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Vigilance-News

Edition 15 – Dec. 2015

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

Once a medicine has been launched on the market, the evaluation of spontaneous reports provides a very useful way of recording the potential risks and adverse drug reactions (ADR) associated with it as quickly as possible.

Thanks to spontaneous reports from everyday practice, the ADR that have not been identified during pharmacological testing and/or clinical trials in the authorisation phase can be collected in pharmacovigilance databases and evaluated. Specific safety signals can then often be detected on the basis of these ADR. In many cases these only emerge after widespread use and/or use

over many years, particularly in patient populations that were not adequately considered in clinical trials.

The importance of this process is demonstrated repeatedly for familiar, long-established medicines, such as combined hormonal contraceptives (CHC) or isotretinoin. ADR monitoring by means of spontaneous reporting plays an even more important role for newly authorised preparations such as hepatitis C treatments.

In Switzerland, spontaneous reports from healthcare professionals, or even directly from patients, are received by the Regional Pharmacovigilance Centres (RPVC), which, in turn, give feedback to the reporting individuals. Ideally, ADR should be reported to the RPVC electronically using ElViS (Electronic Vigilance System). The six RPVC (Bern, Basel, Geneva, Ticino, Vaud and Zurich) record and process the spontaneous reports for Swissmedic's pharmacovigilance database, where they are subsequently evaluated. With the aid of this system it is frequently possible to identify potential drug risks, interactions or other signals and initiate corresponding measures if necessary (see article on rivaroxaban and liver damage). Cooperation with the RPVC is also the focus of our regulatory articles.

We naturally also welcome your suggestions, and look forward to receiving your feedback at news.vigilance@swissmedic.ch.

We wish all our readers a happy festive season and a successful start into 2016.

The Editors

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

Hepatitis C-treatment: New directly acting antivirals

For the past 25 years, interferon-alpha has formed the basis for antiviral treatment in chronic hepatitis C. Initially a monotherapy, it was supplemented at the end of the1990s by ribavirin. For more than 10 years, the standard therapy consisted of a combination of pegylated interferon-alpha and ribavirin (1). Patients with hepatitis C were given this combination treatment over a period of 6–12 months. This treatment achieved a sustained virological response (SVR) in up to 50 % of patients with (HCV) genotype 1 infection and up to 80 % of patients with genotypes 2 or 3. It should also be mentioned, however, that adverse drug reactions (ADR) are frequently reported in connection with this treatment. Notably flu-like symptoms and depressive moods are commonly reported with interferon, while the ADR mainly associated with ribavirin is anaemia.

Boceprevir and telaprevir were authorised in Switzerland in 2011. Both active substances are the first representatives of the group known as protease inhibitors, a subgroup of the directly acting antivirals (DAA). Initially, either one of these active substances was used in a triple therapy regimen with PEG-IFN-alpha and ribavirin. This treatment produced an increase in the SVR rates of non-pretreated patients with genotype 1 infections to approx. 70 %, while at the same time shortening the duration of treatment to 24–48 weeks in around half of the patients (2). This first-generation triple therapy was associated not only with a high pill burden, but also poor tolerability and associated premature discontinuations of treatment (3). The relevant ADR that were reported included various forms of anaemia and a reversible, marked deterioration in kidney function (4, 5).

New DAA authorised by Swissmedic in 2014 and 2015 produced a distinct increase in SVR rates to over 90%. These new drugs included the protease inhibitors simepravir (SMV) and paritaprevir (PTV). The pharmacological target of a second subgroup of DAA is a protein that is important for viral genome replication and virus production (NS5A). This is inhibited by the following new active substances: daclatasvir, ombitasvir (OBV) and ledipasvir (LDV). A further subgroup of DAA comprises the polymerase inhibitors sofosbuvir (SOF) and dasabuvir (DSV), which were recently authorised in Switzerland. The above-mentioned DAA allow a shorter treatment period of 8, 12 or 24 weeks and demonstrate what is currently considered to be a more favourable tolerance profile (6). The patients' response to the new combination therapies is complex due to its multifactorial nature and the dependence on genotype, patients' medical history (phase of hepatic fibrosis, pre-treatment, etc.), viral load, duration of therapy, addition of ribavirin, etc. (2).

Most HCV patients worldwide are genotype 1 carriers. Different therapeutic options for their treatment are available, e.g. the combination of ledipasvir and sofosbuvir or the combination of paritaprevir, ombitasvir, dasabuvir and ritonavir. A fixed-dose combination with the brand name of Harvoni® is authorised for the first combination in a single tablet (LDV–90mg/SOF–400mg). When combined with amiodarone, it can lead to episodes of severe symptomatic bradycardia. Swissmedic has published a Health Professional Communication on this issue on its website: https://www.swissmedic.ch/marktueberwachung/00135/00157/02796/index.html?lang=en

A fixed-dose combination of paritaprevir, ombitasvir and ritonavir is available under the proprietary name Viekirax®, consisting of a single tablet with the following composition: (PTV–75 and 50 mg/OBV–12.5 mg/ritonavir–50 mg). DSV (proprietary name Exviera®) must be taken in an

additional tablet (250 mg) (7). For details of adverse drugs reactions and interactions, readers are referred to the corresponding Information for healthcare professionals, which can be viewed at http://www.swissmedicinfo.ch.

The FDA has recently (22 October 2015) issued a warning concerning the combination product Viekira Pak®, which contains the active substances ombitasvir, paritaprevir, ritonavir and dasabuvir. Apparently, severe liver injury can occur following the administration of this medication, particularly in patients with pre-existing liver disease. Swissmedic is currently evaluating this signal.

The table below provides an overview of the DAA that are currently (1 November 2015) authorised in Switzerland, their mechanism of action and the specific HCV genotypes for which they are effective.

Class	Mechanism of action	Active substances effective for genotype (x)
Protease inhibitors	Inhibit HCV-NS3-4A-protease	Telaprevir (genotype 1) Boceprevir (genotype 1) Simeprevir (genotypes 1 and 4) Paritaprevir (genotypes 1 and 4)
NS5A inhibitors	Inhibit HCV-NS5A	Daclatasvir (genotypes 1–6) Ombitasvir (genotypes 1 and 4) Ledipasvir (genotypes 1, 3, 4, 6)
Polymerase inhibitors	Inhibit HCV-NS5B polymerase	Sofosbuvir (genotype 1–6) Dasabuvir (genotype 1)

In many cases, both international and national guidelines now only regard interferon as second-line treatment for hepatitis C. By comparison, ribavirin is even more substantially integrated into the current guidelines. Under these recommendations, ribavirin can be optionally used as first-line treatment in combination with the new DAA, for example in patients with genotype 1a infections or cirrhosis. For detailed recommendations on the treatment of hepatitis C, please refer to the update to the *Expert Opinion Statement* issued by the *Swiss Association for the Study of the Liver (SASL)* in September 2015:

https://sasl.unibas.ch/guidelines/SASL-SSI_HepC_EOS_Sept2015.pdf

Since little post-marketing experience is currently available for the new DAA, Swissmedic would encourage healthcare professionals in particular to report any ADR that occur during treatment.

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3) Coppola, N et al. Hepatitis C virus markers in infection by hepatitis C virus: In the era of directly acting antivirals. World J Gastroenterol. 2015; 21 (38):10749-59
4) Lupo, F et al. Protease inhibitors-based therapy induces acquired spherocytic-like anemia and ineffective erythropoiesis in chronic hepatitis C virus patients. Liver Int. 2015.doi: 10.1111/liv.12900 [Epub ahead of print]
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Rivaroxaban (Xarelto®) and liver injury

Rivaroxaban is a direct factor Xa inhibitor for the primary and secondary prevention and the treatment of thromboembolic disease. It has been marketed worldwide by Bayer since 2008.

Staff at the Regional Pharmacovigilance Centres (RPVC) in Basel (Clinical Pharmacology and Toxicology, University Hospital Basel) and Zurich (Clinical Pharmacology and Toxicology, University Hospital Zurich) analysed more than 40 individual case reports of liver injury during treatment with rivaroxaban that were submitted to Swissmedic between 2008 and 2013 (1, 2). They also conducted comprehensive searches in several international pharmacovigilance databases. The results show that treatment with rivaroxaban can lead to severe symptomatic liver injury.

Swissmedic accordingly asked the marketing authorisation holder Bayer (Schweiz) AG to provide a comprehensive statement as part of safety signal processing activities. All available data were subsequently analysed and evaluated in an expert report commissioned by Swissmedic. This report fully confirmed the results of the RPVC.

As a risk-minimising measure, the marketing authorisation holder will, in coordination with Swissmedic, add the undesirable effects of cholestasis and hepatitis (incl. hepatocellular injury) to the existing hepatic disorders listed in the Swiss medicinal product information for Xarelto®.

This example highlights the importance of well-documented individual case reports and close cooperation between the RPVC and Swissmedic in the early identification and efficient processing of safety signals.

References

1) Liakoni E, Rätz Bravo AE, Terracciano L, Heim M, Krähenbühl S, Symptomatic hepatocellular liver injury with hyperbilirubinemia in two patients treated with rivaroxaban, JAMA Intern Med 2014; 174: 1683-6
2) Russmann S, Niedrig DF, Budmiger M, Schmidt C, Stieger B, Hürlimann S, Kullak-Ublick GA, Rivaroxaban postmarketing risk of liver injury, J Hepatol 2014; 61: 293-300

Combined hormonal contraceptives (CHC) – update

Updated and harmonised product information, particularly concerning warnings and precautions on the risk of venous and arterial thromboembolism and deletion of references relating to beneficial effects in acne

In the course of two market surveillance procedures involving 84 preparations from 14 marketing authorisation holders, Swissmedic has reviewed, updated and harmonised the product information for healthcare professionals and patients for all combined hormonal contraceptives (CHC) authorised in Switzerland.

The review focused on the warnings and precautions relating to the known risk of venous and arterial thromboembolism (VTE and ATE). However, the procedure also included other safety-related findings and CHC properties.

With this referral procedure, Swissmedic has taken another step forward in raising awareness among users of combined hormonal contraceptives (CHC) and healthcare professionals about the risks associated with these preparations, so that they are able to make an «informed decision» when selecting the most suitable method of contraception. Swissmedic relied on the results and recommendations from the benefit-risk analysis concluded by the European Medicines Agency in January 2014. Swissmedic's evaluation of the risk of VTE and ATE conforms to that of the EU, as do the measures taken to date. When correctly indicated, and provided the contraindications, precautions and individual risk factors are respected, the benefit-risk ratio of these preparations is still positive.

A second procedure reviewed those CHC whose product information have previously listed references relating to beneficial effects in acne (CHC containing chlormadinone acetate or drospirenone). These references to beneficial effects were deleted since the mentioned advantages do not outweigh the potentially life-threatening VTE-risks.

The VTE risk associated with CHC is low. However, given the large number of healthy women who are prescribed CHC, this has significant consequences: In a total of 400,000 CHC-users in Switzerland (2011 estimate), the number of VTE events has been calculated at 200–480 a year according to the latest incidence figures. Around 50 VTE events a year have been notified to the Swiss reporting system in the last five years, i.e. approx. 1 VTE per week (www.swissmedic.ch → Market surveillance → Human medicines → Specific topics → Hormonal contraceptives and thromboembolism).

The conclusion of this procedure marks the achievement of an important regulatory milestone. However, the safe use of contraceptives remains the joint responsibility of all those involved:

- Swissmedic and the Swiss Society of Gynaecology and Obstetrics (SGGG) are jointly committed to providing improved information about the risks associated with CHC.
- When deciding whether to prescribe a CHC for the first time or re-starting the prescription, doctors must evaluate and take account each woman's individual risk factors for VTE at the time of prescription. In this context, the differences in VTE risk between the individual preparations should also be taken into account (see Swissmedic website and updated product information).
- Prescribing doctors must thoroughly inform users about the risks and the steps to take in the event of problems. To this end, Swissmedic strongly recommends the use of the information material published by the SGGG.
- Users must be aware of the important warning symptoms of VTE and seek medical help if they occur and inform doctors about their CHC use; users must be informed about the risk category of the preparation they are taking. The

«SGGG fact sheet for users of combined hormonal contraceptives (version: 6/2013)» and the patient information leaflet for the prescribed CHC can be used for this purpose.

- CHC containing chlormadinone acetate and drospirenone are authorised for contraception and should not be used for acne. Alternative preparations that pose no increased risk of VTE are available for the treatment of acne.

More detailed information on both procedures can be found in the two Swissmedic *Direct Healthcare Professional Communications* (DHPC), available on its website (www.swissmedic.ch → Market surveillance → Human medicines → Specific topics → Hormonal contraceptives and thromboembolism).

Isotretinoin – update on the situation in Switzerland

- It is essential for healthcare professionals to provide information about the risks associated with isotretinoin.
- Since oral isotretinoin preparations are teratogenic, they are contraindicated in women of childbearing age unless proof of at least two negative pregnancy tests has been provided before the start of treatment. Furthermore, reliable contraception is absolutely necessary.
- Packs of 100 units should not be prescribed because isotretinoin may only be dispensed for a period of thirty days

Spontaneous reports of adverse drug reactions (ADR) associated with oral isotretinoin*

Acne is a condition that can have psychological consequences and corresponding repercussions on the patient's social life and quality of life. In the most severe cases, acne can also lead to unsightly scars that make the face look «pock-marked».

Topical treatments – either creams or gels based on benzoyl peroxide and retinoids – are the preferred options for mild or moderate acne. However, an antibiotic (oral doxycycline or lymecycline) may also be prescribed for moderate acne, depending on the individual situation. Isotretinoin is reserved for severe forms of acne (for example acne nodularis, acne conglobata or acne with a risk of permanent scarring) that have proved resistant to the appropriate standard therapeutic cycles of systemic antibiotics. It is very important to stress that acne treatment is generally not immediately effective, and that it can take a few weeks to achieve an improvement. This is why it

is crucial that treatment of any kind should be monitored carefully.

It should be noted that the good efficacy of isotretinoin products is offset by their serious potential for adverse events. Consequently, all the warnings and precautions mentioned in the Information for healthcare professionals for such products must be strictly observed (see following link: http://www.swissmedicinfo.ch).

In Switzerland, all oral isotretinoin preparations are prescribed in dispensing category A: dispensing is subject to non-renewable medical prescription.

Pregnancy, any possibility of pregnancy and breastfeeding represent absolute contraindications to treatment with isotretinoin.

Moreover, patients should be monitored particularly closely for any signs of depression and/or similar symptoms so that these can be identified at an early stage and appropriate treatment started if necessary.

Swissmedic would like to give an updated overview of the reports of adverse drug reactions (ADR) associated with oral isotretinoin recorded in the Swiss pharmacovigilance database between 1 March 2014 and 15 October 2015. A further aim of this article is to reinforce the importance of ensuring that oral isotretinoin is used correctly.

Within the framework of pharmacovigilance, this article focuses on psychiatric disorders, serious skin and liver reactions and exposure during pregnancy, see also Vigilance-News No. 6 (December 2010), No. 8 (December 2011), No. 10 (December 2012) and No. 12 (June 2014).

While the overall profile and distribution between the various organ classes of the adverse events reported for isotretinoin in Switzerland have not changed significantly since the edition of Vigilance-News No. 12 (June 2014), the prevailing frequency of reports has increased. Between 1 March 2014 and 15 October 2015, Swissmedic received a total of forty-two ADR reports.

Psychiatric disorders

A total of seven reports were received for this organ class during the period under review, but none of these involved attempted or completed suicide. Thus, the cumulative total number of reports for oral isotretinoin since the publication in the Vigilance-News No. 10 (December 2012) remains unchanged at twelve for attempted suicide and twenty-one for completed suicides.

Of the seven new reports, two involved depression accompanied by suicidal thoughts, while one concerned a woman whose symptoms of depression were exacerbated one year after starting treatment with isotretinoin against a psychosocial context of relationship break-up and domestic violence. The causality of isotretinoin in the three above-mentioned reports was rated as possible.

Although it is often difficult to establish a link between the administration of isotretinoin and the onset of psychiatric disorders, all patients should be monitored for any signs of depression or mood disorders and appropriate treatment should be provided if required. Particular attention should also be paid to patients presenting with a history of depression. Discontinuing isotretinoin is sometimes not sufficient to alleviate the symptoms, and an additional psychiatric or psychological assessment may be required.

As ever, it is crucial for physicians to watch out for any signs of depression and/or similar symptoms so that these can be identified at a sufficiently early stage.

Furthermore, it is essential to inform patients and their relatives that mood changes or even depression may occur, and that these must be reported immediately to the healthcare professionals treating the patient.

Rare serious skin reactions

During the above-mentioned period, Swissmedic received a total of two reports concerning this organ class. The first report involved a rash, with

no further clinical details, and the link with isotretinoin was assessed as possible. The second report concerned erythema accompanied by sweating of the palms, and again the causality link was rated as possible.

No new rare or serious case was reported for this organ class. The cumulative total of serious skin reactions therefore remains at three.

Serious liver reactions

No new reports of this type of reaction were received during the period under review.

Exposure during pregnancy

Since it is a teratogenic drug, isotretinoin is contraindicated in women of childbearing age. The conditions listed in the pregnancy prevention programme must therefore be strictly observed (see http://www.swissmedicinfo.ch) for information for healthcare professionals on oral isotretinoin preparations). Although isotretinoin should only be dispensed for a period of thirty days, proof of at least two negative pregnancy tests must be provided before treatment starts and reliable contraception is mandatory, fifteen new cases of exposure during pregnancy were reported during the period under review. It should also be noted that two cases of paternal exposure were reported during this period.

Review period from 1 March 2014 to 15 October 2015					
Total number of reports	Number of paternal exposures	Number of maternal exposures	Number of malformed newborns	Number of voluntary terminations of pregnancy	Number of spontaneous abortions
42	2	15	2	5	2

Paternal exposures

Limited information is available for the first report of paternal exposure, which states that the father was taking isotretinoin at the time of conception and the newborn was given a retrospective genetic medical examination for malformation assessment. The baby concerned presented with a congenital anomaly of the right leg. A causal link between the father taking isotretinoin and the bone anomalies in this child cannot be established on the basis of the currently available data; in fact, the sperm of male patients who are taking isotretinoin results in a level of exposure in pregnant women that is not considered sufficient to produce any teratogenic effect.

The second report of paternal exposure concerned a child presenting with mental retardation and cerebral malformations. The father had stopped taking isotretinoin nine months before his partner became pregnant. Since isotretinoin and its active metabolite are largely eliminated six days after the drug is stopped, and spermatogenesis is completed in about two and a half months, the child's malformations do not appear to be associated with the father's treatment.

Maternal exposures

Five of the fifteen new reports of exposure concern patients treated with isotretinoin who then underwent voluntary termination of pregnancy for drug-related reasons.

Of the fifteen aforementioned reports, one concerned the exposure during pregnancy of a patient receiving acne treatment with an oral

isotretinoin preparation. After being born prematurely, the baby concerned presented with serious major cerebral malformations, with consequent neurological deficit and tetralogy of Fallot. These anomalies are compatible with the embryofoetopathies that are associated with retinoids.

The following foetal malformations are generally associated with exposure to isotretinoin: central nervous system abnormalities (hydrocephalus, cerebellar malformations, microcephaly), facial dysmorphia, cleft palate, deformities of the external auditory canal (absence of the auricle, narrow or missing external auditory canal), eye abnormalities (microphthalmia), cardiovascular abnormalities (conotruncal malformations such as tetralogy of Fallot, transposition of the great vessels, septum defects), deformities of the thymus and the parathyroid glands. The incidence of spontaneous abortions is also increased.

Two other reports among the fifteen received during the period under review refer to spontaneous abortions in two patients who were being treated with isotretinoin among other drugs. One of these patients had stopped taking isotretinoin four weeks before conception. The causality of the isotretinoin in this report was rated as unlikely, firstly because isotretinoin and its active metabolite are largely eliminated six days after treatment has ended and, secondly because the child was diagnosed with trisomy.

One other report concerned serious cerebral congenital malformations in a child whose mother had been exposed to isotretinoin during the first trimester of pregnancy. No further information on this case was provided.

To date, a cumulative total of six cases of newborns with retinoid-typical malformations have been reported in Switzerland.

According to the literature, isotretinoin exposure is associated with a risk of malformation of between 25 and 30%. It should also be noted that this risk is much higher than the spontaneous risk rate of 3 to 5% associated with congenital malformation.

Given the high teratogenic risk associated with isotretinoin, it is extremely important to ensure that the precautions described in the Information for healthcare professionals for oral isotretinoin preparations (see http://www.swissmedicinfo.ch) are strictly followed in women of childbearing age. Moreover, isotretinoin preparations should be prescribed to women of childbearing age for no longer than thirty days of treatment, and any continuation of treatment requires a new prescription. **Consequently, packs of 100 units should not be prescribed.**

As a general rule, the main causes of pregnancy in women treated with isotretinoin are non-use of contraception, use of an unreliable or inappropriate contraceptive method or poor observance of contraception.

To prevent foetal exposure to isotretinoin, it is absolutely essential that healthcare professionals inform patients of the risks of teratogenicity associated with isotretinoin using the information material supplied by the authorisation holders for oral isotretinoin preparations. It is also crucial for healthcare professionals to advise women about contraception before treatment starts and to explain the need for pregnancy tests.

Update on alitretinoin, another oral retinoid with a different indication

The active substance alitretinoin, marketed under the brand name Toctino®, is indicated for the «treatment of refractory, severe chronic eczema of the hands in adults who have failed to respond to at least four weeks of extensive local treatment. Pre-treatment measures include avoiding contact with triggers, skin protection and potent topical corticosteroids».

The contraindications, warnings and precautions must be strictly followed, and essentially comprise the same main elements as for isotretinoin, particularly the risk of malformation in the event of pregnancy. All the safety sections in the product information are largely identical with those for isotretinoin.

Of the twenty-nine ADR reports received to date, three concerned depression, while two others involved suicidal thoughts and mood disorders respectively. However, no cases involving the particularly important aspect of drug exposure during pregnancy have been reported.

Conclusion

In this article, Swissmedic has underlined the importance of ensuring proper use of oral isotretinoin and the continuing need to strictly follow all the warnings and precautions described in the Information for healthcare professionals for the aforementioned products (see http://www.swissmedicinfo.ch).

Oral isotretinoin preparations may only be prescribed by physicians who are experienced in the use of systemic retinoids for the treatment of severe acne and who have extensive knowledge of the risks associated with this treatment and the necessary monitoring.

It is crucial to monitor patients particularly closely for any signs of depression and/or similar symptoms so that they can be identified at an early stage and appropriate treatment started.

In view of the high teratogenic potential of isotretinoin, it is essential to follow to the letter the precautionary measures described for women of childbearing age.

Isotretinoin preparations are all prescribed in dispensing category A: dispensing is subject to non-renewable medical prescription. **In this context, Swissmedic reminds prescribers to avoid prescribing packs of 100 units because isotretinoin may only be dispensed for a period of thirty days.**

It goes without saying that oral isotretinoin preparations will remain under intensive surveillance.

Reporting suspected adverse drug reactions

Swissmedic would encourage potential reporters of suspected adverse drug reactions (ADR) to use the portal developed for this purpose. The Electronic Vigilance System ElViS enables reporters to submit their ADR directly. If necessary, paper report forms can still be sent to the Regional Pharmacovigilance Centres. This form is available on the Swissmedic website or can be ordered directly from Swissmedic (Tel. +41 58 462 02 23). All the necessary information can be found on the website.
https://www.swissmedic.ch/marktueberwachung/00135/00160/index.html?lang=en

Full information on warnings, precautions and adverse reactions can be found in the Information for healthcare professionals for oral isotretinoin preparations at: http://www.swissmedicinfo.ch.

**The following oral isotretinoin preparations are currently authorised in Switzerland: Roaccutane®, Curakne®, Tretinac® and Isotretinoin-Mepha®.*

Regulatory

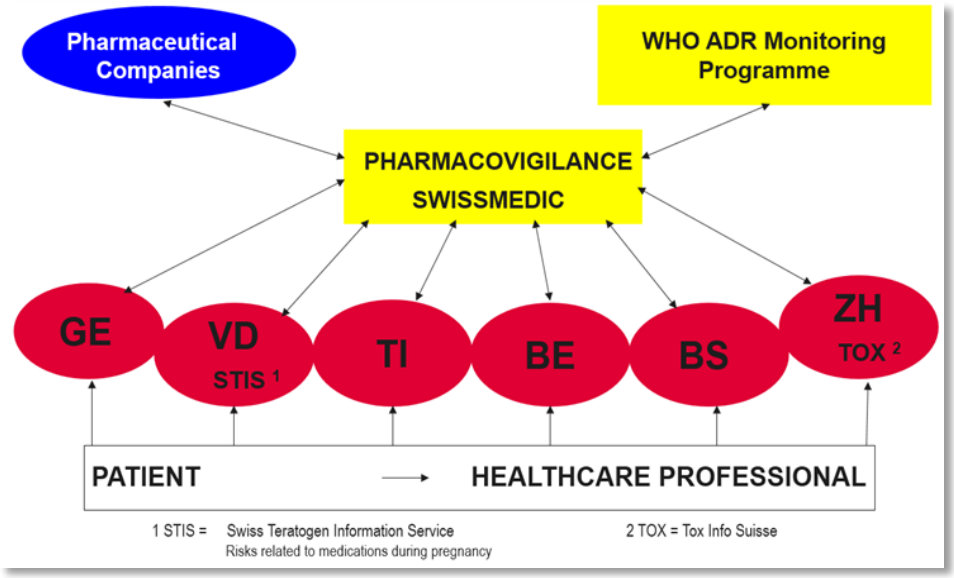
WTO tender for pharmacovigilance services – Outcome and new contract placement from January 2016

Background

The efficacy and safety of new medicinal products are investigated as comprehensively as possible prior to authorisation. Nevertheless, the rarer adverse drug reactions (ADR) only come to light after market authorisation when the products are in use in a much larger population. The most important method for detecting ADR is spontaneous reporting. Even a small number of correctly documented cases can set in motion risk-minimising measures and allow decisions intended to protect patients to be made quickly.

Healthcare professionals and anyone who manufactures, professionally administers or dispenses therapeutic products, are therefore obliged to report the occurrence of any adverse reaction to Swissmedic (Art. 59, (3) TPA). In order to build up and anchor the reporting system at regional level, since 2002, Swissmedic has been collaborating in pharmacovigilance with the pharmacology units at the university hospitals in Berne, Basel, Zurich, Geneva and Lausanne, as well as the regional hospital in Lugano (see graphic below).

These regional centres (RPVC) provide services that essentially form part of Swissmedic's remit, namely recording and evaluating reports, coded entry of reports in the Swissmedic database and report documentation. Important reports that may constitute a safety signal must be forwarded to Swissmedic within 48 hours. These university hospital agencies also provide feedback and advice to reporters and train potential primary reporters on behalf of Swissmedic.



Reports sent to the pharmaceutical industry by healthcare professionals are recorded by the companies in question and forwarded to Swissmedic. As the **national vigilance centre** for Switzerland, Swissmedic is part of the worldwide WHO ADR Monitoring Programme, transfers the structured data to the WHO database and also has access to information on ADR recorded across the globe.

As a result of developments in recent years, there has been a steady increase in the volume of reports, the electronic reporting system (ElViS) has been introduced, and stricter requirements governing the quality of the reports and processing deadlines are in place. Furthermore, in accordance with the stipulations of public procurement legislation, the old contracts have been terminated with effect from 31 December 2015.

WTO tender

An in-depth legal evaluation revealed that the services fall under public procurement requirements by virtue of their volume and are subject to tender via the WTO process. A very detailed requirements specification with clear quality criteria and different report categories was prepared, more lots than the number of existing suppliers were tendered (5 German lots, 3 French, 1 Italian), and bidding consortia were prohibited.

The tendering process started in April 2015 and the outcome was published on 3 July 2015.

Results

All existing RPVC submitted a bid and were considered. The lots were awarded as follows: 3 lots to University Hospital Zurich and 1 lot each to University Hospital Basel and Inselspital Bern. 2 lots were awarded to University Hospital Geneva, 1 lot to University Hospital Lausanne, and the Italian speaking lot went to the EOC (Ente Ospedaliero Cantonale) hospital group in Ticino.

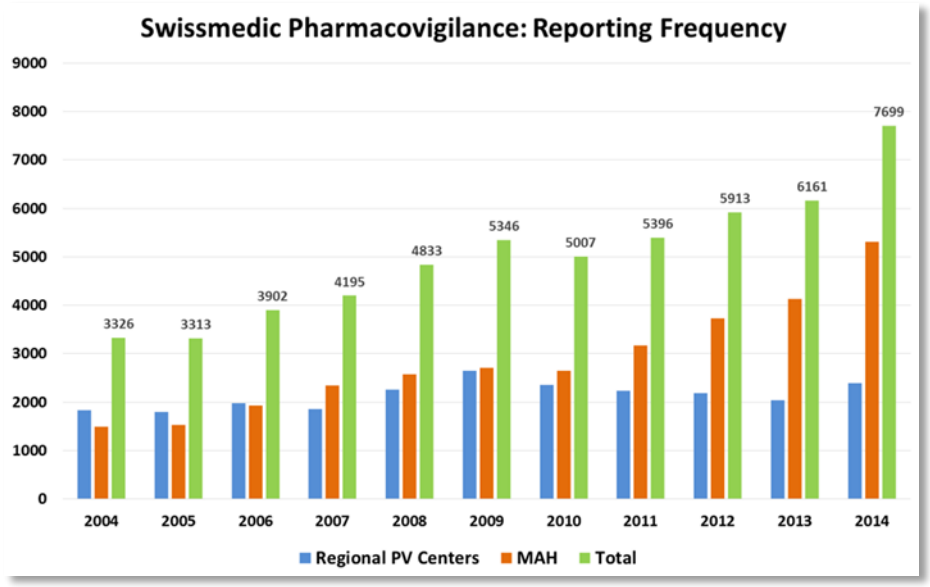
The new contracts include stricter quality requirements, tighter deadlines for report processing and forwarding, a more differentiated remuneration system based on report category (in-depth, simple and minimal investigations, follow-ups), a resulting stronger focus on potential safety signals, and the option of centre auditing by Swissmedic. The contracts run for 5 years, with an option to renew for a further 2 years, and can be cancelled by either side with 6 months' notice. The contracts vary in respect of remuneration (based on the bids received) and order volumes.

To sum up: there will be no changes to the structure of the current RPVC network as of 2016. However, services will now be contracted out in a proper manner in accordance with public procurement law.

Latest developments in electronic reporting in pharmacovigilance

Background

The number of reports of adverse drug reactions (ADR) has steadily increased over the years. This trend has been increasingly observed in Switzerland in recent years as well as in other countries. The increase is primarily attributable to a rise in the number of reports received from the pharmaceutical industry, whereas reports from the regional pharmacovigilance centres have remained fairly constant over the years. We expect 2015 to show another sharp increase in the number of initial reports, as well as a substantial rise in the number of follow-up reports. The revision of the TPA will add to this increase. This presents a major challenge because Swissmedic must be able to keep processing this growing number of reports and identifying any risks promptly.



At almost 1,000 ADR reports per million inhabitants per year, the reporting rate in Switzerland is one of the highest reporting rates in the world. Nevertheless, the number of ADR that go unreported remains high.

Consequences and new developments for authorisation holders

In view of this scenario, Swissmedic will generally give preference to electronic ADR reporting, particularly as regards reports from authorisation holders. The required tools are available in the form of the E2B Gateway and ElViS electronic reporting system.

The E2B Gateway is primarily intended for companies with high report volumes. As of the end of October, 15 authorisation holders were actively using this gateway. Since the reporting system has been optimised, it will be possible to complete the pilot phase by the end of 2015, and companies will not have to pay for activation. As of 2016, companies will be charged CHF 10,000 (equal to the external costs of activation) for each new activation.

The ElViS electronic reporting system is ideal particularly for small to medium-sized companies and has now been in operation for a year. The intention is for companies with fairly low report volumes to report ADR entirely via ElViS as of mid-2016.

From that date, Swissmedic will forward ADR from the regional pharmacovigilance centres to companies entirely electronically via Gateway or ElViS.

Outlook

Both the E2B Gateway and ElViS have proved effective for ADR reporting. ElViS also offers a user-friendly reporting system for healthcare professionals. All service providers are now integrated into the electronic reporting system. We are also encouraging healthcare professionals to submit ADR reports electronically. While hard-copy reports are still possible at present, we are currently evaluating the timepoint from which reports – particularly reports from companies – will have to be submitted electronically.

Information on the Swissmedic website

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

Communications regarding the safety of medicines

- 25.11.2015
  DHPC – Kombinierte hormonale Kontrazeptiva (CHC) mit Chlormadinonacetat oder Drospirenon
  Streichung der Hinweise auf Vorteile bei Akne (Indikation/Eigenschaften) aufgrund des erhöhten Risikos von venösen Thromboembolien (VTE) bei CHC-Anwenderinnen
- 25.11.2015
  DHPC – Kombinierte hormonale Kontrazeptiva (CHC)
  Das Überprüfungsverfahren aller CHC ist abgeschlossen. Die Arzneimittelinformationen sind harmonisiert, insbesondere die Warnhinweise und Vorsichtsmassnahmen zum Risiko venöser und arterieller Thromboembolien (VTE bzw. ATE)
- 21.10.2015
  HPC - Statin-assoziierte immunvermittelte nekrotisierende Myopathie
  In den letzten Jahren wurden Statine (HMG-CoA-Reduktasehemmer) als ein möglicher Auslöser der seltenen immunvermittelten nekrotisierenden Myopathie (Immune-mediated necrotising myopathy, IMNM) identifiziert.
- 20.10.2015
  DHPC – Motilium – Präparate (Wirkstoff Domperidon)
  Risiko von QT-Verlängerung und damit verbundener ventrikulärer Arrhythmien
- 16.10.2015
  Fluarix, Injektionssuspension
  Wichtige Information zur korrekten Anwendung der halben Impfdosis bei Kindern von 6 bis 35 Monaten.
- 20.08.2015
  DHPC – Insulin Hypurin Porcine Präparate (Schweineinsulin)
  Verzicht auf Zulassung und Vertriebseinstellung per 31. Oktober

New on this website

- 16.11.2015
  Modifications to guidance document "Formal requirements" and Modifications to the table "Documents to be submitted"
- 04.11.2015
  Sicherheitshinweis zu ala®octa
  Swissmedic informiert, dass die Firma alamedics ab sofort die Verwendung ihres Produkts ala octa untersagt.
- 27.10.2015
  ICH verkündet organisatorische Veränderungen

- 01.10.2015
  Supplement 11.2 zur Pharmacopoea Helvetica 11 in Kraft
- 29.09.2015
  Suspected criminality associated with medicinal products: Swissmedic investigates in three cantons
  Press release
- 24.09.2015
  Sale of silicone implants manufactured by Silimed suspended
  Press release
- 01.09.2015
  Swissmedic responds to criticism by health insurance provider CSS
- 26.08.2015
  Veterinary medicinal products: Greater clarity and better collaboration
  A new strategy
- 20.08.2015
  Tierische Insuline – Einstellung des Vertriebs in der Schweiz – Information für Patienten
  Per 31. Oktober 2015 verzichtet die Firma CP Pharma (Schweiz) AG auf die Zulassung der Insulin Hypurin Präparate in der Schweiz und stellt deren Vertrieb ein.

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