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Impressum

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

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Important change from 1 January 2021:

New reporting routes for adverse drug reaction reports (see page 4)

Report of an adverse drug reaction (ADR)

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

Online reporting portal ElViS

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Editorial

Dear Reader

The quality, efficacy and safety of a medicinal product must be demonstrated before it can be authorised. The results from clinical trials that were obtained in a controlled manner for a predetermined population are supplemented during post market surveillance by the findings from spontaneous reports in the pharmacovigilance system. By recording adverse events during drug treatment in "real life" in a fairly large number of patients, even rare adverse drug reactions (ADR) can be identified. Therefore, it is important that the healthcare professionals comply with their obligation (pursuant to Article 59, Therapeutic Products Act and Article 63, Therapeutic Products Ordinance) to report ADR, particularly those that are previously unknown or serious.

Swissmedic is currently optimising the electronic recording of ADR which, as of 1 January 2021, can be reported directly to Swissmedic. Corresponding details can be found in the article on "Safety of medicines: New reporting routes for adverse reaction reports by healthcare professionals from 1 January 2021" and, later in the year, on the Swissmedic website.

In this edition of Swissmedic Vigilance News we are illustrating the procedure for recording and evaluating an individual adverse reaction through *Case Reports*. The following factors, where available, play an important role in the assessment of the causal relationship between the ADR and the medicinal product:

- Patient's details and history
- Administered drugs and the period between drug administration and the onset of the ADR *(latency)*
- Course of the ADR
- Severity of the ADR *(serious / non-serious)*
- Outcome *(recovered / not recovered / fatal)*
- Is the ADR already known?

When categorising risks, reference can be made to the *Information for healthcare professionals* and the *Patient information* – which, in Switzerland, can be accessed at www.swissmedicinfo.ch.

The guest articles by the Regional Pharmacovigilance Centres (RPVC) address the little known ADR of "Intravenous iron and osteomalacia" and the subject of "Cytokine release syndrome and immune checkpoint inhibitors".

The 2019 annual statistics for vaccines and human medicinal products deal with vigilance for specific drug groups and/or defined patient populations.

We hope all our readers stay healthy in the new year.

Eva Eyal

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Important change from 1 January 2021

Drug safety: new reporting routes for adverse drug reaction reports by healthcare professionals from 1 January 2021

According to the Therapeutic Products Act (Article 59) and the Therapeutic Products Ordinance (Article 63), healthcare professionals are required to report the occurrence of a serious, or previously unknown, adverse drug reaction (ADR). Until the end of 2020, these reports should be submitted to one of the six Regional Pharmacovigilance Centres.

From 1 January 2021, the ADR reports are to be sent directly to Swissmedic. The electronic vigilance system ElViS and the report form on the Swissmedic website will be modified accordingly. The personnel in the Pharmacovigilance unit will review all incoming reports (triage) and decide, on the basis of defined criteria, whether the ADR report should be sent to a Regional Pharmacovigilance Centre for further processing or whether it can be handled by the Pharmacovigilance unit.

The changes described above do not affect the ADR reports from pharmaceutical companies.

This procedure is designed to establish Swissmedic as the central point of contact for the receipt of all ADR reports, with targeted triage and appropriately adapted task allocation. In addition, better use will be made of the resources and specialist knowledge of the Pharmacovigilance Centres, which will focus on processing reports indicating risks of a drug that are as yet unknown or need to be reassessed. Swissmedic will thereby be making a further contribution to the improvement of drug safety.

Thomas Schwartz, MD

Safety of Medicines division, Swissmedic

Drug safety and signals

Guest article

Cytokine release syndrome associated with immune checkpoint inhibitors

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Introduction

Immune checkpoint inhibitors (ICIs) have proven effective in the treatment of numerous cancer types (1). By inhibiting negative regulators of the immune system, ICIs enhance immune activity against cancer cells and, aberrantly, against host non-cancer cells, resulting in inflammatory side effects called immune-related adverse events (irAEs) (2).

Cytokine release syndrome (CRS) is a systemic inflammatory disease characterised by a massive release of cytokines (3). It can present with a variety of symptoms, ranging from mild (e.g. fever, fatigue, nausea) to life threatening ones (e.g. hypoxia requiring mechanical ventilation), and can sometimes be fatal (4).

CRS can be triggered by a variety of factors such as infections and certain drugs (5). Despite the strict parallelism between ICI mechanism of action and CRS pathophysiology, to date, CRS is an unlabelled irAE and only a few case reports have documented the association between ICIs and CRS onset in cancer patients (6–13).

To describe the burden of ICI-related CRS and raise awareness of CRS as irAE, we performed – and published – a retrospective descriptive observational study in VigiBase, the World Health Organization's (WHO) global database of spontaneously reported suspected adverse drug reactions (ADRs) (14).

Methods

Safety reports associated with ipilimumab, nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab, and cemiplimab, reporting Cytokine release syndrome *(preferred term [PT] "Cytokine release syndrome")* and gathered in VigiBase from database inception through 12 January 2020, were retrieved to assess geographical and temporal patterns of reporting, patient demographics and clinical features, treatment characteristics, CRS clinical presentation, timing, seriousness, and outcome.

Results

We retrieved 58 safety reports of ICI-related CRS, with a heterogeneous geographical reporting pattern across continents, with the highest proportion of ICI-related CRS cases in Australia (3 out of 2,126 ICI-related safety reports, 0.14%). Table 1 summarises baseline characteristics of ICI-related CRS safety reports. Median patient age was 55 years (interquartile range 44–68 years, n=50, 86%), and 34 (59%) cases were in males. ICI-related CRS reporting increased over time, with 27 cases (47%) occurring during 2019. Melanoma (n=17, 29%) and hematologic malignancies (n=16, 28%) were the most common underlying cancers. Regardless of cancer type, ICI-related CRS safety reports were more numerous for antibody monotherapy (46, 79%) compared to ICI combination therapy (8, 14%). Among antibody monotherapy, anti-programmed death-1/programmed death-ligand 1 (anti-PD-1/PD-L1) drugs were involved in 43 (74%) safety reports. ICIs were the solely suspected drugs in 37 (64%) safety reports. Among the other 21

(36%) safety reports with additional suspected drugs, 18 (31%) listed other antineoplastic agents. Concurrent infections were reported in six (10%) patients. ICI-related CRS developed a median of four weeks after ICI initiation (interquartile range 1–18 weeks, n=9, 16%). Except for one case of unknown seriousness and two cases (3%) recorded as not serious, reporters evaluated ICI-related CRS cases as serious in 55 (95%) patients. There were two fatal cases, whereby CRS contributed to worsening the condition of the patients along with infections and tumour progression. Patients with CRS either recovered or were recovering at the time of reporting in 35 (60%) cases. In 20 (34%) safety reports, CRS outcome was unknown and one patient recovered from ICI-related CRS with sequelae.

Discussion

The analysis of the largest-to-date series of CRS cases spontaneously reported in association with ICI treatment showed that ICI-related CRS, taking into account the increasing use of ICIs for a variety of cancer types, is likely to be progressively more easily recognised and diagnosed in association with ICIs, as shown by the peak in reporting in 2019.

Similarly to bispecific antibody constructs and chimeric antigen receptor T (CAR T) cell therapies recently approved for haematological malignancies, for which CRS is known as a serious adverse event (15), we observed that the tumour-specific pattern of CRS onset on ICIs more commonly involved patients with haematological malignancies. Moreover, a considerable number of ICI-related CRS cases were reported in patients with melanoma, probably because of the earlier approval of ICIs for this indication.

A recent review of the largest clinical trials of ICIs found that the frequency of haematological irAEs of all grades (including CRS), was higher with anti-PD-1 (4.1%) and anti-PD-L1 (4.7%) than with anti-cytotoxic T-lymphocyte antigen-4 (anti-CTLA-4) agents (0.5%, $P < 0.0001$) (16). We consistently found that ICI-related CRS safety reports were more numerous on anti-PD-1/PD-L1 antibodies, regardless of cancer type. However, our finding might also reflect a more widespread use of anti-PD-1/PD-L1 agents in clinical practice as compared to anti-CTLA-4 (17).

It is noteworthy that, beyond ICIs, co-suspected drugs were absent in a remarkable proportion of safety reports, suggesting that ICIs could contribute to CRS onset as pharmacological triggers.

Regarding CRS time-to-onset, we described ICI-related CRS as developing with a median of 4 weeks since ICI initiation, which fits well within the 10-week mean time-to-onset described for ICI-related haematological ADRs (16).

Lastly, we observed that patients with ICI-related CRS either recovered or were recovering at the time of reporting in most cases, with only two fatal outcomes.

Because of the limitations inherent to the data source (e.g. reporting biases, missing data, lack of information on the number and demographics as well as clinical characteristics of patients exposed to the drug who either did not develop or did not report ADRs), and due also to the small sample size of the present case series, interpretation of results should be adequately weighted.

Conclusions

Our findings from VigiBase along with the few published case reports suggest that ICIs could contribute to CRS onset in cancer patients as pharmacological triggers. With ICI indications expanding, clinicians and regulatory authorities should be aware of and monitor CRS onset during treatment with ICIs. Further studies are needed to better characterise the incidence of and the mechanisms underlying ICI-related CRS.

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Table 1: Characteristics of safety reports of immune checkpoint inhibitor-related cytokine release syndrome.

Characteristics of safety reports	n (%) (N=58)
Reporting year	
2015	5 (9)
2016	3 (5)
2017	6 (10)
2018	17 (29)
2019	27 (47)
Age	
Reported	50 (86)
Median [IQR], years	55 [44-68]
Not reported	8 (14)

Sex	
Male	34 (59)
Female	21 (36)
Not reported	3 (5)
Cancer type	
Melanoma	17 (29)
Haematologic malignancy[a]	16 (28)
Lung cancer[b]	11 (19)
Other[c]	6 (10)
Not reported	8 (14)
Regimen	
Anti-CTLA-4 (ipilimumab) monotherapy	3 (5)
Anti-PD-1 monotherapy	
nivolumab	21 (36)
pembrolizumab	12 (21)
cemiplimab	1 (2)
Anti-PD-L1 monotherapy	
atezolizumab	7 (12)
avelumab	2 (3)
nivolumab and ipilimumab combination therapy	7 (12)
nivolumab and ipilimumab treatment not definable[d]	2 (3)
pembrolizumab and ipilimumab treatment not definable[d]	2 (3)
pembrolizumab, followed by nivolumab and ipilimumab combination	1 (2)
Duration	
Single administration	10 (17)
Prolonged	10 (17)
Median [IQR], weeks	11 [4-24]
More than 1 year	1 (2)
Not definable[d]	37 (64)
Co-suspected drugs	
Not reported	37 (64)
Reported	21 (36)
Antineoplastic agents[e]	18
Other[f]	4

Abbreviations and footnotes:

IQR interquartile range; CTLA-4 Cytotoxic T-Lymphocyte Antigen 4; PD-1 Programmed cell Death protein 1; PD-L1 Programmed cell Death-Ligand 1

[a] Hodgkin disease (n=5); diffuse large B-cell lymphoma refractory (n=4); diffuse large B-cell lymphoma (n=2); lymphoma, non-Hodgkin's lymphoma refractory, acute myeloid leukaemia, primary mediastinal large B-cell lymphoma, acute lymphocytic leukaemia (all n=1)

[b] Non-small cell lung cancer (n=5); adenocarcinoma of the lung (n=3); pulmonary carcinoma, squamous cell carcinoma of the lung, lung neoplasm malignant (all n=1)

[c] Alveolar soft part sarcoma (n=2); breast cancer metastatic, gastric cancer, squamous cell carcinoma of skin, triple negative breast cancer (all n=1)

[d] Because of partially recorded or missing ICI start and/or end dates

[e] Axicabtagene ciloleucel, cyclophosphamide, fludarabine (n=4); brentuximab vedotin, cobimetinib, vemurafenib (n=2); azacitidine, blinatumomab, carboplatin, dabrafenib, decitabine, IMCgp100, NY-ESO-1, pazopanib, pemetrexed, siltuximab, talimogene laherparepvec, tisagenlecleucel, trametinib (all n=1). Some safety reports had multiple co-suspected antineoplastic agents.

[f] Lisinopril and morphine (n=1); mesna, naloxegol, prednisolone (all n=1)

Guest article

A little-known adverse effect – intravenous iron and osteomalacia

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Clinical case

This 33-year-old female patient presented in August with localised hip pain in the right inguinal fold originating from a bone fissure due to insufficiency. Bone densitometry confirmed low T-scores of -2.3 in the lumbar spine and -3.0 in the left hip, both due to demineralisation rather than osteoporosis in view of the patient's age and the absence of risk factors. Laboratory analysis showed a normalisation of the vitamin D level compared to March, but persistent low blood calcium and phosphate levels. Treatment including high doses of calcium (2 g/day) plus calcitriol produced a transient improvement in the symptoms, but these subsequently returned in identical form. Malabsorption was suspected, but gastroenterology tests did not confirm this hypothesis. In September the patient reported that there had been no improvement, and she still had low levels of vitamin D, calcium and phosphate. She was therefore given phosphate replacement therapy (Phoscap®, 6 mmol 3x/day). In October her calcium and phosphate levels were still as low, with very high markers of bone remodelling, indicating osteomalacia. In addition, fibroblast growth factor (FGF23) was tested and found to be considerably elevated at 171 kRU/L. The division of bone diseases diagnosed phosphate depletion and osteomalacia secondary to injections of ferric carboxymaltose (Ferinject®) received by the patient in the past, with no further details.

The laboratory findings were as follows:

	March	August	September	October
Calcium (2.10–2.60 mmol/L)	2.26	2.30	2.27	2.03
Vit. D (75-220 nmol/L)	48	101		63
Phosphate (0.81-1.61 mmol/L)	0.50	0.60	0.63	0.62
Calcitriol (48-168 pmol/L)			61	
Parathyroid horm.(18.4-80.1 ng/L)			60.4	
FGF23 (26-110 kUR/L)				171

Introduction

In Switzerland, intravenous (IV) iron is available in three distinct forms: ferric carboxymaltose (Ferinject®), iron hydroxide sucrose complex (Venofer®) and iron isomaltoside 1000 (Monofer®). All these forms of IV iron are used to treat iron deficiency when the oral form is ineffective or cannot be used (1). The three forms are complexes of iron(III) and a "sugar". The latter permits the controlled release of the iron to the transport and storage proteins (transferrin and ferritin) (1).

Osteomalacia is a disorder of bone metabolism characterised by impaired bone mineralisation. It may be inherited or acquired. While osteomalacia has multiple aetiologies, the principal causes are vitamin D deficiency and hypophosphataemia, either of which

may be due to different clinical situations (e.g. malabsorption or hypophosphataemic rickets of genetic origin). A diagnosis of osteomalacia is generally based on the clinical symptoms and the results of laboratory tests and radiological imaging. At the clinical level, osteomalacia may be asymptomatic, or patients may present with symptoms such as bone pain, muscle weakness or fractures. Laboratory tests show elevated alkaline phosphatase, FGF23 and parathyroid hormone levels and reduced serum calcium and phosphate. Radiological imaging sometimes shows a low bone mineral density (2).

Iron-induced hypophosphataemia was first described in 1982 in a male patient who had repeatedly been given doses of iron oxide (3). The mechanism of iron-induced hypophosphataemia is complex. Studies suggest that IV iron induces an increase in the concentration of active circulating FGF23. FGF23 is the principal regulator of the plasma concentration of phosphate, regulating its renal excretion and also reducing the formation of active vitamin D (1,25-dihydroxyvitamin D). Higher FGF23 levels lead to increased excretion of phosphate in the urine, a low level of phosphate in the blood and a reduction in serum concentrations of 1,25-dihydroxyvitamin D (3).

IV iron and hypophosphataemia

The *Information for healthcare professionals* for the different Swiss medicinal products varies with respect to hypophosphataemia and the associated risk of osteomalacia. Ferinject® mentions hypophosphataemia as a common adverse effect (<1/10, ≥1/100) that is transient and without clinical symptoms, adding that "Isolated cases of hypophosphataemia requiring treatment have been reported in patients with known risk factors who have received a higher dosage over a prolonged period" (1). The *Information for healthcare professionals* for Venofer® does not mention either hypophosphataemia or osteomalacia. Hypophosphataemia is described as being uncommon (<1/100, ≥1/1,000) and transient with Monofer®. The SmPC mentions that one of the risks of hypophosphataemia is the development of osteomalacia, which has been reported following repeated administration of IV iron, but that Monofer® has not been associated with osteomalacia.

Several studies have evaluated the impact of IV iron on blood phosphate levels (4–7). For example, a randomised controlled study was performed with the aim of comparing ferric carboxymaltose with ferumoxytol, another injectable preparation containing iron. The incidence of severe and extreme hypophosphataemia was significantly higher in patients who had been given ferric carboxymaltose (<2.0 mg/dL, 50.8% vs. 0.9%; <1.3 mg/dL, 10.0% vs. 0.0%; p<0.001). The decrease in phosphate levels in the ferric carboxymaltose group was associated with a concomitant increase in urinary excretion of phosphate which did not appear in the ferumoxytol group. Moreover, FGF23 doubled in the first week and doubled again in the second week in the ferric carboxymaltose group, while it did not change in the other group (mean percentage change in each patient between baseline and the peak in the second week: +302.8 ± 326.2% vs. +10.1 ± 61.0%; p<0.001). Ferric carboxymaltose also induced a significant decrease in the levels of vitamin D and calcium (4).

In a prospective study of eight patients who had been given an injection of iron polymaltose complex, plasma levels of phosphate dropped after the injection of iron from 3.4 ± 0.6 mg/dL to 1.8 ± 0.6 mg/dL one week post-injection (p<0.0001). This was associated with a reduction in the percentages of phosphate and vitamin D reabsorbed in the renal tubules (p<0.001 for both parameters). FGF23 also increased after the injection, from 43.5 pg/mL to 177 pg/mL one

week post-injection ($p<0.001$), and this increase was inversely correlated with the serum levels of phosphate ($r=-0.74$, $p<0.05$) and vitamin D ($r=-0.71$, $p<0.05$) (6).

IV iron and osteomalacia

Several case reports describe the development of osteomalacia during treatment with IV iron – see the article by Zoller et al. for a review of the literature up to 2017 (3). There are two case reports in the literature of two female patients who developed severe hypophosphataemic osteomalacia and multiple fractures after treatment with IV iron (1 g of iron polymaltose complex monthly for 13 and 17 months respectively). FGF23 was measured in one of the two patients and was elevated, at 285 pg/mL (normal: <54 pg/mL). Once the diagnosis of osteomalacia had been made, the injections of iron polymaltose complex were stopped, and the symptoms and laboratory findings improved (8).

In another case report, a female patient developed severe and symptomatic hypophosphataemia and fractures after being given a total of 11 g of ferric carboxymaltose as 1 g infusions over the preceding two years, the last infusion having been given two months previously. The patient also had low calcium levels, vitamin D deficiency and increased urinary excretion of phosphate. She was given phosphate and calcitriol supplements and her treatment with IV iron was replaced by iron administered orally. Follow-up six months later showed a significant improvement in the symptoms and laboratory findings (9).

A male patient who had been given 1 g of ferric carboxymaltose once a month for eight months developed pain and was unable to walk. He presented with elevated FGF23 (226 ng/L), significant hypophosphataemia with low levels of calcium and vitamin D and elevated urinary excretion of phosphate. A connection with his iron therapy was suspected when supplementation with calcitriol and phosphate failed to improve his symptoms. Treatment with IV iron was stopped, and the symptoms and laboratory findings resolved. The patient was given a further infusion of 1 g of ferric carboxymaltose for recurrent anaemia and, one month later, the serum concentration of FGF23 had again increased while the level of phosphate had decreased. However, the patient was asymptomatic and everything had returned to normal two months later (10).

Finally, on 27 November 2019 *Lareb (Netherlands Pharmacovigilance Centre)* published a signal concerning osteomalacia during treatment with IV iron after four reported cases had been entered in the centre's database (11).

Conclusion

Osteomalacia during treatment with IV iron is a little-known adverse effect and is probably poorly reported via the spontaneous pharmacovigilance systems. While this adverse effect seems to occur more frequently with ferric carboxymaltose (Ferinject®), cases have been described in the literature with other IV iron products. The mechanism by which this adverse effect occurs seems to be clear, i.e. via an increase in FGF23 leading to excretion of phosphate and consequent hypophosphataemia. The *Information for healthcare professionals* for the IV iron products available in Switzerland currently mention hypophosphataemia, but there is no recommendation to monitor phosphate levels or mention of osteomalacia as an adverse effect, and these could be added.

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Regulatory

From signal to measure – signal management for human medicinal products as a major contribution to patient safety

In Switzerland, all medicinal products have, by the time they are authorised, undergone an evaluation of their quality, safety and efficacy and received a positive benefit-risk assessment. However, given the known limitations of clinical trials, the complete safety profile of a medicinal product cannot usually be established at the time of authorisation. During the post-marketing period, when the medicinal product is used under real-life conditions, knowledge about the safety profile of the medicine steadily increases over time.

To this end, careful and continuous monitoring of the safety profile of all medicinal products throughout their lifecycle is of crucial importance in identifying and minimising new risks.

Effective monitoring after a medicine is placed on the market is enabled partly through the spontaneous reporting system for adverse drug reactions. These reports – supplemented by other information – form the basis for the ongoing evaluation and improvement of drug safety. They provide information about previously unknown and relatively rare undesirable effects, any increase in their frequency or any changes in the nature or severity of known undesirable effects.

A safety signal refers to any information about new or known adverse drug reactions that may be triggered by a medicinal product and requiring further investigation. However, signals are generated not just from the spontaneous reporting system, but also from other important sources, including clinical trials and the scientific literature.

Signal detection and signal management are core activities during the post-marketing surveillance of a medicine.

If, on evaluation, a signal is confirmed as a new risk, then risk minimisation measures are usually derived.

Risk minimisation measures range from changes to the product information texts, via calls for additional studies through to the market withdrawal of the medicine. Swissmedic is responsible for coordinating the implementation of these measures. Depending on the situation, physicians, patients and other interested parties are then informed through communication measures such as DHPC *(Direct Healthcare Professional Communication)* or publications.

Signal management at Swissmedic

For signal detection purposes, Swissmedic constantly checks the national database for adverse drug reactions reported in Switzerland. These signals are reviewed by Swissmedic and, if necessary, corresponding risk minimisation measures are ordered.

But safety problems involving medicines are not limited by national borders. The evaluation of international signals, which are usually based on much larger data volumes, makes a major contribution to drug safety in Switzerland.

To this end, and as part of signal and risk management, every safety signal relating to a medicinal product or active substance authorised by Swissmedic is considered potentially relevant to the benefit-risk profile of the medicinal product, irrespective of whether the signal is reported in Switzerland or abroad.

Mandatory notification of company signals

The duty to report drug safety signals and time limits for reporting signals by the marketing authorisation holder to Swissmedic are anchored in the Therapeutic Products Act (Art. 59 TPA) and the Therapeutic Products Ordinance (Arts. 61, 62 and 63 TPO).

An important basic requirement in this process is the prompt communication of new signals. The active exchange of information between Swissmedic and marketing authorisation holders about the signals facilitates their fast evaluation and the timely implementation of risk minimisation measures.

The various reporting time limits are based on the risk potential of the signals. For example, signals involving a serious risk potential, i.e. when measures for maintaining drug safety are required in the short term (e.g. informing the public immediately, market withdrawal at short notice) must be reported to Swissmedic at once, at the latest within five days.

For signals without a serious risk potential but still requiring modification of the product information, the marketing authorisation holder is obliged to update its product information in line with the latest scientific and technical findings or new events and evaluations without a specific request by Swissmedic. In this case, the signal reporting obligation is considered to be fulfilled with the submission of an application for modification of the product information, which must be submitted within six months of the closure of the signal evaluation by the marketing authorisation holder.

As part of its work on pharmacovigilance inspections, Swissmedic regularly checks compliance with the reporting obligations by the marketing authorisation holders.

Signals evaluated by foreign authorities

Signal evaluations by international authorities are essential in enabling Swissmedic to implement risk minimisation measures in Switzerland promptly in line with other countries. Marketing authorisation holders are therefore obliged to report to Swissmedic any signals evaluated by foreign authorities (in countries with a comparable drug regulatory authority, particularly EU, EFTA countries and the USA) and with the potential to affect medicinal products authorised in Switzerland.

Signal evaluation by Swissmedic

After receiving the signal notification, Swissmedic evaluates the submitted information and any planned risk minimisation measures. The signal is usually reviewed by active substance and, in certain cases, by the corresponding substance class. If Swissmedic lacks information or data needed to evaluate the signal appropriately, these are requested from the marketing authorisation holder.

As part of the signal evaluation, Swissmedic also relies on information shared with other authorities in regular *International Postmarket Surveillance Teleconferences* (1), during which signals that are of general interest to the participating authorities are discussed.

Implementation of risk minimisation measures

After the signal evaluation has been concluded by Swissmedic, the marketing authorisation holders are informed of the results on national and international signals in respect of risk minimisation measures and their timely implementation (e.g. wording of the modified product information, the deadline for submission of the corresponding application and any other measures, such as DHPC).

The signal process was comprehensively revised in January 2020 (see also Swissmedic website) in order to accelerate the implementation of risk minimisation measures.

As a new feature, as soon as the signal has been evaluated by Swissmedic, official decisions on the final wording for modified medicinal product information and/or packaging are being issued directly as part of the signal process.

The marketing authorisation holder is initially informed in a letter of the wording requested by Swissmedic for the required changes to the product information texts. For international signals, particularly signals reported by the EMA or FDA, the texts specified by these authorities are taken into account unless stricter requirements already exist in Switzerland. Wherever possible, the aim is to issue risk information that is consistent insofar as possible with that in the international environment.

Unless the marketing authorisation holder submits a statement objecting to the specified wording within the specified deadline, the consent of the authorisation holder is assumed, and Swissmedic issues its official decision on the text and on the closure of the signal process.

If the marketing authorisation holder does not agree with the proposed changes to the text, or if Swissmedic requires extensive and complex changes to the product information texts, Swissmedic reviews the company's statement and then informs the company of the result by means of a preliminary decision.

After the official decision, the required changes to the product information texts are implemented directly by the marketing authorisation holder within 30 calendar days by submitting a type C.I.1 a) type IA_{IN} application.

Overall, the number of signal notifications has increased in recent years. Efficient management in processing the signals is therefore all the more important. The implementation times of the necessary risk minimisation measures in Switzerland have been significantly reduced thanks to changes in the signal process.

In addition, an important contribution to the fast implementation is also made by the marketing authorisation holders, who usually report the signals reliably, promptly and with good documentation, thereby creating the basis for efficient signal evaluation by Swissmedic.

The current signal management process guarantees to track efficiently the risk profile of a medicinal product and to undertake continuously required safety-related changes. Since the full lifecycle of the medicinal product is covered, this ensures that safe and effective medicines are made available to patients in Switzerland.

(1) Participating authorities: Australia – TGA *(Therapeutic Goods Administration)*, United Kingdom – MHRA *(Medicines and Healthcare products Regulatory Agency)*, Canada – Health Canada, New Zealand – Medsafe, Switzerland – Swissmedic, Singapore – HSA *(Health Sciences Authority)*, USA – FDA *(Food and Drug Administration)*

Stephanie Storre, MD
Danijela Pavelic Ferretti, PhD

Safety of Medicines division, Swissmedic

Statistical Review 2019

Vigilance of human medicines

Swissmedic records safety signals associated with medicinal products on the basis of reports of adverse drug reactions (ADR) from within Switzerland. If investigation confirms a new risk, Swissmedic initiates the necessary actions following international consultation. As part of the pharmacovigilance network, six regional pharmacovigilance centres (RPVC) assess ADR reports submitted by professionals and patients on Swissmedic's behalf and record them in the national database. Pharmaceutical companies also submit reports on adverse reactions from within Switzerland to Swissmedic.

Activities

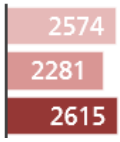
The new VigilanceONE Ultimate database for adverse drug reactions from within Switzerland was upgraded so that it is now possible to carry out specialised data analyses.

International collaboration with other countries' authorities and in multinational specialist organisations was further intensified, for example as part of regular dialogue on safety signals or as part of ICH or WHO activities.

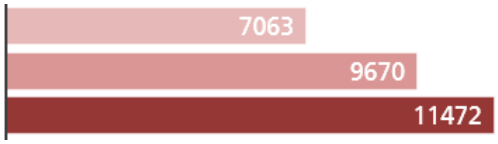
Swissmedic made contributions on drug safety-relevant aspects to the *Swiss National Report on Quality and Safety in Healthcare*.

New service agreements were drawn up for cooperation with the RPVC during 2021 and 2022. The new agreements focus on reports containing safety-relevant aspects.

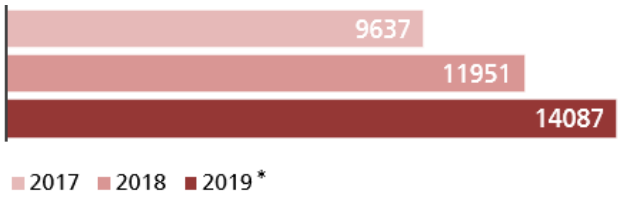
ADR reports from RPVC



ADR reports from pharmaceutical companies



Total ADR reports



* The 2019 figures now also include follow-up reports and are therefore not directly comparable with previous years' figures.

Safety of Medicines division, Swissmedic

Vaccinovigilance

Complete report – link:

Adverse events following immunization – annual report 2019

Summary of adverse events following immunization reported in Switzerland during 2019

During 2019, the Safety of Medicines division of Swissmedic received 273 new case-reports of suspected *adverse events following immunization (AEFI)* from Switzerland. This exceeds the number of cases submitted during 2018 (223 reports) and 2017 (232 reports).

As in the previous year (2018), the AEFI-reports submitted during 2019 were recorded and evaluated in the pharmacovigilance database of Swissmedic – VigilanceONE Ultimate. As no accurate data are available on the total number of vaccines/doses administered during 2019, it is not possible to draw a straightforward conclusion regarding AEFI reporting rates.

As previously, Swissmedic is encouraging spontaneous reporting of AEFIs in high quality, which enables early detection of new safety signals. Important safety issues concerning vaccines – including potential risks – are evaluated with the participation of the *Human Medicines Expert Committee (HMEC)* of Swissmedic, where necessary.

An increased AEFI reporting rate within the database, followed by a scientific evaluation of relevant cases can lead to risk minimisation measures in order to ensure vaccines safety.

Figure 1: Number of AEFI reports by age group and gender, 2019

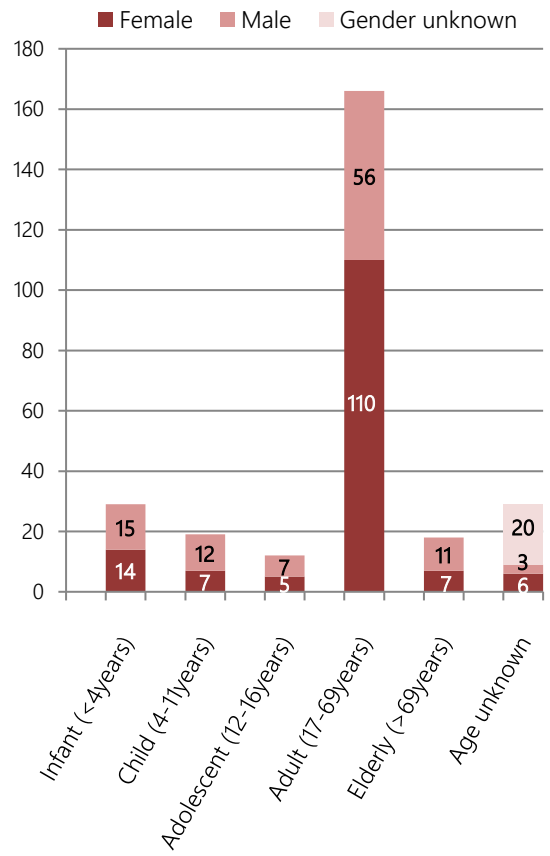


Figure 1 compares the number of reports by age group and gender. The largest number of AEFI reports involved adults (166 reports), followed by infants (29 reports), children (19 reports), elderly (18 reports) and adolescents (12 reports).

Throughout 2019, the number of reports concerning females (149 reports) exceeded the number of reports concerning males (104 reports). In 20 AEFI reports, the gender of the persons remained unknown. In 29 case-reports, the age-group of the patients was not specifically reported.

Figure 2: Number of reports by vaccine group (ATC code) and seriousness, 2019

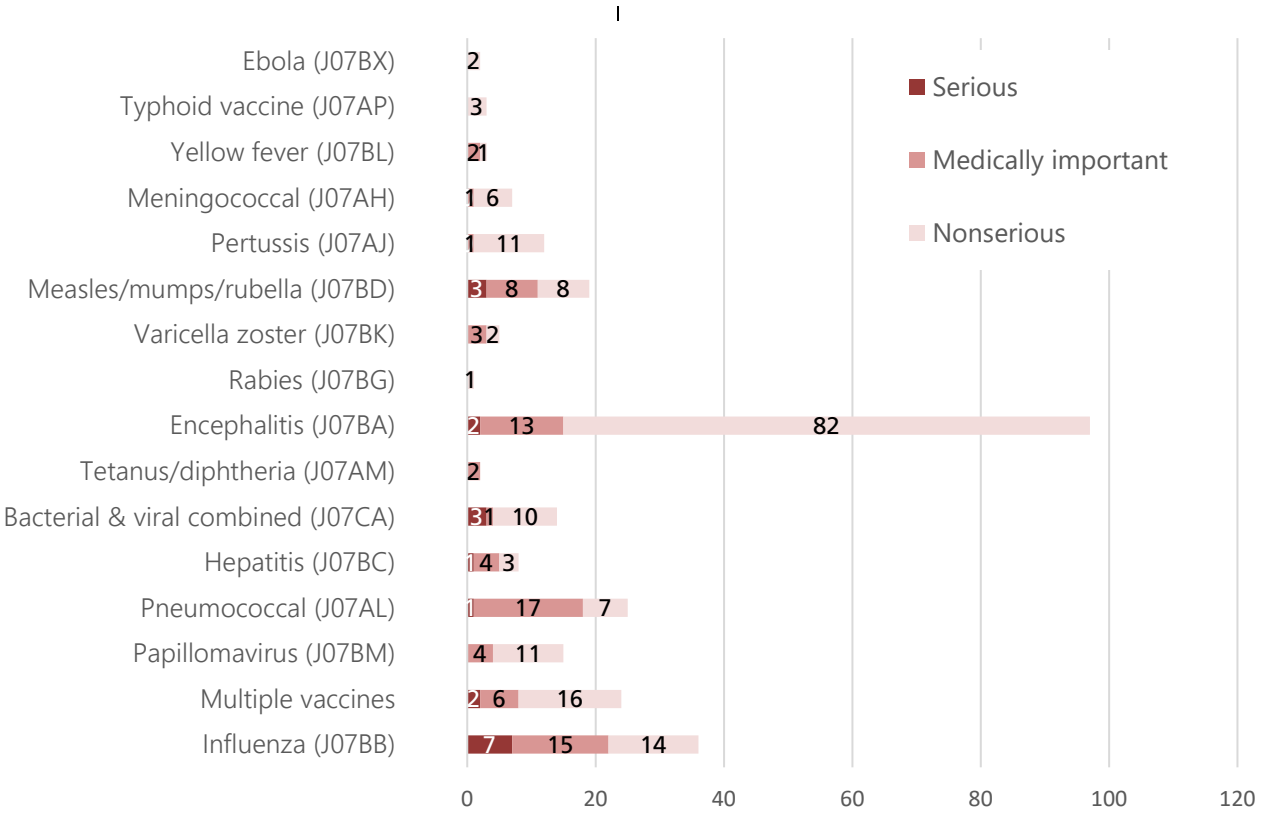


Figure 2 shows the number of spontaneous AEFI reports grouped by vaccine group (ATC code) and seriousness. There are no data available to Swissmedic regarding the number of doses administered in each particular vaccine group in 2019 and therefore this figure does not indicate which vaccine group displayed a higher AEFI rate (as number per 100'000 doses). Generally, a safety report is assessed as "serious" if it involves an adverse event leading to death, hospitalisation or prolongation of an existing hospitalisation, if it was life threatening or if it resulted in a significant or persistent disability or a congenital anomaly.

Furthermore, a report is assessed as "medically important" (and hence as "serious") even if it does not fulfil the criteria for "seriousness" mentioned, but it involves an event considered to be significant by medical judgement. All other reports are assessed as "non serious" (e.g. self-limiting adverse events with good recovery). Of the 273 spontaneous reports received in 2019, 177 (64.8%) were non-serious, 77 (28.2%) involved medically important events and 19 (7%) of the reports involved AEFIs with serious consequences.

Considering all vaccines, the relative frequency (percentage) of "serious" or "medically important" cases taken together decreased as compared to those recorded during the previous year (35.2% in 2019 vs. 52.9% in 2018).

As can be seen in Figure 2, a larger number of cases was submitted in 2019 in relation to the tick-borne encephalitis vaccination. However, the vast majority of these case reports were assessed as "non-serious", whereas the number of "serious" or "medically important" cases regarding encephalitis vaccines was comparable with those received for other vaccine groups.

Figure 3: Number of AEFI reports by reporter qualification and seriousness, 2019

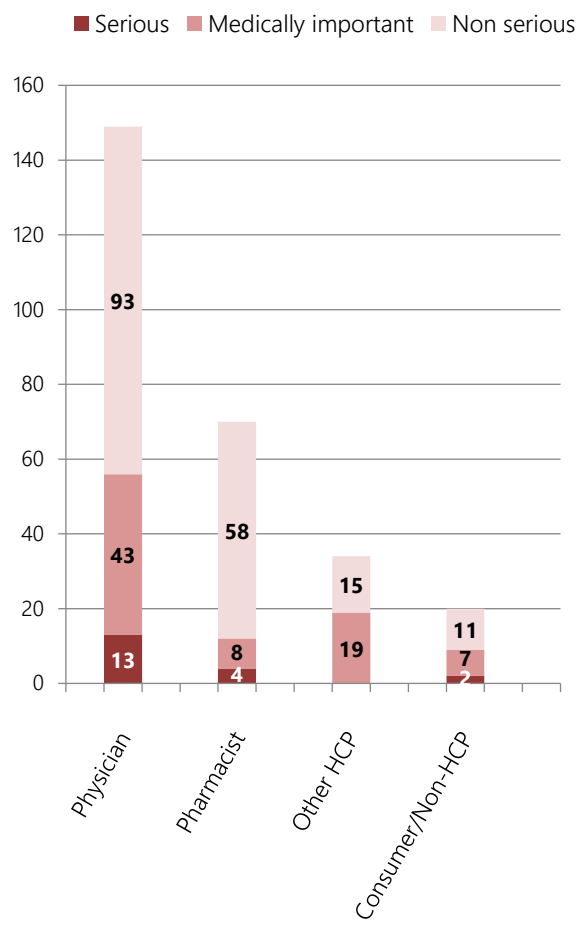


Figure 3 shows the number of Swiss AEFI reports in 2019 grouped by primary reporter and seriousness. Health care professionals - generally providing medically confirmed data and a good quality of individual AEFI reports – were the primary reporters in the vast majority of cases. Physicians reported the largest group of AEFI reports (149 of 273), which also included a larger number of reports assessed as serious or medically important (56 of 149 reports).

Figure 4: Number of AEFI reports by age group and seriousness, 2019

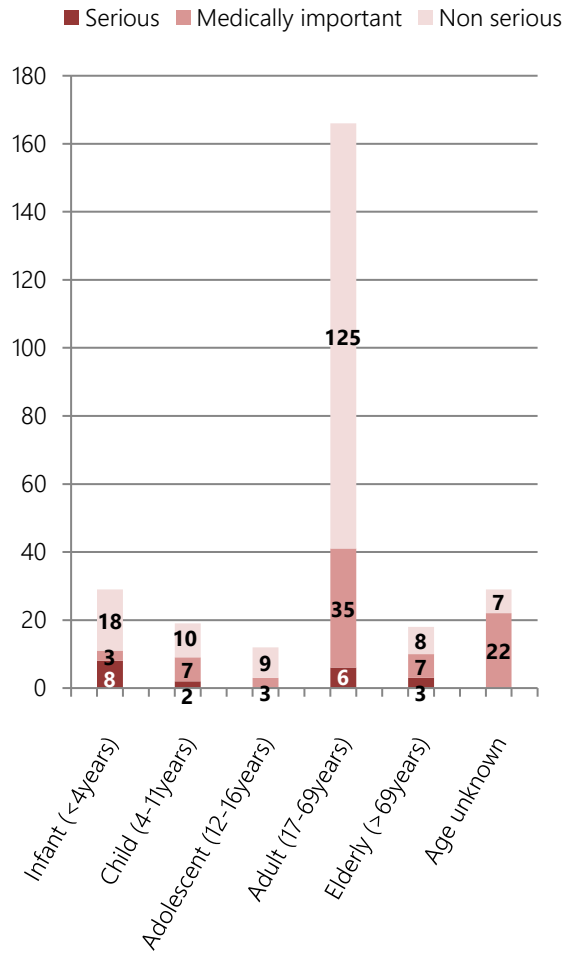


Figure 4 shows the number of spontaneous AEFI reports grouped by age group and seriousness. It becomes apparent that the highest number of "serious" or "medically important" (41 AEFI-reports in total) were recorded in the age group "adults".

However, during 2019, the age group "elderly" exhibits the highest percentage of "serious" or "medically important" cases when taken together (10 of 18 reports, 55.5%) as compared with the other age groups specifically recorded: "children" (9 of 19 reports, 47.4%), "infants" (11 of 29 reports, 37.9%) and "adults" (41 of 166 reports, 24.7%).

Valeriu Toma, MD

Safety of Medicines division, Swissmedic

Vigilance for veterinary medicinal products: adverse reactions reported in 2019

371 reports of adverse reactions to veterinary medicinal products were received during 2019 representing a significant increase of 12.8% compared to the previous year. The majority of these reports described reactions concerning companion animals (215 dogs and 108 cats) as well as cattle (25 reports).

Most of the reported reactions were linked to the use of antiparasitics (201 reports), hormones (37 reports) and anti-infectives (34 reports). 43 of the 371 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). 108 reports about people exposed to veterinary medicinal products were also received.

2 signals were identified from the reports, resulting in revisions of the product information in the sections addressing indications or adverse reactions.

Cedric R. Müntener, D.V.M.

Veterinary Medicines department, Swissmedic

Complete report 2019 (available in German):

Reports of adverse reactions to veterinary medicinal products 2019

Information on the Swissmedic website[1]

Healthcare Professional Communication

11.12.2020
Wichtige Information – Magnesium Gluconate von Fagron
In Gebinden von Magnesium Gluconate von Fagron kann sich Kaliumgluconat befinden

16.10.2020
DHPC – Optiray 300, Injektionslösung in 75 ml Fertigspritzen
Schwierigkeiten beim Aufschrauben der Luer-Lock Adapter

06.10.2020
DHPC – Eylea® (Aflibercept)
Information zur korrekten Vorbereitung und Injektion

28.09.2020
DHPC – Lemtrada (Alemtuzumab)
Einschränkung der Indikation aufgrund schwerwiegender unerwünschter Arzneimittelwirkungen

23.09.2020
DHPC – Ancotil (Flucytosin), Infusionslösung 1% (i.v.)
Neue Kontraindikation und aktualisierte Empfehlungen zur Anwendung bei Patienten mit DPD-Mangel

01.07.2020
HPC – Thiopental Inresa, Pulver zur Herstellung einer Injektionslösung / Infusionslösung

01.07.2020
DHPC – Kürzlich veröffentlichte epidemiologische Studien zur Beurteilung des Risikos von Geburtsfehlern
im Zusammenhang mit der Anwendung Ondansetron-haltiger Arzneimittel

26.06.2020
DHPC – Onivyde (liposomales Irinotecan)
Risiko für Medikationsfehler aufgrund einer geänderten Bezeichnung der Stärke und Berechnung der Dosis

27.05.2020
DHPC – Hydroxychloroquin
QT-Zeit-Verlängerung

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

In focus

08.12.2020
Coronavirus disease (COVID-19) Pandemic
Information on the new coronavirus (SARS-CoV-2)

Announcements

11.12.2020
Benefits and risks of Covid-19 vaccines: rapid authorisations are possible, but premature vaccinations are not the answer for Switzerland
The safety of the Swiss population has top priority

08.12.2020
ICMRA statement on the continuation of clinical trials
ICMRA recommends continued follow-up of study subjects in clinical trials of the SARS-CoV2 vaccine

07.12.2020
Janssen-Cilag AG applies to have its vaccine candidate authorised
Swissmedic is examining Janssen's COVID-19 vaccine in a rolling submission procedure

07.12.2020
New reporting routes for adverse drug reaction reports by healthcare professionals from 1 January 2021
Drug safety

04.12.2020
Access Consortium statement on COVID-19 vaccines evidence
The medicines regulators within the Access Consortium will only authorise vaccines if their benefits outweigh the risks

03.12.2020
Aufsichtsabgabe 2020 – Selbstdeklaration
Eingabefrist: 22. Januar 2021

20.11.2020
Interruption of production at Swiss contract manufacturer may temporarily disrupt supplies
Swissmedic inspection uncovers Good Manufacturing Practice (GMP) deficiencies

20.11.2020
Validity of GMP certificates
during the COVID-19 pandemic

13.11.2020
Swissmedic reviews vaccine candidate from Moderna
Another COVID-19 vaccine under rolling review

26.10.2020
Project Orbis: findings after the first year
Analysis report on regulatory measures to promote innovative cancer drugs

22.10.2020
Discovery of new nitrosamine contamination in tuberculosis drugs: Swissmedic pushes clarification ahead
Traces of the nitrosamine MeNP discovered in rifampicin

20.10.2020
Vigilance for veterinary medicinal products in the year 2019
Reports of adverse reactions to veterinary medicinal products

19.10.2020
Swissmedic receives second application for the authorisation of a coronavirus vaccine
The Swiss therapeutic products agency reviews another vaccine in the rolling submission procedure

14.10.2020
The ACSS Consortium welcomes the U.K. as its newest member
The MHRA is delighted to be joining

07.10.2020
Report on evaluation and reclassification of substances on TAS list
Project for reclassification of products to dispensing category C

06.10.2020
COVID-19 pandemic — Switzerland takes part in "Operation Stop"
Over 130 tonnes of medical face masks inspected

06.10.2020
Swissmedic starts rolling review of a COVID-19 vaccine
First application for authorisation of a COVID-19 vaccine in Switzerland submitted

01.10.2020
Swissmedic extends the MAGHP procedure
The new Light procedure builds on the established MAGHP procedure, but is explicitly applicable to applications for the fast-track authorisation procedure and for temporary authorisation

25.09.2020
Changeover to electronic submission of notifications of major changes: 1 November 2020
(Major changes according to Article 41, paragraph 2 MPLO)

22.09.2020
Warning regarding the "wonder cure" Miracle Mineral Supplements
Experts worldwide warn against taking MMS

15.09.2020
Update – Warning about supposedly herbal products
Swissmedic is issuing an urgent warning regarding slimming products and other supposedly natural products

08.09.2020
New therapeutic products legislation reclassifies patient-specific preparations as non-standardised medicinal products
This new classification replaces an earlier interpretation and classification, based on therapeutic products legislation, of certain autologous serum preparations

18.08.2020
Benchmarking 2020 – Comparison of Swiss approval times for human medicines with the EU and the USA and analysis of national authorisation procedures
Swissmedic compared with the EMA and the FDA and analysis of the national authorisation procedures

23.07.2020
Changeover to electronic submission of notifications of major changes from autumn 2020
Planned changes affecting establishment licence holders

03.07.2020
A study confirms Swissmedic's international Competitiveness
In an international comparison of the processing time for scientific assessments, Swissmedic is on a par with the fastest authorities

02.07.2020
Swissmedic extends the use of remdesivir
With immediate effect, remdesivir can be used more widely in Switzerland for the treatment of COVID-19 patients

02.07.2020
Regulatory authorities step up cooperation in connection with COVID-19
Further details on observational research

01.07.2020
New ruling concerning extensions granted for authorisation applications for human medicinal products
Swissmedic is changing its practice

01.07.2020
Optimisation of labelling phase for human medicinal products
Avoiding text review rounds

01.07.2020
List of medicinal products in dispensing category D dispensed by naturopaths with a federal diploma (NP FD)
Human medicinal products in dispensing category D that may be dispensed by naturopaths

01.07.2020
Virtual meetings instead of ICH meetings in Vancouver during the COVID-19 pandemic
ICH Working Groups continue their activities online

01.07.2020
Submission of DMF updates
Type II variations now possible

01.07.2020
Annexes of two Swissmedic ordinances amended
The Institute Council has put into force the updating of Annexes 3a and 7 of the Medicinal Products Authorisation Ordinance and Annexes 2 and 3 of the Ordinance concerning simplified Marketing Authorisations on 1 July 2020.

26.05.2020
Swissmedic approves first new active substance as part of Project Orbis
Tucatinib for the treatment of a particularly aggressive type of breast cancer reviewed in four months

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