack of efficacy must be reported in accordance with Art. 59 TPA.

Does off-label use have to be reported in Switzerland?

Off-label use in itself does not have to be reported. However, if these cases are reported to Swissmedic, they are entered in the national database. If an ADR occurs, it must be reported under the terms of Art. 59 TPA.

Which therapeutic products have to be reported / stated as suspect?

A company should state not only its own therapeutic product as suspect but also all the therapeutic products stated by the primary reported as being suspect or that are classified as suspect by the company.

When does Swissmedic pass on reports to companies?

Companies generally receive reports submitted to Swissmedic by HCPs and consumers via the regional pharmacovigilance centres (RPVC) and in which the company's therapeutic products are classified as suspect. If only the active substance of the suspect medication is known, the case is generally only sent to the company that holds the first marketing authorisation.

If Swissmedic receives a report from a company in which the therapeutic product of another company is also classified as co-suspect, Swissmedic does not send this report to the second company.

When does Swissmedic pass on enquiries from companies about reports from the Regional Pharmacovigilance Centres (RPVC)?

Swissmedic is receiving a growing number of enquiries from companies about single case reports from the RPVC. These enquiries usually come from head office and are passed on unfiltered to Swissmedic by the company's Swiss branch. Many of these enquiries are irrelevant for medical evaluation of the case, or the information is already contained in the report sent to the company. These enquiries are not answered or passed on by Swissmedic.

However, in individual cases, Swissmedic continues to pass justified enquiries about unclear information, or additional information required to evaluate the case on to the RPVC for processing or reply.

When does Swissmedic pass on questionnaires / information sheets from the companies to the primary reporters?

Questionnaires / information sheets from companies are only passed on to the regional pharmacovigilance centres (RPVC) for further investigation with the primary reporter (healthcare professional) or for completion if a written enhanced PV agreement has been concluded with Swissmedic. These questionnaires must be submitted to Swissmedic for review. Their review by the RPVC / Swissmedic is subject to a fee, which is stipulated in the written agreement.

All other questionnaires are generally not passed on by Swissmedic (this also applies in cases where there is an RMP [Risk Management Plan] commitment by the company but no written enhanced PV agreement with Swissmedic).

- RMP commitment **and** written enhanced PV agreement with Swissmedic: The company sends questionnaires to primary reporters who have submitted reports to the company, and Swissmedic sends the questionnaires to the RPVC for a response.
- RMP commitment **but no** written enhanced PV agreement with Swissmedic: The company sends questionnaires to primary reporters who have submitted reports to the company.

Information sheet regarding reports on adverse events following immunisation (AEFI): see page 20 (available in English only)

Information sheet regarding «Drug exposure during pregnancy» and «Parent-Child reports»: see page 21–22 (available in English only)

General instructions / recommendations for submission of adverse events following immunisation (AEFI)

Suspected **«serious»** and **«non-serious»–«unlabelled»** AEFI are to be reported to Swissmedic according to Swiss legal requirements.

Additionally, reporting of **«non-serious» – «labelled» AEFI** is **strongly recommended** by Swissmedic.

Each AEFI report forwarded to SMC shall contain:

1. In structured data reporting fields

- Dose number (if series) and dates of vaccinations
- Vaccine batch number (this information can be repeated in free-text)
- Most vaccines are a dose series. If an AEFI occurs for each dose in a series:
  1. Enter the vaccine each time as a suspected drug for each dose with different «StartDate/EndDate»
  2. If the AEFI is the same as with the earlier exposure to the vaccine, check «yes» under the field «Rechallenge» for the second vaccine dose.

2. Include in the Case Narrative free-text

- Side of administration: left or right
- Body site of administration (e.g. thigh muscle, deltoid muscle)
- Latency: time from exposure to onset of symptoms and signs
- Vaccination history if relevant or unusual (e.g. delayed schedule, missed childhood immunisations)
- Severity and course/outcome of AEFI
- Results of relevant laboratory, radiological, surgical, pathological, etc. investigations
- Batch Number: request always and if not available, state clearly in case narrative, e.g. «batch number requested but unavailable».

3. New identified **safety signals** (not in form of Individual Case Safety Reports (ICSR) but as concise, critical evaluation of the issue) identified on Swiss or international level:

Not later than 15 calendar days for a new potential risk identified by the **MAH** on Swiss or international level in relation with immunisation (e.g. new potential risk, vaccine use or prescribing problem, increase of abnormal outcomes frequency). This should be considered as an identified **safety signal** for which an **evaluation report** including available data, risk assessment and planned measures must be submitted.

Drug exposure during pregnancy and «Parent-Child reports» from Switzerland – instructions / recommendations of Swissmedic

- In case a drug exposure during pregnancy is suspected, **but:**
  - **no** complication during pregnancy occurred, **and**
  - **no** harmful effect of the foetus/child at the time of the report is suspected,
    - ⇨ The Individual Case Safety Report (ICSR) should be reported as «non-serious» (within 60 days) or «serious/medically important» (within 15 days), **«standard»** (no parent/child) case
    - ⇨ Only the mother should be recorded as «patient»
    - ⇨ Coding options (MedDRA_LLTs) e.g.:
      'Drug exposure during pregnancy'
      'Vaccine exposure during pregnancy'
      'Exposure during pregnancy'
      'Maternal exposure during pregnancy'
      'Maternal exposure during pregnancy, first trimester'
      'Maternal exposure during pregnancy, second trimester'
      'Maternal exposure during pregnancy, third trimester'

- In following situations, pregnancy cases from Switzerland (ICSR) are to be **reported to Swissmedic expedited** (not later than 15 calendar days from receipt):
  - if a **serious** or **medically important** complication/harmful effect during pregnancy concerning the mother is suspected in association with a drug
  - if a **serious** or **medically important** complication/harmful effect during pregnancy concerning the **foetus** (e.g. foetal death, abortion, malformation) is suspected in association with a drug – medically important/serious case – **to be submitted as «Parent-Child report»**
    - ⇨ Coding options (MedDRA_LLTs) e.g.:
      'Foetal exposure during pregnancy'
      'Foetal exposure during pregnancy, first trimester'
      'Foetal exposure during pregnancy, second trimester'
      'Foetal exposure during pregnancy, third trimester'
  - when a harmful effect for the **neonate** is suspected to be drug related–medically important/serious case – **to be submitted as «Parent-Child report»**

- for **any drug exposure during pregnancy** (even without suspected ADR or complication) with a **substance known to be noxious**, i.e. a substance which is contraindicated and should be avoided during pregnancy due to potential risk of adverse reactions for the foetus/child – **«standard» case report, serious (medically important).**

- **Follow-up reports**:

  - New data/information to a case-report concerning **the mother only** should be submitted as **follow-up report of the existing standard** (no Parent-Child) **case**.

  - For new data/information concerning the **foetus/neonate** in relation to a previous standard (mother) case, a **new «Parent-Child report»** should be created and submitted. This new «Parent-Child report» will be **linked to the pre-existing standard case** concerning the mother.

- New **safety signals** concerning exposure during pregnancy (not in form of ICSR but as concise, critical evaluation of the issue) identified on Swiss or international level:

  - **Not later than 15 calendar days** for a new potential risk on Swiss or international level in relation with drug exposure during pregnancy (e.g. signal of possible teratogenic effect, new drug risk, drug use or prescribing problem, increase of abnormal outcomes frequency). This should be considered as a new identified **safety signal** for which an **evaluation report** including available data, risk assessment and planned measures must be submitted.

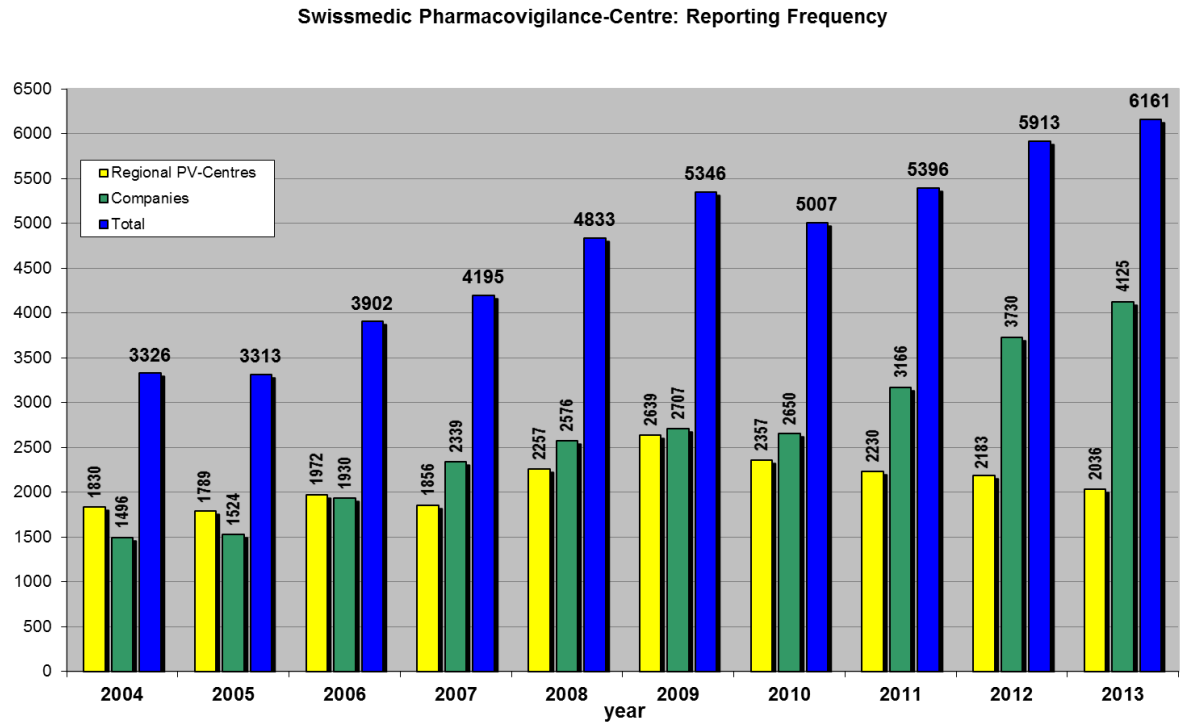
Statistical Review 2013

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 firmsSwissmedic.

Activities

- In 2013, Swissmedic received and assessed 6,161 reports on suspected adverse drug reactions from the 6 RPVCs and industry. The increase of 4.2% compared with the previous year is the result of the increasing number of reports from companies, whereas those submitted by the regional centres continues to decrease.
- Over 10% of the reports from companies were submitted to Swissmedic electronically, using the pharmacovigilance gateway launched the previous year.
- Dr Martina Schäublin replaced Dr Pia Caduff as the head of the Pharmacovigilance division at the beginning of the year.
- The key issues within the division's work included addressing the safety signals that were identified via spontaneous reporting and the FPE II project. The said project permits the electronic reporting of adverse reactions by professionals (and smaller companies), and is being developed in close collaboration with representatives of those submitting the reports.



Vaccinovigilance

Summary of adverse events following immunization

During 2013, Swissmedic received 138 case reports of suspected adverse events following immunization (AEFI) in Switzerland. This is a lower number of reported cases as compared to 2012, which might reflect a decreased incidence of adverse reactions following vaccinations. However, since there are no accurate data available regarding the total number of vaccines/doses administered during 2013 a straightforward conclusion cannot be drawn. In addition, a slightly decreased primary reporting rate due to the absence of new major safety issues concerning vaccines (locally and internationally) and therefore less general focus on this subject last year should be considered. As previously, Swissmedic continues to actively encourage spontaneous reporting of AEFIs in good quality. Since 2010, important topics with regard to AEFIs are evaluated and discussed with experts of the Swissmedic Human Medicines Expert Committee.

Link: Summary of adverse events following immunization reported in Switzerland during 2013

Haemovigilance

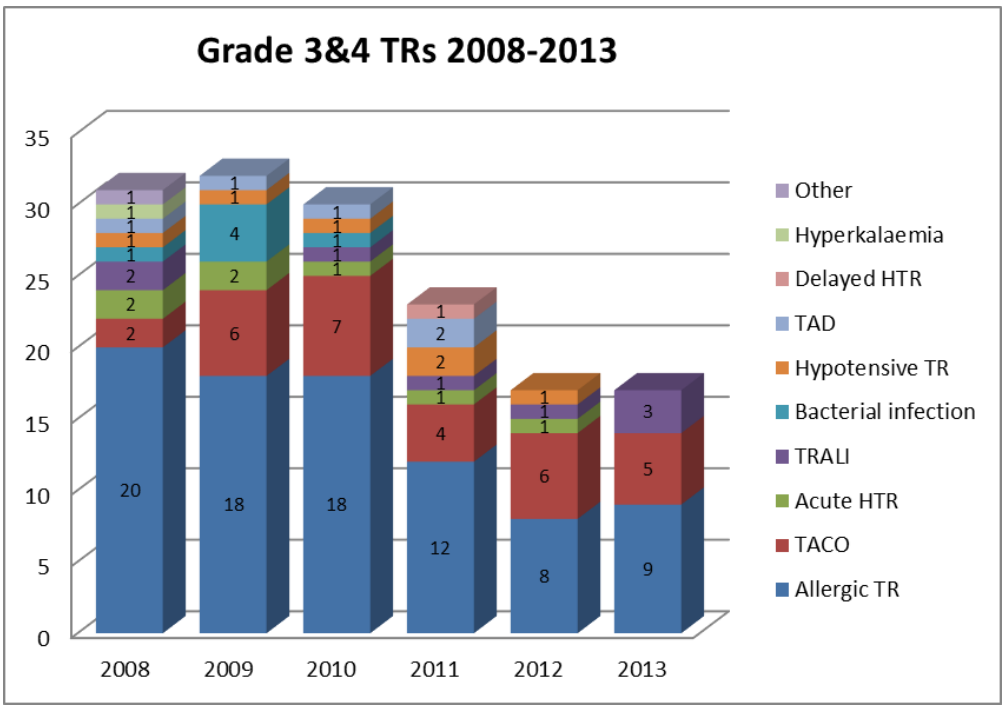
In recent years, the annual requirement for packed red blood cell (pRBC) units and plasma for transfusion in Switzerland has declined steadily. In 2013, approx. 280,000 pRBC units and 45,000 units of plasma were transfused. By contrast, the number of transfused platelet concentrate (PC) units has increased on average by 10% a year. In 2013, approx. 35,000 PC units were administered.

The reporting rate has also risen during this period and is currently 5.6 haemovigilance reports per 1000 delivered blood components.

The most frequently observed events continue to be febrile non-haemolytic transfusion reactions (FNHTR), alloimmunisations and allergic TR. Transfusion-associated circulatory overload (TACO) remains the fourth most frequently reported transfusion reaction.

Whereas the first three types of event are usually unavoidable, the latter reaction can often be prevented by adjusting the transfusion rate or by administering diuretics to patients with evidence of reduced volume tolerance.

The graph illustrates reports of life-threatening or fatal TR since 2008.



In addition to recording the transfusion risks mentioned above, evaluating the efficacy of preventive measures and the targeted evaluation of potential safety signals are becoming increasingly important in haemovigilance.

The «male donor only» strategy was introduced in 2007 with the aim of reducing the incidence of transfusion-related acute lung injury (TRALI). Since then, only plasma from male donors or female donors who have never been pregnant, or whose test results are negative for HLA and HNA antibodies, has been used for transfusions. This strategy is designed to reduce the probability of HLA or HNA antibodies appearing in the plasma, as these can trigger an (immunogenic) TRALI. A comparison of the reporting rates for TRALI in connection with plasma transfusions in the 2002–2007 and 2008–2013 periods shows a marked reduction in the number of cases, while the disproportionality analysis shows a statistically significant relative risk of 0.21.

The efficacy of introducing the Intercept procedure for pathogen inactivation of all PC in Switzerland in 2011 has also been evaluated. The aim of reliably preventing clinically relevant transfusion-transmitted bacterial infections by PC has been achieved. As a result, the number of reports of life-threatening or fatal reactions after PC transfusions has dropped to a statistically significant extent.

Further information on haemovigilance: www.swissmedic.ch → Market surveillance → **Blood components**

Vigilance of Veterinary medicines

250 adverse reactions of Swissmedic-authorised veterinary medicinal products were reported during the year 2013 (2012: 197). Similar to previous years, most of the reactions reported were linked to the use of antiparasitic products (46.4 %) or antiinfectives (12.4 %). 8.4 % of the reports described reactions after reconverted use, mainly in cats. Species concerned were primarily dogs (144 reports), cats (53) and cattle or calves (40). Additionally, 46 reports were generated during consulting by the Swiss Toxicological Information Centre in Zürich. We present a series of serious cases following the use of prostaglandin derivatives in dairy cows and reactions caused by a newly authorised antiparasitic drug for dogs containing amitraz. Finally, the vaccinovigilance program received 160 declarations following the application of various vaccines, mainly to dogs or cats.

Link: Rückblick TAM-Vigilance 2013

Information on the Swissmedic website

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

Communications regarding the safety of medicines

- 22.12.2014
  DHPC Tecfidera (Dimethylfumarat)
  Meldung über progressive multifokale Leukoenzephalopathie (PML) im Rahmen einer schweren prolongierten Lymphopenie.
- 06.12.2014
  DHPC - INOmax, Inhalationsgas
- 03.12.2014
  DHPC – Vectibix® (Panitumumab)
  Wichtige sicherheitsrelevante Information bezüglich Einschränkung der Indikation und Auftreten seltener schwerer Hautreaktionen
- 12.11.2014
  DHPC Invirase® (Saquinavir)
  Neue Empfehlung zur Dosierung und EKG Überwachung bei nicht-vorbehandelten Patienten von Invirase® (Saquinavir)
- 06.11.2014
  Xofigo, Injektionslösung (radium-223 dichloridum)
  Die Firma Bayer (Schweiz) AG informiert, dass während einer Routinekontrolle von Xofigo, Injektionslösung kleine Faserpartikel in den Vials gefunden wurden.
- 30.10.2014
  Impfstoffe gegen humane Papillomaviren (HPV) – aktualisierte Informationen und Hinweise zur Sicherheit
- 24.10.2014
  Taxotere, Infusionskonzentrat
  Die Firma Sanofi-Aventis (Suisse) AG möchte auf einen möglichen Mangel bei der Blisterverpackung von Taxotere 20mg aufmerksam machen.
- 25.09.2014
  DHPC Reminyl® Prolonged Release (Galantamin-Hydrobromid)
  Neuer Warnhinweis: schwere Hautreaktionen (Stevens-Johnson-Syndrom und akute generalisierte exanthematöse Pustulosis) für Reminyl und Generikum* (Galantamin SR Helvepharm)
- 28.08.2014
  DHPC – Hemohes® (Hydroxyethylstärke), HyperHAES® (Hydroxyethylstärke), Tetraspan® 6% (Hydroxyethylstärke), Venofundin® (Hydroxyethylstärke), Voluven® (Hydroxyethylstärke), Voluven® 6% balanced (Hydroxyethylstärke)
  Anwendungsbeschränkung für HES (Hydroxyethlystärke)-haltige Arzneimittel
- 16.07.2014
  HPC – Tresiba Penfill und Tresiba Flex Touch, Injektionslösungen (Insulin Degludec)
  Kardiovaskuläre Sicherheit: Anpassung der Arzneimittelinformation

- 01.07.2014
  DHPC - ARZERRA® (Ofatumumab)
  Tödliche Infusionsreaktionen unter der Behandlung mit ARZERRA® (Ofatumumab)
- 20.06.2014
  DHPC – Inlyta® (Axitinib)
  Wichtige sicherheitsrelevante Information bezüglich kardiopulmonalen Ereignissen und Aufnahme von Herzversagen als unerwünschte Wirkung in die Fachinformation

New on this website

- 19.12.2014
  ICH Steering Committee Meeting in Lisbon, 8 to 13 November 2014
- 10.12.2014
  Manipulated clinical trials by the company GVK Bioscience – minimal impact in Switzerland
- 09.12.2014
  Designer drugs placed on banned list
  So-called designer drugs have been declared illegal in Switzerland since December 1st as part of an effort to crack down on online trading (in German, French or Italian).
- 05.12.2014
  Bundesrat wählt zwei neue Mitglieder in den Institutsrat von Swissmedic
- 16.10.2014
  AIPS-Neuerungen mit Release 2014
  Es werden für die AIPS Zulassungsplattform- und Suchplattform diverse Neuerungen und Verbesserungen eingeführt.
- 06.10.2014
  ElViS Electronic Vigilance Reporting Portal
  Healthcare professionals and companies can now report suspected adverse drug reactions electronically
- 14.07.2014
  Measures for improved patient safety in cardiac surgery
  Press release about heater cooler devices
  Hospitals in Switzerland that perform open heart surgery have taken measures to increase patient safety.
- 09.07.2014
  ICH meeting in Minneapolis, USA: Swissmedic and Health Canada included as new members

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

New Swissmedic telephone numbers in use

From 1 March 2014, the Federal Administration's telephone numbers will be changed in a measure associated with the introduction of the Confederation's new fixed-line telephone facilities. The old telephone numbers will remain valid at least until spring 2015, the Federal Administration can be contacted via both the old and new numbers until spring 2015.

Therefore Swissmedic can be contacted via 058 telephone numbers.

To ensure a gradual changeover, the old telephone numbers will remain valid at least until spring 2015. Existing mobile telephone numbers will not be affected by this renumbering for the time being.

The new telephone numbers of the Federal Administration can be looked up individually on the website of the Federal IT Steering Unit (FITSU).

Federal Administration's new telephone numbers

Online inquiry of the numbers old - new

With few exceptions the new Swissmedic phone numbers including the area code 058 start with 46 (058 46x xx xx).