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In this edition

Impressum

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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

Drug safety plays a vital role in many areas of healthcare provision. In the past, it was the authorities and the pharmaceutical industry that were primarily involved in identifying and evaluating adverse drug reactions. Nowadays, as well as healthcare professionals, affected patients are also taking the initiative when it comes to assessing the risks associated with medicinal products and the resulting measures (e.g. changing the Information for healthcare professionals and Patient Information texts). An overview of the responsibilities of the individual stakeholders can be found in the article on "Drug safety: Shared responsibility".

Adverse drug reactions (ADR) can be described in individual reports, as illustrated by the reports on statin-associated IMNM (immune-mediated necrotising myopathy) or the example of intestinal angioedema after the administration of ramipril. Sometimes the suspicion of an ADR cannot be confirmed, and a completely different cause is determined. One such case is presented in the article on "Ferjol's asthenia".

Certain ADR are particularly important for the benefit-risk profile of a medicinal product, and their occurrence triggers a safety signal. A potential risk is often communicated to healthcare professionals by means of a DHPC (Dear Healthcare Professional Communication). This information can also be made available to the public by publishing the DHPC on the Swissmedic website.

Just how important these safety-related reports issued by Swissmedic and the authorisation holders are is demonstrated by the examples of the risk of multiple vertebral fractures and reduced bone mineral density after discontinuation of treatment with denosumab, or the occurrence of a DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) after the administration of minocycline.

The 2016 annual statistics for pharmacovigilance, vaccinovigilance, haemovigilance and the monitoring of veterinary medicines provide a retrospective overview of the changes in drug safety for human medicines, vaccines, blood products and veterinary medicines.

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

We wish all our readers a happy festive season and a successful start to 2018.

The Editors

Drug safety and signals

"Ferjol's asthenia"

Introduction

The importance of pharmacovigilance is known and recognised. In accordance with the current Therapeutic Products Act, side effects of medicinal products observed in daily medical practice must be reported so that safety data, which are still inevitably incomplete when the medicinal products are brought to the market, can be collated by Swissmedic.

It is extremely important to consider, in the differential diagnosis, the possibility of adverse drug reactions in a patient. Obviously, pathological conditions can be caused by a variety of factors. The following description of the history of the illness in a patient has been conceived and written on the basis of a minimally documented report in order to illustrate this point.

Case narrative

The report concerns a 25-year-old woman who was working as a healthcare professional in a hospital. She received treatment with an antidepressant, a selective serotonin reuptake inhibitor, at a dosage of one 50 mg tablet once a day for about three months following a moderate depressive episode. Although the symptoms, including depressed mood, sleeping problems, palpitations and weight loss associated with a loss of appetite, improved on this antidepressant treatment, the patient continued to complain of fatigue and, moreover, appeared very pale. Following a blood test, the doctor diagnosed microcytic, hypochromic iron deficiency anaemia.

Despite various additional tests, including gynaecological and gastrointestinal investigations, no aetiology could be established, nor could any source of bleeding be found. Oral treatment with ferrous sulfate was initiated since the patient refused any injectable form of iron supplementation. A blood test after four weeks of treatment showed a slight improvement in the haemoglobin and serum ferritin levels, from 8 to 9 g/dL and from 20 to 25 µg/L respectively. A few weeks later, a new blood test showed no further improvement in the haemoglobin or ferritin levels. In view of this clinical picture of anaemia of unknown origin that failed to respond to medical treatment, it was decided to admit the patient to a hospital. During the second night of her hospital stay, a nurse spontaneously entering the patient's room noticed the patient standing over the washbasin cutting her arms and legs and bleeding profusely. First aid was administered. On the following day, a psychiatric opinion was requested and, a few days later, she was diagnosed with "Ferjol's asthenia". The patient's admission to the hospital prevented her from employing the strategies that she had devised to lose blood, and supplementation with iron produced a rapid improvement in the haemoglobin level and, therefore, her anaemia. Psychiatric treatment has been arranged.

Discussion

As regards the differential diagnosis, it should be noted that abnormal cases of bleeding such as bruising and purpura have been reported for SSRIs (selective serotonin reuptake inhibitors) (1), including reports of gastrointestinal and gynaecological bleeding, in some cases with a fatal outcome. Caution is therefore indicated in patients taking SSRIs, particularly if they are used concurrently with drugs known for their effects on platelet function (e.g. atypical antipsychotic agents and phenothiazines, most tricyclic antidepressants, acetylsalicylic acid and non-steroidal

anti-inflammatory drugs), and also in patients with a history of clotting disorders.

However, the diagnosis of "Ferjol's asthenia" (2) was clearly appropriate in the patient whose history is briefly described above once all other possible causes of anaemia had been ruled out.

The syndrome of "Ferjol's asthenia" is a factitious, or pathomimetic, disorder characterised by hypochromic iron-deficiency anaemia secondary to episodes of bleeding that are both induced and concealed in women, usually between the ages of 15 and 35, and who are typically employed in the healthcare professions. Pathomimia is often difficult to diagnose because it first has to be considered as a possibility.

Conclusion

In the differential diagnosis, it is important to consider the possibility of adverse drug reactions in a patient. Making a diagnosis at an early stage is important given that a variety of causes may explain a pathological picture. As illustrated by the course of the illness in this patient, multiple – including invasive – supplementary investigations often need to be arranged in view of the complexity of "Ferjol's asthenia", and the primary objective is to avoid any clinical deterioration or, more particularly, a fatal outcome.

Strict vigilance is therefore indicated when an adverse drug reaction is suspected, as should be the case in every medical differential diagnosis.

Literature

(1) See the product information for the active substance sertraline under the following link: swissmedicinfo.ch (status September 2017).

(2) It was the famous Professor Jean Bernard, a French haematologist, who first described the syndrome of "Ferjol's asthenia" in the 1960s, taking the name from a heroine in the novel "Histoire sans nom" [The story without a name] written in the 19th century by Barbey d'Aurevilly.

(3) Barbey d'Aurevilly Jules Amédée, "Histoire sans nom", Paris 1882.

(4) G. Haddad, "Monsieur Jean", Ed. Hémisphères Zellige, March 2017.

(5) M. Karamanou et al, Lasthénie de Ferjol syndrome: a rare disease with a fascinating history, Internal Medicine Journal 40 (2010) 381-382.

(6) C. Agostini et al, Syndrome de Lasthénie de Ferjol et maladie relationnelle : à propos d'un cas, Annales Médico-Psychologiques 166 (2008) 297-301.

(7) L. Farcy et al, L'anémie par spoliation sanguine volontaire : le syndrome de Lasthénie de Ferjol, Rev Med Liege 2005; 60:9: 719-723.

Risk of multiple vertebral fractures and reduced bone mineral density after discontinuation of treatment with Prolia® (denosumab), solution for injection

Prolia® is authorised for the treatment of osteoporosis in postmenopausal women for the prevention of vertebral and non-vertebral fractures.

In mid-December 2016, the marketing authorisation holder Amgen Switzerland AG, in consultation with Swissmedic, sent a DHPC (Dear Healthcare Professional Communication) concerning the risk of multiple vertebral fractures and the reduction in bone mineral density following the discontinuation of treatment with Prolia®. On 21.12.2016, the DHPC was published on the Swissmedic website (available in German/ French only).

The DHPC was prompted by various reports from the regional pharmacovigilance centres about patients with substantial bone mineral density loss, in some cases to a level below that present at the start of Prolia® treatment. Between autumn 2015 and the end of November 2016, Swissmedic received a total of 67 reports on this issue from the regional pharmacovigilance centres in its ADR database. The loss of bone mineral density was associated with increased bone turnover and with vertebral fractures following the discontinuation of treatment. Most of these complications were observed at the follow-up checks 9, 12 or 15 months after discontinuation of longstanding treatment with Prolia®.

Summary of the key points of the DHPC:

- Multiple vertebral fractures (MVF) following the discontinuation of Prolia® in female patients with osteoporosis have been reported in clinical trials and after market authorisation.
- These MVF usually arise in association with the loss of bone mineral density that occurs after treatment with Prolia® is stopped, particularly in patients with a history of vertebral fractures.
- In accordance with the pharmacological properties of Prolia®, the effects on bone density (BD) and bone turnover regress after discontinuation. In clinical trials, the BD returned to the values measured before treatment after Prolia® was discontinued. In some patients, however, the BD dropped, within a year, to a level below the baseline measured before the start of the Prolia® treatment.

Measures

In consultation with Swissmedic, Amgen Switzerland AG has now updated the Information for healthcare professionals (IHP) and the Patient Information (PI). These contain important new information about the risk after discontinuation of treatment and new requirements concerning the use of the preparation.

The new IHP and PI were published on the Swissmedic publication platform www.swissmedicinfo.ch on 09.07.2017.

To ensure that professionals and the public were informed promptly, Swissmedic published an HPC on its website on 06.09.2017 (available in German/French only):

Summary of the key points of the HPC:

A *Boxed warning* at the start of the "Warnings and Precautions" section in the Information for healthcare professionals contains the following new text:

Important information: Multiple vertebral fractures (MVF) and a reduction in bone mineral density (BMD), in some cases to below pre-treatment levels, can occur following discontinuation of treatment with Prolia®.

Before treatment with Prolia® is started and before it is discontinued, an individual benefit-risk profile should be assessed in light of these risks. Patients should be advised not to interrupt Prolia® therapy without their physician's advice.

The Patient Information includes the following new text under the heading "When should you be especially careful when using Prolia®?"

Bone fractures, particularly in your spine, can occur after you stop taking Prolia® (multiple vertebral fractures), and the bone mineral density can start falling again, possibly even below the initial level. Please therefore do not, under any circumstances, stop taking the treatment with Prolia® without first discussing this with your doctor. If your Prolia® treatment is stopped, your doctor will talk to you about the possibility of switching to another medicine. Careful follow-up, e.g. including the determination of bone mineral density, is also required.

Recommendations for healthcare professionals

- Advise your patients not to interrupt treatment with Prolia® without medical advice.
- Before discontinuing Prolia®, you should carry out an individual benefit-risk analysis in light of the points mentioned above.
- Limited data are available from clinical trials suggesting that bone mineral loss can be reduced by switching from Prolia® to another antiresorptive treatment (e.g. bisphosphonates). However, there are reports of patients who failed to respond sufficiently to bisphosphonates. At present, insufficient data are available to enable more specific recommendations to be issued on the procedure after the discontinuation of Prolia®.

Minac® capsules and Minocin® acne tablets (minocycline): Risk of a drug reaction with eosinophilia and systemic symptoms (DRESS)

Minac® capsules and Minocin® acne tablets are authorised in Switzerland for the treatment of acne vulgaris, particularly for papulopustular and cystic forms.

In mid-June 2017, the marketing authorisation holders Galderma Schweiz AG (Minac®) and Drossapharm AG (Minocin®), in consultation with Swissmedic, issued a DHPC (Dear Healthcare Professional Communication) on the risk of DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) and severe systemic hypersensitivity reactions during treatment with minocycline. On 26.06.2017, the DHPC was also published on the Swissmedic website (available in German/French only).

The trigger for the DHPC was a report from a regional PV centre in Switzerland. A 26-year-old woman taking Minac® 50 mg capsules developed DRESS syndrome with eosinophilic myocarditis and pneumonia. The young patient subsequently died of the complications of a heart transplant necessitated by the eosinophilic myocarditis.

Systemic hypersensitivity reactions are a very important feature of the risk profile of minocycline and should be taken into account when deciding whether the drug is indicated. The Swissmedic database of adverse drug reactions (ADR) includes a total of 82 reports with 199 ADR connected with the oral administration of minocycline. About half of the ADR concern systemic hypersensitivity reactions with organ involvement (liver, skin, blood count, vasculitic manifestations, heart and anaphylaxis).

Summary of the key points of the DHPC

- Minocycline can lead to serious systemic hypersensitivity reactions with organ involvement, including DRESS syndrome. The latter usually manifests as a drug rash with eosinophilia and systemic symptoms, e.g. liver damage.
- DRESS syndrome is potentially life-threatening.
- If DRESS syndrome or other hypersensitivity reaction is suspected, the treatment with minocycline should be discontinued immediately and permanently, and appropriate therapeutic measures should be initiated.
- Patients should be informed of the possible warning symptoms, such as fever or the occurrence of a skin rash, and they should contact a doctor as soon as such symptoms occur.
- The blood count and renal and hepatic parameters must be checked at regular intervals.

Since minocycline was launched, cases of DRESS syndrome during the administration of minocycline preparations, in some cases with a fatal outcome, have appeared in the worldwide literature. Since 1970, the VigiBase database managed by the Uppsala Monitoring Centre (the WHO ADR database) has received a total of 127 reports of DRESS syndrome associated with minocycline, with a fatal outcome in 19 cases.

In Switzerland, of the estimated 235,000 patients who have been treated with minocycline over the past 10 years, only one is known to have developed DRESS syndrome associated with the use of minocycline, as described in the report above.

Measures

In consultation with Swissmedic the marketing authorisation holders Galderma Schweiz AG (Minac®) and Drossapharm AG (Minocin® Akne) have now amended and updated the "Warnings and precautions" and "Undesirable effects" sections of the Information for healthcare professionals (IHP) and Patient Information (PI). A new "Hypersensitivity reactions" section was added with the following wording:

Warnings and precautions

Hypersensitivity reactions

Minocycline can lead to serious systemic hypersensitivity reactions with organ involvement. These include acute reactions, possibly progressing to anaphylactic shock (including with a fatal outcome).

One serious hypersensitivity reaction with organ involvement is DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms). This can involve a drug rash with eosinophilia and systemic symptoms, often occurring several weeks after the start of treatment, and can manifest as skin reactions (e.g. rash or exfoliative dermatitis), fever, lymphadenopathy, eosinophilia and inflammatory involvement of one or more organs (e.g. hepatitis, pneumonitis, nephritis, myocarditis, pericarditis, myositis, encephalitis or pancreatitis).

A protracted course or recurrences over a period of several months after discontinuation of treatment, including fatalities in rare cases, are possible. In the event of a skin rash or other allergic manifestations (e.g. swelling of the face or other parts of the body), the treatment should be discontinued immediately and permanently, and appropriate therapeutic measures should be initiated.

The blood count and renal and hepatic parameters must be checked at regular intervals.

Other hypersensitivity reactions with organ involvement, but without eosinophilia or skin involvement, can also occur, e.g. drug-induced lupus, vasculitis and agranulocytosis.

The new IHP and PI for the two preparations Minac® and Minocin® Akne are available on the Swissmedic website at http://www.swissmedicinfo.ch.

Statin-associated immune-mediated necrotising myopathy (IMNM) – New Swiss cases

In our Swissmedic Vigilance-News Edition 18 in May 2017, we reported on the epidemiology, pathophysiology, clinical features and treatment of IMNM. We now highlight two more Swiss cases that have been reported to Swissmedic in connection with pharmacovigilance.

Case 1

A 69-year-old man complained of muscle weakness in his legs that was increasingly restricting his mobility. He also noticed declining strength in his arms. Two years previously he had been diagnosed with type 2 diabetes and hyperlipidaemia, for which treatment with metformin 1700 mg/d and atorvastatin 40 mg/d had been initiated. Blood tests showed elevated transaminases: ASAT 395 U/L (ref. <50 U/L), ALAT 229 U/L (ref. <50 U/L) and an elevated CK of 12,253 U/L. The treatment with atorvastatin was immediately terminated. A muscle biopsy and a positive test result for anti-HMGCR autoantibodies led to the diagnosis of a statin-associated IMNM. Initial prednisone treatment proved unsuccessful. The same applied to the additional use of azathioprine. Only the renewed administration of rituximab managed to produce a distinct improvement in the muscle weakness. Subsequently, maintenance treatment with prednisone and azathioprine resulted in a further improvement of his symptoms.

Case 2

A proximal muscle weakness in all four extremities was diagnosed in a 66-year-old man. At this time he had been taking atorvastatin 40 mg for 18 months as secondary prophylaxis in view of chronic venous insufficiency in the right middle cerebral artery territory. The electromyogram showed abnormal spontaneous activity with fibrillation potentials and positive sharp waves. A paraneoplastic syndrome was ruled out by whole-body PET. He was known to suffer from polymyositis, and an MRI of the upper and lower leg muscles showed a diffuse oedema over the whole of the gluteal and thigh muscles. A significant rise in the CK level (20,000 U/L) and positive anti-HMGCR autoantibodies were key test results that enabled a statin-associated IMNM to be diagnosed. The treatment with atorvastatin was stopped immediately and replaced with treatment with steroids, azathioprine and intravenous immunoglobulins. Despite a slight improvement on this immunosuppressive therapy, the patient did not initially recover completely from the illness.

Discussion

Both of the patients described above showed muscle weakness of the major muscles on clinical examination. Key diagnostic features were muscle symptoms and elevated CK, including after the statin was discontinued. In such cases an autoimmune myopathy should be considered. The diagnosis is confirmed either by a recently developed blood test for anti-HMGCR autoantibodies or by a muscle biopsy. The required treatment of statin-associated IMNM varies from one individual to the next. While immunosuppressive treatment is potentially required, the specific immunosuppressant that produces the best results varies from patient to patient. As described for the first case, the use of the monoclonal antibody rituximab can also produce a distinct improvement in the patient. Treatment is not usually successful in the short term. The extent to which an early diagnosis of this condition influences its course is currently not clear. Nor can the incidence or prevalence be estimated on the basis of the individual case descriptions.

A potential underdiagnosis is also conceivable, given that the specific antibody test is only available in specialised laboratories.

In this connection, we would like to encourage healthcare professionals to consider this serious ADR, with hitherto unknown incidence, during statin therapy and to confirm the diagnosis if myopathy is suspected. In the event of a positive result, the treating physicians should report this to their regional Pharmacovigilance Centre in Switzerland.

Clinically important factors such as the duration of statin treatment, a change in the statin therapy, dosage, co-medication with other cholesterol-lowering drugs, latency period, symptoms, laboratory results or histological findings, the exclusion of other differential diagnoses, treatment of symptoms and the course after discontinuation and during immunosuppressive therapy are important in this connection.

An interesting case: ACE inhibitor-induced intestinal angioedema

ACE inhibitors are a standard treatment for hypertension and chronic heart failure. Known side effects include a dry cough (common) and angioedema of the face and oropharynx (uncommon). A study group from Lugano describes a fairly rare case of isolated intestinal angioedema triggered by an ACE inhibitor.

A 92-year-old woman was admitted to hospital as an emergency with intractable diffuse abdominal pain. The pain began one month before admission, occurred intermittently and was only partially responsive to painkillers. No further gastrointestinal symptoms were present. The patient had a history of coronary heart disease and hypertension with consequent left ventricular dysfunction. At the time of admission, she was taking the following medication: acetylsalicylic acid, ramipril, nicorandil, escitalopram and pantoprazole.

On admission, the patient was in a poor general condition and complaining of severe, diffuse abdominal pain. Peritoneal irritation was ruled out, laboratory tests showed moderate renal insufficiency and a plain abdominal radiograph was unremarkable. Ultrasound revealed cholelithiasis without signs of cholecystitis or biliary tract dilatation.

Attempted treatment with fentanyl transdermal patches proved unsatisfactory. Other radiological investigations (CT scan of the abdomen, contrast esophagram) did not reveal any irregularities.

During further investigations, it emerged that ramipril had been prescribed to treat heart failure four months before the symptoms started. Ramipril was discontinued because ACE inhibitor-induced intestinal angioedema was suspected. The abdominal pain situation progressively resolved, cardiac compensation was good, and the patient remained free of symptoms for one year after discharge.

Although typical radiological abnormalities such as oedema of the bowel wall and ascites were absent, the temporal relationship between the prescription of ramipril and the occurrence of the symptoms and the rapid improvement in symptoms after the discontinuation of ramipril led to the justified exclusion of other differential diagnoses.

Emergency doctors, surgeons, internists and general practitioners should consider ACE inhibitors in the differential diagnosis of unexplained abdominal pain. The early discontinuation of the medication can prevent further complications and even unnecessary surgical interventions in some cases.

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

Literature

Dietler V, Fusi-Schmidhauser T, Intestinal Angioedema in a palliative care setting, American Journal of Medicine, 2016: 129 (11): e 293-4

Regulatory

Drug safety: Shared responsibility

Numerous stakeholders

The safety of medicines is a major concern for all stakeholders in healthcare, not just for patients. In Switzerland, safety issues around oral contraceptives, medicines containing isotretinoin and the use of valproate in pregnancy have been the focus of public attention in recent years.

Numerous frequently investigated factors are important in ensuring the success of drug treatments. The responsibility for the various aspects of compliance-relevant drug safety is shared across all stakeholders for ethical and scientific reasons, on the basis of legal requirements (Therapeutic Products Act) and out of obvious self-interest. Important aspects concerning the responsibility of individual stakeholders are outlined below.

Authorities

Swissmedic and cantonal agencies are the authorities responsible for drug safety. *As a regulatory and monitoring authority* Swissmedic is responsible for ensuring that medicinal product information is correct and updated by the authorisation holders (1). This includes the Information for healthcare professionals and Patient Information for medicinal products authorised in Switzerland and prompt communication in the event of newly discovered drug risks. In the event of any safety-relevant findings, Swissmedic must also ensure that healthcare professionals (via DHPC) and the public are informed without delay. If necessary, and also in consultation with foreign partner authorities, Swissmedic can also take safety-relevant measures such as restricting the authorised indications, modifying the product information, making changes to the labelling of drug packaging or, if applicable, reclassifying an OTC preparation as a prescription-only medicine. An authorisation holder can also be required to produce material that promotes safe use, such as patient cards or checklists for prescribing. Communicating adequately to the right target audience is important here. In this context, efforts are under way worldwide to increase transparency, including for the general public, by making information for patients and their relatives more understandable.

The *cantonal authorities*, on the other hand, are tasked with ensuring compliance with the legal requirements and medical due diligence obligations, particularly by prescribers and dispensing outlets, i.e. in hospitals, medical practices, pharmacies or homes for the elderly (1).

Medical professionals and their professional associations

Medical personnel and *healthcare professionals* make an important contribution to drug safety. In hospitals, medical practices and pharmacies, but also in nursing homes and the community nursing service, and depending on their role in each case, these individuals are responsible for the correct prescribing, dispensing and use of medicines (1, 2). The clarification of possible risk factors before prescribing is just as important here as providing patients with accurate information. Any helpful materials such as checklists (e.g. for prescribing oral contraceptives) or patient cards (e.g. on the use of valproate in pregnancy, or of methotrexate in non-oncological indications) provided by Swissmedic, authorisation holders or medical professional organisations should be used consistently, and the published warnings (medicinal product information and supplementary DHPC) must be observed (3).

If notifiable adverse reactions are observed in a patient receiving drug treatment, these

must – despite the extra work for the primary reporter – be reported to the authorities in order to improve drug safety, not just because this is a legal requirement but for ethical reasons as well.

Meticulous documentation of drug treatment is also important, particularly at interfaces such as hospital admissions or discharges. Valuable projects have been conducted in this area, for example *progress! Safe medication at interfaces* by Patient Safety Switzerland (4). Quality assurance strategies such as the systematic comparison of medicines are very helpful in improving the safety of medicines. However, they do require corresponding resources, and this is one of the key challenges, as hospitals would need to allocate resources for this type of quality management. At the same time, the proven financial benefit of reducing the consequences of adverse drug reactions (5) is not accrued directly, but results in a lowering of the general costs for the insured persons.

Medical professional associations can also make an important contribution to drug safety by alerting their members, as needed, to safety-relevant publications by Swissmedic or authorisation holders (multiplier effect) (6). Another very welcome development is the professional sharing of information on specific issues around identified safety-relevant risks.

Patients and their organisations

A wholesale rethink has taken place in recent years on the part of *patients* and their relatives. On the one hand, patients and their organisations are demanding a greater say in their treatment and, as a precondition, greater transparency from the manufacturers and the authorities specifically as regards the safety of "their" medication. Easy-to-understand package leaflets are important in this context, as is the publication of additional safety-relevant information (e.g. the Risk Management Plan Summaries). On the other hand, patients and their relatives can be assumed to possess a certain amount of self-initiative. Competent patients read the package leaflets for the medicines, often obtain information on the Internet and dare to ask their doctor or dispensing professional questions about a particular drug treatment and its risks. They might also, for example, consult www.swissmedicinfo.ch as a reliable source of information. In the event of suspected adverse drug reactions, patients should also be encouraged to make use of their reporting right and inform the doctor or pharmacist (1).

Patient organisations are very important in voicing the concerns of those who are affected, particularly those suffering from rare illnesses. Thanks to their much-frequented networks, these organisations can quickly reach those affected and their relatives – and they can also serve as a reliable source of information on drug safety.

Conclusion

Drug safety is a valuable asset and involves numerous stakeholders. The tasks of the individual stakeholders are known and also clearly regulated. Compliance with the legal obligations, and also quality management, involves effort, but this is essential for ensuring safe drug treatment.

References

(1) Federal Act on Medicinal Products and Medical Devices (Therapeutic Products Act, TPA), as at 1 January 2014

(2) Federal Act on University Courses for Medical Professions (Medical Professions Act, MedPA), as at 1 January 2016

(3) Swissmedic Market Surveillance: www.swissmedic.ch/swissmedic/en/home/humanarzneimittel/marktueberwachung.html

(4) Patient Safety Switzerland: http://www.patientensicherheit.ch/de/themen/Pilotprogramme-progress--/progress--Sichere-Medikation.html

(5) Conference of the Patient Safety Switzerland Foundation on 1 June 2017, presentation by Martina Anditsch
http://www.patientensicherheit.ch/de/themen/Pilotprogramme-progress--/progress--Sichere-Medikation/Tagung-Sicheres-Medikationsmanagement.html

(6) Swiss League Against Epilepsy
https://www.epi.ch/page.php?pages_id=1251&language=de

Submission of risk management plans (RMP), RMP updates and RMP summaries

With effect from 24 March 2017, Swissmedic published online the amendments to the information sheet RMP/ICH E2E(1) – Information for submissions (MU103_10_002d_MB, available in German and French only).

The information sheet has been restructured and updated to reflect current practice. It explains to authorisation holders the formal and regulatory aspects of submitting the RMP, RMP updates and RMP summaries. There are important changes in the following areas:

The obligation to submit an RMP with applications for "major variations" has been specifically delimited:

An RMP/RMP update must only be submitted if the major variation results in changes to the RMP that affect the following aspects:

- Safety concerns
- Pharmacovigilance activities
- Risk minimisation measures

Fundamentally, however, Swissmedic may request an RMP/RMP update at any point in the life cycle of a medicinal product if there are concerns about its benefit-risk ratio.

Content and format of the RMP/RMP-update specified in greater detail:

- The risk management of a medicinal product must be viewed as a global activity. Differences may, however, still arise, particularly as a result of different indications in different countries, specific features of healthcare systems or target populations, for example. For this reason, different versions of the RMP for a medicinal product may be valid in certain regions.
- The content and form of the RMP that must be submitted to Swissmedic must be based on the ICH E2E Guideline *Pharmacovigilance Planning* and the *European Medicines Agency* (EMA) Guideline *Good pharmacovigilance practices (GVP): Module V – Risk management systems*.
- If an RMP has been submitted to, or approved by, the EMA, this should be forwarded to Swissmedic.

Regulatory aspects of submitting an RMP summary specified in greater detail:

An RMP summary must be submitted for the following authorisation applications:

- New active substances for synthetic human medicines and herbal human medicines
- Human medicines manufactured using biotechnology (including biosimilars)
- Human vaccines

The submission of the RMP summary is a requirement that is specified with the approval of the application. The RMP summary must be submitted to Swissmedic as a separate document written in English: via the Portal, on a CD by post or as an eCTD (*Electronic Common Technical Document*).

The RMP summaries will be published on the Swissmedic website www.swissmedic.ch > Human medicines > Market surveillance > Vigilance of medicines > Risk Management Summaries and linked on www.swissmedicinfo.ch. The publicly accessible summaries of the risk management plans enable interested parties, i.e. both professionals and lay people, to see what measures are currently being employed to minimise the risks associated with a given medicinal product.

Statistical Review 2016

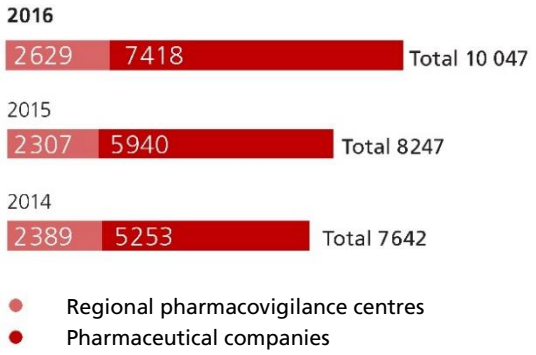
Vigilance of human medicines

Within the framework of the pharmacovigilance network, the direct reports from healthcare 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

- Swissmedic received 10,047 initial reports of suspected adverse drug reactions (ADR) in 2016. 2,629 of them were sent by the six regional pharmacovigilance centres (RPVC), 7,418 by the industry. As in previous years, there was again a sharp rise in the number of reports received (+21.8 %), due to an increase in the volume reported by companies. In addition, the number of follow-up reports increased by 41.7 % compared with the previous year to 3,056. This puts Switzerland in 6th place worldwide in terms of reporting rate.
- The percentage of industry reports notified electronically to Swissmedic rose to more than 90 %, most of them arriving via the pharmacovigilance gateway. A further six companies were given gateway access in 2016, bringing the total number using this reporting route to 24 in February 2017.
- The second electronic reporting route, the online reporting portal ElViS (Electronic Vigilance System), was launched in October 2014, enabling healthcare professionals to report ADR online to one of the regional pharmacovigilance centres. In 2016 Swissmedic received 204 reports from healthcare professionals via the portal. By the end of 2016, most of the pharmaceutical companies without access to the gateway were also reporting via ElViS. At the end of the year, 108 companies had access to this reporting route, twice the number in 2015.

Figure 1: Adverse drug reactions, human medicinal products



Vaccinovigilance

Summary of adverse events following immunization reported in Switzerland

During 2016, Swissmedic received 209 case reports of suspected "adverse events following immunization" (AEFI) from Switzerland. This is fewer than the number of cases submitted during 2015 (278 reports) and 2014 (296 reports). However, 80 of the 278 reports submitted in 2015 were retrospective, involving cases occurring in previous years. Similarly, 106 of the 296 case reports submitted in 2014 were retrospective. No such retrospective reporting occurred during 2016 and hence all 209 case reports contain recently occurring AEFI. Notably, there are no accurate data available regarding the total number of vaccines/doses administered during 2016 and therefore a straightforward conclusion regarding AEFI reporting rates cannot be drawn. As in the past, Swissmedic encourages spontaneous, high-quality reporting of AEFI to enable early detection of new safety signals. Members of the Swissmedic Human Medicines Expert Committee (HMEC) have been discussing and evaluating important safety topics concerning vaccines since 2010. An increased AEFI reporting rate followed by a scientific evaluation of relevant cases can enable risk minimisation measures to be adopted where necessary in order to ensure vaccines safety.

Complete report: Summary of adverse events following immunization reported in Switzerland during 2016

Haemovigilance

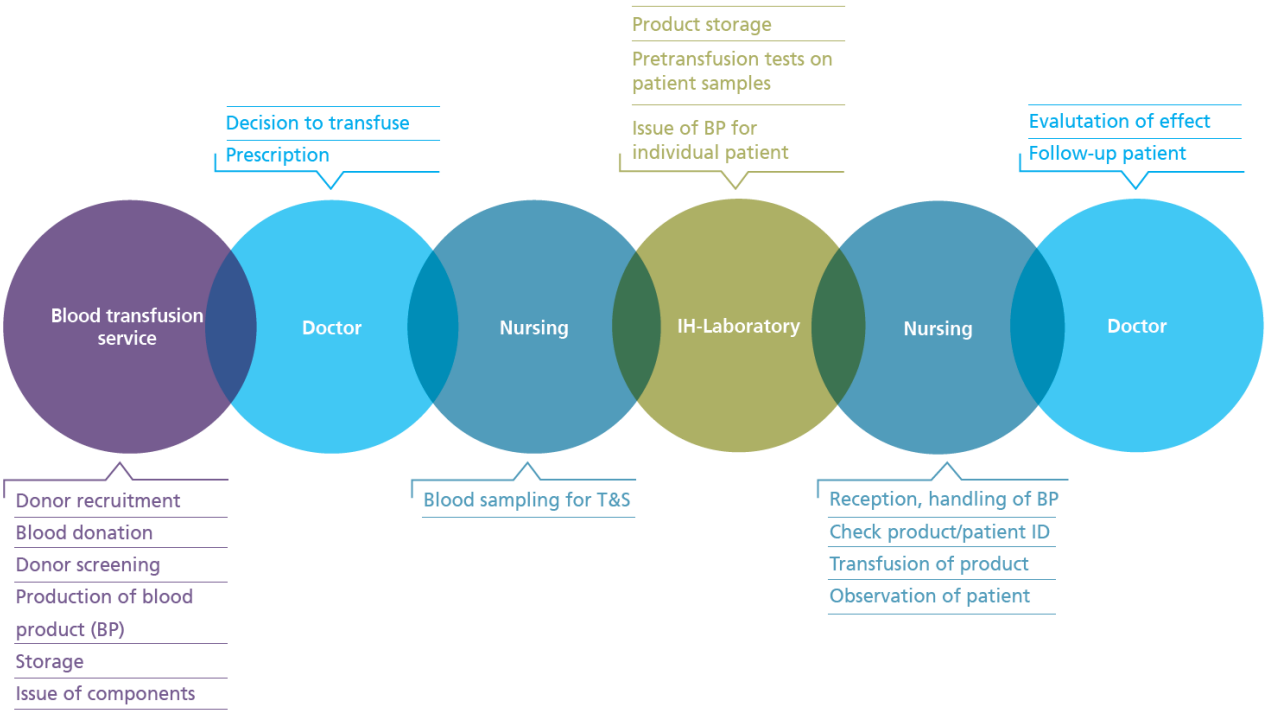
New information about transfusion safety in Switzerland

Overview

Haemovigilance reports permit the implementation of targeted measures to improve safety in the use of blood and labile blood products. The reporting rate rose again in 2016 and currently stands at 10 reports per 1,000 transfusions. Reports cover both transfusion reactions and transfusion errors, near misses (which may also result in quality assurance measures), donor reactions and protective measures against infectious diseases.

The causes of these events are found throughout the transfusion chain (Figure 1). The figure shows which professions are involved in a transfusion and thus in the prevention of events.

Figure 1: Transfusion chain



Transfusion reactions

A total of 1,777 transfusion reactions were reported in 2016.

Figure 2 shows their distribution by reaction category.

Figure 2: Transfusion reactions (TR) reported in 2016 by category

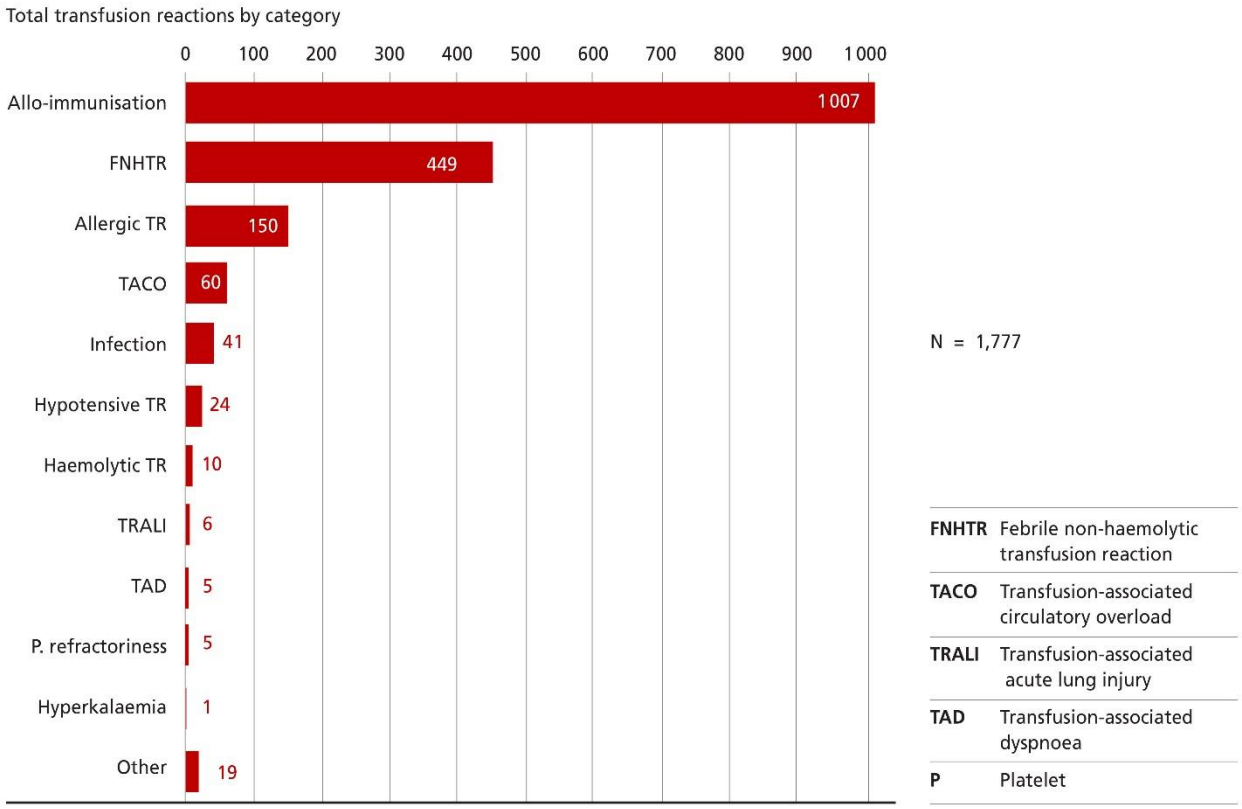


Figure 2 shows the distribution of the transfusion reactions reported in 2016 among the different categories. All 1,777 cases are shown, irrespective of imputability (causality). With the exception of 2 cases with "possible" imputability, all 41 cases of infections were suspected cases which were classified as "unlikely" or "excluded" following investigation.

Hepatitis E

In 2016 there were again no reports of transfusion-transmitted hepatitis E in Switzerland. However, the donor pathogen prevalence is estimated as being in the order of 1 viraemic donation per approx. 2,000 donations (1, 2). This means that a high level of under-reporting of (often asymptomatic) transfusion-related transmission is likely. The disease can lead to complications in immunosuppressed patients or those with pre-existing liver disease, e.g. due to the development of liver cirrhosis.

A Swiss working group has developed recommendations for the prevention of (transfusion-related) hepatitis E. Its first step was to publish a Healthcare Professional Communication (HPC) warning of the possible complications in immunosuppressed patients, particularly those who are transplant recipients.

Link to HPC – Hepatitis E in transplant recipients

The working group has also recommended HEV testing (not relevant for release) of all blood donations in 96-donation pools. This would mean that the results of an estimated 80% of blood components would be known before the transfusion took place, and that a large proportion of positive products could

be destroyed in time. This type of testing in mini-pools of 96 donations does not detect contaminated blood products with a viral load below approx. 2000 IU/mL. Overall, this residual risk attached to undetected low viral loads would appear to be acceptable since the likelihood of a patient being infected by foodstuffs is substantially greater.

Internationally, comprehensive hepatitis E testing is done only in Ireland and in the United Kingdom of Great Britain and Northern Ireland (UK). However, introduction of the tests is under discussion in many other European countries (e.g. the Netherlands, France, Germany; last revised July 2017).

Findings and prevention

The section on "findings and prevention" in the annual report focuses on issues that have a major impact in the practical setting:

- Transfusions in children
- New guidelines for quality assurance in transfusion practice
- Current information about transfusion-transmitted infections

Haemovigilance annual report 2016

Literature

(1) Gallian P, Piquet Y, Assal A, Djoudi R, Chiaroni J, Izopet J, Tiberghien P. [Hepatitis E virus: Blood transfusion implications]. [Article in French]. Transfus Clin Biol 2014 Nov; 21(4-5): 173-7.

(2) Hewitt PE, Ijaz S, Brailsford SR, Brett R, Dicks S, Haywood B, Kennedy IT, Kitchen A, Patel P, Poh J, Russell K, Tettmar KI, Tossell J, Ushiro-Lumb I, Tedder RS. Hepatitis E virus in blood components: a prevalence and transmission study in southeast England. Lancet 2014 Nov 15; 384(9956): 1766-73.

Vigilance of veterinary medicines

Reports on veterinary medicinal products authorised by Swissmedic

A total of 253 reports were recorded in 2016, equivalent to a 13% reduction compared to 2015 (292 reports). Distribution by sources remains comparable with previous years, with 72.3% of the reports (N=183) being submitted by distributors/marketing authorisation holders, 13.4% by practising veterinarians (N=34) and 12.6% (N=32) by Tox Info Suisse (the Swiss poisons information centre in Zurich) as part of their advisory service. The dominant position of the industry as the main source of vigilance reports for veterinary medicinal products is also observed in neighbouring countries. In a publication on the years 2011 to 2013, the overwhelming majority of reports in Germany originated from the pharmaceutical industry (1). In Switzerland, the remaining reports for 2016 were submitted either directly by animal owners (1.2% or N=3) or by a public office (0.4%, N=1).

Small animal species continue to be most affected, with 178 reports (70.4%) of adverse reactions recorded for dogs and 32 (12.6%) for cats. A small animal share of approx. 80% is also observed in foreign systems. In the UK, 4,329 (76.8%) out of a total of 5,638 reports were recorded for small animals in 2015 (2). In decreasing order, the rest of the reports from Switzerland involved cattle and calves (17 reports) and horses (10 reports). All other target animal species featured in fewer than 5 reports across the whole year. No reports were received in 2016 on reactions in users or animal owners.

Table 1 presents the submitted reports, sorted by medicinal product classes according to the ATCvet code. Adverse reactions were most frequently reported after the administration of antiparasitics (145 reports, 57.2%). These were followed by hormone preparations (26 reports, 10.3%), anti-infectives (19 reports, 7.5%) and products for the treatment of the musculoskeletal system (17 reports, 6.7%, usually as non-steroidal anti-inflammatory drugs). Fewer than 15 reports (5% of the total) were received for all the other product groups.

In 2016, Tox Info Suisse provided advice on 39,543 occasions; 2,002 cases involved animals. In accordance with a long-standing agreement with Swissmedic, all cases involving both animals and veterinary medicinal products are periodically forwarded to Swissmedic. In 2016 there were 80 such cases. Distribution by medicinal class remains comparable with previous years: antiparasitics were most frequently involved, accounting for 36.1% of the cases, followed by anti-inflammatory drugs (25.5%) and anti-infectives (12.1%). 40% of the cases (N=32) fulfilled the minimum criteria for inclusion in the system. In 17 cases, tablets, usually in excessive doses, were accidentally ingested by 15 dogs and 2 cats. Anti-inflammatory medication was most frequently involved (10 cases, 58.8% of cases of accidental ingestion). The largest quantity described was for a 6-year-old Appenzeller dog weighing 25 kg, which consumed 80 tablets each containing 100 mg of carprofen. The total quantity of 8 g was equivalent to 57 times the recommended dose (228 mg/kg) and resulted in apathy and loss of appetite. No further information was available on the outcome of this case. In most cases, since the animals were asymptomatic or had already vomited up the tablets by the time the advice was given, additional information on the subsequent outcome was rarely received. All cases describe an unwanted consequence of adding flavouring agents to tablets. Although this improves voluntary ingestion by the animals, it also entails a risk of accidental overdosage, since the animals associate the tablets with a reward and deliberately seek them out. Newly authorised orally administered products containing flavouring agents

therefore routinely include a corresponding warning (3).

For 43 reports (17% of the total) it was possible to establish a clear link between the use of a product and the adverse reaction; in 86 cases (34%) at least one possible alternative cause was identified (causality "possible"), and in 13 cases (5.1%) it was possible to unequivocally rule out a connection between the product and the adverse reaction. In the other 111 cases (43.9%) there was too little information to definitively determine causality. A total of 5 safety signals were identified, 3 from periodic safety reports, one from submitted reports and one from another source. All signals resulted in the "Adverse reactions" or "Contraindications" sections being modified.

Table 1

Distribution of adverse reactions reported in 2016, sorted by ATCvet code and providing specific data for dogs and cats. The fictitious code QZ makes it possible to specifically group adverse drug reaction reports involving reconverted products (i.e. not used for the authorised animal species and/or indication).

Category of medicines according to ATCvet code		Number of reports (% of total)					
		All species		Dog		Cat	
QA:	Alimentary tract	4	(1.6%)	2	(1.1%)	0	
QB:	Blood and blood forming organs	5	(2.0%)	0		0	
QC:	Cardiovascular system	13	(5.1%)	12	(6.7%)	1	(3.1%)
QG:	Genito-urinary system and sex hormones	2	(0.8%)	1	(0.6%)	0	
QH:	Hormonal preparations (excl. sex hormones and insulins)	26	(10.3%)	21	(11.8%)	4	(12.5%)
QJ:	Anti-infectives	19	(7.5%)	5	(2.8%)	0	
QL:	Antineoplastic and immunomodulating agents	3	(1.2%)	3	(1.7%)	0	
QM:	Musculo-skeletal system	17	(6.7%)	13	(7.3%)	2	(6.3%)
QN:	Nervous system	5	(2.0%)	2	(1.1%)	2	(6.3%)
QP:	Antiparasitics	145	(57.2%)	114	(64.1%)	20	(62.4%)
QR:	Respiratory system	1	(0.4%)	0		0	
QS:	Sensory organs	5	(2.0%)	5	(2.8%)	0	
«QZ»:	Reconverted products	8	(3.2%)	0		3	(9.4%)
Total		**253**		**178**		**32**	

Literature

(1) Palm J., Von Krüger X., Ibrahim C.: Pharmakovigilanzreport Tierarzneimittel. Spontanmeldungen unerwünschter Arzneimittelwirkungen im Zeitraum 2011 bis 2013. Dtsch Tierärzteblatt 2014, 2014 (11): 1540-48.

(2) Cooles S., Diesel G., Blenkinsop J.: Suspected adverse events, 2015. Vet. Rec. 2017, 180: 467-69.

(3) Tierarzneimittelkompendium der Schweiz: Hrsg. D. Demuth & C. Müntener, Institut für Veterinärpharmakologie und –toxikologie der Universität Zürich, 2017. Zugänglich unter www.tierarzneimittel.ch.

Information on the Swissmedic website

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

Healthcare Professional Communication

18.10.2017
DHPC – Orencia® (Abatacept)
Risiko von Plattenepithelkarzinom, Hautpapillom, Lymphom und maligne Neoplasie der Lunge

26.09.2017
DHPC – ReoPro Injektionslösung (Abciximab)
Wichtige sicherheitsrelevante Information – Lieferunterbruch

22.09.2017
DHPC – Präparate mit Wirkstoff Voriconazol
Aktualisierte Warnhinweise zum Risiko von Plattenepithelkarzinomen der Haut

06.09.2017
HPC – Prolia® (Denosumab) Injektionslösung in Fertigspritzen mit Nadelschutz
Risiko multipler Wirbelfrakturen sowie Schwund der Knochenmineraldichte nach Absetzen einer Therapie mit Prolia®

18.08.2017
DHPC – Digoxin-Sandoz, 5 Ampullen zu 0.5mg/2ml (Packungsbeilage Charge K0028)
Diese Verpackung enthält eine veraltete Version der Fachinformation.

09.08.2017
DHPC – Zinbryta (DACLIZUMAB beta)
Einschränkung der Anwendung aufgrund des Risikos von fulminantem Leberversagen

28.07.2017
DHPC – Tecentriq (ATEZOLIZUMAB)
immunbedingte Myokarditis

13.07.2017
HPC – Cough and cold preparations containing codeine or dihydrocodeine
Update of the product information

11.07.2017
DHPC – Uptravi® (Selexipag)
Neue Kontraindikation: Gleichzeitige Anwendung von Selexipag mit starken CYP2C8 Inhibitoren kontraindiziert.

30.06.2017
DHPC – Cinryze 500 U (C1-INAKTIVATOR HUMAN)
Empfehlungen aufgrund eines möglichen Lieferengpasses

26.06.2017
DHPC – Minocin® Akne und Minac® (MINOCYCLIN)
Risiko schwerwiegender Überempfindlichkeitsreaktionen inkl. DRESS (Drug Rash with Eosinophilia and Systemic Symptoms)

15.06.2017
HPC – Litarex® Retard Tabletten (Wirkstoff: Lithiumcitrat 564 mg corresp: Lithium 6 mmol)
Schweizweite Einstellung des Vertriebs.

31.05.2017
DHPC – Angiox® (Bivalirudin): Wichtige sicherheitsrelevante Information
Neue Warnhinweise betreffend des Risikos einer akuten Stentthrombose (AST) bei Patienten mit ST-Hebungsinfarkt (STEMI) die sich einer primären perkutane Koronarintervention (PCI) unterziehen und neue Anwendung- und Dosierungsempfehlungen für alle PCI-Patienten sowie entsprechende Vorsichtsmassnahmen.

Announcements

19.10.2017
Summary of adverse events following immunization reported in Switzerland during 2016
New edition

17.10.2017
Increase of antibiotic resistance - Antibiotic Awareness Week highlights the risks
The global fight against antibiotic resistance

12.10.2017
Haemovigilance annual report 2016
New information about transfusion safety in Switzerland

01.10.2017
Information on changes to the guidance document (formerly Information sheet) on the Fast-track authorisation procedure

01.10.2017
Optimisation of labelling phase
Pilot phase, for human and veterinary medicinal products.

29.09.2017
Cross-border inspections
Implementation of Art. 64a revTPA brought forward

25.09.2017
"Operation PANGEA" – Switzerland participates for the 10th time in an international week of action targeting illegal sales of medicines
Press release

13.09.2017
ICH General Meeting approves Guideline E11(R1) and the questions and answers to Q11
ICH Meeting in Montreal on 27 May to 1 June 2017

08.09.2017
Illegal pharmaceuticals: Investigators from the European therapeutic products agencies meet in Switzerland
Some 80 experts from authorities in 26 countries attended a meeting of the Working Group of Enforcement Officers (WGEO) in Montreux.

30.08.2017
Stéphane Rossini wird Präsident des Institutsrats von Swissmedic
Stéphane Rossini ersetzt Christine Beerli, die auf Ende 2017 aus dem Institutsrat zurücktritt.

04.08.2017
New eGov CPP service: Planned change for ordering product certificates (CPP) via the Swissmedic eGovernment Portal
Once the new eGov CPP service has been launched, orders will no longer be accepted via e-mail.

14.07.2017
Manufacturer information data quality (update): Continuous improvement
Experience with the new forms; IDMP study; discontinuation of the one-off updating of manufacturer information

10.07.2017
Leitfaden für die Qualitätssicherung in der Transfusionspraxis
Schweizerische Arbeitsgruppe Qualitätssicherung in der Anwendung von Blutprodukten

10.07.2017
Modification of the form "Application for Authorisation / Variation, human medicines"
The new versions of the documents in question enter into force on 1 July 2017.

10.07.2017
Requirements and information relating to combination products (medicinal products with a medical device component) in the form Application for authorisation / variation, human medicinal products
The preconditions specified above are also explained in section 2.5.14 of the Guidance document Formal requirements.

08.07.2017
Extended option for applying the procedure with prior notification (PPN) – PPN now also applicable for Art. 12 para. 4 TPLO preparations
The corresponding guide to Procedure with prior notification has been modified and will enter into force in its revised form on 1 July 2017.

06.07.2017
In der Schweiz zugelassene Kontrazeptiva - Übersicht (Update)
Die Übersicht der in der Schweiz zugelassenen hormonalen Verhütungsmittel wurde aktualisiert.

05.07.2017
ICH Assembly in Montreal, Canada (May/June 2017)
ICH starts work on medicines for children and better clinical trials; Chinese authority CFDA joins ICH.

01.07.2017
Nachtrag 9.2 der Europäischen Pharmakopöe in Kraft
Der Institutsrat hat den Nachtrag 9.2 der Europäischen Pharmakopöe auf den 1. Juli 2017 in Kraft gesetzt.

30.06.2017
Updated PDF forms and preliminary information on eGov service
In accordance with its strategic IT plan (Annual Report 2011), Swissmedic constantly strives to optimise its processes and extend its platforms.

21.06.2017
Implementing regulations in the therapeutic products area: Start of consultation procedure for Federal Council and Agency Council Ordinances
The consultation procedure for the Therapeutic Products Ordinance Package IV will last from 21 June May to 20 October 2017

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