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Vigilance News

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Report of an adverse drug reaction (ADR)

Swissmedic recommends using the reporting portal (direct-entry or XML file upload).

Online reporting portal ElViS: www.swissmedic.ch/elvis

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Editorial

Dear Reader

There are various phases and methods in the life cycle of a medicinal product for recording potential risks.

When applying for the authorisation of a new medicinal product, the prospective authorisation holder has to submit documentation on efficacy, quality and drug safety. The benefit-risk profile is established by means of pharmacological testing and, in particular, by clinical trials during the authorisation phase.

However, since it is not possible to identify all risks, e.g. in certain patient groups and/or rare risks, during clinical trials, spontaneous reports on unexpected adverse reactions (ADR) after the authorisation of a medicinal product provide valuable evidence of a particular safety signal.

The recording of individual ADR reports and observational studies after widespread or long-term use play an important role. Known existing risks and the resulting risk minimisation measures should be checked at regular intervals, particularly in order to determine whether new findings might require a modification of the risk-benefit profile. This condition applies equally to new active substances, such as the antidotes for the substance class of direct oral anticoagulants (DOAC), and to familiar medicinal products that have been around for a long time. In this edition of Swissmedic Vigilance News we report on updates to isotretinoin and psychiatric disorders, the risk of overdose arising from confusion between amphotericin B formulations and on the toxicity profile of morclofone.

A periodic overview of the evaluation of any risks and signals is provided by the PSUR (Periodic Safety Update Report) for a medicinal product, which is prepared by the corresponding authorisation holder. An article on PSUR takes a closer look.

Current changes in drug safety are also shown by the 2017 annual statistics for pharmacovigilance and vaccinovigilance.

In vigilance in particular, it is extremely important to provide information to, and obtain feedback from, the affected patient groups and healthcare professionals. The "Guidelines for Quality Assurance in Transfusion Practice" were developed to protect patients from transfusion errors and resulting harm.

Monitoring on site in hospitals, as in other institutions, is essential to ensure that therapeutic products remain safe. This fact is highlighted by the guest article on quetiapine in retirement homes in Ticino prepared by the Regional Pharmacovigilance Centre (RPVC) in Ticino.

Another guest article, this time from the RPVC in Zurich, describes in detail the work of "RPVC collaboration", illustrated by a case report. The exchange of information and communication between healthcare professionals and patients, the RPVC and the national Pharmacovigilance Centre at Swissmedic and the authorisation holders are key factors in assessing the potential risks associated with a medicinal product.

The Editors

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Drug safety and signals

Medical monitoring of psychiatric disorders in patients taking oral isotretinoin for severe acne – Update

Introduction

During the clinical development of a drug, only the most common adverse reactions which are primarily attributable to the pharmacological mechanism can be identified.

Once a drug is launched on the market, the patients receiving the drug become more numerous and heterogeneous, potentially altering the safety profile of the drug.

Therefore, side effects of medicines observed in daily medical practice must be reported, in accordance with the current Therapeutic Products Act, so that safety data, which are still inevitably incomplete when the medicines are launched on the market, can be collated by Swissmedic.

The following patient history was taken from an adverse drug event report forwarded to Swissmedic by a regional pharmacovigilance centre. The aim of this article is to use this specific example to illustrate the potential risk of the onset of psychiatric side effects during oral treatment with isotretinoin.

Completed with due care and attention, this article is intended to alert healthcare professionals to the problem and provide them with useful information for patients suffering from severe acne and for whom oral treatment with isotretinoin is indicated.

Case narrative

The report concerns a 15-year-old male adolescent with a severe form of acne that failed to respond to standard therapeutic cycles, including systemic antibiotics and topical treatment. Treatment with oral isotretinoin was started in April 2016. The patient was not taking any other medication. Three weeks after starting the treatment, in May 2016, the patient attempted to commit suicide with his mother's painkillers, specifically ibuprofen tablets, although the total ingested dose is not known. He was admitted to the emergency department the same day and remained clinically stable. The laboratory test results showed no abnormalities. He was transferred to a psychiatric hospital a few days later. Although it was difficult to obtain a history from the patient because he was very withdrawn, he did not describe any previous psychiatric problems. Nor did the history taken from his parents reveal any relevant issues. The treatment with isotretinoin was discontinued in this young patient following his suicide attempt. The adolescent, who remained in hospital for several weeks, showed a slight improvement in mood, with the disappearance of suicidal thoughts, following the introduction, according to the history, of a quetiapine-based antidepressant in the form of tablets.

Discussion

Acne is a disabling facial skin disorder, particularly in its severe form that can have significant social and psychological consequences and also interfere with the activities of daily living.

The term "depression" covers a large and wide variety of possible meanings. The nuances range from sadness to despair, via inertia, lack of energy, with the possibility of black thoughts and even suicide.

Isotretinoin, the treatment of choice for severe cases of acne, is a systemic retinoid.

Although abundant medical literature is available on the subject of psychiatric disorders, the onset of depression and mood disorders, the causality of oral isotretinoin is still a matter of debate, particularly since

acne itself can lead to depressive symptoms. Indeed, the rate of depressive symptoms is higher in patients suffering from acne than in non-sufferers. The incidence of suicidal thoughts and mental health problems is higher in adolescents with severe acne than those with little or no acne. Consequently, the age of the target population has to be taken into account as a confounding factor.

It is acknowledged that the data available on the subject of psychiatric disorders and treatment with oral isotretinoin are associated with a significant number of limitations that make it difficult to establish a clear link of causality. Numerous spontaneous reports of adverse events involve confounding factors, such as the concomitant medication and/or a medical history of psychiatric disorders. Moreover, depending on the indication concerned, the epidemiological studies do not allow confounding factors to be ruled out. Nevertheless, the data presented in the form of case series, spontaneous reports of adverse drug events and the individual experience of patients are considered to be essential.

For the patient whose history is described in this article, a compatible chronology suggests that the causality of isotretinoin in this clinical picture may be rated as possible.

Moreover, the product information for orally administered isotretinoin-based drugs mention the rare onset of depression, aggravation of a pre-existing depression, mood alterations, anxiety, tendency to aggressiveness, and the very rare occurrence of suicide attempts and suicide. The corresponding information on these drugs can be found via the following link:
www.swissmedicinfo.ch.

Provided they are considered as judicious, Swissmedic broadly supports the application of the measures decided in Europe (1) in relation to products containing isotretinoin and, more generally, retinoid-based products.

Medical monitoring

In view of the target population and a possible underlying risk of psychiatric disorders, it is essential for healthcare professionals to warn their patients about the potential risk of psychiatric reactions associated with treatment with oral isotretinoin. In this context, particular attention should be paid to patients suffering from, or with a history of, depression. It is also essential to look out for signs and symptoms that are precursors of depression during the course of treatment and to monitor these patients. If a patient develops psychiatric problems, the treatment with oral isotretinoin may need to be stopped and, if necessary, appropriate treatment initiated.

Authors of the relevant literature usually report that the symptoms appear from a few days to a few weeks after the start of treatment and disappear following its termination. It is possible, however, that stopping the treatment with oral isotretinoin may not be sufficient to reduce the depressive symptoms, and that psychiatric or psychological measures may need to be put in place. Cases involving the reappearance of the symptoms when the treatment with oral isotretinoin was resumed have also been reported.

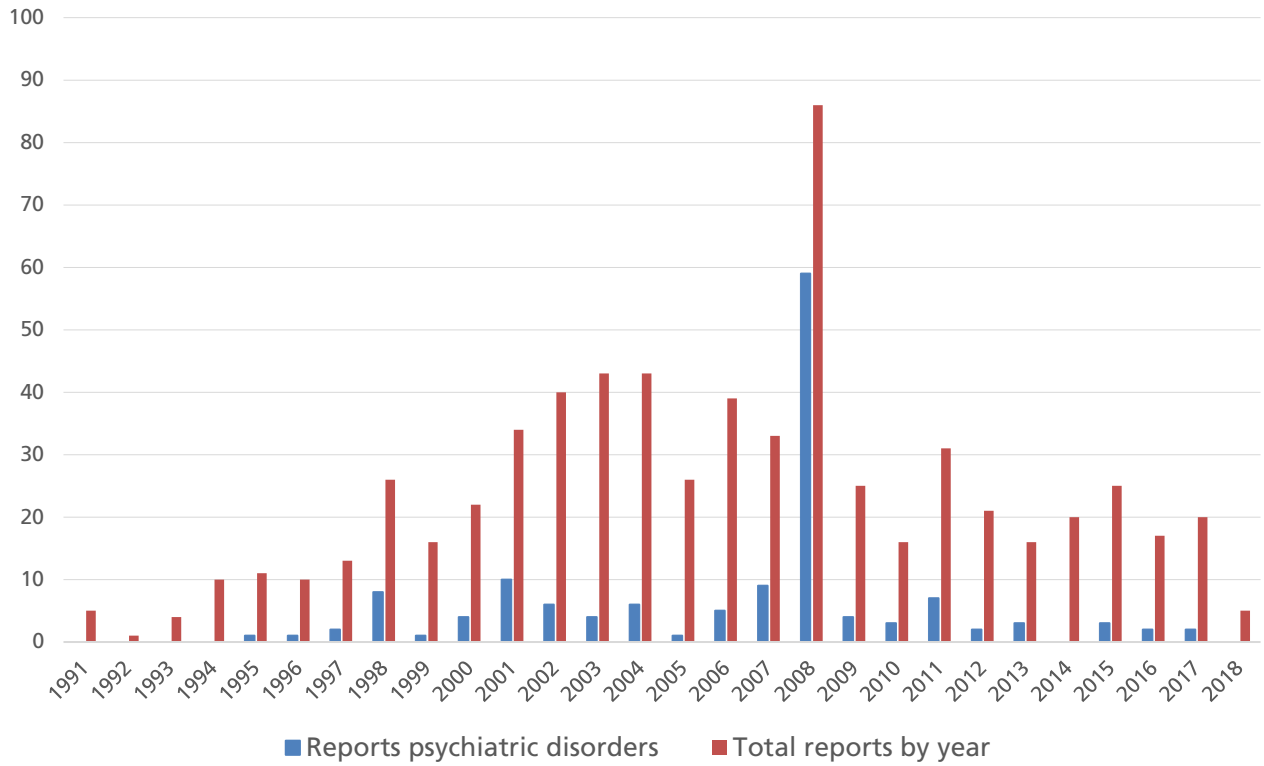
All sound reasons, therefore, to undertake close medical monitoring of patients treated with oral isotretinoin for the onset of depressive and suicidal thoughts. Ideally, the patient's own physician, as well as the dermatologist, should also be involved in this monitoring. Before treatment is started, the patients themselves should be warned of the risks associated with the treatment in general, and the risks of psychiatric side effects in particular.

Pharmacovigilance data in Switzerland on oral isotretinoin and psychiatric disorders

As at April 2018, Swissmedic had received a total of 658 reports since 1991, 143 of which concern psychiatric side effects. In these reports, oral isotretinoin was the suspected drug. In most cases the reports were submitted spontaneously. However, in 2008, following a media appeal by a patient organisation, an increased number of solicited reports of side effects were submitted to Swissmedic, as shown in figure 1. Disregarding that particular year, the reporting rate for psychiatric side effects is relatively stable, averaging 10 reports a year. Reports involving psychiatric problems represent around 20% of all the reports submitted to Swissmedic for oral isotretinoin.

It should be mentioned that the spontaneous reporting system does not allow the incidence of psychiatric side effects to be evaluated on the basis of the accumulated data (figure 1), nor does it allow any clear and definitive causal relationship to be established between the psychiatric symptoms and the administration of oral isotretinoin treatment.

Figure 1: Oral Isotretinoin – Swiss reports from 1991 until April 2018



Conclusion

Severe acne is far from being a trivial illness since it can have significant social and psychological consequences for the sufferers.

When these patients are treated with orally administered isotretinoin, it is important for healthcare professionals to be particularly vigilant in watching for possible signs of depression and/or similar symptoms so that they are detected at an early stage, followed by their close medical monitoring and, if necessary, the initiation of appropriate treatment.

Reporting adverse drug reactions

Swissmedic recommends the use of its specially designed online portal for reporting adverse drug reactions (ADR). The Electronic Vigilance System (ElViS) is used to report ADR. All the necessary details can be found at www.swissmedic.ch.

Literature

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Development, authorisation and safety of antidotes for the substance class of direct oral anticoagulants (DOAC) – Update

Since DOAC are being used with increasing frequency in clinical practice (1), the availability of an effective antidote is of considerable medical importance. The indications for these antidotes are life-threatening bleeds, emergency surgical procedures and elective procedures where the aim is to minimise the time needed to reverse the anticoagulation (1). We would now like to provide an overview of the current situation.

Praxbind® (active ingredient idarucizumab), the antidote for the factor IIa inhibitor Pradaxa® (active ingredient dabigatran), was authorised in Switzerland in July 2016. We reported previously on the authorisation studies in our Vigilance News, edition 16 (May 2016). Since these antidotes were authorised, Swissmedic has received a total of four reports (as at 12 June 2018) of adverse drug reactions that were classified as serious. These involved the cardiovascular system, including one thromboembolic event, and the nervous system. For all four reports the causal link with the administration of Praxbind® was rated as possible. At this point, it should be stated that, in order to be able to draw conclusions about the safety and tolerability of a drug, the underlying prescribing figures, which we do not have, need to be taken into account.

Until recently, no specific antidote to factor Xa inhibitor has been available anywhere in the world. In May 2018, this changed following the approval of **andexanet alfa** by the FDA (2). This antidote is capable of reversing the effect of direct (apixaban, edoxaban and rivaroxaban) and indirect (fondaparinux and low molecular weight heparins) factor Xa inhibitors (3). In a 2-arm phase III study, ANNEXA-A for apixaban and ANNEXA-R for rivaroxaban, the efficacy and safety of andexanet alfa were tested in 145 healthy volunteers aged between 50 and 75 in a placebo-controlled trial (3). In the test subjects treated with rivaroxaban, there was a median reduction of 97 % in factor Xa activity, while a median reduction of 92 % was observed in those treated with apixaban (4). No thrombotic events occurred in any of the study participants. Antibodies to factor Xa were not detected in any of the trial subjects. Nor were any neutralising antibodies to andexanet observed. Non-neutralising antibodies to andexanet were detected in 1 of 44 trial participants receiving placebo and in 17 of 101 study subjects who were prescribed andexanet. The fact that these antibodies disappeared again after 15–30 days suggests that andexanet is not associated with significant immunogenicity. D-dimers and prothrombin fragments were temporarily detected in increased amounts, but returned to normal levels after 24–72 hours (3).

Ciraparantag is a third antidote still under clinical trial. Structurally, it is a small, water-soluble, synthetic molecule. Compared to andexanet alfa, ciraparantag is supposed to be capable of additionally reversing the effect of factor IIa inhibitors (Pradaxa®), and thus serves as an antidote for all DOAC and for both unfractionated and low molecular weight heparins (1, 5). A phase I study investigated the efficacy and safety of ciraparantag (100–300 mg) after an initial dose of edoxaban (60 mg). The study enrolled 83 healthy volunteers between 18 and 65 years old, 67 of whom received ciraparantag and 16 placebo. A single dose of ciraparantag was able, after 10 minutes, to reverse the effect of edoxaban for 24 hours (5). No serious adverse drug reactions were observed, and no trial subject terminated the study prematurely due to such reactions. No significant blood count or ECG changes were registered. Procoagulant activity, measured by

specific changes in the D-dimers and prothrombin fragments 1 and 2, remained absent. Facial flushing was observed in a few subjects immediately after the intravenous administration of ciraparantag (5). A phase II study that investigated the efficacy and safety of ciraparantag after the administration of rivaroxaban is scheduled to end in July 2018 (6).

There is hope that many patients can now benefit from successful treatment with these agents, which have recently become available for routine clinical use in the treatment of life threatening complications caused by haemorrhage. For a detailed assessment of the safety profile of the antidotes mentioned beforehand, final results from ongoing clinical trials with ciraparantag must become available. Moreover, postmarketing data for all new antidotes over a prolonged period of time is crucial to elucidate their safety profile.

Literature

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Favourable acute toxicity profile of morclofone in children

Morclofone has been used since the 1980s as a centrally acting antitussive, mainly as a syrup in children with a dry non-productive cough. The standard single dose is 50 mg in children up to 3 years old and 150 mg in older children.

A study group at *Tox Info Suisse* retrospectively analysed 29 cases of acute intoxication with morclofone in children that were reported to *Tox Info Suisse* between January 1997 and June 2016. These reports involved 10 girls and 19 boys with an average age of 3 years (1.6–6 years).

Eight children were asymptomatic and 21 only had mild symptoms. The administered dose was known in 21 cases and ranged from 31 to 171 mg/kg body weight (mean: 64 mg/kg body weight), which corresponds to between 4 and 36 times the single therapeutic dose. The observed symptoms of vomiting (n=15), nausea (n=4), abdominal pain (n=4), drowsiness (n=6), ataxia (n=1) and tachycardia (n=1) were of short duration and regressed spontaneously. In 9 patients, gastrointestinal decontamination was performed with a single dose of activated charcoal, producing mild symptoms in 7 patients.

Conclusion: Morclofone has a favourable acute toxicity profile, and significant overdoses of up to 171 mg/kg body weight resulted only in mild symptoms. Therefore, the monitoring of patients at home, without gastrointestinal decontamination, seems reasonable following the administration of doses below 171 mg/kg body weight.

Literature

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Clinical Toxicology 55.5 (2017): 460 of the 37th International Congress of the European Association of Poisons Centres and Clinical Toxicologists

An interesting case: Unexpected cause of shock in a patient with tachycardiomyopathy

A study group at Basel University Hospital has reported on a 76-year-old male patient who had been referred to the emergency department by his GP (general practitioner) due to exercise-induced dyspnoea (NYHA grade II) lasting for 10 days. He took no medication and had not received any medical treatment for the past 25 years.

His GP noted the presence of tachycardia (140 bpm) and hypertension (146/107 mmHg). The jugular veins were slightly distended, and blood gas analysis and respiratory rate were normal.

Since an ECG showed atrial fibrillation, the patient was given 1 mg metoprolol intravenously every 5 minutes to control his heart rate. After the administration of 3 mg of metoprolol, the patient developed severe orthopnoea. Blood pressure, heart and respiratory rates (up to 50/min) rose substantially, and the jugular veins were markedly distended. The ultrasound showed signs of right heart failure, while ruling out a pneumothorax and a pericardial tamponade. His blood pressure subsequently dropped to the point where it was no longer measurable, and his extremities were cold. The treating physicians assumed that the shock had been caused by pulmonary embolism and administered 10 mg rt-PA (recombinant tissue-type plasminogen activator), which produced an improvement in the patient's clinical condition. A pulmonary embolism was subsequently ruled out by a CT scan. Echocardiography showed tachycardiomyopathy of unknown origin, with a left ventricular ejection fraction of only 17 %.

Conclusion: Even low doses of a beta blocker can provoke shock in patients with tachycardiomyopathy and a very low left ventricular ejection fraction. The authors assumed that the clinical improvement was attributable to the short half-life of the intravenous metoprolol or a hypothetical interaction with rt-PA that diminished the effect of metoprolol.

This literature report was submitted to us by a pharmaceutical company that distributes metoprolol in Switzerland. Like traditional spontaneous reports, Swissmedic continuously assesses literature reports and reviews them in particular for their signal impact.

Literature

Spiegel R, Haefelfinger R, Sutter R, Bingisser R. An unexpected cause of shock in a patient with tachycardiomyopathy. Critical Care Medicine. 2018;46(1):143. DOI: 10.1097/01.ccm.0000528341.94497.d1.

Confusion between amphotericin B formulations: Risk of overdose

Amphotericin B

Amphotericin B is a polyene antibiotic isolated from Streptomyces nodosus. Its mechanism of action is based on the reaction with the sterols in the cell membranes of sensitive fungi, thereby disrupting the membrane function and partially damaging the membrane structure. Amphotericin B is indicated for the treatment of patients with invasive fungal infections. The most frequent side effects include hypersensitivity reactions, inflammation of the tongue, nausea, vomiting, diarrhoea and skin rashes; the most problematic feature is the pronounced nephrotoxic potential of the substance (1, 2).

Since amphotericin B is hardly absorbed at all from the gastrointestinal tract, amphotericin B must be administered parenterally for the treatment of systemic fungal infections. Amphotericin B is therefore marketed in non-liposomal and liposomal forms.

Despite the fact that both contain the same active substance and identical antimycotic spectrum of action, the dosages of amphotericin B are product-specific and must not be applied to other medicines containing amphotericin B: For conventional (non-liposomal) amphotericin B, the maximum daily dose of 1.5 mg/kg body weight should not be exceeded (1); for liposomal amphotericin B, on the other hand, the maximum dosage is 3 to 6 mg/kg/day (2).

Reports of mix-ups between medicines containing amphotericin B and liposomal amphotericin B, with serious adverse events, including cases with a fatal outcome, are described in the literature (3, 4).

DHPC in France

On 22 May 2017, Bristol-Myers Squibb (BMS), Gilead Sciences and Acino Pharma, in consultation with the French authority ANSM *(Agence nationale de sécurité du médicament et des produits de santé)*, distributed a *Direct Healthcare Professional Communication (DHPC)* in France concerning the risk of overdosage of amphotericin B (5). Mix-ups had occurred between non-liposomal and liposomal parenteral forms. Since the preparation of the infusion solutions, the dosages and the rate and duration of administration differ between the formulations, there is a risk of drug errors. These errors mainly involve the administration of Fungizone® and the possibility of amphotericin B overdose with potentially serious cardiac and renal damage as a result of a mix-up.

Situation in Switzerland

Current risk-minimising measures

Following the publication of the DHPC in France, marketing authorisation holders and the competent drug regulatory authorities in all countries where differing amphotericin B formulations are marketed are investigating whether changes need to be made to the relevant summaries of product characteristics (SPC) and whether the risks need to be communicated to corresponding healthcare professionals via a DHPC, as in France.

The following parenteral formulations of amphotericin B are currently available on the market in Switzerland: Bristol-Myers Squibb SA distributes Fungizone® (non-liposomal amphotericin B), the conventional form based on deoxycholate amphotericin B. Gilead Sciences Switzerland Sàrl distributes AmBisome®, which contains liposome-bound amphotericin B.

In order to highlight the risk of confusion, the Swiss Information for healthcare professionals for Fungizone® already contains the following warnings:

"Multiple parenteral forms of the active substance amphotericin B exist. Please check the preparation name and dosage before use. Caution during Fungizone dosing: Under no circumstances should a total daily dose of 1.5 mg/kg body weight be exceeded. An overdose can result in potentially fatal cardiac or respiratory arrest. "

In view of the higher permitted dosage of AmBisome®, the problem of overdose arises when Fungizone® is administered at the AmBisome® dosage. By contrast, using AmBisome® instead of Fungizone® can lead to underdosage. The product information for AmBisome® explicitly refers to this in the dosage section:

"Since the dosage of AmBisome is product-specific it may NOT be applied to other medicines containing amphotericin B. "

Case reports

The product information texts and packaging elements of Fungizone® and AmBisome® already include sufficient references to the risk of confusion and the associated risk of overdose. Nevertheless, there are two known cases in Switzerland where the dosage recommendations for liposomal amphotericin B were applied to the administration of non-liposomal amphotericin B.

In 2015, a 39-year-old woman received an overdose with non-liposomal amphotericin B, resulting in multiple life-threatening events (ventricular tachycardia, cardiac arrest, hyperkalaemia, acute kidney injury, liver cell damage, haemolytic anaemia and thrombocytopenia). By the time of the report, the patient had recovered from the cardiac arrest and hyperkalaemia, but not from the acute liver damage, haemolytic anaemia or thrombocytopenia.

In a case from Switzerland published in 2016, an immunosuppressed 9-year-old boy recovering from a bone marrow transplant suffered diarrhoea, vomiting, acute renal failure, fever and shivering as a result of an amphotericin B overdose. The patient had been given Fungizone® instead of the prescribed intravenous AmBisome®. Consequently, the patient had received ten times the recommended dose. After rehospitalisation and several weeks of treatment, the child recovered completely (6).

Conclusion

The purpose of a *Direct Healthcare Professional Communication (DHPC)*, formerly termed a *Dear Doctor Letter (DDL),* is to inform health professionals about important, newly identified drug risks – particularly if these are unexpected – and corresponding risk minimisation measures, with a view to prompting a relevant change in approach. In this case, the product information texts and packaging elements for the drugs concerned already contained sufficient references to the risk of confusion and thus the associated risk of overdose. The risk of confusion is known in professional circles and published in the literature. The information in these texts should already have been taken into account by the treating professionals. In this specific case, Swissmedic is therefore not sending out a DHPC, but would like to remind professionals of the risk of mix-ups between non-liposomal and liposomal parenteral forms of amphotericin B. Since the dosage of amphotericin B preparations is product-specific it may not be applied to other medicines containing amphotericin B. In view of the parallel use of different amphotericin B solutions in hospitals, measures should be taken to make it impossible, or at least more difficult, to confuse these preparations.

Literature

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Guest article

Pharmacovigilance, drug safety and knowledge transfer: The Swiss RPVC Approach

Stefan Weiler (1), (2)
as part of the Swiss RPVC collaboration, consisting of the Regional Pharmacovigilance Centres in Geneva, Lausanne, Bern, Basel, Ticino, Zurich

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(2) Tox Info Suisse, Associate Institute of the University of Zurich

"The doctor prescribes medicines about which he knows little to patients about whom he knows even less."

Ahmed Wilfried Waba, WHO, 1984

Diagnosis: "Adverse Drug Reaction"

Adverse drug reactions (ADR) are medication-induced conditions whose symptoms mimic those that can themselves be caused by illnesses. Headache, dizziness, diarrhoea or vomiting are temporary and reversible symptoms that can occur as part of a viral infection for example. By contrast, other conditions such as carcinogenesis are protracted processes that can be promoted by various factors. It is often difficult to separate out the various aetiologies and weigh up the risks factors on both sides. Physicians are trained to diagnose, define and "successfully" treat diseases. Medicines are developed and manufactured to cure patients, or at least improve their condition. But the other side of the pharmacological coin can soon be forgotten.

"If it is claimed that a substance has no side effects, then there is a strong suspicion that it does not have any principal effect."

Gustav Kuschinsky, 1904-1992

Diagnostic investigations of adverse reactions are usually based on the exclusion of other causes. Laboratory markers that clearly diagnose an adverse reaction are not present in many cases. Like other tests, such diagnostic methods – e.g. HIT antibody assay – possess a sensitivity and specificity that allows for the possibility of false-positive and false-negative results. So it's not so easy to pinpoint the culprit (the suspected drug)!

And this is what pharmacovigilance is all about: Criteria such as latency period, course of the reaction, frequency, severity, reproducibility, mechanism or nature of the adverse reaction strengthen the diagnosis of a drug-induced illness.

Descending from the ivory tower: Knowledge transfer in pharmacovigilance

Acting on behalf of Swissmedic, the Regional Pharmacovigilance Centres (RPVC) are responsible in Switzerland for receiving and processing ADR reports from healthcare professionals, patients and consumers. The RPVC are usually linked with the Clinical Pharmacology and Toxicology departments of the university hospitals. Clinical pharmacology is a medically and scientifically established discipline in Switzerland that addresses the rational and safe use of pharmaceutical products in humans. Drug safety and pharmacovigilance are core areas of clinical pharmacology and toxicology, where you will find experts who help record, prioritise and process ADR. They support the detection of potential signals and the flow of information to the primary reporter, the authorities and, under certain circumstances, to the public as well. On the other hand, those who

frequently report ADR are patients who are, or were, themselves affected or professionals who use or dispense therapeutic products on a commercial basis. The latter are also obliged by the Swiss Federal Act on Medicinal Products and Medical Devices to report serious or previously unknown ADR. But numerous wide-ranging reasons are presented for nevertheless not reporting ADR. These include:

- erroneous assumptions that only safe medicines are on the market and that an ADR is therefore not possible.
- fear of becoming entangled in a legal dispute or of losing the patient's trust.
- subjective feelings of guilt that a medicine may have harmed more than helped.
- personal ambition to collect and publish case reports *(publish or perish)*.
- unwillingness to report a drug-induced reaction solely on the basis of a suspicion without a definite connection, or simply the lack of time and interest: *"The bureaucracy and completion of forms won't help improve my patient's situation."* Primary reporters are also not reimbursed for their time and intellectual input.

Many of these possible reasons involve an active reluctance to report an ADR. However, an unintentional reticence should not be overlooked: the lack of knowledge concerning pharmacological principles, pathophysiological explanations of dose-dependent effects and side effects, the fundamental inclusion of an ADR in the differential diagnosis during the investigation of symptoms. In 2017 in Switzerland, 36,900 physicians (32,586 full-time equivalents) were employed in a wide variety of fields (SMF 2018; 99 (13-14): 408-413). 51% of these work in the outpatient environment and 47% in the inpatient sector. Many use medicines as treatments – but how many of them possess a sound knowledge of pharmacological principles that goes beyond the respective indication, dosage and certain warnings?

So in 2016 all RPVC in Switzerland and *Tox Info Suisse* – the National Poisons Centre responsible for all questions and information related to overdoses – merged in a collaborative venture with the aim to focus people's attention on drug safety (see SMF 2016;16(37):757–763). Together with the Swissmedic National Pharmacovigilance Centre, the decision was taken to provide regular educational articles consisting of clinically relevant pharmacovigilance cases with a subsequent pharmacological or toxicological explanation. The medium chosen for this purpose was the official training organ of the Swiss Medical Association (FMH), i.e. the most widely read medical education journal in Switzerland. The "Swiss Medical Forum" appears weekly in German and French, with a total circulation of 38,110 copies in Switzerland. This ensures that issues of relevance to drug safety are given the widest possible dissemination. The existing pharmacological and toxicological expertise is provided to refresh drug-related knowledge, place it in a clinical context and present it concisely and succinctly using case-based analyses. The higher-level aim is to improve drug safety in Switzerland, maintain standards of prescribing and, last but not least, increase national patient safety.

Decant and carafe: Choosing the right vessel

Every day physicians take countless histories. They ask questions about current symptoms, previous illnesses, familial predisposition, work, risk factors and many other matters. So physicians listen to countless histories from their patients. But they also like to read patient (hi)stories, since they are much more familiar with them from their daily clinical work than with statistics or methodological indicators. The RPVC collaboration therefore

agreed on the format of a brief case description of the ADR: How old? How serious? What medicine was used, why and at what dosage? What was the latency period prior to what symptoms? What was investigated in the differential diagnosis? What happened then? Were countermeasures initiated? Were there any predisposing factors, such as allergies, renal impairment or liver disease?

Subsequent to the case report, a clinically-based pharmacological or toxicological assessment of the case is provided, in which classical sources are presented as helpful guidance. The assessment is based on the Swiss product information of the drug which, in contrast with many other countries, is freely available on the Internet, at www.swissmedicinfo.ch. Depending on the clinical case and the ADR, drug-drug interactions, drug-herb interactions, drug-food interactions and drug-disease interactions are also discussed. A failure to recognise the ADR can result in prescribing cascades. Risk factors for the respective ADR – e.g. advanced age, poor compliance, substances with a narrow therapeutic range, multimorbidity, hepatic/renal impairment and polypharmacy – are included in the analysis. These factors may be associated with an increased risk of altered pharmacodynamics in terms of an increased response, pharmacokinetic and pharmacodynamic interactions or the patient's limited compensation mechanisms. Other medical causes that may not yet have been excluded are also presented, together with case-related evidence and the pathophysiological plausibility for the respective reaction. The question as to whether the reaction could have been avoided is often posed. Were potential sources of error present, such as system-related risk factors with transcription errors, mix-ups, incorrect administration or multiple prescribing? Are there medical/pharmacological alternatives to the drug that may have caused the reaction?

An example of such a case description with subsequent assessment is shown below.

The clinical case: Acute hepatitis during the administration of amoxicillin/clavulanic acid

The 58-year-old male patient presented at the hospital with severely itching jaundice and general malaise. Following a yellow fever vaccination (3 months previously), he had travelled to Tanzania, where he had developed swallowing difficulties two weeks ago. He also suffered from a blocked nose and earache. As treatment he took Triofan® (carbocisteine, xylometazoline) nasal spray, Mebucaine® f (tyrothricin, cetylpyridinium, oxybuprocaine), Voltaren® Dolo liquid Caps 12.5mg (diclofenac) and two sachets of Neo-Citran® (phenylephrine, pheniramine, ascorbic acid, paracetamol). Since the symptoms continued to deteriorate, he returned home prematurely after a few days and visited his physician, who diagnosed an upper respiratory tract infection and bilateral otitis media. The C-reactive protein level (CRP) was 48 mg/L (normal: <5 mg/L). The streptococcal rapid test was negative, and the EBV serology did not show any evidence of an acute infection. Antibiotic treatment was initiated with Co-Amoxi Mepha® (amoxicillin/clavulanic acid) 1g twice daily. He also took Spiricort® (prednisolone) 5mg, Neo Spirig® HC nasal spray (xylometazoline) and Olfen® 50mg (diclofenac) to reduce swelling. While the patient's symptoms had improved on the antibiotic treatment that he had been taking up until a week previously, his urine turned a dark beer-colour for the first time after a few days and he was sleeping poorly. Two days before presenting at the hospital, the patient noticed itching for the first time. On the following morning he became increasingly listless and had a diminished appetite.

During the previous week he had lost 2 kg in weight despite following a normal diet.

On admission to hospital, the patient then passed a whitish stool for the first time. Laboratory tests showed elevated liver parameters:

	Reference	Admission	+4 days	+8 days	+15 days	+26 days
ALT	<50 U/l	395	253	330	81	22
AST	<50 U/l	120	120	137	25	22
GGT	<61 U/l	494	360	246	126	65
ALP	40-129 U/l	403	488	329	170	98
Bilirubin (total)	<21µmol/l	72	37.5	19.4	14.1	13.8

Table 1: Course of liver function parameters in relation to the day of admission. ALT alanine aminotransferase, AST aspartate aminotransferase, GGT γ-glutamyl transferase, ALP alkaline phosphatase

The hepatitis serologies and the HIV, CMV, HSV, EBV, syphilis screening tests and the malaria rapid test were negative. The INR was 1.2, albumin was normal, the eGFR was 79ml/min/1.73 m^2.

On the abdominal ultrasound scan the liver appeared normal apart from a known haemangioma in the left lobe. Acute hepatitis was diagnosed on the basis of the laboratory results and the patient's symptoms (table 1). Already by the 5th day after admission, i.e. 11 days after the antibiotic had been discontinued, the pruritus had started to regress and the patient's stools were less white. However, the patient's urine remained a dark colour. The liver enzymes subsequently also regressed: 32 days after discontinuation of the antibiotic, the transaminase levels, bilirubin and ALP had all returned to the reference range.

The patient had suffered an episode of acute cholestatic hepatitis three years previously. At that time a cefuroxime-induced cause had been suspected in the aetiology. The patient's mother had suffered from jaundice in the past.

Clinical pharmacological / toxicological assessment

Drug-induced liver injuries (DILI) are predominantly idiosyncratic and do not show dose-dependency for the substances used – comparable to a hypersensitivity reaction, e.g. with interstitial nephritis. Dose-dependent exceptions for DILI apply in the case of a hepatotoxic effect due to the paracetamol metabolite NAPQI. DILI is currently an exclusion diagnosis, since no specific biomarkers are yet available (Weiler et al. 2015). Three categories are differentiated: hepatocellular, cholestatic or mixed liver injury. The injury pattern can be determined using the ratio R, where R = ALT/ULN_ALT/ALP/ULN_ALP, according to the enzyme configuration for

alanine aminotransferase and alkaline phosphatase. An R ≥ 5 is indicative of a hepatocellular injury, which often occurs in paracetamol poisoning, with anti-infective agents such as ciprofloxacin, isoniazid, antihypertensive substances such as lisinopril, or statins. Amoxicillin/clavulanic acid, erythromycin, steroids, oral contraceptives, clopidogrel, irbesartan and tricyclic antidepressants often lead to a cholestatic pattern (R ≤ 2). Mixed forms of hepatic injury (R >2 and <5) are found, for example, during treatment with nitrofurantoin, anabolic steroids, verapamil, enalapril, carbamazepine and phenytoin, but also erythromycin or amoxicillin/clavulanic acid. In this case, there was a mixed pattern on admission (on admission R=2.5) with an elevated bilirubin level. In the differential diagnosis, serology tests and ultrasound showed no evidence of any other possible causes in this case.

The following relevant adverse drug reactions are described in the Swiss Information for healthcare professionals for amoxicillin/clavulanic acid:

"Co-Amoxi® Mepha:

Uncommon: Moderate rises in the AST and/or ALT levels, temporary rise in lactate dehydrogenase and alkaline phosphatase levels.

Rare: Hepatitis and cholestatic jaundice."

Treatment with diclofenac and paracetamol usually results in purely hepatocellular cell damage, whereas beta-lactam antibiotics such as amoxicillin/clavulanic acid show a predominantly mixed to cholestatic pattern (Hussaini et al. 2014).

The incidence of this adverse reaction to amoxicillin/clavulanic acid is approx. five times higher than for amoxicillin alone, and is estimated to occur in approx. 1 in 2,500 prescriptions. According to "NIDDK Livertox", the combination of amoxicillin/clavulanic acid is currently the most frequent cause of DILI in most large case series in Europe and the USA. The symptomatic onset typically involves the appearance of fatigue, mild fever, nausea and abdominal pain, followed by pruritus and jaundice. The latency period ranges from a few days to eight weeks after the start of treatment, i.e. usually after the cessation of the antibiotic treatment. While the mechanism for the liver damage is not known, an immunoallergic origin is suspected. Fever, joint pains, skin rash and eosinophilia are described as accompanying signs and symptoms. The risk appears to be slightly increased with a prolonged treatment period, age ≥ 65 years and in men. An HLA association is suspected (DRB1*15:01-DRB5*01:01-DQB1*06:02). The symptoms and findings (particularly elevated ALP and GGT levels) are usually reversible – as in the case described above (approx. 1 month after discontinuation of the antibiotic).

Although a temporal relationship with the Triofan®, Mebucain® f, Voltaren® Dolo, NeoCitran®, Spiricort®, Neo Spirig® HC and Olfen® cannot formally be ruled out, the patient had already suffered an episode of cholestatic hepatitis a good two years previously, when cefuroxime had been suspected as the cause. As a cephalosporin, and like the broad-spectrum penicillin amoxicillin/clavulanic acid, cefuroxime is also a beta-lactam antibiotic with a similar structure (Weiler & Corti 2014). Köklü and colleagues described a 23-year-old male patient who experienced cholestatic hepatitis after taking cefuroxime. The same patient had previously suffered an episode of cholestatic hepatitis while taking ampicillin. A cross-reactivity with an idiosyncratic reaction due to toxic metabolites was suspected in this case.

Given the temporal relationship, the typical picture of liver injury, the very good documentation in the literature and the previous

episode of hepatitis while taking the beta-lactam cefuroxime, the causality between the acute hepatitis and amoxicillin/clavulanic acid was formally rated as probable according to the CIOMS/WHO criteria.

The following measures were recommended: the issuing of an allergy card for beta-lactams, the alternative use of other antibiotic groups with no structural similarity, such as macrolides or fluoroquinolones, or the administration of beta-lactams only in life-threatening situations.

The Swiss RPVC Approach: Lessons for the future

The Swiss spontaneous reporting system for postmarketing safety monitoring enables medical professionals to report ADR to pharmacovigilance centres. Such systems allow physicians and pharmacists to become directly involved in the safety monitoring system and can help them in their duty to report reactions as required by the Swiss Federal Act on Medicinal Products and Medical Devices. Detailed information on relevant symptoms, diagnostic results, history details, concomitant medication and the subsequent clinical outcome of the ADR can be reported using these systems. This detailed information directly from the healthcare professional is particularly important for ADR that are serious or rare, and is also an essential component of the postmarketing pharmacovigilance system. The remit is very broad and encompasses all medicines that are used by the general public (table 2).

ADR	Medicine(s)	Reference	URL
Pancytopenia	Methotrexate	Schweiz Med Forum 2017;17(2829):594-596	https://medicalforum.ch/de/article/doi/smf.2017.03013/
Type II thrombocytopenia	Heparin	Schweiz Med Forum 2017;17(33):676-677	https://medicalforum.ch/de/article/doi/smf.2017.03036/
Perforated duodenal ulcer	Naproxen	Schweiz Med Forum 2017;17(36):756-759	https://medicalforum.ch/de/article/doi/smf.2017.03053/
Overdose after administration error	Buprenorphine	Schweiz Med Forum 2017;17(38):806-807	https://medicalforum.ch/de/article/doi/smf.2017.03055/
Bilateral achillodynia	Ciprofloxacin	Schweiz Med Forum 2018;18(06):123-124	https://medicalforum.ch/de/article/doi/smf.2018.03201/
Hemiballism	Cinnarizine	Schweiz Med Forum 2018;18(07):145-146	https://medicalforum.ch/de/article/doi/smf.2018.03198/
Restlessness, malaise and tremors in opioid withdrawal syndrome	Nalmefene	Schweiz Med Forum 2018;18(1314):295-296	https://medicalforum.ch/de/article/doi/smf.2018.03206/
Palpitations	Xylometazoline	Schweiz Med Forum 2018;18(1920):415-416	https://medicalforum.ch/de/article/doi/smf.2018.03255/
Extrapyramidal symptoms	Metoclopramide	Schweiz Med Forum 2018;18(10):220-221	https://medicalforum.ch/de/article/doi/smf.2018.03204/
Weakness, bradycardia, visual disturbance, hyperkalemia	Digoxin	Schweiz Med Forum 2018;18(22):460-462	https://medicalforum.ch/de/article/doi/smf.2018.03200/
Haemorrhage and Vitamin-K deficiency	Orlistat	Swiss Med Forum. 2018;18(23):479-481	https://medicalforum.ch/de/article/doi/smf.2018.03293/
Acute liver failure	Repeated paracetamol	Schweiz Med Forum 2018;18(21):437-439	https://medicalforum.ch/de/article/doi/smf.2018.03257/

Table 2: Examples of adverse drug reactions with corresponding medicines

Despite the advances made in the field of biomarkers or pharmacogenetics and pharmacogenomics, a comprehensive history of previous intolerances will definitely continue to be essential in future. So the right questions will still need to be asked even when specific tests and biomarkers for detecting adverse reactions become available.

The transfer of knowledge from the expert to the prescribing physician with a basic pharmacological understanding of side effects intends to strengthen the system, while the knowledge from routine clinical practice should help improve the detection of safety signals. The future will show how the development of a wide variety of communication resources can contribute towards the optimisation of medicines and patient safety, not to mention the benefit-risk assessment both in the individual and in large parts of the population.

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Author's note

The author is a also member of the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA). The aspects and the views expressed here are the author's personal views, and may not be understood or quoted as being made on behalf of the PRAC or reflecting the position of the PRAC. The author declares that there are no conflicts of interest.

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Consumption, off-label use and prescribers of quetiapine in retirement homes in Ticino

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Introduction

In recent years, the use of second-generation neuroleptic agents, also known as atypical neuroleptics, has been steadily on the rise in the western world, including in connection with off-label prescriptions – i.e. outside the officially authorised indications (treatment of schizophrenia and manic-depressive episodes in bipolar disorder) and particularly for the treatment of agitation, dementia, insomnia, personality disorders, generalised anxiety disorders, obsessive compulsive disorders, eating disorders, post-traumatic stress disorders and substance abuse. In this context, quetiapine is one of the atypical neuroleptics that is most frequently prescribed for off-label use, particularly at low dosages (1–6). This is especially relevant in the elderly, since the risk of receiving inappropriate medication is higher in this group in view of their numerous co-morbidities and the associated polypharmacy. Such cases have been observed particularly in elderly residents in retirement homes (2–3, 5, 7–11).

Quetiapine is not without side effects, and its use in the elderly, even at low doses, is associated with numerous serious adverse reactions, including hip fractures, orthostatic hypotension or bouts of pneumonia (2–3, 5–8, 12). The risk of drug interactions is also increased due to the polypharmacy that is frequently associated with these patients (7, 11, 13). Various studies have shown a 1–2 % increase in the mortality rate in elderly dementia patients treated with neuroleptics, even at low dosages, which prompted the US Food and Drug Administration (FDA) to issue a warning as early as 2005 (2–5, 7–8). Moreover, hardly any evidence confirming efficacy is available for the various off-label indications of quetiapine. For example, various studies have shown not only that quetiapine is no better than placebo – from either the statistical or clinical standpoint – in treating agitation or psychoses in elderly dementia sufferers (15–20), but also that the long-term use of quetiapine is associated with significant cognitive and functional deficits in elderly dementia patients compared to groups of comparable individuals that were not treated with quetiapine (15–17).

The problem of the too frequent prescribing of quetiapine and its off-label use is not only discussed extensively at international level, but is also important at the local level: Specifically, a report produced in 2011 on the state of health of elderly residents in retirement homes in Ticino showed that neuroleptics are prescribed much more frequently, on average, in Ticino than in Switzerland as a whole (14). The widespread off-label use of this drug in our canton has also been confirmed for hospitals: A project undertaken in 2016 at the larger hospitals in the Cantonal Hospital Network (Ente Ospedaliero Cantonale, EOC) revealed that 54.6 % of the investigated prescriptions for quetiapine were for non-officially authorised indications.

Objective

The aim of this project was to ascertain the situation regarding the use of quetiapine in retirement homes in Ticino by analysing data on the consumption and, in particular, on the indications and the prescribers.

Method

The collected and fully anonymised data were provided by the pharmacies in 15 retirement homes in Ticino. The following was recorded: treatments with quetiapine in relation to the overall number of retirement home residents, the prescribed dosage and posology (baseline and/or as-needed), the indication, the prescriber and demographic data.

The study covered the period from September to November 2016 and included all residents in the retirement homes who received a baseline and/or as-needed treatment with quetiapine on the key date of the data survey. The statistical analysis of the frequency of off-label treatments with quetiapine according to prescriber (general practitioner or specialist) was carried out with a 2x2 contingency table with calculation of the odds ratio, a confidence interval of 95 % and determination of the p value by Fisher's exact test.

Results

The data from 1,173 retirement home residents were analysed. 379 (32.3 %) of these patients were treated with quetiapine, and there were a total of 476 prescriptions (baseline and/or as-needed). 73.4 % (n=278) of the patients treated with quetiapine were women, and the average age was 85.8 years. 58.8 % (n=223) of the retirement home residents received quetiapine as baseline treatment, 15.6 % (n=59) on an as-needed basis only and 25.6 % (n=97) both as baseline and as-needed medication.

In the majority of the prescriptions (87.8 %, n=418), the dosage of quetiapine was less than 100 mg/day; the most commonly prescribed dosages were less than 25 mg/day (53.6 %, n=255). Dosages of over 200 mg/day, as recommended for the indications officially recognised by Swissmedic, accounted for 4.4 % (n=21) of the prescriptions (see figure 1).

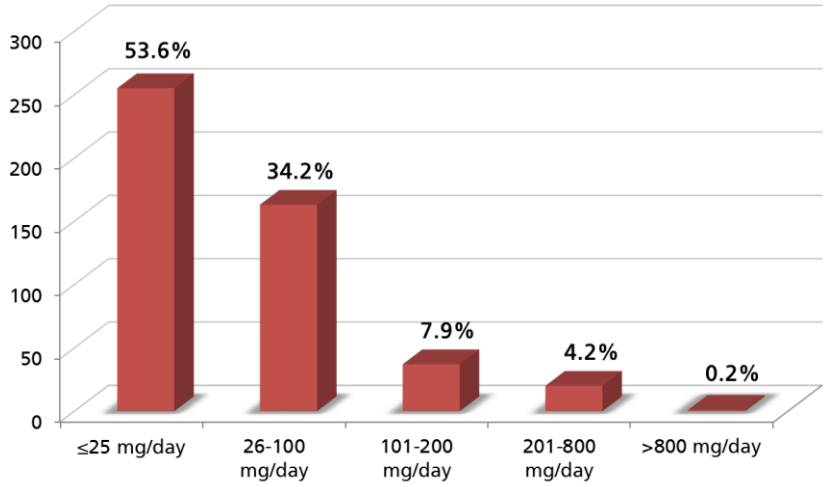

Figure 1: Prescribed daily dose for quetiapine (N_{tot}=476), as-needed and baseline

As far as the indications are concerned, quetiapine was prescribed for officially authorised indications (on-label) in 4.8 % (n=23) of cases, whereas an off-label indication was involved in 94.3 % (n=449) of cases, particularly for the treatment of agitation (31.3 %, n=149), dementia (30.3 %, n=144), anxiety states (15.3 %, n=73), depression (12 %, n=57), insomnia (6.7 %, n=32) and episodes

of delirium (4 %, n=19). Smaller percentages resulted for other indications, including substance abuse, post-traumatic stress disorders or obsessive compulsive disorders (see figure 2).

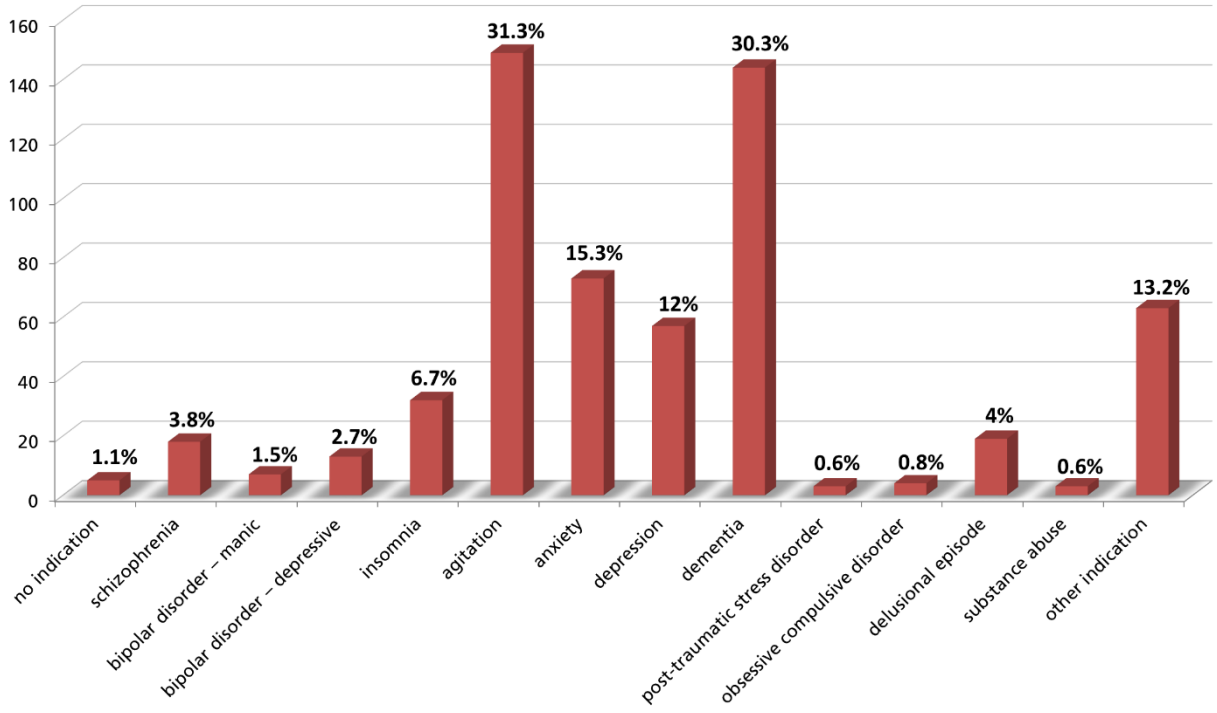

Figure 2: Indications for quetiapine (N_{tot}=476)

As far as the prescribers are concerned, quetiapine was prescribed by general practitioners (family doctors or physicians working for the retirement homes) in 75 % (n=295) of cases, and by specialists (in geriatrics or psychiatry) in 13.2 % (n=52) of cases. In 11.7 % (n=46) of cases, the prescribers could not be determined because the corresponding information was missing, or because the drug had been prescribed during a previous hospital stay (see figure 3). A statistically significant link emerged between off-label prescribing of quetiapine and prescribing by general practitioners (OR 3.01; 95 % CI, 1.09–8.31; p=0.039).

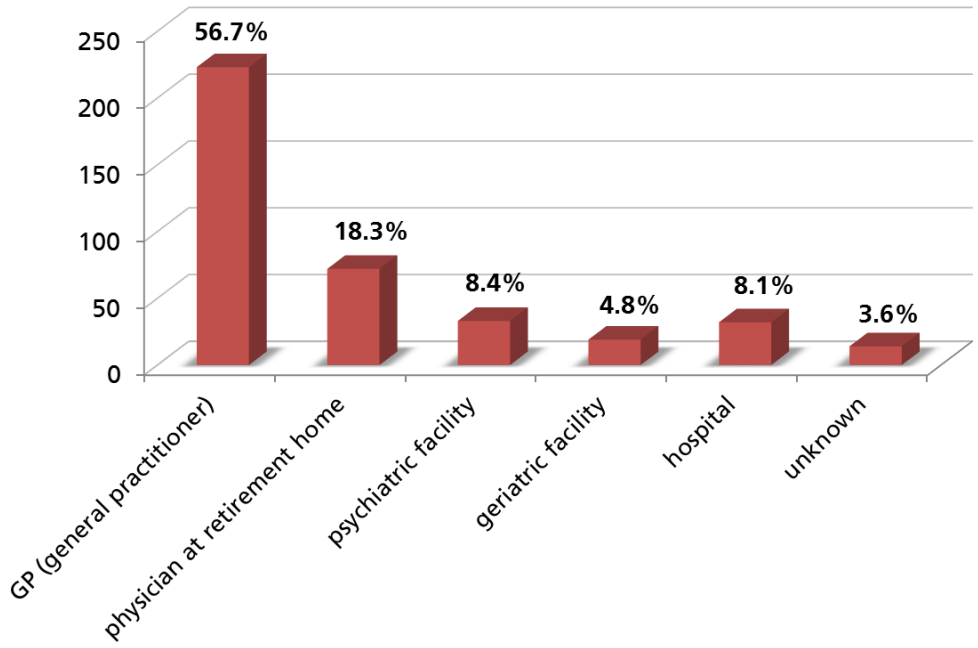

Figure 3: Prescriber of quetiapine (N_{tot}=476)

Conclusion

The results confirm that quetiapine is widely used in retirement homes in Ticino: A third of the residents are treated with this medicine. Quetiapine was administered mainly at low dosages for an off-label indication, particularly for the treatment of agitation and dementia.

A statistically significant link also emerged between the off-label prescribing of quetiapine and the prescribing by general practitioners compared to specialists.

Efforts to raise awareness among general practitioners about the off-label use of quetiapine and, possibly, the increased involvement of specialists in the prescribing of drugs in retirement homes may help reduce the frequency of prescription of this drug in inappropriate cases, and thereby improve the care of the elderly.

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Regulatory

The Guidelines for Quality Assurance in Transfusion Practice – An introduction with examples

Introduction

Quality assurance in the context of blood transfusions is crucial to providing patients with the best possible treatment, avoiding transfusion errors and preventing harm to patients. Hence the formation in 2015 of the Swiss "Quality Assurance in the Use of Blood Products" working group. The group first published the "Guidelines for Quality Assurance in Transfusion Practice" in June 2017.

Composition of the working group

The working group comprises representatives from among the Cantonal Medical Officers, Cantonal Pharmacists, Haemovigilance Officers and Swissmedic experts. The final guidelines have been approved by all the bodies responsible for oversight of transfusion activities: the Association of Cantonal Medical Officers, Association of Cantonal Pharmacists, Swissmedic and the Swiss Transfusion Medicine Association (STMA).

Binding nature of the guidelines

The guidelines take account of the status of the legislation and knowledge at the time of publication and are designed to help the transfusion institutions (users) set up or check the legally stipulated QA system. The users may implement procedures that deviate from these recommendations if, on the basis of the latest scientific findings, it can reliably be assumed that the desired quality and safety goals in these guidelines are achieved to the equivalent extent or better.

Classification and definition

Article 39, paragraph 4 of the Swiss Therapeutic Products Ordinance (TPO) requires users to observe the following:

"Institutions that use labile blood products shall establish a quality assurance system for the use of labile blood products according to the current state of medical science and technology. They shall designate an individual who is responsible for fulfilling the reporting obligations."

These guidelines specify the minimum requirements for this quality assurance in transfusion practice in the form of a list of criteria. They also specify further requirements and recommendations. The following deserve particular mention: Transfusion medicine laboratory tests on patient samples, recommendations of the STMA and the Blood Transfusion Service of the Swiss Red Cross for professionals, laboratories and medical institutions on immunohaematology and molecular investigations on patients' blood samples. These recommendations and the guidelines largely complement each other and cover all the processes in the transfusion chain from the standpoint of the user.

Haemovigilance data

In addition to international data and guidelines, the key themes and content of the Swiss guidelines are based on Swiss haemovigilance data – specifically reports from hospitals concerning not just transfusion reactions, but also reports of transfusion errors and "near misses". Near misses are errors or deviations from standard operating procedures or directives that are discovered before initiating a transfusion and that could have resulted in a transfusion error or a transfusion reaction in the recipient if the error/deviation had not been detected and corrected.

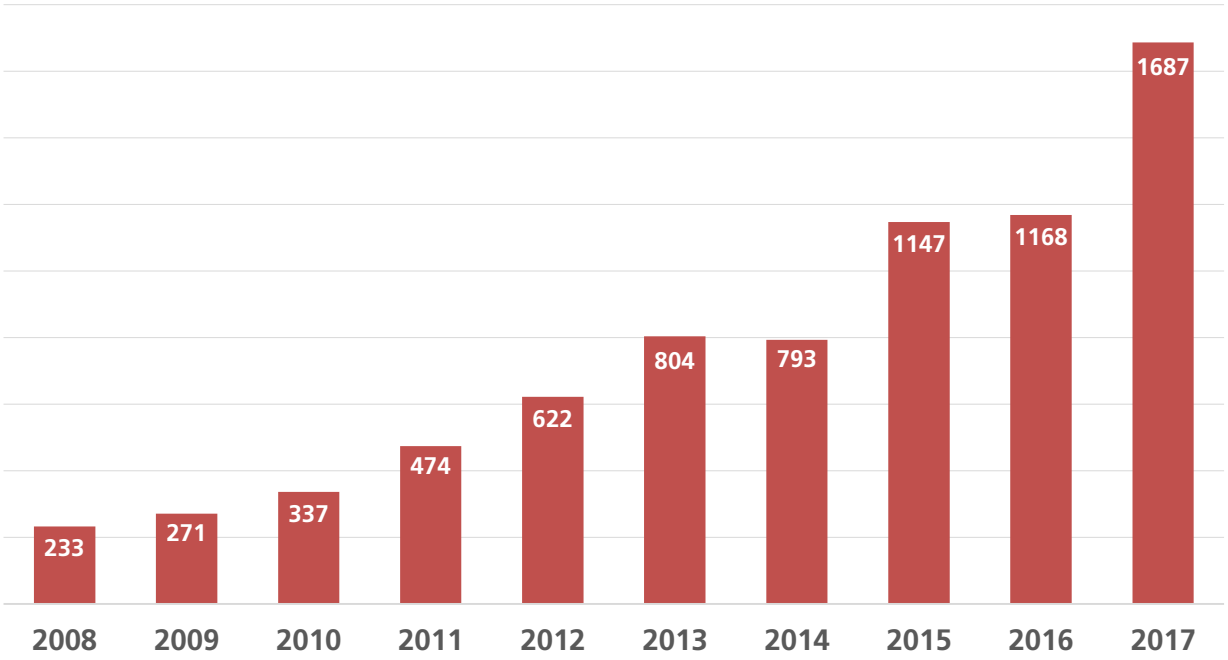


Figure 1: Near miss reports in Switzerland 2008–2017

Figure 1 shows the near misses reported since 2008:

Around 15% of the cases involve a grade 3 near miss, i.e. they are potentially life-threatening (in absolute figures: 2015: 147; 2016: 150; 2017: 272).

Most of the grade 3 near misses involve "Wrong Blood in Tube" (WBIT) cases, which means that mix-ups occurred in respect of patients or samples taken before transfusion (1).

These mix-ups can lead to ABO-incompatible transfusion errors if the error is not discovered before the transfusion.

Due to under-reporting, it can therefore be assumed that several hundred such mix-ups occur in Switzerland each year and threaten the lives of patients. Quality assurance measures are therefore essential.

Example 1: Duplicate blood group (BG) determinations

ABO-incompatible transfusion errors are life-threatening, even though the earlier mortality rate of approx. 10% probably no longer applies thanks to better monitoring (2). The present rate cannot be determined precisely since such incidents are so rare. One of the most important measures for avoiding transfusion errors in Switzerland is duplicate blood group determination. This severely limits the greatest risk, namely the mix-up of samples or patients during sampling. In Switzerland – in contrast to Germany, for example – the BG check is only rarely performed at the patient's bedside *(bedside test)*.

Quote from the guidelines:

"At least two blood group determinations are needed for each transfusion of labile blood products in order to detect any mix-ups. If the blood group is not yet known, one complete blood group determination should always be carried out on two independently taken blood

samples with separate patient identification for each sample.

The QA system stipulates which external documents are accepted as BG determinations (e.g. BG cards) and which are not…. "

Example 2: Checks when hanging up the transfusion

The above-mentioned WBIT errors are the most commonly reported grade 3 near misses. However, there is another important cause of transfusion errors that are actually observed in practice: According to the Swiss haemovigilance data, more than half of ABO transfusion errors (ABO incompatible or compatible only by chance) result from incorrect patient identification just before initiation of the transfusion (1).

Quote from the guidelines:

"The checks before the administration of the transfusion should be carried out by two registered nurses (vocational college/university of applied sciences) who have been trained for and are authorised to perform this task, one of whom may still be in training. Both individuals should check independently of each other; a registered nurse (vocational college/university of applied sciences) executes the transfusion [….]

The patient's identity and blood group (on the bag and on the documentation) are checked at the patient's bedside and immediately before the transfusion, usually by two people:

- *Identify the patient by asking him/her to state his/her name (if possible).*
- *Check the blood group compatibility between the product and patient.*
- *Check the conformity of the patient's details (first name, surname, full date of birth) with the current blood group card or laboratory report, the blood bag sticker and the details on the blood product.*
- *Check the validity of the pre-transfusion tests.*

An electronic patient identification system can replace one of the two checkers as an independent check prior to administration at the patient's bedside. In addition to the electronic check, the registered nurse (vocational college/university of applied sciences) must also ask the patient to state his/her name. "

Link to the guidelines

Guidelines for quality assurance in transfusion practice (Link to PDF)

The guidelines are also available on the websites of the following bodies that are responsible for monitoring transfusion activities:

- Association of Cantonal Pharmacists
- Association of Cantonal Medical Officers in Switzerland
- Swissmedic
- Swiss Transfusion Medicine Association

Literature

1) Haemovigilance Workshop 2017: Presentations
2) Davenport DD. Hemolytic Transfusion Reactions. In: Popovsky M. (Ed.). Transfusion Reactions. Fourth Edition. AABB Press 2012
3) Haemovigilance Annual Report 2016

Periodic Safety Update Reports (PSUR) – Important mainstay of drug safety

For many years, the market surveillance of an authorised medicinal product has included the need for the marketing authorisation holder to submit a PSUR to Swissmedic at regular intervals as a condition of the authorisation. While this applies to both human and veterinary medicinal products, the present article deals only with human medicines.

The submission procedure at Swissmedic has changed over time. In previous years, PSUR used to be submitted twice a year, starting from the day of authorisation in Switzerland, and each report covered a period of six months. Swissmedic subsequently switched to the annual submission of two six-monthly PSUR. PSUR usually have to be submitted for a period of five years. In the event of a relevant indication extension, e.g. from use in adults to use in children as well, the obligation to submit PSUR was extended for a further five years from the date of the official decision approving the indication extension. Swissmedic also has the option of extending the obligation to submit PSUR in connection with a review procedure or signal investigation, or to reset the obligation when it has already expired.

The structure of a PSUR is determined by the *International Conference on Harmonisation (ICH).* For details refer to ICH E2C(R2) dated 17 December 2012. Aspects that are directly or indirectly associated with drug safety include completed clinical trials, long-term follow-up, new safety data related to combination therapies and signals.

For signals, the author of the PSUR is required to state, clearly and comprehensively, the reasons for or against a causal relationship with the product and to arrive at an evaluation of one of the following three options:

- The signal is refuted since the available evidence argues against a causal relationship.
- The signal is declared to be an identified risk since the evidence is sufficient to indicate an association with the product.
- The signal is declared to be a potential risk. There are reasons for suspecting a relationship, but this cannot yet be confirmed/proved.

One important mandatory aspect of a PSUR is *"Actions Taken in the Reporting Interval for Safety Reasons".* The actions that were taken during the reporting interval for safety reasons and that need to be included in the report relate to the MAH *(Marketing Authorisation Holder)*, the sponsor of a clinical trial, Data Monitoring Committees, ethics committees and, of course, regulatory authorities. The actions cover both regular market use and new therapeutic areas *(investigational use)*.

In the section *"Level of Detail Within PBRER"*, the ICH Guideline gives the author a certain amount of leeway regarding the scope and depth of the presentation. It is clear that no single benchmark can be set for the numerous products subject to the PSUR obligation. On the other hand, the responsibility for correctly interpreting this leeway therefore rests with the author. It is not just the description that is needed but, above all, the medical evaluation – and here it is important to avoid focusing solely on one's own product.

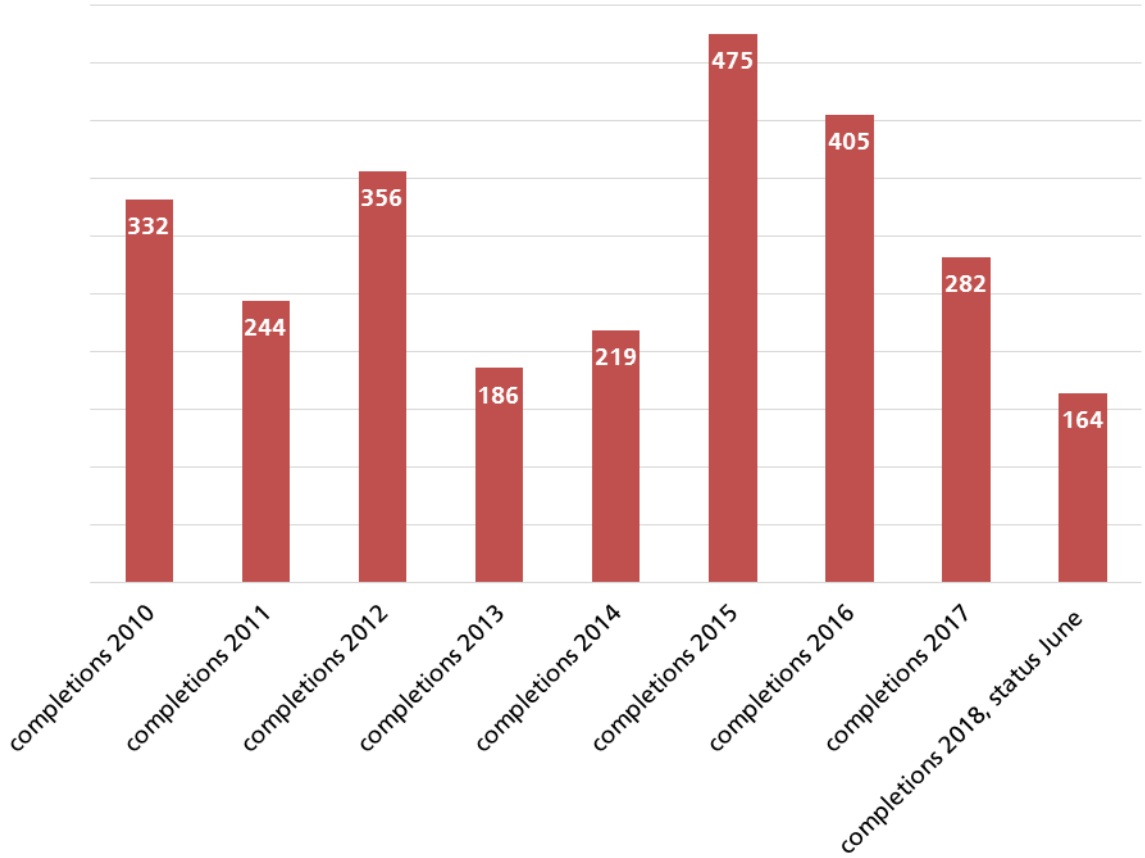
The author should also take a conscientious look at similar preparations, other therapeutic options, new findings in diagnosis or treatment, and the options for prevention, in each case taking into account the risk, impact on the patient, options for the physician and the life cycle of the product.

It is also desirable to think about the target readership, i.e. the authority's individuals who process the PSUR. Clearly presented text and tables and the use of helpful illustrations

can assist the Clinical Reviewer, but possibly also the MAH itself. At the very least, it leaves a good impression if a PSUR for a "difficult" product is well presented.

During the ICH Assembly in Kobe/Japan from 1-7 June 2018, the E19 EWG on *Optimization of Safety Data Collection* met, in addition to other working groups. The meeting aimed to separate the " wheat from the chaff" in connection with data collection, i.e. to record only the relevant safety data while preserving the risk-based approach.

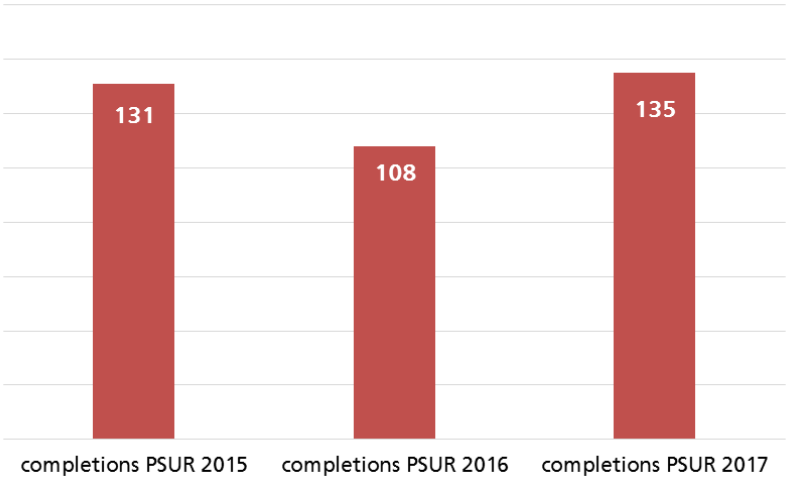
Development of PSUR completions from 2012 to June 2018



Thanks to the extended IT support and internal improvements at Swissmedic, the **processing time** has shortened appreciably in recent years, and is currently six weeks on average (42 calendar days).

For some years now, PSUR submissions to Swissmedic have been accompanied by a new version of a Risk Management Plan (RMP), known as an RMP Update. The simultaneous submission not only simplifies matters for the processing specialist, but also enhances the efficiency of the assessment and thus, ultimately, improves drug safety.

Overview of PSUR completions including RMP Updates in recent years



In a new RMP Update, the author not only reviews the changes compared to the previous version and their implications for the safety profile, but also checks whether changes need to be made to the RMP Summary, which the authorisation holder makes available to Swissmedic for publication on the Agency's website.

A key component of an RMP is the *Summary of Safety Concerns.* This is where the important identified risks, important potential risks and missing information are presented in a table together with a summary description. This section is linked to the PSUR in that all points in the Safety Concerns must be re-addressed and reassessed in every PSUR. As a result, no risk can be "hidden" in what is often a very voluminous PSUR.

Companies are required to submit relevant RMP Updates only. In this context, it is helpful to include a specific reference to this either in the mandatory Swissmedic PSUR form or in the cover letter.

What is the aim of PSUR submissions? What are the implications for drug safety?

- While preparing the PSUR, the MAH discovers that the product information in Switzerland needs to be modified in respect of a particular adverse reaction.
- While evaluating the PSUR, Swissmedic discovers that immediate action needs to be taken in respect of an adverse reaction, or that certain points must be clarified in the next PSUR, e.g. through additional evaluations, more detailed description (including graphs) and an in-depth evaluation by the company.
- While comparing the Safety Concerns of the RMP and PSUR, Swissmedic discovers that the risk minimisation measures described by the company in the RMP do not lead to the desired objective.
- The effectiveness of a product under market conditions produces results that differ from those from the clinical trials that led to the authorisation.

- For *Orphan Drugs* the data pool is very limited due to the rarity of the disease and starts to grow only after market launch. The growing experience is reflected in the PSUR.

For various reasons it is not appropriate to publish statistics on the countable results or results that are visible to third parties (*outcome* of drug safety). These reasons include overlaps in content with authorisation processes or the poorly quantifiable effect of publication of a *Direct Healthcare Professional Communication (DHPC).*

The new Therapeutic Products Act, TPA 2, will shorten the mandatory period for submitting PSUR in Switzerland from the standard five years to four years. Swissmedic believes that this decision will not adversely affect drug safety.

One reason is the more comprehensive and improved pharmacovigilance as a result of:

- increased reporting frequencies in recent years,
- reports of adverse reactions by patients as well,
- the reporting of signals by authorisation holders, which is independent of the PSUR obligation,
- intensive international collaboration.

Conclusion: PSUR remain an intellectual and ethical challenge, both for those who produce them and those who evaluate them.

Statistical Review 2017

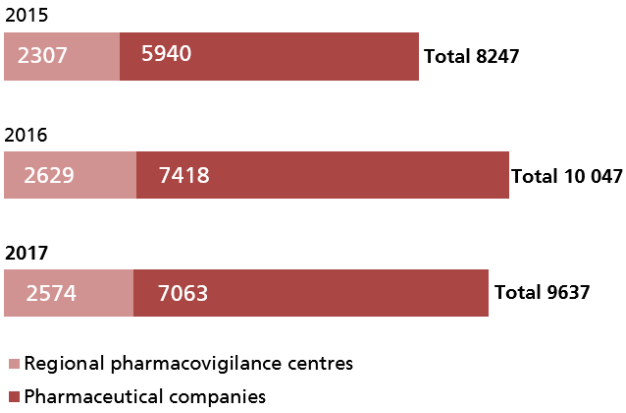
Vigilance of human medicines

Within the framework of the pharmacovigilance network, the direct reports from professionals and patients on adverse drug reactions are assessed in six regional pharmacovigilance centres (RPVC) on behalf of Swissmedic and recorded in the national database. The professionals who submit the reports receive appropriate feedback. Reports on adverse reactions from within Switzerland are also sent to Swissmedic by the pharmaceutical companies.

Activities

- In the year under review, Swissmedic received 9,637 initial reports of suspected adverse drug reactions (ADR) associated with medicinal products, evaluated them and recorded them in the national VigiFlow database. The regional pharmacovigilance centres (RPVC) sent 2,574 reports, the pharmaceutical industry 7,063. In addition, 4,207 follow-up reports were processed and evaluated.
- The proportion of reports from the pharmaceutical industry that were submitted electronically increased to nearly 100 %. 90 % of these reports reached Swissmedic via the Pharmacovigilance Gateway (25 firms), the remainder via the online reporting portal ElViS (electronic vigilance system).
- The preparations for the introduction of a new, modern pharmacovigilance database in 2018, which took place in parallel to day-to-day business, represented a particular challenge and dominated the working day in the year under review.

Figure 1: Adverse drug reactions, human medicinal products: Number of initial reports from



Vaccinovigilance

Summary of adverse events following immunization reported in Switzerland

During 2017, Swissmedic received 232 case reports of suspected adverse events following immunization (AEFI) from Switzerland. This is a higher level than the number of cases submitted during 2016 (209 reports) but lower as compared to 2015 (278 reports). However, during 2015, 80 of 278 reports had been retrospectively submitted cases occurring in previous years. Since no retrospective reporting occurred during 2017, all 232 case reports contain recently occurring AEFI. Notably, there are no precise data available regarding the total number of vaccines/doses administered during 2017 and therefore a straightforward conclusion regarding AEFI reporting rates cannot be drawn. As previously, Swissmedic is encouraging spontaneous reporting of AEFI with high quality, which enables early detection of new safety signals. Since 2010, important safety topics concerning vaccines – including potential risks – are being discussed and evaluated by experts of the *Swissmedic Human Medicines Expert Committee (HMEC)*.

An increased AEFI reporting rate followed by a scientific evaluation of relevant cases can lead to new risk minimisation measures in order to ensure vaccine safety, if necessary.

Complete report:

Vaccinovigilance – Adverse events following immunization – annual report 2017

Information on the Swissmedic website[1]

Healthcare Professional Communication

22.09.2018
DHPC – Litak® 10 (Cladribin)
Risiko einer progressiven multifokalen Leukenzephalopathie (PML)

19.09.2018
DHPC – Spinraza® (Nusinersen)
Berichte über das Auftreten eines kommunizierenden Hydrozephalus, der nicht mit einer Meningitis oder Blutung in Verbindung steht

07.09.2018
DHPC – Remodulin (Treprostinil) Infusionslösung
Anpassung der Arzneimittelinformation

06.09.2018
HPC – Condrosulf® (Chondroitinsulfat), Structum® (Chondroitinsulfat)
Abschluss der Überprüfung Chondroitinsulfat-haltiger Arzneimittel – Anpassung der Indikation

24.08.2018
DHPC – Esmya® (Ulipristalacetat)
Indikationseinschränkung, neue Kontraindikation und Notwendigkeit zur Durchführung von Leberfunktionstests bei der Anwendung von Ulipristalacetat, Esmya® 5 mg Tabletten

22.08.2018
DHPC – Thiopental Inresa
As a precautionary measure, the use of Thiopental Inresa should be strictly indicated until further notice

14.08.2018
DHPC – ZINBRYTA® (Daclizumab beta)
Berichte über immunvermittelte Enzephalitis, einschliesslich Anti-NMDA-rezeptorvermittelte Enzephalitis, mehrere Monate nach Absetzen

08.08.2018
DHPC – Cinryze® 500 IU, Pulver und Lösungsmittel
Shire Switzerland GmbH informiert über die eingeschränkte Verfügbarkeit

13.06.2018
DHPC – Perenterol 250 (Saccharomyces boulardii) Kapseln und Beutel
Neue Kontraindikation von Saccharomyces boulardii bei schwerkranken Patienten

13.06.2018
DHPC – XGEVA (Denosumab)
Risiko multipler vertebraler Frakturen (MVF) im Zusammenhang mit Knochenmineralverlust nach Absetzen / Risiko für neue primäre maligne Erkrankungen (NPM)

08.06.2018
DHPC - Tivicay® (Dolutegravir) /Triumeq® (Dolutegravir/Abacavir/Lamivudin)
Dolutegravir: Neuralrohrdefekte (Neural Tube Defect, NTD) bei Neugeborenen von Frauen, die zur Zeit der Konzeption im Rahmen der Tsepamo-Studie mit Dolutegravir behandelt wurden

Announcements

05.11.2018
Valsartan: Proprietary medicines on the Swiss market containing sartans are safe in respect of NDMA
Analytical results to date for the proprietary medicinal products containing the active substances valsartan, losartan, olmesartan, candesartan and irbesartan

05.11.2018
Analytical results for NDMA tested medicinal products with sartans
Analytical results in respect of NDMA for the proprietary medicinal products containing the active substances valsartan, losartan, olmesartan, candesartan and irbesartan.

[1] Most of the links are available in German/French only

05.11.2018
Aktueller Stand bei Zulassungen von homöopathischen und anthroposophischen Arzneimitteln ohne Indikation

02.11.2018
Federal Council approves Swissmedic's strategic goals for 2019–22
Swissmedic guarantees efficient, independent therapeutic products oversight.

01.11.2018
New application forms for operating licences available

01.11.2018
Update of eCTD and eDok specification documents
Documents are valid with immediate effect.

23.10.2018
Operation "PANGEA XI": Switzerland participates in international week of action against illegal trading in medicines
Successful operation against illegal online sales

01.10.2018
Valsartan: Extended investigations – products on Swiss market tested to date give no cause for concern
Like the previously analysed products with valsartan, products with losartan, olmesartan and candesartan that have been investigated do not contain elevated NDMA levels.

30.09.2018
Procedure for submitting applications according to HMV4 before 1 January 2019
As of 1 December 2018 Swissmedic will accept submissions with the documents updated according to HMV4.

30.09.2018
Updating of various specification documents connected with HMV4
Various eDok and eCTD specification documents are being updated

30.09.2018
Revision of the Therapeutic Products Act (TPA): Publication of the specification documents and forms for authorisation applications
Owing to the revision of the TPA and the corresponding implementing ordinances (Therapeutic Products Ordinance Package IV), Swissmedic has adapted the specification documents and forms for authorisation applications.

25.09.2018
New process GMP/GDP-certificates
As of 1 January 2019 GMP/GDP certificates to be ordered exclusively via eGov GMP-GDP service

21.09.2018
Therapeutic Products Ordinance Package IV: Publication of the ordinances
The Federal Council has approved Therapeutic Products Ordinance Package IV. Swissmedic and the FOPH publish the revised documents

18.09.2018
Publikumswerbung für zugelassene Komplementärarzneimittel ohne Indikation
Regulierende Massnahmen von Swissmedic

14.09.2018
New application forms for operating licences available from November 2018

14.09.2018
Swissmedic agrees closer collaboration in therapeutic products field with Dutch partner authority
Swissmedic intends to intensify collaboration with its partner authority in the Netherlands

13.09.2018
Adverse events following immunization – annual Vaccinovigilance report
Summary of adverse events following immunization reported in Switzerland during 2017

07.09.2018
F&A Umteilung Abgabekategorien

06.09.2018
Swiss eCTD: Updating of Module 1 as of January 2019
Changes to the specifications (folder structure) in Module 1 of the Swiss eCTD module due to the revision of the Therapeutic Products Ordinances

01.09.2018
Amendments to the "MB Swissmedic eGov Portal – Standard Functions" information sheets
OS000_00_001d_MB / OS000_00_002dMB

31.08.2018
Swissmedic eGovernment services: New customer portal
System enhancements and new eGov service as of September 2018

27.08.2018
Abteilung Betäubungsmittel Info & News 2018
Swissmedic Veranstaltung

24.08.2018
Medicinal products containing valsartan: First analytical results
Preparations with valsartan that are currently available on the market satisfy the requirements

17.08.2018
Investigation of Valsartan medicinal products for evidence of active substance contamination – an update
Additional recall of batches in Europe – no products in Switzerland affected to date

15.08.2018
Revision des Heilmittelgesetzes (HMG)
Informationsveranstaltung 2018

09.08.2018
Spontanmeldungen aus der Schweiz zu hormonalen Kontrazeptiva und venösen Thromboembolien
aktualisierte Zahlen mit Stand 30.06.2018

07.08.2018
Individual distinguishing features and safety precautions on the packaging of medicinal products
two-dimensional barcodes (data matrix)

03.08.2018
(BIA-ALCL) Anaplastic large cell lymphomas in connection with breast implants – updated information
Affected products: Breast implants, all types, makes and models of all manufacturers

03.08.2018
Safety notice: Recall of three varieties of latex-free condoms – Durex Natural Feeling (pack of 10 condoms), Durex Love Collection (pack of 31 condoms) and Durex Natural Feeling Easy Glide (pack of 12 condoms) – produced by Reckitt Benckiser Healthcare (UK) Limited

18.07.2018
Adaptation of the Guidance document «Time limits for authorisation applications» to be submitted immediately
ZL000_00_006e_WL

12.07.2018
List of authorised products containing valsartan as active substance
List of preparations and batches affected by the batch recall

10.07.2018
Änderungen der Liste der dokumentierten traditionellen asiatischen Stoffe
Liste TAS gemäss Anhang 6 Art. 29 Abs.1 (KPAV; SR 812.212.24) und des Vorworts zur Liste TAS

10.07.2018
Changes to the Guidance document on time limits for authorisation applications
The changes to the Guidance document take immediate effect.

06.07.2018
Impurities in valsartan products: risks currently being investigated
Certain preparations containing the active substance valsartan produced by a Chinese manufacturer are in some cases being recalled in Europe

04.07.2018
ICH Assembly in Kobe, Japan, 2 to 7 June 2018
ICH continues membership expansion, and advances harmonisation work in electronic standards and pharmaceutical quality

01.07.2018
Nachtrag 9.5 der Europäischen Pharmakopöe in Kraft
Der Institutsrat hat den Nachtrag 9.5 der Europäischen Pharmakopöe auf den 1. Juli 2018 in Kraft gesetzt.

29.06.2018
Warning regarding eye contact with the veterinary medicinal product Osurnia® ad us.vet.
In both humans and dogs, the ear gel for dogs coming into contact with eyes can result in eye irritation, redness of the eye and in very rare cases corneal ulcers

18.06.2018
HIV self-test kits now also available in Switzerland
Media release

04.06.2018
Swissmedic Annual Report 2017: achieving success through collaboration
"The Agency fulfils its mandate reliably and professionally"

The complete list is available at the following web address www.swissmedic.ch/updates-en