

# Vigilance-News

Edition 22 – May 2019

---

## In this edition

---

- Current case report
- WHO – 41st annual pharmacovigilance meeting
- Communication of medicinal product risks
- Information for patients
- International collaboration on the safety of medicines

---

## Sign up for e-mails

---

Subscribe to Swissmedic's Vigilance News and register for the **newsletter on drug safety!**

You will be constantly kept up to date by e-mail with information from the fields of pharmacovigilance (Health Professional Communication) and market monitoring (batch recalls, out-of-stock announcements): [www.swissmedic.ch/newsletter-en](http://www.swissmedic.ch/newsletter-en)

---

## Impressum

---

### Editorial team

Martina Schäublin, Eva Eyal, Helena Bill

### Authors

Véronique Ditesheim, Eva Eyal, Christoph Küng, Cedric Müntener, Martina Schäublin, Thomas Schwartz, Valeriu Toma

We would like to thank all colleagues for their contribution to producing this edition of Swissmedic Vigilance News.

### Contact

Please send any suggestions or feedback on this issue of Swissmedic Vigilance News to [news.vigilance@swissmedic.ch](mailto:news.vigilance@swissmedic.ch).

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

## Contents

<b>Editorial</b>	<b>3</b>
<b>Current case report</b>	<b>4</b>
Rhabdomyolysis with myoglobinuria in two patients with Duchenne muscular dystrophy after treatment with zoledronate	4
<b>Congress report</b>	<b>5</b>
WHO: 41st annual pharmacovigilance meeting in Geneva	5
<b>Regulatory</b>	<b>7</b>
Communication of medicinal product risks by Swissmedic	7
Patients – stay informed!	10
Swissmedic and international collaboration on the safety of medicines	14
<b>Statistical Review</b>	<b>16</b>
Vigilance of veterinary medicines	16
<b>Information on the Swissmedic website</b>	<b>21</b>
Healthcare Professional Communication	21
Announcements	22

---

## Editorial

---

Dear Reader

Audience-appropriate communication between Swissmedic and the public – i.e. patients, medical professionals, the media and politicians – is a topic of constant discussion.

One of Swissmedic's important tasks is to provide information about potential risks associated with medicinal products and the resulting measures. To enable medical professionals and patients to correctly categorise this new information and carefully weigh up whether to use a particular medicinal product, a description of the background, updated medicinal product information and practical implications for patients is given. The aim is to depict the situation precisely and with scientific accuracy, but without overloading it with too much data.

One of the articles in this edition of Swissmedic Vigilance News looks at the issue of patient information. Another deals with the issue of communicating medicinal product risks to professionals by means of Direct Healthcare Professional Communications (DHPC).

Risk minimisation measures do not end when signals or safety information are published.

Just how effective a measure is becomes apparent over the next few months or years through reports of adverse drug reactions (ADR) or summary reports such as Periodic Safety Update Reports (PSUR).

It goes without saying that Swissmedic does not just observe signals in Switzerland, but also internationally. International cooperation with other regulatory authorities is a relevant factor in assessing potential risks. Swissmedic's involvement in international working groups plays an important role here, as the article on "International post-market surveillance teleconference" illustrates. A further opportunity is afforded by networking at meetings and congresses, where it is possible to network with colleagues from all over the world (see report on the WHO Meeting in Geneva in November 2018).

We hope that this latest issue of Swissmedic Vigilance News once again provides you with new and interesting information.

The Editors

Please send any suggestions or feedback on this issue of Swissmedic Vigilance News to:  
[news.vigilance@swissmedic.ch](mailto:news.vigilance@swissmedic.ch).

## Current case report

### Rhabdomyolysis with myoglobinuria in two patients with Duchenne muscular dystrophy after treatment with zoledronate

Duchenne muscular dystrophy (DMD) is an inherited muscle disorder that occurs in one in 3,600–10,000 male births. While corticosteroids remain the standard treatment, in combination with the underlying illness they increase the risk of reduced bone density which, in turn, leads to pain, fractures and an impaired quality of life in the affected patients. Bisphosphonates are usually used in these patients to improve bone density.

A study group from the university hospitals in Lausanne and Bern reports on two adolescent patients who developed rhabdomyolysis with myoglobinuria while receiving treatment with zoledronate.

Patient 1 is a 14-year-old boy who had been treated with corticosteroids since the age of 9. Treatment with zoledronate for bone pain and low bone density was started when he was 13. Two days after the second infusion (6 months after starting treatment), the patient developed flu-like symptoms accompanied by diffuse muscle pain, vomiting and dark brown urine.

Patient 2 is a 13-year-old boy who had been treated with corticosteroids since the age of 4. Treatment with zoledronate for back pain and low bone density was started when he was 13. The first infusion was followed by the onset of muscle pain, fever, nausea and dark brown urine.

The symptoms experienced by both patients suggest the presence of transient rhabdomyolysis with myoglobinuria.

Rhabdomyolysis is not described in the Information for healthcare professionals for medicines containing zoledronate. According to the authors, no similar reports, particularly involving patients with DMD, have been published. Possible mechanisms under discussion include drug-induced hypophosphataemia and/or a myotoxic effect of nitrogen-containing bisphosphonates. Low calcium and vitamin D levels may also play a contributory role. Hypophosphataemia and hypocalcaemia are known side effects of medicines containing zoledronate.

**Conclusion:** In rare cases, zoledronate can cause rhabdomyolysis with myoglobinuria in DMD patients. The authors point out that calcium, phosphate and vitamin D levels should be within normal limits before the infusion.

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

#### Literature

Ivanyuk A., Segarra N., Buclin T., Klein A., Jacquier D., Newman C., Bloetzer C., Myoglobinuria in two patients with Duchenne muscular dystrophy after treatment with zoledronate: a case report and call for caution, *Neuromuscular disorders* 2018; 28: 865-867



---

## Congress report

---

### WHO: 41st annual pharmacovigilance meeting in Geneva

---

The WHO celebrated several anniversaries during 2018. Not only had the organisation itself been founded 70 years previously, its “Programme for International Drug Monitoring” was established in 1968, while the “Uppsala Monitoring Centre (UMC)” was set up in 1978.

The celebratory meeting to mark the half-centenary of the “WHO Programme for International Drug Monitoring” was combined with the “41st Annual Meeting of Representatives of National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring”, which was held in Geneva in November. Both meetings were organised by the WHO in conjunction with Swissmedic, which represented the host country of Switzerland.

The meeting to mark the 50th anniversary of the “WHO Programme for International Drug Monitoring” was held at the WHO headquarters in Geneva on 5 November 2018. The celebrations were attended by more than 200 former and current representatives of national pharmacovigilance centres, international PV experts, representatives of diplomatic missions and WHO staff members.

A WHO retrospective of the preceding decades was followed by an exploration of the changes that the aims of pharmacovigilance had undergone during this period. Various panel discussions and pharmacovigilance success stories from certain countries rounded off the 50th anniversary celebrations.

The next three days, 6 to 8 November, were devoted to the “Annual Meeting of Representatives of National Pharmacovigilance

Centres participating in the WHO Programme for International Drug Monitoring”. Around 180 representatives from over 80 of the 160 countries participating in the Programme had travelled to Geneva for the Meeting.

Following the welcome addresses by Dr Küng (Swissmedic) and Dr Ondari (WHO), two representatives from Uganda reported on the previous year’s meeting in Kampala and the activities that had resulted from the Working Groups’ recommendations in 2017.

A series of plenary sessions shed light on various highly topical facets of pharmacovigilance, such as reporting systems for substandard and counterfeit medical devices, packaging and labelling measures to prevent medication errors, and data protection. Once again, a lot of time was devoted to “Signals of current interest”. Representatives of various authorities had an opportunity to present interesting signals or PV measures from their countries and to hold animated discussions of them with colleagues from other authorities.

Like previous events, the meeting featured Working Group sessions, with no less than eight groups sharing information and planning for the future. Meeting participants had a choice of four different Working Groups on each of two days. The groups addressed topical issues once more, including “Improving communication”, “Strategies for improving the quality of information in Individual Case Safety Reports”, “Monitoring medicines safety in special populations”, “Reporting and preventing medication errors” and “Reporting quality problems”. The Working Groups then presented the outcomes of their discussions and recommendations for the WHO in a plenary session.

The Meeting was rounded out by a series of tutorials, which gave participants an opportunity to brush up and expand their knowledge of PV. The topics covered by the

tutorials included benefit-risk assessment, signal detection, “VigiLyze” and “MedDRA”.

The Meeting ended with the announcement of, and a presentation on, the host country

for the next Meeting. In October 2019, representatives of the National Centres will have another opportunity to meet, discuss current pharmacovigilance-related issues and learn from each other in Bogotá, Colombia.

## Regulatory

### Communication of medicinal product risks by Swissmedic

The Therapeutic Products Act (1) defines one of the central tasks of Swissmedic as follows: *“The Agency shall be responsible for monitoring the safety of therapeutic products. To this effect, it shall in particular collect the notifications referred to in Article 59, evaluate them, and take the necessary administrative measures.”* The **notifications referred to in Article 59** are reports of serious or previously unknown adverse drug reactions and events. The administrative measures include the provision of information to healthcare professionals and the public about the risks associated with medicinal products that have been ascertained and the corrective actions.

Notifications of adverse drug reactions originating from medical practice are an important element in the task of identifying new risks arising from the use of medicinal products in Switzerland. This is why the Therapeutic Products Act contains a requirement for authorisation holders, doctors, pharmacists and other professionals to submit such notifications.

Swissmedic is also notified of risks associated with medicinal products from abroad, both by authorisation holders in accordance with the requirements of the Therapeutic Products Ordinance (2) and by partner authorities in other countries. International collaboration is being expanded on an ongoing basis as a result of agreements to exchange information; it leads to a prompt response and functions smoothly.

As soon as a new medicinal product risk is identified, appropriate action must be taken. This action is determined by the potential risk for patients and also by the evaluation of benefits and risks, including the

availability of alternative medicines. The range of possible actions is accordingly varied, from a simple modification of the information for healthcare professionals and the package leaflet through a warning letter to healthcare professionals to restrictions on use of the medicinal product or even withdrawal of the product from the market.

The question here is: what is the most effective way of informing healthcare professionals and patients or the public? This information must be provided promptly on a broad front and in a coordinated fashion. Serious adverse drug reactions and important safety information are communicated to healthcare professionals in the form of warning letters known as *Direct Healthcare Professional Communications (DHPC)*. DHPC are sent directly to healthcare professionals by the authorisation holders. *Healthcare Professional Communications (HPC)* are distributed in the form of information provided on the Swissmedic website and circulars sent to the Swiss Medical Association FMH, the Swiss Pharmacists' Association Pharmasuisse, the Federal Office of Public Health (FOPH), the cantonal medical officers and the cantonal pharmacists. Every year around 25 warning letters are issued, containing information about the risk that has been identified, the resulting actions and, in many cases, initial recommendations on how healthcare professionals and affected patients should respond.

If the potential risk is high, a DHPC is distributed through four different information channels simultaneously:

1. Swissmedic publishes the DHPC on its own website. The warning letter is accessible to the public at (<https://www.swissmedic.ch/swissmedic/de/home/human-arzneimittel/marktueberwachung/health-professional-communication--hpc-.html>).

Interested professionals and members of the public can subscribe to warning letters of this type on our website.

2. Swissmedic informs the cantonal medical officers and the cantonal pharmacists in advance by e-mail one day before the DHPC is published on the website. These cantonal offices also provide information on important topics within their area of responsibility.
3. Swissmedic publishes DHPC in the two major publications issued by the professional associations, *Schweizerische Ärztezeitung* and *pharmaJournal*.
4. The affected authorisation holders are required to send the DHPC by post specifically to the healthcare professionals. These warning letters are sent not only to all the members of the respective medical societies but usually also to medical directors and heads of department at hospitals and to pharmacies and hospital pharmacies. Only letters of this type from authorisation holders are permitted to bear the words "Important communication" and are thus easy to distinguish from promotional material sent by the companies.

The purpose of communicating recently identified medicinal product risks in parallel through four channels is to ensure that all the doctors concerned, and the public as well, are informed of risks associated with medicinal products shortly after they have been identified.

Despite all these measures, a DHPC containing information about a recently identified risk of light skin cancer associated with therapy with hydrochlorothiazide (a blood pressure-lowering medicine) that was sent at the end of 2018 failed to reach numerous doctors and pharmacists.

Investigation by Swissmedic showed that the authorisation holders had made mistakes when putting together the mailing list. This was corrected by supplementary mailings, and the intention is for the corresponding processes to be reviewed more thoroughly than in the past during the regular pharmacovigilance inspections held on the authorisation holders' premises.

But why were the other three communication channels not sufficient on their own? Possible questions in search of an answer:

- Are the functions performed and information offered by Swissmedic relating to drug safety not adequately known?
- Are there technical hurdles that make it difficult to obtain information, or is the Swissmedic website not user-friendly enough?
- Should Swissmedic use other communication channels, such as social media?
- Does the heavy everyday workload of healthcare professionals turn their obligation to seek out information relating to drug safety into a need for this information to be actively provided?
- Is it the challenge of filtering out important warning letters from the flood of information and advertising that reaches the doctor's practice or the pharmacy?
- How could the medical societies be involved more effectively?
- And in the longer term: Shouldn't awareness of the topic of drug safety be established at an early stage and more intensively in the university and clinical training of medical and pharmacy students?

A representative from East Africa at last year's WHO *Annual Meeting of Representatives of National Pharmacovigilance Centres* summed up the issue very nicely when she said, "Catch them young!"



The shared and most important goal can only be the following: for therapeutic products to be used with awareness of the currently known risks – for the good of patients!

## References

- 1) Art. 58, para. 3 TPA
- 2) Art. 61, para. 4 TPO

## Patients – stay informed!

### Introduction

One of the purposes of the Federal Act on Medicinal Products and Medical Devices (Therapeutic Products Act, TPA of 15 December 2000 in the version of 1 January 2019) is to ensure that high-quality, safe and effective therapeutic products are placed on the market in order to protect human health (1).

As part of its market surveillance activities, Swissmedic reviews the safety signals it receives in reports of suspected adverse drug reactions in Switzerland, and it also evaluates international data on medicinal product safety. If its investigations confirm the existence of a new risk, the Agency takes action accordingly.

The information for healthcare professionals and the information for patients supplied with human medicinal products are modified and updated if new knowledge about the medicinal products in question requires healthcare professionals and patients to be informed of this risk.

### Information for patients relating to human medicinal products

Any form of therapy with medicinal products requires the patient to be informed appropriately by healthcare professionals.

Yet it is equally important for a patient to have access to any information that is useful, relevant and reliable in the context of his/her treatment with medicines. This aspect is fundamental for patients, no matter what medical conditions they have.

Information for patients (2) is generally provided as an insert in the package in which the medicine is sold. In most cases it is supplied in the form of a leaflet, but it may equally take the form of a booklet or a combination of a label and a package insert. The information is available in German, French

and Italian and must not contain any form of advertising. It is a reference document that the patients can consult and read whenever they wish.

A website (3) is also available which hosts information for patients and information for healthcare professionals relating to human medicinal products. This website can be accessed using the following link: [www.swiss-medinfo.ch](http://www.swiss-medinfo.ch).

### Examples

This seems to be a good point at which to mention two examples which demonstrate how beneficial and advisable it is for patients to read the information intended for them and to be aware of the advice and explanations contained in this information.

The **first example** is Iberogast® oral liquid, a herbal medicine used to treat dyspepsia and functional digestive disorders.

The section “When should Iberogast not be used or used only with caution?” in the information for patients states the following:

*“Products based on celandine (Chelidonium) have in very rare cases been associated with liver damage (see the section “What side effects can Iberogast cause?”).*

*If you have or have had a liver disorder, or if you have been treated with another medicine that affects the liver, you must talk to your doctor before taking this medicine.*

*Be attentive to signs and symptoms that may point to impaired liver function. If you notice the following signs or symptoms you must stop the treatment and consult your doctor because they may point to impaired liver function: loss of appetite, unusual tiredness (particularly with the following symptoms), pain in the upper right quadrant of your abdomen, yellow discolouration of the skin/whites of the eyes, unusually dark urine, light-coloured stools.”*

The **second example** is Esmya® 5 mg tablets, a medicinal product based on ulipristal acetate for the symptomatic treatment of uterine fibroids in adult women of childbearing age (a therapeutic product in dispensing category B).

In the section “What precautions should be taken when using Esmya?” of the information for patients the precautions are stated as follows:

*“Before starting treatment with Esmya, blood tests are done to see if your liver is working properly. Your doctor will decide whether or not Esmya is suitable for you on the basis of the results of these tests. The tests will be repeated every month during the first two cycles of treatment. In the subsequent cycles your liver function will be checked once before each new cycle of treatment and also if you develop any of the symptoms described below. Your liver function must additionally be checked between 2 and 4 weeks after you finish the treatment. The following symptoms may be signs that your liver is not working properly: loss of appetite, pain in the upper abdomen, nausea and vomiting, jaundice (yellow discolouration of the eyes or skin), dark-coloured urine, itching. If you develop one or more of these signs during treatment, you must stop the treatment and immediately contact your doctor, who will check your liver function and decide if you can continue the treatment.*

*Equally, intense tiredness or a sudden feeling of physical exhaustion may be the first sign of liver damage. In this case, too, you must immediately inform your doctor, who will arrange for liver tests to be performed and then decide if you can continue the treatment with special monitoring. As the medicine Esmya is associated with a rare risk of liver damage, you should not drink alcohol while you are being treated with Esmya*

*(or during the intervals between the treatment cycles).”*

### **The importance of patients reading the information provided for them**

The two examples above show that the information supplied in the packaging of a medicinal product, whether obtained by the patient with or without a prescription, provides vital information about using the product correctly and about patient safety. This information identifies the potential risks associated with the medicinal product and, if possible, shows how to avoid or minimise them. It is therefore crucial to advise patients to read the information provided with a medicinal product.

### **Additional surveillance**

Following the entry into force of the current Therapeutic Products Licensing Requirements Ordinance (TPLRO of 9 November 2001 in the version of 1 January 2019), a black inverted equilateral triangle ▼, in particular, in the information for patients (2) identifies a medicinal product that is subject to additional surveillance. This triangle is accompanied by the statement *“This medicinal product is the subject of additional surveillance”* and the following short text: *“This medicinal product is the subject of additional surveillance to permit the rapid identification of new safety-related information. You can help by reporting all side effects. Please see the section “What side effects can it cause?” at the end of this information to find out how to report side effects.”* The triangle symbol, the statement and the short text are placed immediately before the first section of the information for patients.

## Packaging for medicinal products for human use

Healthcare professionals also need to draw patients' attention to the fact that pictograms or short safety warnings may be present on the packaging of medicinal products (2).

### Examples

Here are three examples of packaging bearing pictograms and warnings.

The **first example** involves medicines based on valproate that are classified as antiepileptics.



### WARNING FOR WOMEN AND GIRLS

- There is a risk of serious developmental problems and foetal malformations if taken during pregnancy!
- It is vital to use reliable contraception!
- Inform your doctor immediately if you are planning to have a baby or if you are pregnant.
- Do not stop taking valproate without consulting your doctor.

The **second example** refers to medicinal products based on isotretinoin taken orally for treatment of severe forms of acne.

#### Attention:

- Pregnancy forbidden.
- Risk of serious malformations for the unborn child!
- Strict contraceptive measures absolutely necessary.

The **third example** concerns methotrexate, which needs to be taken in a low dosage for rheumatoid arthritis and psoriasis – once a week to avoid accidental overdosage.

In case of rheumatoid arthritis and psoriasis  
To be taken only once a week  
Day of intake: \_\_\_\_\_

### Pictograms and visual warnings

As the three examples above show, it is helpful to look at the packaging of a medicinal product since it features important information such as pictograms which provide visual warnings about safety precautions that need to be observed during treatment with medicinal products.

### Conclusion

It is essential for patients to remain vigilant and to actively request information about medicinal products from healthcare professionals.

It is equally important to know that useful, relevant and reliable information about how to use medicinal products and their safety is available in the information for patients. It should be remembered that a website (3) is available which hosts information for patients and information for healthcare professionals relating to human medicinal products. This website can be accessed using the following link: [www.swissmedicinfo.ch](http://www.swissmedicinfo.ch).

### Notice of adverse drug reactions

Swissmedic encourages those concerned to report all suspected adverse drug reactions using the reporting tool developed for this purpose. The Electronic Vigilance System ELViS enables reporters to submit an ADR. All the necessary information can be found at [www.swissmedic.ch](http://www.swissmedic.ch).

## References

- (1) [www.swissmedic.ch/swissmedic/en/home/legal/legal-basis.html](http://www.swissmedic.ch/swissmedic/en/home/legal/legal-basis.html)[ch/fr/home/legal/bases-juridiques.html](http://www.swissmedic.ch/swissmedic/fr/home/legal/bases-juridiques.html)
- (2) Product information about human medicinal products and packaging TPO4: [www.swissmedic.ch/documents/humanarzneimittel\\_hmv4.html](http://www.swissmedic.ch/documents/humanarzneimittel_hmv4.html)
- (3) [www.swissmedicinfo.ch](http://www.swissmedicinfo.ch)



## Swissmedic and international collaboration on the safety of medicines

### Introduction

For a variety of reasons, some of them obvious, internationally recognised regulatory authorities have been pursuing for some years a strategy to improve networking progressively.

- The therapeutic products industry develops and produces medicinal products worldwide and is therefore reliant on internationally harmonised standards and regulations.
- The market surveillance of authorised medicines is also a global operation and is constantly bringing to light new findings and information about their efficacy and safety that have to be taken into account in the regulatory environment.
- In order to guarantee the safety of individual patients in accordance with the latest findings, cross-border sharing of data on drug safety is essential. Together with other internationally recognised regulatory authorities, Swissmedic has therefore set up collaborative projects at this important level and is constantly seeking to intensify this collaboration.

In various international bodies, Swissmedic discusses important aspects of drug safety among the partner authorities. In the event of newly emerging drug safety risks, the Agency aims to share information quickly and at an early stage and coordinate the measures to be taken with other authorities. Particularly at an early stage when new drug risks or new aspects of known risks (so-called safety signals) are suspected, the international exchange of information can enable the necessary measures to be implemented quickly and effectively in Switzerland as well.

### Multilateral international collaboration / initiatives

International collaboration on drug safety does not take place only between individual authorities at a bilateral level, but increasingly also multilaterally on different platforms. Multilateral platforms for harmonising drug safety can take the form of international initiatives or private associations set up and funded by several national therapeutic products authorities or international organisations such as the WHO or the Council of Europe.

Swissmedic is actively involved in the commissions and working groups relevant to the Agency's role, which have been set up by such platforms. The precondition for the active participation of the Safety of Medicines Division is a concrete benefit in terms of fulfilling its legal remit and service mandate in order to ensure the protection of the population's health.

Important initiatives (examples) in this connection:

#### The ACSS Consortium

Swissmedic is part of the ACSS Consortium, which, in addition to Swissmedic, includes the following medicines agencies:

- Therapeutic Goods Administration (TGA), Australia
- Health Products and Food Branch (HPFB) of Health Canada
- Health Sciences Authority (HSA), Singapore

The Consortium was formed in 2007 by "like-minded" regulatory authorities with the aim of promoting closer collaboration and harmonising regulatory requirements.

The primary objectives are to maximise international cooperation and eliminate duplication. The individual authorities should also be in a better position to provide the public

with high quality, safe and effective therapeutic products. The members regularly take part in informal teleconferences, during which they share information on regulatory issues and difficulties.

The Consortium also reviews the options for projects on information sharing and on co-operation in various areas, including the safety surveillance of therapeutic products.

Confidential information is shared in accordance with the provisions of existing agreements and in accordance with the legal regulations of the individual authorities on information sharing with partner authorities.

#### International Post-Market Surveillance teleconference

Following discussions between the authorities in the USA and Canada in November 1997, the first pharmacovigilance videoconference took place between the FDA (Food and Drug Administration) and Health Canada in February 1998. The Australian authority, the TGA (Therapeutic Goods Administration), has participated in these videoconferences since November 2001 and the New Zealand authority, Medsafe, since January 2002, after which the conference was referred to as a "4-way Pharmacovigilance Videoconference". In September 2008 the format was changed from a videoconference to a teleconference. The HSA (Health Sciences Authority) from Singapore joined in July 2011, and Swissmedic has participated since March 2017, when the conference was renamed the "*International Post-market*

*Surveillance Teleconference*". Since February 2018, the UK agency MHRA (Medicines and Healthcare products Regulatory Agency) has also taken part.

The mandate of the *International Post-market Surveillance Teleconference* primarily consists of the following tasks:

- Serve as a forum for sharing and discussing pharmacovigilance topics that are of general interest to the participating authorities.
- Coordinate the regulatory pharmacovigilance activities between the national authorities.

The aim of the *International Post-market Surveillance Teleconference* is to identify and address problems associated with ad hoc and known pharmacovigilance issues, where the available information can be shared internationally:

- Pharmacovigilance of specific medicinal products. In rare cases, questions on herbal medicines, food products and other health-related products are also discussed.
- Ongoing regulatory processes, e.g. guidelines, instructions, etc., that do not relate to a single specific medicinal product.

Since Swissmedic joined the *International Post-market Surveillance Teleconference* (March 2017), the division "Safety of Medicines" has actively contributed to all conference-rounds, sharing available information and regulatory experience on numerous safety-related issues.

## Statistical Review

### Vigilance of veterinary medicines

This article is an abridged version of the publication in the journal *Schweizer Archiv für Tierheilkunde* (Swiss Archive of Veterinary Medicine): Müntener C.R., Kupper J., Naegeli H., Gassner B. Vigilance der Tierarzneimittel: Adverse reactions reported in 2017. *Schweiz. Arch. Tierheilk.*, 2019 161: 107-112.

### Adverse reactions reported in 2017

A total of 306 reports of adverse reactions to veterinary medicinal products were received during 2017, representing an increase of 21% compared to the previous year. The majority of these reports described reactions concerning companion animals (180 dogs and 59 cats), cattle (38 reports) and horses (14 reports). Most of the reported reactions were linked to the use of antiparasitics (158 reports), hormone products (30 reports) and anti-inflammatory products (25 reports). 40 reports were generated from consultations with Tox Info Suisse in Zurich and mainly involved the excessive intake of flavoured tablets and, in some cases, the use of products under the cascade regulation (applied to a species other than that authorised). Nine signals were identified from the reports, resulting in revisions of the product information in the sections addressing contraindications or adverse reactions.

### Introduction

Reactions that occur very rarely (defined as an incidence of no more than 1 event per 10,000 uses) are of particular interest for veterinary vigilance because the incidence is so low that they are not observed during authorisation studies (due to the small number of animals investigated). Swissmedic and the Institute of Virology and Immunology (IVI in Mittelhäusern) are responsible for monitoring veteri-

nary medicinal products in Switzerland. Marketing authorisation holders and healthcare professionals (veterinarians and pharmacists) are required to submit reports, while third parties such as animal owners may participate on a voluntary basis (Art. 59 para. 3 and 4 Therapeutic Products Act). Evaluation of recent years (1) has shown that many reports originate from veterinarians but are very often entered in the system by the responsible companies. Animal owners can also consult Tox Info Suisse in Zurich if they need immediate advice. All consultations involving both an animal and a veterinary medicinal product are passed on periodically to Swissmedic. Following receipt, each notification is reviewed for a causal relationship between use and reaction (ABON system) (2) and, as a result of this review, revisions may be made to the product information in the sections addressing adverse reactions, precautions or contraindications. The aim of this revision is to improve safety for animals and users alike. Where products for livestock are concerned, withdrawal periods may also be revised in the interest of food safety. The vaccine vigilance office of the IVI is responsible for the safety of vaccines and revision of the associated product information in Switzerland.

Below is an overview of the 306 reports relating to veterinary medicinal products received by Swissmedic in 2017 with an evaluation of the animal species affected, class of medicinal product and causal relationship between use and adverse reaction. Relevant examples are given in summary form.

### Reports on veterinary medicinal products

**Figure 1** shows how the number of reports developed between 2003 and 2017. In the last of these years a total of 306 reports were received, representing a 21% increase compared with the 253 reports in 2016 (1). The

distribution of reports throughout the year followed the pattern established in previous years (1): 67.3% of the reports (N=206) were submitted by companies/marketing authorisation holders, 18.3% directly by practising veterinarians (N=56) and 13.1% (N=40) were recorded as a result of consultations with Tox Info Suisse. This distribution pattern is also seen in other countries. In Germany, reports submitted by companies in 2016 accounted for 71% of the total (1039 of 1453) (3). In Switzerland, the remaining reports were submitted either directly by animal owners (1% or N=3) or by a public office (0.3%, N=1). The distribution of the animal species affected has also remained stable over the years (1): In 2017 reports of adverse drug reactions were submitted most often for dogs (180 reports, 58.8%) and cats (59 reports, 19.3%), followed by cattle (38 reports, 12.4%) and horses (14 reports, 4.6%). The large proportion of reports referring to reactions in companion animals (78.1% in Switzerland) is also seen in other European countries, with this category accounting for 78.5% of reports submitted in the United Kingdom in 2015 (4329 of a total of 5512 reports) (4). A publication by the European Medicines Agency also reported that 82% of the notified adverse drug reactions occurred in dogs and cats in 2016 (5). Finally, four reports were submitted concerning reactions in users. Three of them involved contact between an antiparasitic liquid intended for topical application and the user's fingers. The liquid is very sticky and difficult to remove, yet the users showed no symptoms.

**Table 1** shows the submitted reports, arranged by medicinal product classes according to the ATCvet code. Adverse reactions were most frequently reported after the administration of antiparasitics (158 reports, 51.6%). This high proportion was observed in all previous years and was due largely to the regular administration of these products both to companion animals and to livestock (1).

Fifty reports of this type referred to the presumed lack of efficacy of the product, particularly its inability to control ticks in companion animals. Reports of this type are due basically to the fact that, according to the current guidelines, a product is still considered to be effective if individual live ticks are found on the animal in the first 24 to 48 hours after application (6). Most of these reports were archived following assessment as "possible" or "insufficient information", in the latter case particularly if the latency period between application and observation of ticks on the animal was not known. We received one notification of a serious skin lesion associated with spot-on treatment with the insecticidal substance fluralaner. "Asbestos-like scales" (original wording of the notification) developed over the entire body of an 11-year-old cat two days after administration, as did large areas of erosion on the animal's pads and erythema on the nipples and ears. Histological examination of punch biopsies from the chest, a nipple and the mucocutaneous border of the lip showed an interface dermatitis. According to the histology reports, erythema multiforme could have been the cause, but a differential diagnosis of exfoliative dermatitis could not be excluded. A thymoma, in particular, could have been the cause of the latter in the cat (7). The cat was euthanised at the owner's wish approximately 3 weeks after the initial notification because of the extensive and pronounced skin lesions. It was not possible to exclude a neoplasm as the cause since a necropsy was not performed. However, X-ray images showed no evidence of this. The causal relationship was assessed as "possible" because of the appropriate latency period and the histological findings. The most common categories of medicinal products following antiparasitics were hormone products (30 reports, 9.8%), products to treat the musculoskeletal system (25 reports, 8.2%, usually in the form of non-steroidal anti-inflammatory agents) and anti-infectives (21 reports, 6.9%).



21 reports (6.9%) concerned undesirable effects following use under the cascade, i.e. cases in which the product was used in a target species other than that for which it was authorised. Seven applications of this type occurred in cats. In two cases spot-on products containing up to 500 mg permethrin per pipette were used by mistake. The dermal LD50 for mammals is in the range of 1 to 1.5 g/kg (8). However, cats are very poor eliminators of the active substance as the result of a glucuronidation defect (9) and are therefore more susceptible. In addition, the intensive grooming habit of cats leads to repeated oral ingestion, which plays an additional role. One cat was brought to the veterinarian with impaired balance, in another the mistake was noticed immediately and the cat was washed with shampoo and subsequently showed no symptoms. For 58 reports (19% of the total) it was possible to establish a clear relationship between the use of a product and the adverse reaction ("probable" causality); in 105 cases (34%) at least one possible alternative cause was identified ("possible" causality); and in 15 cases (5%) it was possible to unequivocally rule out a relationship between the product and the adverse reaction. In the other 128 cases (42%) there was too little information to definitively determine causality. In 2017 a total of nine signals were identified that led to revision of the product information in the sections addressing adverse reactions or contraindications

### Consultations with Tox Info Suisse

Tox Info Suisse held 40,309 consultations in 2017. 2058 of these involved cases in which animals had been exposed to toxins either deliberately or accidentally. A veterinary medicinal product was involved in 111 of the cases in the latter category. The distribution of medical product categories in these cases is in line with a pattern that has been known for years (1) and with the distribution of authorisations for veterinary medicinal products.

Antiparasitics were most frequently involved, accounting for 33% of cases, followed by anti-inflammatory drugs (27%) and anti-infectives (10%). Of the 111 cases notified, only 40 met the minimum criteria for inclusion in the system. In 30 cases, excessive doses of flavoured tablets were ingested by 24 dogs and 6 cats. Anti-inflammatory drugs were involved in 16 of these cases. One dog swallowed 150 tablets each containing 100 mg carprofen, equivalent to approx. 600 mg per kg bodyweight (an approx. 150-fold overdose). It was not possible to establish how such a large quantity could have been ingested since it was substantially larger than the largest authorised pack, which contains 100 tablets. The animal was made to vomit, subsequently had slightly elevated liver enzymes and ultimately recovered. Other cases described the ingestion of 29 tablets each containing 100 mg carprofen (21 were vomited up again) or 20 tablets each containing 2.5 mg pimobendan (ingested with 10 chewable strips; the dog was slightly apathetic but otherwise asymptomatic). There were also isolated reports of this kind involving cats. Tablets containing 100 mg carprofen (maximum ingestion approx. 143 mg/kg bodyweight) and 60 or 600 mg cefalexin (maximum ingestion 600 mg/kg bodyweight) were swallowed. In this context attention is drawn to the corresponding warning about flavoured products in the information about the medicinal product (10).

### References

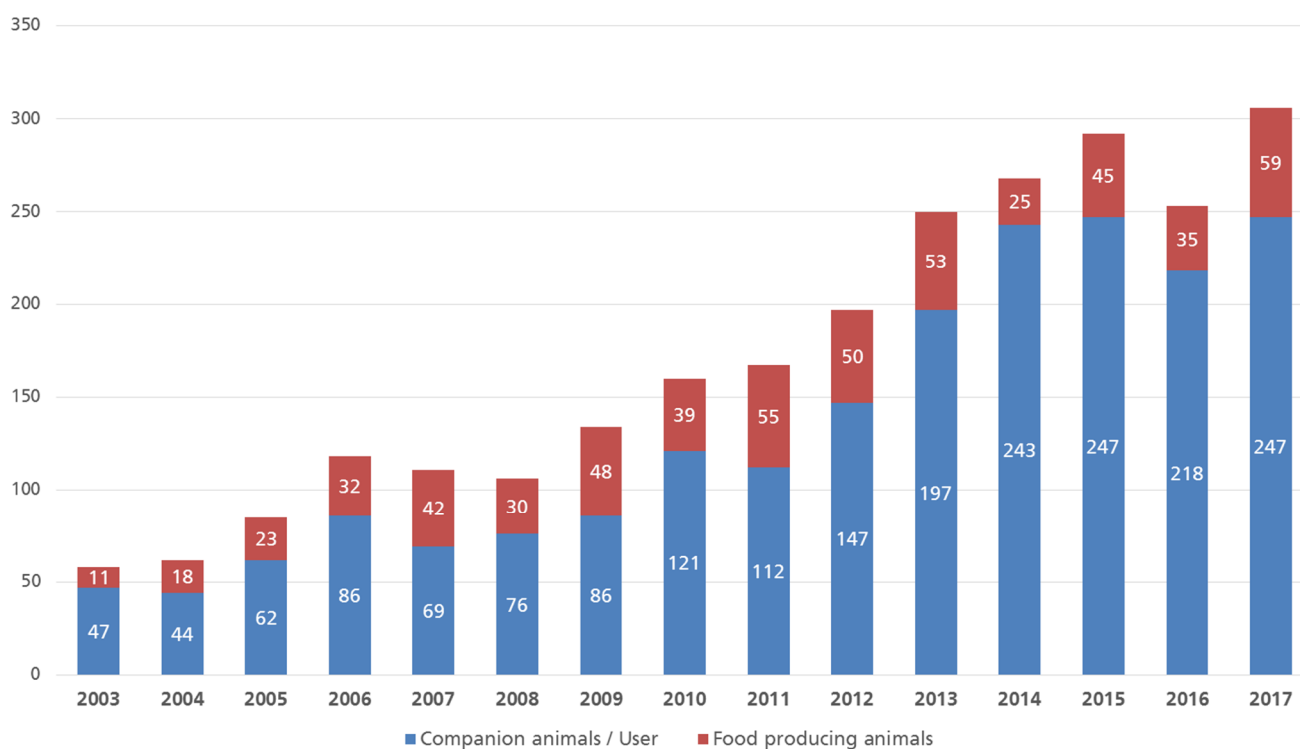
- (1) Müntener C., Kupper J., Naegeli H., Gassner B.: *Vigilance der Tierarzneimittel: Gemeldete unerwünschte Wirkungen im Jahr 2016*. Schweiz. Arch. Tierheilk. 2017; 159: 581-585.
- (2) EMEA/CVMP/552/03: *Guideline on causality assessment for adverse reactions to veterinary medicinal products*, 2003.
- (3) BVL, Bundesamt für Verbraucherschutz und Lebensmittelsicherheit: *Pharmakovigilanzreport Tierarzneimittel 2016. Spontanmeldungen unerwünschter Arzneimittelwirkungen in Deutschland*. Dtsch Tierärzteblatt. 2018; 9: 1254-1260.



- (4) Cooles S., Diesel G., Blenkinsop J.: Suspected adverse events, 2015. *Vet. Rec.* 2017; 180: 467–469.
- (5) EMA, European Medicines Agency: Veterinary pharmacovigilance 2016. Public bulletin. EMA/568976/2016, 2017.
- (6) EMEA/CVMP/EWP/005/2000-Rev.3: Guideline for the testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestation in dogs and cats, 2016.
- (7) Rottenberg S., Tschärner von C., Roosje PJ. Thyoma associated Exfoliative Dermatitis in Cats. *Vet. Pathol.* 2004; 41: 429–433.
- (8) Ungemach F. R.: Antiparasitika. In: *Pharmakotherapie bei Haus- und Nutztieren*, Ed. W. Löscher, F. R. Ungemach und R. Kroker, Parey Buchverlag, Berlin, 2003.
- (9) Richardson J. A.: Permethrin spot-on toxicoses in cats. *J. Vet. Emerg. Crit. Care.* 2000; 10: 103–106.
- (10) *Tierarzneimittelkompendium der Schweiz*: Ed. D. Demuth & C. Müntener, Institut für Veterinärpharmakologie und –toxikologie der Universität Zürich, 2017. Zugänglich unter [www.tierarzneimittel.ch](http://www.tierarzneimittel.ch).

**Figure 1**

Development of number of reports submitted between 2003 and 2017, divided into companion animals and livestock



**Table 1**

Distribution of adverse reactions reported in 2017, arranged by ATCvet code and providing specific data for dogs, cats and livestock. The fictitious code QZ makes it possible to specifically group adverse drug reaction reports involving reclassified products (i.e. not used for the authorised animal species and/or indication; use under the cascade regulation).

ATCvet group	Number of reports (% of each total)			
	All species	Dogs	Cats	Food producing animals <sup>1</sup>
QA: Alimentary tract and metabolism	7 (2.3%)	1 (0.6%)	1 (1.7%)	5 (11.1%)
QB: Blood and blood forming organs	5 (1.6%)	0	0	5 (11.1%)
QC: Cardiovascular system	6 (2.0%)	5 (2.8%)	1 (1.7%)	0
QD: Dermatologicals	9 (2.9%)	6 (3.3%)	0	1 (2.2%)
QG: Genitourinary system and sex hormones	10 (3.3%)	4 (2.2%)	1 (1.7%)	5 (11.1%)
QH: Systemic hormonal preparations, excl. sex hormones and insulins	30 (9.8%)	24 (13.3%)	5 (8.5%)	0
QJ: Antiinfectives for systemic use	21 (6.9%)	5 (2.8%)	2 (3.4%)	12 (26.7%)
QL: Antineoplastic and immunomodulating agents	1 (0.3%)	1 (0.6%)	0	0
QM: Musculo-skeletal system	25 (8.2%)	17 (9.4%)	3 (5.1%)	2 (4.4%)
QN: Nervous system	9 (2.6%)	5 (2.8%)	3 (5.1%)	0
QP: Antiparasitic products, insecticides and repellents	158 (51.6%)	100 (55.5%)	35 (59.3%)	12 (26.7%)
QS: Sensory organs	9 (2.9%)	9 (5%)	0	0
QV: Various	1 (0.3%)	0	1 (1.7%)	0
«QZ»: Use under the cascade	21 (6.9%)	3 (1.7%)	7 (11.8%)	3 (6.7%)
<b>Total</b>	<b>306</b>	<b>180</b>	<b>59</b>	<b>45</b>

<sup>1</sup>Cattle, dairy cows, calves, sheep, goats and pigs

## Information on the Swissmedic website

### Healthcare Professional Communication

06.05.2019

[DHPC – Tecentriq® \(Atezolizumab\)](#)

Fälle von immunbedingter Myositis im Zusammenhang mit Tecentriq®

30.04.2019

[DHPC – Dantrolen i.v., Injektionslösung](#)

Neue Filtrationsvorrichtung, um eine schnellere Vorbereitung für die Verabreichung an die Patienten zu ermöglichen

30.04.2019

[DHPC – Darzalex® \(Daratumumab\)](#)

Neu festgestelltes Risiko einer Hepatitis-B-Virus Reaktivierung

26.04.2019

[DHPC – Xeljanz® \(Tofacitinib\)](#)

Erhöhtes Risiko von Lungenembolie und Mortalität bei Patienten mit rheumatoider Arthritis, die in einer klinischen Prüfung 10 mg 2x täglich erhielten

17.04.2019

[DHPC – Néo-Mercazole® \(Carbimazol\)](#)

Risiko einer akuten Pankreatitis und Verstärkung der Empfehlung zur Kontrazeption

20.03.2019

[DHPC – Haemocomplettan® P \(Fibrinogen aus Humanplasma\)](#)

Vorsichtsmassnahme: geänderte Lagertemperatur

15.03.2019

[HPC – Iberogast® Tinktur](#)

Risiko von Leberschädigungen: weitere Anpassung der Arzneimittelinformation

13.02.2019

[DHPC – Mydrane® \(Tropicamid, Phenylephrin, Lidocain\)](#)

Risiko eines Irisprolapses, insbesondere bei Patienten mit einer flachen Vorderkammer mit Gefahr eines Verschlusses des Iridokornealwinkels

04.02.2019

[HPC – Systemisch und inhalativ angewendete Fluorochinolone](#)

Risiko für Aortenaneurysmen und Aortendissektionen

Aufnahme eines neuen Warnhinweises in die Arzneimittelinformation

01.02.2019

[DHPC – Lartruvo® \(Olaratumab\)](#)

Die Ergebnisse der beauftragten klinischen Phase 3 Studie, die nach der Zulassung durchgeführt wurde, bestätigen nicht die klinische Wirksamkeit von Olaratumab in der zugelassenen Indikation.

14.01.2019

[DHPC – Prezista® \(Darunavir\)](#)

Erhöhtes Risiko für Therapieversagen und für eine Mutter-Kind-Übertragung der HIV-Infektion während der Schwangerschaft

10.01.2019

[DHPC – Xofigo® \(Radium-223-Dichlorid\)](#)

Neue risikominimierende Massnahmen in der Fachinformation von Xofigo® in Bezug auf die Kombination mit Abirateronacetat plus Prednison/Prednisolon

12.12.2018

[DHPC – Valproat \(Depakine®, Depakine Chrono®, Valproate Chrono Sanofi®, Orfiril®, Valproat Chrono Desitin®, Valproat Sandoz®, Convulex®\)](#)

Valproat: Neue Anwendungseinschränkungen; Einführung des Schwangerschaftsverhütungsprogramms

<sup>1</sup> Most of the links are available in German/French only

30.11.2018

[DHPC – Hydroxyethylstärke \(HES\)-haltige Infusionslösungen](#)

(Tetraspan 6%, Infusionslösung, Venofundin 60 mg/ml, Infusionslösung, Voluven 6% balanced, Infusionslösung)

27.11.2018

[DHPC – Ferinject®, Injektionslösung zur i.v. Verabreichung](#)

Die Firma Vifor (International) AG informiert über das Auftreten eines Ferinject-Vials (Ampulle) mit blauem Inhalt (blau anstelle von dunkelbraun) in einer Klinik in Spanien.

21.11.2018

[DHPC – Präparate mit Wirkstoff Hydrochlorothiazid \(HCTZ oder auch HCT genannt\)](#)

Präparate mit HCT – Risiko für nicht-melanozytäre Malignome der Haut (Basalzellkarzinom, Plattenepithelkarzinom)

## Announcements

---

13.05.2019

[Classification of permethrin-containing preparations for topical application in animals](#)

These products shall in future come under the therapeutic products legislation in Switzerland

02.05.2019

[Statistics illegally imported medicinal products 2018](#)

Potency preparations remain at the top of the list of illegally imported substances

25.04.2019

[Round Table Innovation \(RTI\)](#)

Forum for multi-stakeholder dialogue

16.04.2019

[Treatment of peripheral arterial disease with paclitaxel-coated balloons and paclitaxel-eluting stents](#)

Potential association with increased mortality

11.04.2019

[DHPC – Flunixin ad us. vet., Injektionslösung](#)  
DEA in Tierarzneimitteln

09.04.2019

[Adaptation of the Guidance document Orphan Drug HMV4](#)

ZL100\_00\_002e\_WL

08.04.2019

[Reallocation of dispensing category C medicinal products to other dispensing categories](#)

Publication of the decisions

05.04.2019

[Breast implant associated-anaplastic large cell lymphoma \(BIA-ALCL\) – updated information](#)

Swissmedic statement

03.04.2019

[The Agency Council has appointed a new head of Communication and Networking](#)

Jörg Schläpfer appointed as the successor to Petra Dörr

01.04.2019

[Discontinuation of sale of mesh produced by C.R. Bard, Inc. for pelvic organ prolapse and stress urinary incontinence, and its removal from hospitals and distribution centres](#)

28.03.2019

[DHPC – Vetaflumex 50 mg/ml ad us. vet., Injektionslösung](#)

DEA in Tierarzneimitteln

07.03.2019

[DHPC – Meflosyl ad us. vet., Injektionslösung](#)

Wichtige sicherheitsrelevante Informationen

06.03.2019

[DHPC – Finadyne ad us. vet., Injektionslösung](#)

Wichtige sicherheitsrelevante Informationen

06.03.2019

[F&A Umteilung Abgabekategorien](#)

27.02.2019

[Update: Correction of the new eCTD specification documents Swiss M1 Specification and Swiss eCTD Validation Criteria](#)

18.02.2019

[Breast implant associated-anaplastic large cell lymphoma \(BIA-ALCL\) – updated information](#)

18.02.2019

[Pelvic floor meshes and slings – Reference to expert letters sent by the SGGG \(Swiss Society of Gynaecology and Obstetrics\)](#)

08.02.2019

[Publications](#)

Rückblick TAM-Vigilance 2017

Müntener C.R., Kupper J., Naegeli H., Gassner B.  
Vigilance der Tierarzneimittel: Gemeldete unerwünschte Wirkungen im Jahr 2017. Schweiz. Arch. Tierheilk., 2019 161: 107-112

01.02.2019

[DHPC – Vetagent ad us. vet., Injektionslösung](#)

Anpassung von Dosierung, Therapiedauer und Absetzfristen

01.02.2019

[DHPC – Pargenta-50 ad us. vet., Injektionslösung](#)

Anpassung von Dosierung, Therapiedauer und Absetzfristen

08.01.2019

[Hospital inspections: Priority issue reprocessing of flexible endoscopes](#)

Announcement

28.12.2018

[New form for reporting serious incidents for manufacturers & placers on the market](#)

14.12.2018

[Swissmedic laboratory publishes test method for nitrosamines in sartans](#)

Test method for active substances and finished medicinal products

13.12.2018

[ICH Meeting in Charlotte, USA, 10–15 November 2018](#)

Continuation of harmonisation efforts in an increasingly global International Council for Harmonisation

08.12.2018

[Authorised narcotics](#)

Jahresrechnung 2018

04.12.2018

[Reclassification of medicinal products from dispensing category D to E: evaluation concluded](#)

More medicines available for sale over the counter – Patient safety paramount

30.11.2018

[Betäubungsmittelverzeichnis um 16 neue psychoaktive Substanzen ergänzt](#)

Press release

23.11.2018

[Temporary authorisation to use medicinal products](#)

Temporary authorisation to use medicinal products in accordance with Article 9b para. 1 TPA

23.11.2018

[Ordinance on Licensing in the Medicinal Products Sector: publication of the text](#)

The Federal Council has approved the MPLO. Swissmedic and the FOPH publish the revised text as prior information.

23.11.2018

[Analysis of the valsartan batches recalled in July 2018 confirms NDMA contamination](#)

Presence of impurities in recalled valsartan products now proven

16.11.2018

[Reclassification of veterinary medicinal products in dispensing category C: evaluation concluded](#)

The actual reclassification of the medicinal products will take place in early 2019, once the revised Therapeutic Products Act has entered into force and in the course of normal administrative procedures.



16.11.2018

[Reclassification of therapeutic products in dispensing category C: Evaluation concluded](#)

The prevailing supply category C will be eliminated.

14.11.2018

[Renewed discovery of impurities in valsartan-containing medicines](#)

Swissmedic laboratory discovers contamination with N-nitrosodiethylamine above the tolerated level in certain valsartan batches

The complete list is available at the following web address [www.swissmedic.ch/updates-en](http://www.swissmedic.ch/updates-en)