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swissmedic

In this edition

swissmedic

In this edition

46 Information on the Swissmedic website

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swissmedic

Editorial

Dear Reader

Recently, a report on hospitalisations in Switzerland due to adverse drug reactions was published in the international Drug Safety Journal *(Hospitalisations Related to Adverse Drug Reactions in Switzerland in 2012–2019: Characteristics, In-Hospital Mortality, and Spontaneous Reporting Rate)*. This demonstrated the importance of spontaneous reports by healthcare professionals for pharmacovigilance, but also for the systematic evaluation of data by means of analyses. In the pharmacovigilance system, different methods are used to identify and evaluate potential risks.

In a prospective observational cohort study, possible problems with pregnancy after the use of GLP-1 agonists in the first trimester were suspected. Initial results are discussed in the article "Pregnancy outcomes after GLP-1 agonist exposure in early pregnancy". "Sex differences in outcomes of intravenous thrombolysis in acute ischaemic stroke patients with preadmission use of antiplatelets" are the subject of another cohort study from RPVC Ticino.

In respect of "drug-induced pancreatitis", the reports of adverse drug reactions (ADRs) recorded at RPVC Geneva were assessed for their causality, taking into account the relevant literature. An article in this edition deals with the rare "Kounis syndrome" ADR, which is defined by the occurrence of an acute coronary syndrome accompanied by an allergic reaction.

Case reports contribute to a better understanding of medicinal products and their side effects. One report relates to a rare interaction between febuxostat and azathioprine, and the resulting pancytopenia.

In pharmacovigilance, it is not only the recording of the ADRs that have occurred and the active substances or medicinal products involved that plays a role, but also the subsequent scientific assessment of the frequency and causality of the reported risks. In this edition, you will find articles to support the risk evaluations, e.g. on the correct application of the term "medically important" in AEFI (adverse events after immunization) reports on COVID-19 vaccines. The problem of the "masking effect" in pharmacovigilance due to the numerous AEFI reports on COVID-19 vaccines is addressed in another article.

According to the "Swissmedic requirements for the medical assessment of individual case reports", reporting quality in the pharmaceutical industry is to be improved. The article "Reporting of adverse effects and the competent authority, depending on the suspected product" is also intended to facilitate the reporting of ADRs, e.g. those of cannabidiol-containing products.

An overview of the ADRs reported for human medicines and vaccines can be found in the respective 2022 annual statistics.

Swissmedic urges you to continue submitting reports of ADRs and AEFIs. You can find all the relevant information on submitting reports at www.swissmedic.ch.

We hope you find this an interesting read and wish you all the best for the approaching winter.

Eva Eyal

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Safety of medicines and case reports

Pregnancy outcomes after GLP-1 agonist exposure in early pregnancy

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Introduction

Glucagon-like peptide 1 (GLP-1) agonists, including dulaglutide, exenatide, semaglutide, liraglutide, albiglutide and beinaglutide, are extensively used for the management of type 2 diabetes mellitus. Beyond their use in improving blood glycaemic control, some GLP-1 agonists are also used for facilitating weight reduction among individuals with excess weight.

These medications are also commonly prescribed for women of reproductive age. In a Swiss administrative claim database study, GLP-1 receptor agonists accounted for approximately 20% of the prescribed blood glucose-lowering medications in pregnancies where antidiabetic medications were dispensed for pregestational diabetes mellitus (1). Given that many pregnancies are unplanned, there has been an increasing number of unexpected exposures to these drugs during the early stages of pregnancy. Consequently, the Swiss Teratogen Information Service (STIS) and other Teratology Information Services (TISes) worldwide, are observing an increasing number of requests concerning the potential risks associated with these drugs in early pregnancy. At present, providing guidance to these patients and their healthcare providers is challenged by the limited availability of data. Regarding liraglutide, a single case of exposure during the first trimester of pregnancy has been documented, with a favourable outcome observed for the newborn (2). Furthermore, an exenatide pregnancy registry recorded seven cases of exposure during pregnancy, although comprehensive follow-up information remains unavailable (3).

GLP-1 agonists are characterised by a large molecular size, ranging from 3,700 Da (liraglutide) up to 63,000 Da (dulaglutide): placental transfer is not expected a priori, unless specific mechanisms exist. However, findings from animal studies indicate the potential for reproductive toxicity at doses causing polymorphic maternal toxicity for semaglutide, dulaglutide, exenatide and liraglutide. For liraglutide and semaglutide, an increased risk of birth defects (fetal vessel, kidney, liver and skeletal abnormalities) was observed at doses equivalent to those administered in humans (4–6).

Given the limited availability of data, we intended to investigate whether GLP-1 agonists were associated with adverse pregnancy outcomes. This led us to initiate a multicentre, prospective, observational cohort study involving members of the European Network of Teratology Information Services (ENTIS). ENTIS, a non-profit organisation that coordinates TIS activities, is dedicated to providing evidence-based information to patients and their caregivers concerning medication safety and risks during pregnancy and breastfeeding. TISes collect patient data, including information on pregnancy outcomes. This promotes collaborative research that contributes significantly to our understanding of risks associated with drugs during pregnancy.

Methods

This prospective, observational cohort study was conducted involving seven participating centres in six countries: Australia, Germany, Israel, Italy, Switzerland and the United Kingdom. We studied pregnant women exposed to GLP-1 agonists during the first trimester. We compared their pregnancy outcomes to two reference groups: one with diabetes exposed to non-GLP-1 agonist antidiabetic drugs, and another of overweight or obese patients

exposed to non-teratogenic drugs. Data collection involved two phases: initial contact with the TIS and post-expected delivery date. We used standardised questionnaires given to patients or their healthcare providers to gather information. This included maternal characteristics, medical history, drug exposure details and concurrent medications during the first TIS contact. After the expected delivery date, follow-up was carried out through structured questionnaires and telephone interviews to obtain data on pregnancy outcomes, gestational age, birth weight, birth defects and neonatal complications. Birth defects were classified using the European Network of Population-based Registries for the Epidemiological Surveillance of Congenital Anomalies (EUROCAT) ICD10-BPA system (7).

Preliminary results

Whilst the analysis is ongoing, preliminary results based on data from 173 pregnant women exposed to a GLP-1 agonist during the first trimester of pregnancy, along with two reference groups (comprising pregnant women with diabetes and overweight or obese pregnant women), suggest that there is neither a significant increase in the rate of major birth defects nor in the risk of pregnancy loss for women exposed to GLP1 agonists.

Discussion

To the best of our knowledge, this observational prospective multicentre study represents the first evaluation of the reproductive safety of early pregnancy exposure to GLP-1 agonists. ENTIS is in a unique position to conduct independent post-marketing surveillance of drugs during pregnancy. Given the scarcity of data on drug exposure in pregnancy, which often takes considerable time to emerge in the literature, studies like this prospective multicentre cohort investigation are essential for enhancing our understanding of the potential risks. We would like to highlight that the detailed analysis of our findings is currently underway, and we anticipate publishing the full results in the near future.

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Drug-induced pancreatitis: Assessment of ADR reports and review of the literature

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Introduction

Drug-induced pancreatitis is rare, although its actual incidence is not known since its causality is difficult to establish. However, it is thought to be less than 5%, accounting for around 2% of acute cases of pancreatitis. Various pathophysiological mechanisms are associated with drug-induced pancreatitis: immunological reactions (6-mercaptopurine, aminosalicylates, sulfonamides), direct toxic effect (diuretics, sulfonamides), accumulation of a toxic metabolite (valproic acid, didanosine, pentamidine, tetracycline), ischaemia (diuretics, azathioprine), intravascular thrombosis (oestrogens) and an increase in the viscosity of pancreatic secretions (diuretics and corticosteroids). The drugs most often responsible include antibiotics such as tetracycline and the sulfonamides, as well as immunosuppressants such as corticosteroids and azathioprine (1, 2).

Pancreatitis can develop from a few days to a few weeks after the start of a treatment and be mediated by an immunological mechanism; in this case, the patient may also present with a skin rash and eosinophilia. By contrast, other patients may only develop pancreatitis after several months in the case of chronic accumulation of toxic metabolites (e.g. with valproic acid) (3).

Methods

We analysed cases of drug-induced pancreatitis reported over a period of 18 months, between January 2022 and June 2023, to the Geneva Regional Pharmacovigilance Centre (RPVC), and reviewed the scientific literature on the subject. Causality was evaluated according to the WHO-UMC causality assessment system. The suspected drugs were classified according to the categories proposed by Wolfe et al. in 2020 for drug-induced pancreatitis (4). These categories enable the drugs to be classified according to their propensity to trigger pancreatitis, based on a review of the literature (1, 4–6). Thus, according to the most recent classification including data up to 28 March 2019 (4), four classes have been proposed by Wolfe et al. (2020):

Ia) at least one case report with a positive rechallenge after ruling out all other causes (alcohol, hyperlipidaemia/hypertriglyceridaemia, gallstones and other treatments)

Ib) at least one case report with a positive rechallenge without having ruled out other causes

Ic) at least one case report without a positive rechallenge (no rechallenge or a negative rechallenge) after ruling out other causes

II) at least two case reports without a positive rechallenge (no rechallenge or a negative rechallenge) without having ruled out other causes, consistent latency

III) at least two case reports without a positive rechallenge (no rechallenge or a negative rechallenge) without having ruled out other causes, inconsistent latency

IV) at least one case reported in the literature, drugs not fitting into the previously described classes

Results

Between January 2022 and June 2023, RPVC Geneva received a total of 798 reports of adverse drug reactions, including 11 reports of suspected drug-induced pancreatitis. The majority of cases concerned women (n=7, 64%), and the average age was 55 (min-max: 27–92 years).

At the time of the report to the pharmacovigilance centre (the investigations were still in progress for several of the cases), drug causality was assessed as probable in two cases and as possible in nine cases (Table 1). We reviewed all these cases remotely for follow-up. In view of the additional investigations and dechallenge results, we were able to update the causality assessment. Thus, drug causality could be ruled out (unlikely) in four cases, remained possible for four cases and was probable for three cases.

Table 1: Characteristics of pancreatitis individual case safety reports (n=11) processed by RPVC Geneva between January 2022 and June 2023.

		Number
Age (years)	≥ 80	1
	50-79	6
	30-49	2
	0-29	2
Sex	Female	7
	Male	4
Causality assessment at declaration	Probable	2
	Possible	9
Causality assessment after follow-up	Probable	3
	Possible	4
	Unlikely	4

The reasons stated for reclassifying the cases as unlikely after follow-up were as follows:

- a negative rechallenge (enalapril) was observed, and an unknown aetiology with underlying biliary lesions after a cholecystectomy was suggested.
- a recurrence of pancreatitis despite the discontinuation of the suspected drugs (valsartan/hydrochlorothiazide). Moreover, this patient was known to be a regular consumer of alcohol and had a history of several episodes of pancreatitis (four episodes in all).
- a positive resolution despite the continuation of the suspected drug (azathioprine) with the presence of polyps in the gall bladder.
- a positive resolution despite the continuation of the suspected drugs (sitagliptin, metformin and dapagliflozin) in a patient with a history of pancreatitis and cholecystectomy.

We are not aware of any positive rechallenge for the 11 reports of pancreatitis in our centre. The characteristics of the other cases (causality possible or probable after follow-up) are detailed in Table 2.

Table 2: Causality assessment (after follow-up), underlying conditions that may have predisposed to acute pancreatitis and potential risk factors for acute pancreatitis or drug-induced pancreatitis.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Suspected drugs	empagliflozin	dapagliflozin	ceftriaxon	metronidazole	paracetamol/codeine	semaglutide	valproate
Drug classification for assessment of association with DIP* (according to Wolfe et al. 2020)	Not classified	Not classified	II	Ia	Ia	Not classified	Ia
Causality assessment	Probable	Possible	Probable	Possible	Possible	Possible	Probable
Potential risk factors:							
Previous cholecystectomy	No	Yes	Yes	No	Yes	No	No
Previous episode of pancreatitis	No	Yes	No	No	No	No	No
Possible renal dysfunction	No	Yes	Yes	No	No	No	Yes
Hepatic disease	No	No	No	No	No	No	No
Gall stones / biliary disease	No	No	No	Yes	No	No	Yes
History of moderate to heavy alcohol use or abuse	No	No	No	Yes	No	No	No
Pre-existing conditions:							
Crohn's disease/ inflammatory bowel disease	No	No	No	Yes (suspicion)	No	No	No
Diabetes	Yes	No	Yes	No	No	No	No
Hepatitis	No	No	No	No	No	No	No
HIV/AIDS	No	No	No	No	No	No	No
Hyperlipidaemia/ hypercholaesterolemia/ hypertriglyceridaemia	Yes	Yes	No	No	No	No	Yes
Immune disorder	No	No	No	No	No	No	No
Infection	No	Yes	Yes	No	No	No	No

*DIP : drug-induced pancreatitis

Among those cases in which drug causality was retained, five out of the seven patients had at least one comorbidity predisposing them to the onset of pancreatitis, and five out of seven had at least one risk factor for acute or drug-induced pancreatitis.

In three cases, the suspected drugs were classified in category Ia according to Wolfe et al. (2020), i.e. at least one case report with a positive rechallenge, consistent latency and other causes having been ruled out. In one case the suspected drug was classified in category II. Finally, the suspected drugs in the last three cases were not included in the classification tables for assessing the association with drug-induced pancreatitis (4–6).

Discussion

As mentioned in the introduction, cases of drug-induced pancreatitis are rare. Their progression is usually benign, but they can become life-threatening in isolated cases. Therefore, a knowledge of those drugs capable of triggering pancreatitis can be useful for clinicians and enable them to identify this rare aetiology and, most importantly, refrain from re-administer the implicated drugs to their patients.

In February 2023, drug-induced pancreatitis was also the subject of a new section, "Pharmacovigilance in the spotlight", published on the Swissmedic website (7). This section presents three case reports involving isotretinoin (class II), azathioprine (class Ia) and semaglutide (not classified) (4). It serves as a reminder that this adverse drug reaction should be considered in the differential diagnosis as a possible cause of acute pancreatitis.

The determination of drug causality in cases of pancreatitis can be complex to establish. Similar to other adverse drug reactions, it involves an exclusion diagnosis, and it is advisable to first rule out other potential causes such as biliary (gallstones) or alcoholic aetiology, paying particular attention to their frequency (1). A biliary origin should be suspected, particularly if the transaminase levels are abnormal. In elderly patients, obstruction of the pancreatic ducts by a tumour should be considered, although this scenario is rare. In young patients, an infectious origin should be explored systematically. Other aetiological causes that should also be taken into account include hypertriglyceridaemia, autoimmune factors, hyper/hypocalcaemia, a malignant tumour, a genetic cause, a complication of endoscopic retrograde cholangiopancreatography, and trauma (8).

Alongside the aetiological investigations, the chronology of the symptoms in relation to the start of the implicated drug, the clinical outcome upon discontinuation and the results of biological tests are also useful in establishing the diagnosis. It should be noted, however, that a latency of several months does not rule out a drug-related aetiology.

The drugs implicated in the cases reported to RPVC Geneva include treatments that are commonly known to be associated with the onset of acute pancreatitis, such as metronidazole, paracetamol/codeine and valproate, as well as ceftriaxone, although the acknowledged association with the latter is considered to be less strong. The three other cases involve anti-diabetic drugs that were recently placed on the market and that are therefore not yet included in the various classification systems: semaglutide (a glucagon-like peptide 1 analogue [GLP1]), empagliflozin and dapagliflozin (sodium-glucose transport protein 2 inhibitors [SGLT-2]), although it should be noted that drugs belonging to the same classes – liraglutide and canagliflozin – are already classified in category Ic.

In fact, several case reports involving the use of GLP-1 receptor agonists can be found in the literature (9–13), and acute pancreatitis is listed as an uncommon adverse reaction (≥1/1,000, <1/100) to semaglutide (14). GLP-1 agonists stimulate the GLP-1 receptors directly in the pancreatic islet beta cells and exocrine duct cells, which can cause an overgrowth of the cells covering the smaller ducts, leading to hyperplasia, increased pancreatic weight, duct occlusion, back pressure and acute or chronic pancreatic inflammation (15). According to two meta-analyses, GLP-1 analogues are not considered to be more likely to trigger acute pancreatitis compared to placebo (16, 17). The first, published in 2017, included studies with all the GLP-1 agonists in diabetic patients; no difference was observed in the risk of onset of acute pancreatitis between the treated group vs. control (OR 0.93, 95% CI 0.65-1.34) (16).

However, in two other meta-analyses, again with diabetic patients, cases of pancreatitis are described as rare side effects of semaglutide. Only few studies exist and, according to the authors, further assessment supported by pharmacovigilance studies is needed (18, 19).

While pancreatitis is not a known side effect of SGLT-2 inhibitors, there have been several reported cases associating their use with pancreatitis (20–23), including one case with positive rechallenge and dechallenge in a 51-year-old man with a history of type 2 diabetes, dyslipidaemia and a cholecystectomy (24). He was hospitalised for pancreatitis and, following investigations, an alcoholic and biliary origin, as well as hypercalcaemia and hypertriglyceridaemia, were ruled out. Dapagliflozin had been started five days before his admission, in addition to his long-term treatment with insulin detemir, sitagliptin, metformin and rosuvastatin. His symptoms disappeared after the sitagliptin and dapagliflozin were stopped. One year later, following an increase in his HbA1c levels, it was decided to re-administer the dapagliflozin. Subsequently, the patient developed another episode of acute pancreatitis. His symptoms resolved after the dapagliflozin was discontinued. An analysis investigating the association between SGLT-2 inhibitors and acute pancreatitis utilised the postmarketing data collected between 2013 and 2021 in the American FAERS database (FDA Adverse Event Reporting System) (25). In this study, employing various statistical methods, the authors concluded that the administration of SGLT-2 inhibitors may increase the risk of onset of acute pancreatitis (with RORs of 5.37 for canagliflozin, 4.8 for dapagliflozin and 4.78 for empagliflozin). In most cases, this side effect occurred within the first six months after treatment initiation. When SGLT-2 inhibitors were combined with dipeptidyl peptidase-4 inhibitors (gliptins), GLP-1 analogues or angiotensin converting enzyme inhibitors, the risk of onset of acute pancreatitis was greater compared to the administration of SGLT-2 inhibitors as monotherapy. However, the data currently available do not allow any definitive conclusion to be drawn concerning the role of SGLT-2 inhibitors in the occurrence of pancreatitis.

Conclusion

Although drug-induced pancreatitis accounts for a small proportion of pancreatitis cases, it is important to consider it in the differential diagnosis of acute pancreatitis, so that the potentially responsible drug(s) can be withdrawn. Nevertheless, establishing a causality link is not always easy in view of the presence of other, more prevalent causes, particularly in patients with multiple comorbidities and underlying risk factors. Moreover, in many cases a conclusive association between a pancreatitis and a particular drug cannot be determined due to the absence of a rechallenge or an inconclusive chronology. In such situation, the periodically updated systems for classifying the association between an adverse effect and treatment can greatly assist clinicians, particularly for events that are as rare as drug-induced pancreatitis.

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Sex differences in outcomes of intravenous thrombolysis in acute ischaemic stroke patients with preadmission use of antiplatelets

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The article presented below is an abbreviated version of the original article published by Noseda R. et al., 2023 (1).

Introduction

Intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator (rtPA) is the only approved pharmacological reperfusion treatment for acute ischaemic stroke (AIS) (2). Clinical outcomes of IVT with rtPA rely strictly on patient individuality, which encompasses biological sex, among others (3, 4). Sex differences have been investigated in relation to safety and functional outcomes of IVT with rtPA in patients with AIS, but with heterogeneous and unsettled findings (5–7).

Although the use of antiplatelets (single or dual) before stroke onset has been associated with an increased risk of haemorrhagic complications following IVT (7), preadmission use of antiplatelets is not considered a contraindication for IVT with rtPA in eligible patients with AIS (2). Data on the association of preadmission use of antiplatelets with safety and functional outcomes after IVT with rtPA in patients with AIS are also contradictory (8–11).

Platelet count and reactivity are higher in females (12–14), therefore females with preadmission use of antiplatelets and AIS may respond differently from males to IVT. There is a lack of studies specifically evaluating the interaction between patient sex and preadmission use of antiplatelets in relation to both safety and functional outcomes of IVT in patients with AIS.

The aim of this cohort study was to compare safety and functional outcomes after IVT between females and males with regard to preadmission use of antiplatelets in a large multicentre Swiss cohort reflecting daily clinical practice in acute stroke care.

Methods

Consecutive patients admitted from 1 January 2014 to 31 January 31 2020 to hospitals participating in the Swiss Stroke Registry (SSR) (15) presenting with AIS and receiving IVT without endovascular treatment were included. Patients who used anticoagulants before admission and patients with missing data on age, sex and preadmission use of antiplatelets were excluded. The study population was divided into two groups based on patient biological sex and thereafter compared in terms of preadmission use of antiplatelets.

The safety outcome was in-hospital symptomatic intracerebral haemorrhage (sICH) occurring within seven days of AIS onset. The functional outcome was functional independence, defined as a modified Rankin Scale (mRS) score of 0 to 2, at three months after hospital discharge. The mRS is an ordinal scale that ranges from 0 (no symptoms) to 6 (death), which is widely used to measure functional outcomes (16).

Multivariable logistic regression models were fitted to assess the association between patient sex and each outcome according to preadmission use of antiplatelets (single vs no use or dual vs no use). With this aim, interaction variables between patient sex and preadmission use of antiplatelets (either single or dual) were introduced. Regression models were adjusted for meaningful demographic and clinical patient variables that could potentially influence outcome measures. These variables included age, National Institutes of Health Stroke Scale (NIHSS) score at admission, pre-stroke disability (defined by mRS score), medical history of hypertension,

hyperlipidaemia, diabetes, coronary heart disease, smoking, atrial fibrillation, previous sICH and previous stroke, and in-hospital acute treatment with anticoagulants.

Results

Of 5,412 patients with AIS receiving IVT and admitted to stroke units or stroke centres from the SSR network between 1 January 2014 and 31 January 2020, 4,996 (92.3%) patients met the inclusion criteria. Of these, 2,124 (42.5%) were females and 2,872 (57.5%) were males. Table 1 summarises the baseline characteristics of the study population according to patient sex.

In-hospital sICH

Overall, 136 (2.7%) patients presented in-hospital sICH after IVT, with similar proportions of females and males, both as crude rates (3.1% vs 2.5%, p=0.19) and after risk adjustment (adjusted odds ratio, aOR 0.93; 95% confidence interval, CI, 0.63-1.39). In the multivariable logistic regression analysis on the association of baseline patient characteristics with the probability of in-hospital sICH, preadmission use of a single antiplatelet agent did not significantly increase the odds of in-hospital sICH compared with no preadmission use of antiplatelets (aOR 1.40; 95% CI 0.90-2.19). By contrast, preadmission use of dual antiplatelets was associated with higher odds of in-hospital sICH compared with no preadmission use of antiplatelets (aOR 2.72; 95% CI 1.04-7.10), with a statistically significant trend from preadmission use of single to dual antiplatelets (p=0.04). No interaction was found between patient sex and preadmission use of either single or dual antiplatelets regarding in-hospital sICH (p=0.94 and p=0.23, respectively).

Table 1: Baseline characteristics of the study population according to patient sex.

Characteristics	Females (n=2,124)	Males (n=2,872)	*p* value
Age, years			
Median, min-max	79, 16-102	71, 16-98	<0.0001
Preadmission use of antiplatelet(s), no. (%)	848 (39.9)	1160 (40.4)	0.7402
Single	807 (38.0)	1087 (37.9)	
Dual	41 (1.9)	73 (2.5)	
Medical history, no. (%)			
Previous stroke	289 (13.6)	454 (15.8)	0.0387
Previous sICH	32 (1.5)	38 (1.3)	0.5667
Hypertension	1,575 (74.2)	1,984 (69.1)	<0.0001
Diabetes	356 (16.8)	580 (20.2)	0.0031
Hyperlipidaemia	1,271 (59.8)	1,869 (65.1)	0.0004
Smoking	258 (12.2)	678 (23.6)	<0.0001
Atrial fibrillation	456 (21.5)	497 (17.3)	<0.0001
Acute coronary disease	266 (12.5)	594 (20.7)	<0.0001

Pre-stroke disability, no. (%)			
mRS score 0 – No symptoms at all	1,158 (54.5)	1,852 (64.5)	<0.0001
mRS score 1 – No significant disability despite symptoms at all	278 (13.1)	324 (11.3)	
mRS score 2 – Slight disability	163 (7.7)	169 (5.9)	
mRS score 3 – Moderate disability	198 (9.3)	137 (4.8)	
mRS score 4 – Moderately severe disability	58 (2.7)	52 (1.8)	
mRS score 5 – Severe disability	11 (0.5)	4 (0.1)	
NIHSS at admission, no. (%)			
0-4	707 (33.3)	1,227 (42.7)	<0.0001
5-10	867 (40.8)	1,068 (37.2)	
11-15	264 (12.4)	302 (10.5)	
16-21	191 (9.0)	190 (6.6)	
≥22	91 (4.3)	78 (2.7)	
Pathogenic subtype of AIS, no. (%)			
Large artery atherosclerosis	197 (9.3)	424 (14.8)	<0.0001
Cardioembolism	593 (27.9)	688 (24.0)	
Small vessel occlusion	179 (8.4)	241 (8.4)	
Stroke of other determined aetiology			
Two or more causes identified	86 (4.1)	147 (5.1)	
Negative evaluation	452 (21.3)	553 (19.3)	
Incomplete evaluation	334 (15.7)	382 (13.3)	
In-hospital acute treatment with anticoagulants, no (%)	33 (1.6)	47 (1.6)	0.9675

Abbreviations: sICH, symptomatic intracerebral haemorrhage; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; AIS, acute ischaemic stroke

Functional independence at three months after discharge

The proportion of patients who were independent at three months after discharge (mRS score 0-2) was 44.2% (939/2124) of females and 54.7% (1571/2872) of males (p<0.0001). In the multivariable logistic regression analysis on the association of baseline patient characteristics with the probability of functional independence at three months after discharge, the odds of reaching functional independence at three months was higher in males than in females (aOR 1.34; 95% CI 1.09-1.65). Preadmission use of either a single antiplatelet agent or dual antiplatelets increased the odds of functional independence at three months after discharge (aOR 0.88; 95% CI 0.70-1.12 and aOR 1.62; 95% CI 0.72-3.62, respectively). No interaction was found between patient sex and preadmission use of either single or dual antiplatelets in relation to the primary functional outcome (p=0.41 and p=0.58, respectively).

Discussion

This study found no sex differences in the safety of IVT in AIS patients in relation to preadmission use of antiplatelets. Males showed higher odds of functional independence at three months than females after IVT; however, the sex difference was apparently not explained by a sex-specific mechanism related to preadmission use of antiplatelets.

Since both antiplatelets and IVT interfere with the haemostatic balance, concern regarding an increased risk of haemorrhagic complications in AIS patients with preadmission use of antiplatelets

when treated with IVT is high, all the more so because of the heterogeneous findings from previous studies (9). Consistent with the only earlier study that used subgroup analysis to assess the effect of patient sex on the risk of in-hospital sICH in relation to preadmission use of antiplatelets (8), the present study confirmed that preadmission use of dual antiplatelets increased the odds of in-hospital sICH following IVT, with a trend from single to dual antiplatelet therapy without sex differences.

In contrast, better benefits of IVT were observed in males compared to females, confirming some previous observations (6). Nevertheless, sex differences in IVT efficacy apparently were not explained by a sex-specific mechanism related to preadmission use of antiplatelets. The reasons for sex disparities in IVT responses may be found in the patients' living situation, family and caregiver support, and social background; however, these assumptions are beyond the scope of this study and are not documented in the SSR.

The results of this study are important in the era of precision and gender medicine, where biological sex is considered a health and disease modifier (17) and adds new data to the ongoing debate regarding the impact of sex differences on the safety and functional outcomes of IVT in females and males in relation to preadmission use of antiplatelets (3). In the context of personalised medicine, optimisation of IVT therapy should not disregard the biological sex of AIS patients given that cellular, anatomical, hormonal and behavioural differences exist between the sexes and are associated with pharmacological responses and health (17, 18).

However, the study has several limitations. Owing to small sample sizes, separate analyses for individual antiplatelet agent regimens could not be performed. Adherence to antiplatelets could have influenced stroke onset; however, this information is not recorded in SSR, which also lacks detailed radiological findings regarding the subtypes of haemorrhagic transformations.

In conclusion, when clinicians use IVT to treat AIS patients, worse safety and functional outcomes in females compared to males are not to be expected on the basis of the notion of preadmission use of antiplatelets. Future studies are needed that aim to discern the mechanism(s) that underpin(s) the better functional outcomes observed in males with AIS following IVT.

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Febuxostat and azathioprine: A rare interaction with severe consequences

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Summary

The concomitant use of azathioprine (AZT) and a xanthine oxidase (XO) inhibitor without an appropriate dose reduction may cause a drug interaction leading to adverse haematological changes. This case report describes a female patient aged about 70 who developed pancytopenia after concomitant treatment with azathioprine and febuxostat. Based on the known interaction of the two active ingredients, the improvement of the pancytopenia after the discontinuation of the drugs, the lack of plausible alternative aetiologies and the high levels of the haematotoxic AZT metabolite 6-thioguanine nucleotide, causality was judged to be established with certainty. This case report reinforces the importance of clearly listed interactions in the medicinal product information.

Introduction

Febuxostat (FX) and allopurinol, which belong to the class of selective and non-selective xanthine oxidase (XO) inhibitors respectively, are used to treat gout. When choosing the right therapy, it is important to consider possible drug interactions. One such interaction is between azathioprine (AZT) and an XO inhibitor (1).

In Switzerland, AZT is approved *inter alia* for the treatment of severe primary chronic polyarthritis, lupus erythematosus visceralis and autoimmune haemolytic anaemia. Its mechanism of action is based on immunosuppression. A cytotoxic agent, it interferes with the formation of nucleic acids (2). The metabolism of AZT is complex and proceeds via several metabolisation pathways, which are described in detail in the discussion. Both the haematotoxicity and immunosuppressive effect of AZT are primarily caused by the thioguanine nucleotide (6-TGN) metabolites that remain within the body's cells for several weeks. These metabolites are formed in greater quantities when XO is inhibited (1, 2). Clinically, vomiting, nausea and, above all, haematological changes (e.g. anaemia, leukopenia, thrombocytopenia) are characteristic of interactions between these drug classes (3). In Switzerland, two cases of pancytopenia have been reported to date after concomitant administration of AZT and FX (4).

Case report

In 2023, the Regional Pharmacovigilance Centre (RPVC) in Zurich received a report of a case of pancytopenia following the concomitant administration of AZT and FX. Pancytopenia is a deficiency of all three types of blood cells (erythrocytes, leukocytes and platelets) in peripheral blood (5).

The female patient, who was about 70 years old, had been treated for an extended period with 80 mg Adenuric® (febuxostat) daily due to recurrent gout. She was also prescribed 100 mg Imurek® (azathioprine) due to ANCA-associated vasculitis with eye involvement. Pancytopenia was detected during a routine check-up a few weeks later. The lowest levels of haemoglobin were 66 g/L (reference 117-153 g/L), platelets 89 G/L (reference 143-400 G/L) and leukocytes 1.32 G/L (reference 3.0-9.6 G/L). Symptomatically, the patient presented with exertional dyspnoea, which had started a few weeks earlier and was readily explained by the anaemia. The patient denied any occurrences of bleeding. The pancytopenia was thought to be caused by the combination of azathioprine and febuxostat. Both drugs were therefore discontinued and the patient was hospitalised and put into protective isolation. Her thioguanine nucleotide levels were measured a few days later: Her 6-TGN levels were 937 pmol/8*10^8 RBC, above the level of

450 pmol/8*10^8 RBC considered to be a potential haematotoxic threshold. 6-methyl-mercaptopurine (6-MMP) metabolites associated with hepatotoxicity were not elevated at 469 pmol/8*10^8 RBC (hepatotoxic threshold: 5,000 pmol/8*10^8 RBC). Prior to treatment, the patient's TPMT activity was measured and was normal at 63 nmol MTG/g*Hb*h(-1). Given the presence of chronic renal insufficiency, the possibility of renal anaemia was also considered, but this would not have explained the depletion of the other cell lines. As a therapeutic measure, the patient was given an erythrocyte transfusion to stabilise her haemoglobin level. Stimulation with granulocyte colony stimulating factor (G-CSF) was not performed, as a relevant effect was not considered likely due to the high 6-TGN levels. The patient's blood count normalised over the course of the treatment and she was discharged in an improved condition.

The patient was treated simultaneously with sulfamethoxazole/trimethoprim, amlodipine, carvedilol, pantoprazole, candesartan, torasemide and heparin. These drugs can also cause cytopenias, but as the cell lines recovered with continued therapy, they are not to be suspected as an aetiological factor. The patient has the following relevant pre-existing conditions: membranous glomerulonephritis with chronic renal insufficiency (KDIGO classification G3a A3), arterial hypertension, a prediabetic metabolic state, normochromic and normocytic anaemia, and hypothyroidism. The patient is also known to have a penicillin allergy.

Discussion

In the presence of glutathione, azathioprine, which is chemically and structurally similar to thiopurines, is converted by the glutathione S-transferase (GST) into 6-mercaptopurine (6-MP) (6, 7). Further degradation occurs via three different metabolic pathways: The first pathway is via thiopurine methyltransferase (TPMT), whereby TPMT modifies the resulting 6-MP into 6-MMP by S-methylation. Another possibility is the oxidation of 6-MP by XO, which produces the degradation product 6-thiourea acid, an inactive form. As a third form of metabolisation, active thiopurine intermediates are formed by hypoxanthin-guanin-phosphoribosyl-transferase (HGPRT), with 6-TGN being most active in erythrocytes. 6-TGN is immunomodulatory, and the incorporation of the metabolite into the genetic information of immune cells is the key factor in the cell-damaging properties of azathioprine, which can lead to DNA damage in the long term. (6, 8). 6-TGN levels above 450 pmol/8*10^8 RBC can have a toxic effect on bone marrow. (9). Two cases of acute bone marrow failure associated with elevated intracellular 6-TGN levels due to AZT therapy have been reported in the literature. Haematological side effects such as leukopenia are known with long-term azathioprine therapy, but pancytopenia and severe anaemia after short-term AZT therapy are rare. (10). TPMT, which as one of three key enzymes for the metabolisation of AZT S-methylates the substance, is influenced by a genetic polymorphism. This polymorphism was already described in the 1970s. (8, 10, 11). This genetic condition causes different enzymatic activity in different patients. In an older study, 88.6% of a randomly selected group of patients had high enzymatic activity, 11.1% had moderate TPMT activity and 0.3% had none at all. The researchers also postulated that TPMT enzymatic activity in erythrocytes could be inherited in an autosomal codominant manner (12).

Xanthine oxidase, which can alternatively inactivate AZT, is little affected by genetic polymorphisms; previous studies have shown little variation between individuals (8, 10).

Concomitant use of allopurinol may shift metabolism adversely by inhibiting the metabolising enzyme xanthine oxidase. This is also the case with febuxostat. This inhibition favours the formation of cytotoxic 6-TGN. According to Logan et al. in 2020 in the USA, the guidelines for the management of potential adverse drug interactions between thiopurines, such as azathioprine, and febuxostat were not comparable to those for allopurinol. While the US prescribing information for febuxostat contraindicates concomitant administration with azathioprine, the package leaflet for thiopurines does not mention this interaction (1). The Swiss information for healthcare professionals for Adenuric® (febuxostat) currently contraindicates concomitant treatment with febuxostat and azathioprine (as well as mercaptopurine), as this can lead to elevated plasma concentrations and potentially toxic effects. In contrast, the Swiss information for healthcare

professionals for Imurek® does not contraindicate concomitant administration of azathioprine and febuxostat (2, 13). The interaction between azathioprine and allopurinol is well documented in the literature (1, 14–16). The available literature recommends reducing the dosage of thiopurines or refraining from concomitant administration altogether (1). Switzerland makes a similar recommendation. The Swiss information for healthcare professionals for Imurek® recommends reducing the dose of azathioprine to ¼ of the original dose if AZT is co-administered with allopurinol (2).

Conclusion

Serious haematological side effects are to be expected if azathioprine and XO inhibitors such as febuxostat are coadministered, because of the adverse metabolism of azathioprine to the haematotoxic 6-TGN. At present, this interaction is only described in the Swiss medicinal product information for Adenuric® (febuxostat), but not for Imurek® (azathioprine). This case report shows once again how important it is to read the medicinal product information for all medicines taken in order to avoid such serious interactions wherever possible.

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COVID-19 vaccines: Is the seriousness criterion "medically important" applied correctly in reports, and are there differences between reports from healthcare professionals and patients?

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Introduction

When reporting adverse drug reactions (ADRs), their seriousness has to be graded. According to the Guidelines on Good Pharmacovigilance Practices (GVP), suspected serious adverse drug events are those that are **fatal, life-threatening**, **lead to or prolong hospitalisation**, result in **persistent or significant disability/incapacity**, or lead to a **congenital anomaly/birth defect** (1). Other situations can also be classified as serious according to the medical assessment using the criterion "medically important" (1). "Medically important" reactions are situations that could endanger the patient or require an intervention to prevent one of the other seriousness criteria listed above (1).

The EudraVigilance Expert Working Group provides a list of "important medical events" (IMEs) (2). The IME list can help as a standardisation tool for classifying "medically important" reactions and is meant for guidance only (2). In general, the seriousness of a report is indicated by the reporter, whereby more than one criterion can be selected per case (3). In contrast to seriousness, severity indicates the extent or degree of a reaction and is generally not sufficient on its own to classify a reaction as a serious ADR.

In Switzerland, on the one hand there is a reporting obligation for healthcare professionals (HCPs) under the Therapeutic Products Act and, on the other, patients and relatives are allowed to report ADRs (4). Since 2021, the reports from both sources (HCPs and patients/relatives) can be sent directly to Swissmedic (Swiss Agency for Therapeutic Products) (5).

During the COVID-19 vaccination campaign, Swissmedic received approximately 50% of the spontaneous reports from HCPs and 50% directly from patients/relatives. The rate of ADRs following COVID-19 vaccination categorised as serious by the reporters is 37% in Switzerland and thus significantly higher than e.g. in the US (6.6%), while reporting rates for fatal outcome are comparable (1.4% vs. 1.3%) (6).

A large proportion of the cases labelled as serious in Switzerland was classified based on the category "medically important". Since this criterion is used very commonly but is less distinct than the other seriousness criteria, the objective of this analysis was to evaluate the appropriate use of this criterion in ADR reports from healthcare professionals compared to patients/relatives following COVID-19 immunisation.

Methods

All serious ADR reports received between 1 January 2021 and 31 December 2021 following immunisation with a COVID-19 vaccine were extracted from the Swiss national database at Swissmedic. Cases categorised solely as "medically important" were further analysed. We extracted the preferred term (PT) of the reported ADRs according to the Medical Dictionary for Regulatory Activities (MedDRA) (7) and matched them with the IME list (EMA list dated 8 March 2022, MedDRA version 25.0) (8). The significance between proportions was measured using the Z-test for proportions.

Results

Between 1 January 2021 and 31 December 2021, Swissmedic received 11,115 ADR reports concerning COVID-19 vaccines. Table 1 shows the number of reports per vaccine type and the number of reports per 1,000 administered doses, respectively (9).

Table 1: Type of COVID-19 vaccine and number of reports

COVID-19 vaccine	Number of reports (per 1,000 administered doses)
Spikevax® (elasomeran) Moderna	7,667 (1.0)
Comirnaty® (tozinameran) Pfizer	3,143 (0.8)
COVID-19 vaccine Janssen	77 (0.7)
Unknown	224

An overview of this analysis is shown in Figure 1. Half of the reports were received by HCPs (n = 5,582), the other half by patients/relatives (n = 5,533).

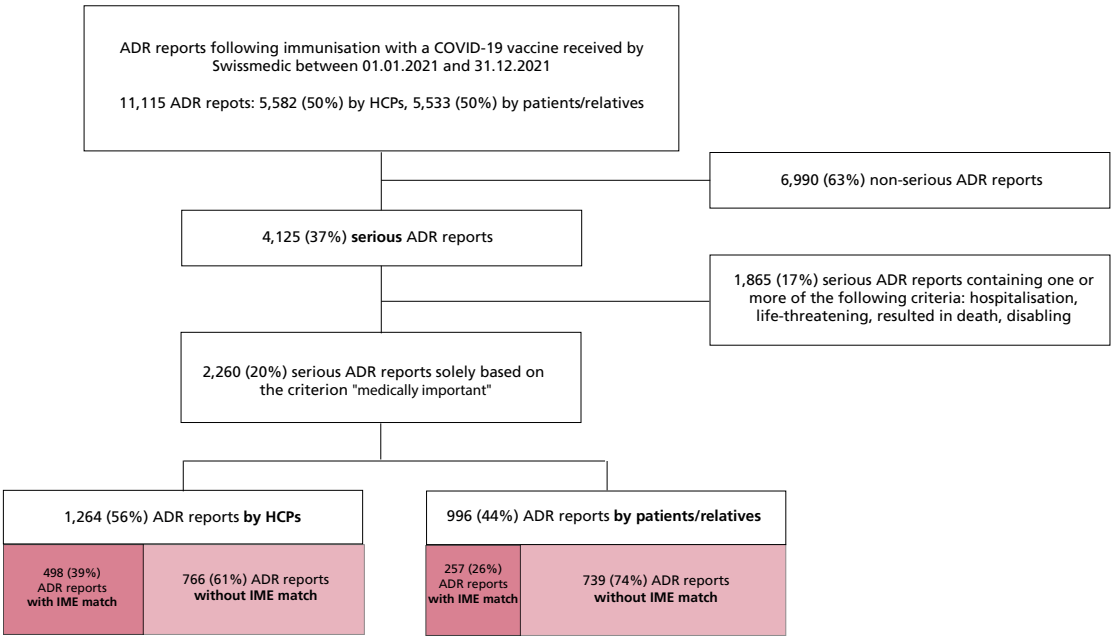

Figure 1: Overview of results, including number (%) of cases reported by HCPs and patients/relatives with and without IME match, respectively

A total of 4,125 reports (37% of all reports concerning COVID-19 vaccines) were categorised as serious. The total numbers for the seriousness criteria within these serious reports are shown in Figure 2. It should be noted that more than one seriousness criterion could have been selected for each report.

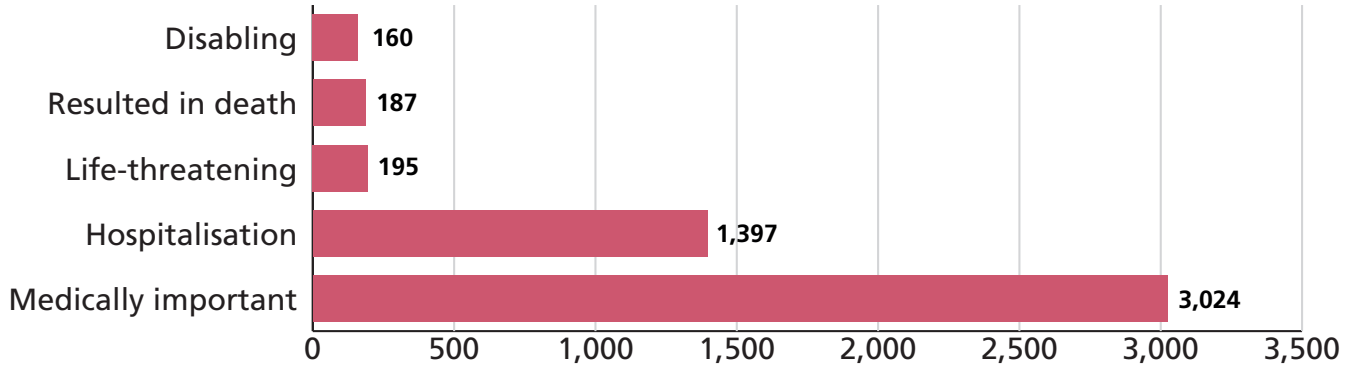

Figure 2: Total numbers (n) of the criteria for the serious reports

In 2,260 of the serious reports, the categorisation "serious" was based solely on the criterion "medically important". These 2,260 cases contained 7,675 ADRs. 1,264 (56%) reports were submitted by HCPs (46% physicians, 9% pharmacists, 1% other HCPs) and 996 (44%) by patients/relatives. In 498 of 1,264 reports by HCPs (39%) and in 257 of 996 (26%) by patients/relatives, the reported seriousness matched with the IME list. As shown in Figure 1, the proportion of correctly categorised ADRs is significantly higher ($p<0.0001$) for reports from HCPs compared to patients/relatives.

The ten most frequent reactions without an IME match from HCPs and patients/relatives are shown in Figure 3 and Figure 4.

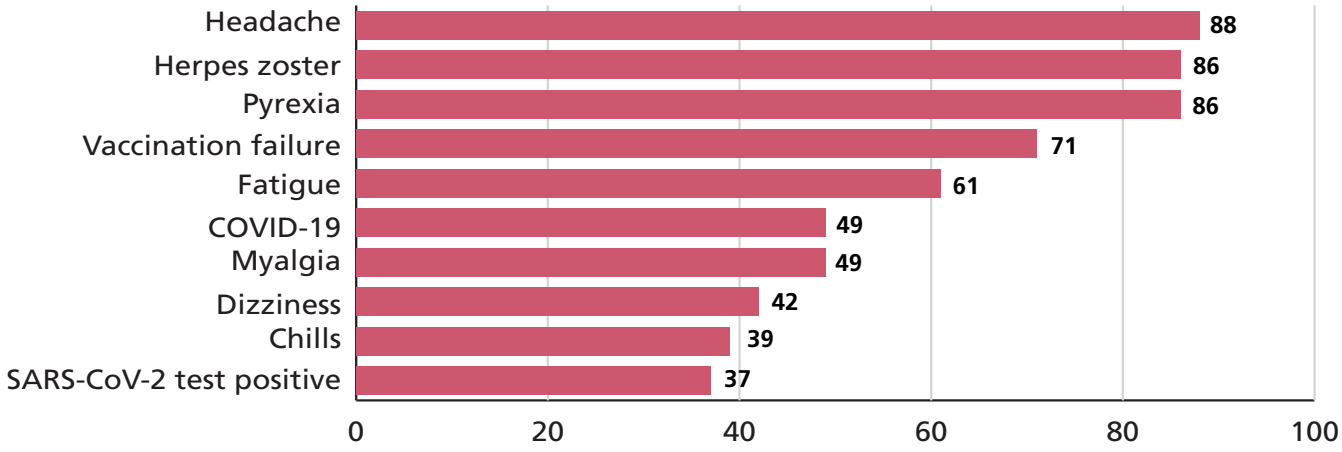

Figure 3: Top 10 reactions from HCPs without an IME match

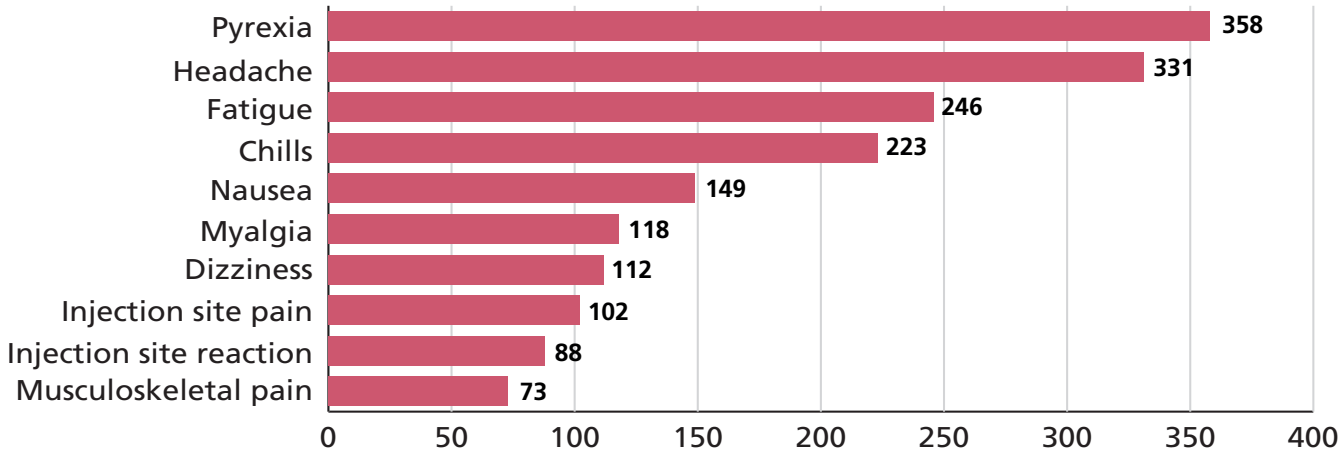

Figure 4: Top 10 reactions from patients/relatives without an IME match

Discussion

In Switzerland, more than one third of all reported ADRs related to COVID-19 vaccination during the period analysed were classified as "serious" by the primary reporters. Of these reports, 2,260 cases were classified as "serious" on the basis of the criterion "medically important" alone. In comparison, an analysis of the US VAERS database revealed 6.6% serious reports (7.9% serious reports including deaths) (6). In that analysis, reports were classified as "serious" only by the more unequivocal criteria (i.e. inpatient hospitalisation, prolongation of hospitalisation, permanent disability, life-threatening illness, congenital anomaly or birth defect, or death) (6). The criterion "medically important" was not applied in the VAERS analysis to classify a case as serious, which explains the lower rate of serious reports.

Other analyses also show a significantly lower proportion of serious reports compared to Switzerland. However, seriousness was not defined in the same way in all studies, and the criterion "medically important" was not included (10, 11). Analyses using relatively short data periods at the beginning of vaccination campaigns tend to show a higher

proportion of serious cases (12, 13). Overall, comparability of data remains difficult due to the use of different criteria to define seriousness.

In our analysis, approximately two thirds of the cases classified as "medically important" are not "serious" according to the IME list. This misclassification may lead to a general overestimation of serious adverse reactions. The proportion of correctly categorised ADRs is significantly higher in reports from HCPs. However, HCPs frequently reported herpes zoster as a serious reaction using the criterion "medically important". According to the IME list, herpes zoster involving one dermatome without complications like ophthalmic involvement is not considered "serious" (8). In addition, HCPs often classified reactions such as vaccination failure, COVID-19 disease or a positive Sars-CoV-2 test as "medically important".

With regard to patients/relatives, the most frequent reactions without IME match reflect the known ADR profile of mRNA COVID-19 vaccinations (14). Local reactions such as "injection site pain" and "injection site reactions" were also frequently reported as "medically important" by patients/relatives. In these cases, seriousness and severity might have been used interchangeably, and the reporters may have tried to emphasise the severity of the reaction.

In concordance with other studies, our analysis reveals that many reports classified as "serious" due to the criterion "medically important" may in fact have been misclassified (15). Thus, the use of the category "medically important" in reports by patients/relatives requires a general revision. Moreover, additional information and training for HCPs appears necessary as well to improve the seriousness categorisation in ADR reports. Guidelines regarding the handling of reports by patients/relatives are needed to tackle the increasing number of reports by patients/relatives.

Conclusion

The analysed Swiss reports concerning COVID-19 vaccines show a significantly higher proportion of adverse reactions labelled as "serious" by the primary reporters compared to other countries/ analyses. Since a large proportion of the cases was labelled as "serious" based on the "medically important" criterion, an overestimation of serious reports from Switzerland can be assumed. In order to improve the validity of spontaneous reports in the future, measures to increase the rate of appropriate seriousness categorisation by patients/relatives as well as HCPs are considered necessary.

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Kounis syndrome: A less familiar adverse drug reaction

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Introduction

Early detection of adverse drug reactions by healthcare professionals is of the utmost importance for patient safety. Kounis syndrome is a little-known side effect, with a reported incidence of 4.33 cases/100,000 inhabitants, as based on 52 cases documented over a period of four years in a region of Greece numbering 300,000 inhabitants (1). In Switzerland, a total of three cases of Kounis syndrome have been reported to Swissmedic to date (2).

Kounis syndrome is defined as the occurrence of an acute coronary syndrome accompanied by an allergic reaction. For this reason it is also known as "allergic angina pectoris syndrome".

In the pathophysiological background are mast cells (1), which are present both in the heart muscle tissue and in atheromas of the coronary vessel wall. (3–4). If these are activated, they release inflammatory mediators such as histamine, which can trigger spasm of the coronary arteries. If this persists, severe heart muscle cell damage may occur, which is associated with increased troponin levels (1).

Risk factors for Kounis syndrome include a positive history of allergic reactions, arterial hypertension, diabetes mellitus, dyslipidaemia and nicotine abuse.

Three forms of Kounis syndrome have been described (5):

- Type 1 is the most frequent variant (72.6%), generally occurring in younger patients with a known diathesis for allergic reactions. Underlying this form is the triggering of a coronary spasm without coronary sclerosis;
- Type 2 occurs in 22.3% of all affected patients and is characterised by coronary spasms in the presence of known coronary sclerosis. In these cases, inflammatory mediators can destabilise existing plaques and cause an acute myocardial infarction;
- Type 3 occurs in 5.1% of all cases and is limited to patients who have undergone stent implantation, in whom stent thrombosis or stent restenosis occurs in the context of an allergic reaction.

Kounis syndrome may be triggered by food, environmental factors or medicinal products (Table 1) (6).

Table 1: Active substances authorised in Switzerland which, according to Swiss medicinal product information, may trigger Kounis syndrome (7).

Medicinal product group	Active substance
Analgesics	Metamizole
Antibiotics	Amoxicillin, amoxicillin / clavulanic acid, aztreonam, benzylpenicillin, cefaclor, cefazolin, cefepime, cefpodoxime, ceftaroline, ceftazidime, ceftazidime / avibactam, ceftobiprole, ceftolozane / tazobactam, ceftriaxone, cefuroxime, ertapenem, flucloxacillin, imipenem / cilastatin, meropenem, meropenem / vaborbactam, phenoxymethylpenicillin, piperacillin / tazobactam
Contrast media	Iobitridol, iodine, iodixanol, iohexol, iomeprol, iopromide, iopamidol, ioversol, gadobenic acid, sodium amidotrizoate / meglumine, sulfur hexafluoride
Non-steroidal antirheumatics (NSARs)	Diclofenac, lysine acetylsalicylate
Thrombocyte aggregation inhibitor	Clopidogrel
Other	Iron, rocuronium

In line with the three forms of Kounis syndrome, the clinical picture of Kounis syndrome is always associated with an allergic reaction. However, the clinical symptoms of angina pectoris are always strongly determined by localisation and the duration of the coronary spasm (Table 2) (1).

Table 2: Clinical, electrocardiographic and laboratory signs of Kounis syndrome (1).

Clinical symptoms	Clinical signs	Electrocardiographic signs	Laboratory signs
• Acute chest pain • Chest discomfort when swallowing • Dyspnoea • Faintness • Headache • Malaise • Nausea • Pruritus • Skin itching • Syncope • Vomiting	• Bradycardia • Cardiorespiratory arrest • Cold extremities • Diaphoresis • Hypotension • Pallor • Palpitations • Skin rash • Sudden death • Sweating • Tachycardia	• Atrial fibrillation • Bigeminal rhythm • Heart block • Nodal rhythm • Sinus bradycardia • Sinus tachycardia • ST segment depression or elevation • T-wave flattening and/or inversion • QRS complex prolongation • QT segment prolongation • Ventricular ectopics • Venticular fibrillation	• Coronary angiography (spasm, thrombosis) • Eosinophilia • Increased cardiac enzymes and especially CPK-MB • Increased troponins • Cardiomegaly in chest X-ray • Dilated cardiac chambers in echogram • Eosinophils and/or mast cells in coronary biopsy • MRI: subendocardial gadolinium concentration • SPECT: detects ischaemia

Conclusion

Diagnosing Kounis syndrome presents a challenge in clinical practice. In practice, it can be difficult to distinguish mild angina pectoris symptoms from hypersensitivity syndrome; on the other hand, if an allergic reaction is mild, it may be wrongly diagnosed as being "only" classic angina pectoris. The situation is also exacerbated by the variability of the latency time between allergic reaction and angina pectoris symptoms in Kounis syndrome. This is shown by case studies in which patients have developed Kounis syndrome symptoms immediately after taking a medicinal product (8–10), while one case study describes a patient who untypically suffered an acute coronary event 48 hours after the allergic reaction (11).

Diagnosis of Kounis syndrome always requires further investigations, such as laboratory tests, electrocardiography or angiography, in addition to the clinical symptoms (Table 2). Against this background, it should be remembered that laboratory parameters such as serum concentration of tryptases can only be investigated for a limited period of time, and if Kounis syndrome is suspected, assessment should take place promptly (12).

In summary, it is critically important that Kounis syndrome be taken into account as a differential diagnosis in the case of specific clinical symptom constellations. Correct diagnosis allows early intervention to prevent myocardial damage.

Reporting adverse reactions

Healthcare professionals are requested to report serious and/or previously unknown adverse drug reactions to Swissmedic. Please use the "ElViS" Electronic Vigilance Reporting Portal for this purpose.

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Regulatory

The masking effect in pharmacovigilance: A signal detection challenge amidst the COVID-19 vaccine rollout

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The COVID-19 pandemic has been a global health crisis necessitating rapid development and deployment of vaccines to curb its spread. The broad use of COVID-19 vaccines and the considerable attention to potential safety issues in the media and among the public led to an unprecedented large number of reports of suspected adverse events. All these reports are evaluated and stored in databases on a national and international level in order to identify previously unknown adverse effects. In this context, a known phenomenon called the "masking effect" has presented a challenge as regards statistical signal detection in databases of adverse event reports. This “masking effect” is caused by the large number of COVID-19 vaccines but applies to signal detection for other medicines or the vaccines amongst each other in the database.

In order to detect potential safety issues in databases containing adverse event reports, a statistical and a scientific analysis are combined. A statistical disproportionality analysis enables screening of a database of reported adverse events for patterns that may indicate a larger number of certain adverse events than expected for certain medicinal products. An identified “disproportionality” will then be substantiated by a clinical review of cases and screening of the scientific literature and studies. There are different statistical methods for the disproportionality analysis. One of the most common of these is the reporting odds ratio (ROR), which is based on a 2x2 contingency table. The ROR corresponds to the ratio between the odds of an adverse event of interest with a certain medication or vaccine to the odds of the same adverse event with all other medicinal products and vaccines in the database (Table 1).

Table 1: Calculation of the reporting odds ratio (ROR)

	Adverse event of interest	All other adverse events
Medication or vaccine of interest	a	b
All other medications and vaccines	c	d

$$ROR = \frac{a/b}{c/d}$$

When the lower limit of the 95% confidence interval is greater than 1, the chosen adverse event of interest could be a signal. A prerequisite for the ROR to work is that there is a randomly scattered background rate.

Since the COVID-19 pandemic, the large amount of adverse event reports has impacted databases worldwide and affected signal detection for other medicines based on disproportionality analysis by significantly changing the background rates of reports in the databases. This phenomenon is called the “masking effect”: The signal detection ratio for a specific drug event of interest, identified through quantitative methods, is reduced or inhibited due to the presence of another product (e.g. COVID-19 vaccines) in the database, with overrepresented reporting of the event in question. Masking effects may complicate the interpretation of adverse event data by potentially obscuring safety issues and thus delay timely intervention.

As an example, we calculated the ROR of myocarditis, pericarditis and myopericarditis for the antipsychotic agent clozapine in our database with and without inclusion of the COVID-19 vaccines in the background rates. Since myocarditis, pericarditis and myopericarditis are known adverse reactions to clozapine, a statistical disproportionality in the database is expected. Table 2 shows that the ROR is nearly 3.5 times higher after excluding the COVID-19 vaccines from the analysis. Thus, the signal for clozapine becomes more evident.

Table 2: ROR of the preferred terms (PT) myocarditis, pericarditis, myopericarditis and the substance clozapine with inclusion and exclusion of COVID-19 vaccines

	Including all ICSRs in the database	Excluding ICSRs related to COVID-19 vaccines
ROR	8.1	27.7
Lower limit confidence interval (95%)	5.9	18.4
Upper limit confidence interval (95%)	12.0	41.9

One strategy to mitigate the masking effect is the omission of the offending agents from the disproportionality analysis. However, removing the COVID-19 vaccines from an ROR analysis, may reduce the overall sensitivity of the signal detection system (1). Other authors suggest using a different statistical approach for signal detection such as regression, where the analysis can be adjusted for the presence of other medicinal products (2).

Conclusion

The masking effects of COVID-19 vaccine reports may present a challenge when using and interpreting a disproportionality analysis for other medicines based on a 2x2 contingency table. Therefore, more robust analyses like regression-based calculations have to be further developed to ensure the validity of statistical signal detection in large databases.

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Information for private individuals, healthcare professionals and the pharmaceutical industry regarding the reporting of adverse effects and the competent authority, depending on the suspected product

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The use of therapeutic products, foodstuffs and cosmetic products may be associated with adverse effects. Unlike therapeutic products, however, adverse effects of foodstuffs and cosmetic products do not have to be reported. It is therefore important that the person submitting the report correctly classifies the suspected product used before reporting an adverse effect.

Therapeutic products include medical devices and medicinal products. Medicinal products include not only conventional medicinal products but also complementary medicines (i.e. homeopathic, anthroposophic and Asian medicinal products) and herbal medicines. These are subject to the KPTPO in the TPA (Complementary and Phytotherapeutic Products Ordinance, Therapeutic Products Act) and thus fall under the responsibility of Swissmedic (for further information see Herbal medicinal product, swissmedic.ch). Relevant lists of the currently authorised complementary and herbal medicines are available under Lists and directories, swissmedic.ch.

If severe and/or previously unknown adverse effects occur after use of a medicinal product, healthcare professionals and pharmaceutical companies are obligated to report these according to Art. 59 TPA. Under the Swiss TPA, consumers, patients and their organisations and interested third parties can also report adverse effects and incidents to Swissmedic.

Both foodstuffs and cosmetic products (cosmetics) are subject to the Foodstuffs Act and are regulated in food legislation. These products are therefore the responsibility of the Federal Food Safety and Veterinary Office (FSVO). Foodstuffs include, among others, nutritional supplements and novel foods (such as cañihua and protein extracts from insects), etc. Cosmetic products include perfuming products and products used to cleanse and care for the skin, hair, teeth and mucous membranes.

There is no duty to report the occurrence of adverse effects for foodstuffs (including nutritional supplements and novel foods) or cosmetic products.

In the specific case of a serious and/or previously unknown adverse effect report in which the suspected product contains both a medicinal product and a foodstuff or cosmetic product, this must also be reported and the report should primarily be made to Swissmedic.

Products containing cannabidiol (CBD) are not only available in Switzerland as authorised medicinal products but also as (currently non-marketable) foodstuffs (including nutritional supplements) and cosmetic products (Products containing cannabidiol (CBD) – Overview, swissmedic.ch). Two medicinal products containing CBD are currently authorised by Swissmedic in Switzerland: Epidyolex® and Sativex®. If adverse effects occur in connection with products containing cannabinoids, Swissmedic receives these reports. The products are classified as necessary under the relevant legislation by the Delimitation Specialist Group and – if they are not medicinal products – fed into the correct channel.

In summary, Swissmedic would like to highlight the following:

Suspected product	Responsible authority for reporting suspected adverse reactions
Complementary and herbal medicines (medicinal products)	Swissmedic Pharmacovigilance Hallerstrasse 7 3012 Bern E-mail: vigilance@swissmedic.ch Reporting adverse drug reactions for healthcare professionals or submit the report via the online reporting form for patients and relatives
Foodstuffs incl. nutritional supplements, Cosmetic products	Federal Food Safety and Veterinary Office (FSVO) Schwarzenburgstrasse 155 3003 Bern E-mail: info@blv.admin.ch Website: www.blv.admin.ch
Products containing cannabidiol (CBD) are - among others - available as medicines: • Authorised medicines: Epidyolex® and Sativex®	Swissmedic

You can find further information on the assignment of specific products to the relevant category under Questions on delimitation (swissmedic.ch) and Delimitation criteria (admin.ch).

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Important change as of 1 January 2024
Drug safety: Swissmedic requirements for the medical assessment of individual case reports will be adapted

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The medical assessment of individual case reports improves report quality and is important for early detection of safety signals. Swissmedic has adapted the requirements and expects pharmaceutical companies to provide a medical assessment with the following information for individual case reports as of 1 January 2024 (Table 1):

1. **Expectedness of the adverse drug reaction (ADR)**
   The following information is required for all reported ADRs: details regarding the "labelledness" in the Swiss information for healthcare professionals (IHP) or, in the case of ADRs not described there, additional information on the "listedness" in the Company Core Safety Information (CCSI).

   In addition, for "serious and unlabelled" ADRs: literature findings, class effects, similar cases in the database, etc.

2. **Assessment of causality**
   This should be provided for serious ADRs. It should take into account factors such as temporal association, information on dechallenge and rechallenge and alternative causes. An assessment as "unrelated" or "not assessable" is only justifiable based on plausible and comprehensible arguments. In this respect, an "implied causality" should be assumed for spontaneous reports.

3. **Need for risk-minimising measures (including signal evaluation)**
   The need for risk-minimising measures should be discussed for serious ADRs that are not labelled in the Swiss information for healthcare professionals (serious/unlabelled).

Swissmedic recommends entering the medical assessment in the "Sender's comment" field.

Table 1

Adverse reactions (ADRs)	Medical assessment requirements
Non-serious / unlabelled	Expectedness of the ADR (limited to IHP + CCSI)
Serious / labelled	Expectedness of the ADR (limited to IHP + CCSI) Assessment of causality
Serious / unlabelled	Expectedness of the ADR Assessment of causality Risk minimising measures

References

- Art. 58, 59 TPA
- Art. 61, 65, 66 TPO
- International Guidelines on Good Case Management Practice (EMA Module VI, CIOMS V, ICH E2D)

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Update to the guidance document “RMP ICH E2E Information submission HMP”

The guidance document “RMP ICH E2E Information for submission HMP” has been fully revised. The most important change concerns the obligation to submit RMPs, which now only applies to first authorisation applications for new active substances and their indication extensions.

There is no RMP obligation for known active substances without/with innovation or for biosimilars.

Other changes include clarifications regarding the submission of RMP updates and concerning the implementation of the RMP, as well as additional risk-minimisation measures.

The changes take effect on 1 November 2023.

Guidance document RMP / ICH E2E – Information for submission of RMP HMP

swissmedic

Statistical review 2022

Pharmacovigilance: Human medicinal products

Swissmedic evaluates safety signals associated with medicinal products and vaccines on the basis of reports of adverse drug reactions (ADRs) from within Switzerland. If its investigations confirm a new risk, Swissmedic initiates the necessary actions (for example amending the medicinal product information), often after first consulting its international partner authorities. As part of the pharmacovigilance network, all reports from medical professionals and, in increasing numbers, patients are entered in the national database and evaluated by specialists. Some are also assessed on Swissmedic's behalf at six regional pharmacovigilance centres (RPVCs). Pharmaceutical companies also submit a large number of reports of adverse reactions from within Switzerland to Swissmedic.

Activities

Once again, surveillance activities centred on COVID-19 vaccines. However, the number of reports of suspected ADRs declined substantially on the previous year (Figure 1).

The VigilanceONE Ultimate database used to process ADR reports from Switzerland was upgraded so that it can perform specialised analyses to detect new safety signals. The new tool launched in 2022 to enable patients to report ADRs themselves has proven valuable in practice.

A new tender for pharmacovigilance services for the 2023–2027 period was issued, a heavy focus being placed on specific specialised medical skills.

Close collaboration with other countries' authorities and in multinational specialist organisations continued, for example as part of a regular dialogue on safety signals. Swissmedic regularly briefed the public on reports connected with COVID vaccines and the findings obtained. By the end of 2022, it had published 28 COVID-19 reports as well as other associated information and answered a large number of enquiries from the public and the media.

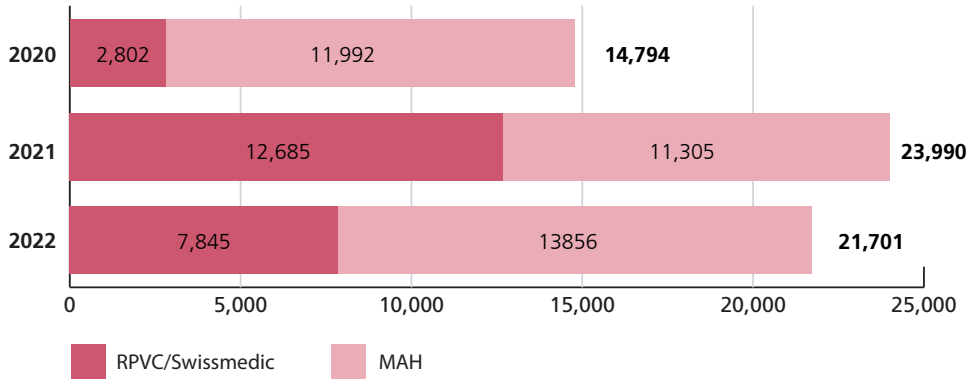

Figure 1: Number of ADR reports (initial and follow-ups) in Switzerland per primary recipient

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Vaccinovigilance

Valeriu Toma

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Complete report:

Vaccinovigilance - Adverse events following immunization – annual report 2022

Summary of adverse events following immunization reported in Switzerland during 2022

During 2022, the Pharmacovigilance Unit of Swissmedic received a high number of case reports of suspected "adverse events following immunization (AEFIs)" from Switzerland. As in 2021, the vast majority of these reports (> 5,000 cases) were submitted in relation to COVID-19 vaccines during the vaccination campaign which continued throughout 2022. In addition to that, 217 AEFI reports were submitted in Switzerland for **non**-COVID vaccines during 2022, which is a higher number compared to 2021 (159 reports), but lower than in 2020 (271 reports). These figures are not unexpected and are probably still a consequence of the large scale COVID-19 vaccination and information campaign, with the main attention focused on COVID-19 vaccines. However, most of these reports describe well-known reactions following COVID-19 immunisation such as fever, chills or administration site reactions. This summary report has its main focus on the **non**-COVID vaccine AEFIs since several COVID-19 vaccine safety reports have been regularly published as cumulative updates on Swissmedic's website. Nevertheless, a brief summary of COVID-19 AEFI reports received during 2022 is presented in the final section of this document.

Similar to the previous year, AEFI reports submitted during 2022 were recorded, assessed and analysed in the pharmacovigilance database of Swissmedic. However, no accurate data were available regarding the number of vaccine doses administered in Switzerland during 2022 for different **non**-COVID vaccine groups and therefore a straightforward conclusion regarding AEFI reporting rates cannot be drawn. As previously, Swissmedic is encouraging spontaneous high-quality reporting of AEFIs, which enables early detection of new safety signals. Important safety issues concerning vaccines are being evaluated in international collaboration with other foreign agencies and/or with the participation of the Human Medicines Expert Committee (HMEC) of Swissmedic, if necessary. An increased AEFI reporting rate within the Swiss database, followed by an assessment of relevant cases, can lead to risk minimisation measures in order to ensure vaccine safety.

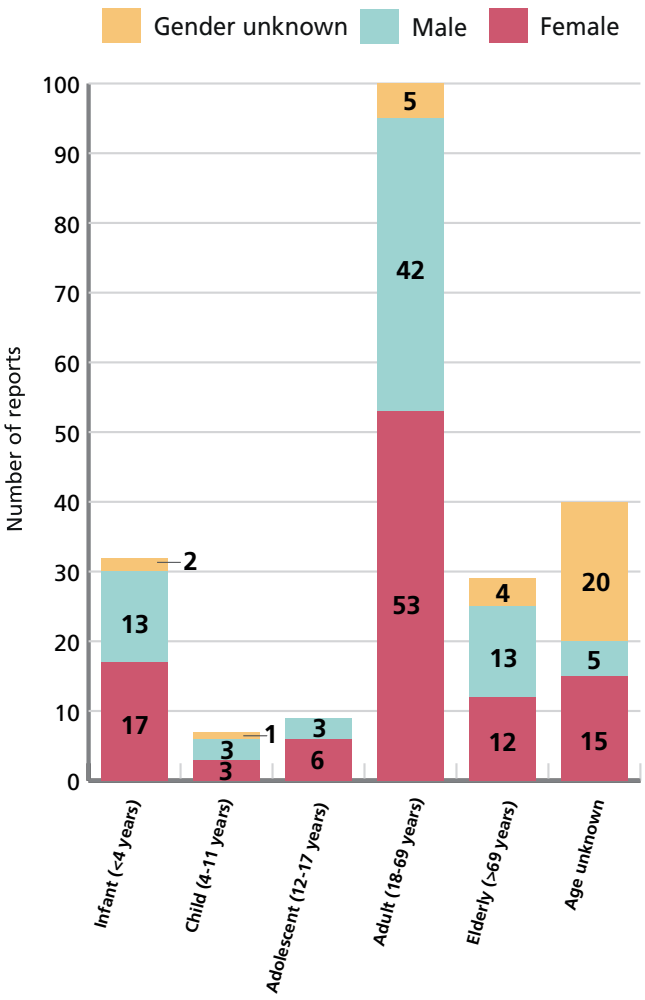

Figure 1: Number of AEFI reports by age group and gender, 2022

Figure 1 compares the number of reports by age group and gender. The largest number of AEFI reports involved adults (100 reports), followed by infants (32 reports), the elderly (29 reports), adolescents (9 reports) and children (7 reports). Throughout 2022, the number of reports concerning females (106 reports; 48.8%) exceeded the number of reports concerning males (79 reports; 36.4%). In 32 AEFI reports (14.7%), the gender of the persons remained unknown. In 40 case reports (18.4%), the age group of the patients was not recorded.

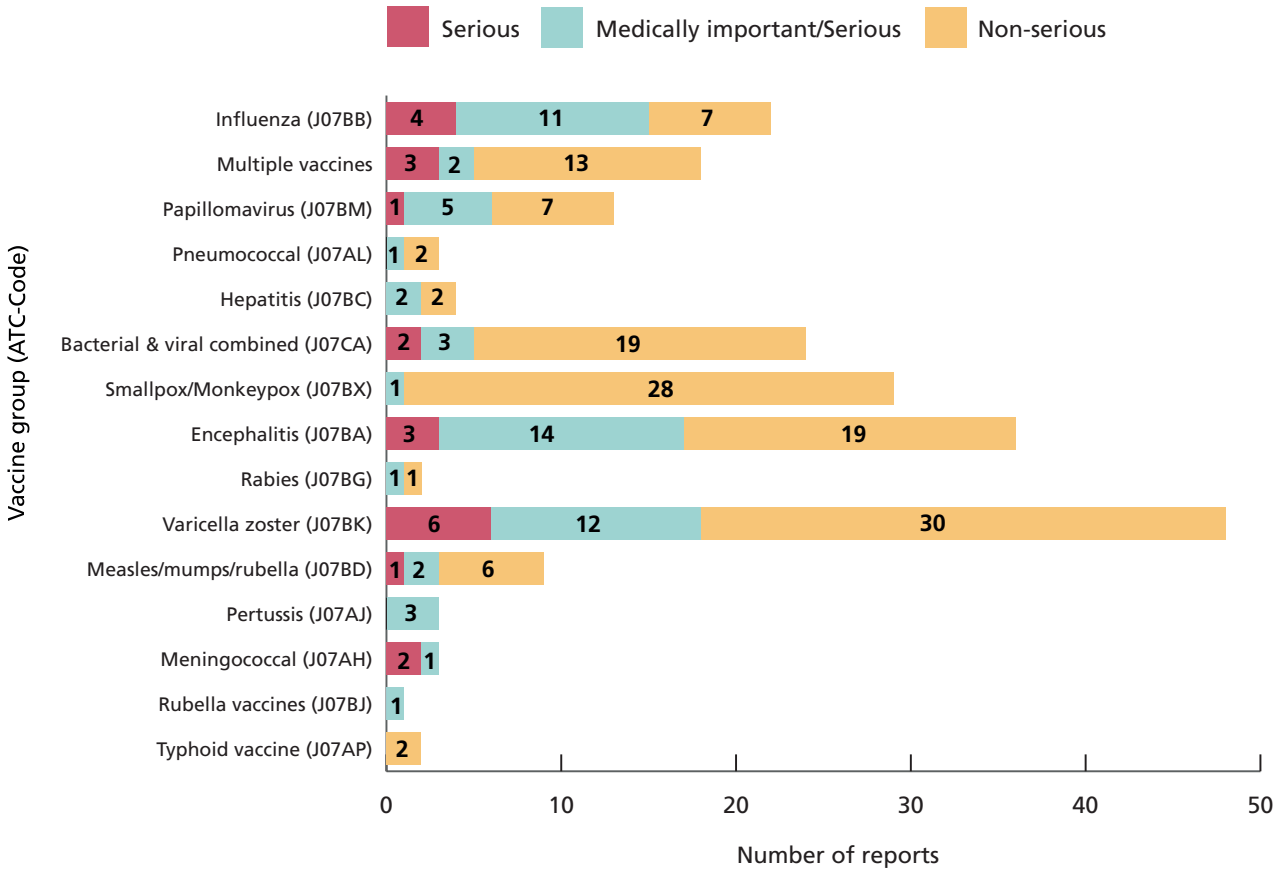

Figure 2: Number of reports by vaccine group (ATC code) and seriousness, 2022

Figure 2 shows the number of spontaneous AEFI reports by vaccine group (ATC code) and seriousness. There are no accurate data available to Swissmedic regarding the number of doses administered in each particular non-COVID 19 vaccine group in 2022 and therefore this figure does not indicate which vaccine group displayed a higher AEFI rate (e.g., as the number per 100,000 doses). Generally, a safety report is assessed as "serious" if it involves an adverse event leading to death, to hospitalisation or to prolongation of an existing hospitalisation, if it was life threatening or resulted in a significant or persistent disability or a congenital anomaly. Furthermore, a report is assessed as "medically important" (and therefore, also as "serious") even if it does not fulfil the criteria for "seriousness" mentioned, but 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 217 spontaneous reports received in 2022, 136 (62.7%) were "non-serious", 58 (26.7%) included only medically important events and 23 (10.6%) of the reports involved AEFIs with serious consequences.

Generally, by considering all vaccines in 2022, the relative frequency (percentage) of "serious" including "medically important" cases taken together (81 reports; 37.3%) was higher compared to 2021 (32.1%) and 2020 (29.9%).

Case reports where several (n >1) different vaccines have been administered and have been reported in relation with suspected AEFIs are shown in Figure 2 as "Multiple vaccines".

As compared to previous years, during 2022 a higher number of cases was submitted in relation to the herpes zoster vaccination, shown in Figure 2 as ATC code "Varicella zoster (J07BK)", and to the monkeypox vaccination, shown in Figure 2 as "Smallpox/

Monkeypox (J07BX)". These reporting figures are not surprising, since a new herpes zoster vaccine had been authorised by Swissmedic toward the end of 2021.

Furthermore, during 2022 a new smallpox vaccine, which was authorised in Europe and the US, could also be administered in Switzerland to high-risk individuals as a preventive measure against infection with the monkeypox virus. The majority of these case reports were assessed as "non-serious" for the herpes zoster vaccines (30 of 48 cases; 62.5%), and almost all reports in relation to the smallpox/monkeypox vaccination (28 of 29 cases in 2022) contained only "non-serious" AEFIs (1).

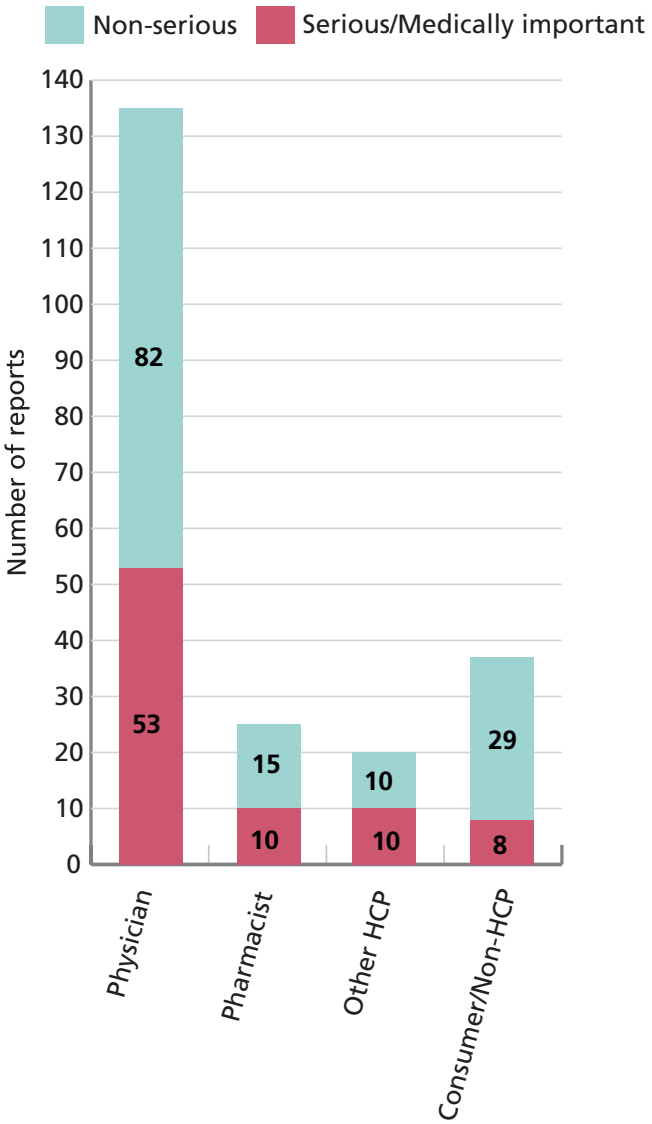

Figure 3: Number of AEFI reports by reporter qualification and seriousness, 2022

Figure 3 shows the number of Swiss AEFI reports in 2022 grouped by primary reporter and seriousness. Healthcare professionals – providing medically confirmed data and good quality individual AEFI reports – were primary reporters in the vast majority of cases. Physicians submitted the largest group of AEFI reports (135 of 217), also comprising a higher number of reports assessed as "serious" or "medically important" (53 of 135 reports). Notably, consumers/patients submitted the second-highest number (37) of non-COVID AEFI reports to Swissmedic during 2022.

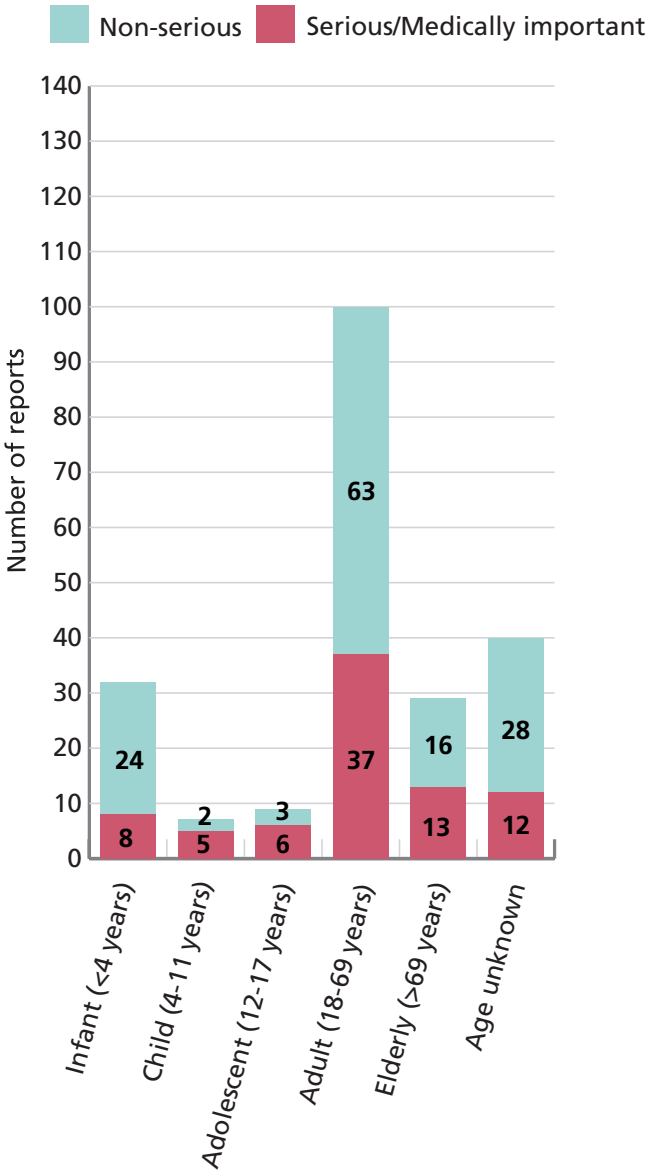

Figure 4: Number of AEFI reports by age group and seriousness, 2022

Figure 4 shows the number of spontaneous AEFI reports by age group and seriousness. It becomes apparent that the highest number of "serious" or "medically important" (37 of 100 AEFI reports in total) were recorded in the age group of "adults", followed by the elderly (13 of 29 reports), infants (8 of 32 reports), adolescents (6 of 9 reports) and children (5 of 7 reports).

AEFI reports received by Swissmedic in 2022 following COVID-19 vaccinations

In Switzerland, the COVID-19 vaccine rollout continued during 2022 and the AEFI reports received (>5,000 cases) reflect the spontaneous reporting on COVID-19 vaccines in the second year of the national immunisation campaign.

During 2022, Swissmedic published eight "Update Reports of suspected adverse reactions to COVID-19 vaccines in Switzerland"; the last one – "Update 28" – was published on 25 November 2022 (2). Each of these reports presents in a cumulative manner a summary of the suspected adverse drug reactions following COVID-19 immunisation, in the time period from 1 January 2021 to the publication of the respective report by Swissmedic.

The Update Reports include statistical data (overall figures), the presentation and ranking of suspected reactions by individual vaccines and by vaccination dose, as well as updated information from Swissmedic on particular safety aspects of COVID-19 vaccines.

Altogether, the reports of adverse reactions received and analysed by the end of 2022 did not alter the positive benefit-risk profile of the COVID-19 vaccines used in Switzerland, largely confirming their known side effects profile. Known side effects of COVID-19 vaccines are listed in the continually updated Swiss product information texts published (3).

As an important safety topic, "myocarditis/pericarditis" was particularly addressed in "Update 28", since very rare cases of myocarditis and pericarditis have been reported following vaccination with the COVID-19 mRNA vaccines. These cases generally occurred within 14 days of vaccination and more frequently after the second vaccination dose and in younger men. "Update 28" draws the attention of healthcare professionals to the signs and symptoms of myocarditis and pericarditis in order to inform vaccinated persons that they should seek immediate medical advice and assistance in the event of chest pains, shortness of breath or palpitations. Strong physical exertion should be avoided if such symptoms occur until the cause of the symptoms has been ascertained.

By 22 November 2022 (date of data lock for "Update 28"), 416 cases of myocarditis and/or pericarditis with a suspected link to vaccinations had been reported in Switzerland and evaluated out of a total of around 16.7 million vaccine doses administered. Of these reports, 94 were temporally related to Comirnaty (18 of which were after the third dose) and 306 to Spikevax (25 of which were after the third dose); in 12 cases, the vaccine has not been identified, while 4 cases concerned the COVID-19 vaccine from Janssen. The large majority of cases involved males (n = 300, 72.11%), and the mean age was 36.64 years (median 34, range 14 to 88 years). The persons affected received medical treatment and most have recovered. There was no evidence that the number of reports of myocarditis and/or pericarditis received by Swissmedic would increase following booster shots/third vaccinations (5). Various studies have shown that inflammation of the heart muscle and heart sac in those under 30 years of age was observed more frequently after vaccination with Spikevax than after vaccination with Comirnaty.

Another safety topic occurring in 2022 and published in "Update 26" on 1 July 2022 (4) refers to reports of urticaria (hives, nettle rash) received by Swissmedic following COVID-19 booster vaccinations. Overall, the profile of the adverse effects reported after a vaccine booster/third dose largely resembled the profile after the first and second vaccine doses. There was, however, an exception: cases of urticaria reported to Swissmedic, mostly after booster vaccinations with Spikevax.

Up to 28 June 2022 (date of data lock for "Update 26"), 1,228 such reports had been received in temporal relation with the vaccination (interval of 0-72 days), most of which (approx. 78%) were sent by the affected persons themselves. The case reports often relate to urticaria that appeared on various parts of the body with a time lag (on average around 11 days after the booster vaccination), and with episodes recurring over a lengthy period. The clinical picture as described in many of the reports corresponds most closely to acute (< 6 weeks) or chronic (> 6 weeks) spontaneous urticaria. On average, the reports were submitted 32 days after the onset of symptoms and in most of the affected persons the symptoms had not yet resolved by the time of reporting. 60% of the reports were related to women and 40% to men. The mean age was approximately 40 years.

Findings on the occurrence of urticaria following booster vaccination with Spikevax have since been included in the product information (3).

An additional, currently most recent cumulative safety "Update 29" on COVID-19 vaccines was published by Swissmedic on its website on 24 February 2023 (6).

References

(1) Reports of suspected adverse reactions following monkeypox vaccination; Swissmedic Vigilance-News Edition 30 – May 2023

(2) Reports of suspected adverse reactions to COVID-19 vaccines in Switzerland – update 28; Swissmedic Website, 25.11.2022

(3) AIPS (www.swissmedicinfo.ch)

(4) Reports of suspected adverse reactions to COVID-19 vaccines in Switzerland – update 26; Swissmedic Website, 01.07.2022

(5) Reporting rates of myocarditis and/or pericarditis following basis and booster vaccinations with COVID-19 mRNA vaccines in Switzerland; Swissmedic Vigilance-News Edition 28 – May 2022

(6) Reports of suspected adverse reactions to COVID-19 vaccines in Switzerland – update 29; Swissmedic Website, 24.02.2023

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Vigilance for veterinary medicinal products

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Complete report:

Vigilance for veterinary medicinal products – Annual report 2022

Adverse reactions reported in 2022: A summary of the main points

- 422 reports, increase compared with 2021: 23%
- Most frequently affected species: 254 dogs, 104 cats, 31 cattle
- Most frequent medicinal product types: antiparasitics (141), hormone products (103), products to modulate the nervous system (76), antiinfectives (21)
- 139 cases of suspected lack of efficacy, largely for antiparasitics and hormone products
- 47 cases passed on by Tox Info Suisse
- 30 cases of accidental ingestion of flavoured tablets by dogs/cats
- 104 cases of human exposure to veterinary medicinal products
- 6 signal procedures initiated

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Information on the Swissmedic website

Pharmacovigilance in the spotlight

Learning from adverse reaction reports – cases from pharmacovigilance

17.11.2023
Hypotonic-hyporesponsive episode and basic immunisation in infants

29.09.2023
Parenteral iron products and hypophosphataemia

11.08.2023
Tizanidine and clinically relevant interactions

07.07.2023
Betaseptic and burns

01.06.2023
Combined hormonal contraceptives (CHC) and thromboembolic events

09.05.2023
Metamizole and agranulocytosis

11.04.2023
Loperamide and intentional overdose

08.02.2023
Drug-induced pancreatitis

26.11.2022
Fluoroquinolones and tendon inflammation/ruptures

21.11.2022
Amiodarone and hyperthyroidism

Find out more on our website:
www.swissmedic.ch/pv-in-the-spotlight

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Healthcare Professional Communication

Some links are available in German/French only

25.10.2023
DHPC – Gavreto® (Pralsetinib)
Nicht-Verlängerung der befristeten Zulassung in der Indikation «Medulläres Schilddrüsenkarzinom mit RET-Mutation»

24.10.2023
DHPC – Nulojix® (Belatacept)
Änderung der Erhaltungsdosis von 5 mg/kg auf 6 mg/kg aufgrund eines neuen Herstellungsverfahrens

20.10.2023
DHPC – Integrilin® (Eptifibatid)
Einstellung der Produktion von Integrilin Infusionslösung und Integrilin Injektionslösung: Zunahme der Anzahl Fälle von Übelkeit und/oder Erbrechen nach Verabreichung von Integrilin

04.10.2023
DHPC – Vaxneuvance® (Pneumokokken-Polysaccharid-Konjugatimpfstoff [15 valent, adsorbiert])
Wichtige Information bezüglich der Möglichkeit des Bruchs der Vaxneuvance Fertigspritze

29.09.2023
HPC – Propofol (Disoprivan®, Disoprivan PFS®, Propofol Labatec®, Propofol-Lipuro®, Propofol MCT Fresenius®, Recofol EDTA®)
Risiko für Sepsis bei Mehrfachentnahme aus einem Behälter

26.09.2023
DHPC – Nordimet® (Methotrexate)
Safety-related information for the product NORDIMET® Fertigpen (PEN)

29.08.2022
DHPC – Simulect (basiliximabum)
Update – Important information on Simulect preparation for injection 10 mg and 20 mg

23.08.2022
DHPC – Valproat (Depakine®, Depakine Chrono®, Valproate Chrono Sanofi®, Valproat Chrono Desitin®, Orfiril® long, Orfiril®, Valproat Sandoz®, Convulex®)
Potenzielles Risiko für Kinder von mit Valproat behandelten Vätern – Neue Informationen zum potenziellen Risiko für neurologische Entwicklungsstörungen bei Kindern von mit Valproat behandelten Vätern im Vergleich zu Kindern von Vätern, die mit Lamotrigin oder Levetiracetam behandelt wurden

23.06.2022
DHPC – Opdualag® (nivolumab, relatlimab)
Error in section "Other information, Instructions for handling" in the Information for healthcare professionals

swissmedic

Announcements

27.11.2023
Warning about imports of melatonin and DHEA by private individuals
Self-prescribed use of sleep hormones or supposed "anti-ageing" products can be harmful to health

13.11.2023
Meeting of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)
Excellent Progress made on ICH harmonisation activities in Prague, Czech Republic

07.11.2023
New information on submitting vigilance reports for medical devices
Swissmedic has revised the information on submitting vigilance reports (incidents, trend reports and FSCA reports) for products according to the Medical Devices Ordinance (SR 812.213) and the Ordinance on In Vitro Diagnostic Medical Devices (SR 812.219).

06.11.2023
Access Consortium's Advanced Therapy Medicinal Products Working Group
In 2023, the Access Consortium established a working group for advanced therapy medicinal products (ATMPs)

02.11.2023
Products containing cannabidiol (CBD) and other cannabinoids that are not subject to narcotics legislation – Overview and implementation guide
This information sheet applies not only to CBD, but to all cannabinoids of herbal, synthetic or semi-synthetic origin, provided they are not subject to narcotics legislation

01.11.2023
Swissmedic confirmed as WHO Listed Authority
Swissmedic, already considered as stringent regulatory authority, is now listed as a WHO Listed Authority (WLA) and recognised in all regulatory functions

31.10.2023
Operation Pangea XVI: International campaign against falsified and illegally imported medicinal products
Authorities checked shipments of medicinal products worldwide from criminal online sales

09.10.2023
Falsified Ozempic diabetes medication in circulation
The Regional Council in Freiburg im Breisgau, Germany, has warned against the use of counterfeit Ozempic® pens

09.10.2023
Health risks of designer drugs: further psychoactive substances prohibited
Ten individual substances and one substance group added to the Narcotics List

01.10.2023
Changes to the guidance document Mobile technologies and the related form
Training documents according to the most recently approved RMP are considered to be information required by therapeutic products legislation

01.10.2023
Modifications to guidance document Formal requirements
Clarification on submission via eDOK and eCTD for co-marketing medicinal products; correction to submission deadline for variations without assessment (VMP)

28.09.2023
Swissmedic approves Moderna Switzerland GmbH coronavirus vaccine Spikevax XBB.1.5
Spikevax XBB.1.5 approved for persons aged 18 and over

25.09.2023
Swissmedic offers Scientific Advice for Weight-of-Evidence Approach described in the Addendum of ICH Guideline S1B(R1)
Scientific Advice for Weight-of-Evidence Approach

22.09.2023
Swissmedic approves Pfizer coronavirus vaccine Comirnaty XBB.1.5
Comirnaty XBB.1.5 approved for persons aged 12 and over

15.09.2023
Changes to the guidance document Temporary authorisation of human medicinal products
Clarification regarding authorised medicinal products, harmonised deadlines for applications before expiry of temporary authorisation and changes to terminology

10.09.2023
SwissGMDP database
Swissmedic is bringing a SwissGMDP database into operation, similar to the European Medicine Agency's (EMA) EudraGMDP database

06.09.2023
Complementary and herbal medicines containing ethanol in paediatric populations
The benefits of the use of the medicinal product containing ethanol must outweigh the potential risks

01.09.2023
Allocation of medicinal product groups for CHM
has been updated

24.08.2023
Potential risk to children whose fathers have taken the active substance valproaten
Precautionary change to the medicinal product information for valproate products

17.08.2023
Benchmarking study 2022
International comparison of Swiss authorisation times

02.08.2023
Swissmedic participation in the European Medicines Agency (EMA) OPEN initiative
Opening procedures at EMA to non-EU authorities (OPEN) initiative

27.07.2023
MRA between Switzerland and the USA on the manufacturing practice for medicinal products takes effect
Mutual recognition in principle of inspections by Swissmedic and the FDA

26.07.2023
Establishment licence for Dr. Heinz Welti AG: Suspension of establishment licence at Bubendorf site lifted
Suspension for Dr. Heinz Welti AG fully lifted

26.07.2023
Switzerland becomes Official Observer in the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH)
Swissmedic amends donation criteria at request of Swiss Transfusion SRC

25.07.2023
New blood donation criteria for men who have sex with men
Swissmedic amends donation criteria at request of Swiss Transfusion SRC

14.07.2023
Trips abroad with medications – what you need to know
Anyone who relies on medication should find out about the regulations in their destination country and any countries they travel through before taking a trip abroad

07.07.2023
Public Consultation on ICH Reflection Paper launched in Switzerland
International Harmonisation of Real-World Evidence Terminology and Convergence of General Principles Regarding Planning and Reporting of Studies Using Real-World Data, with a Focus on Effectiveness of Medicines

05.07.2023
Nitrosamine impurities in medicinal products: Swissmedic sets up specialist group
"Nitrosamine Specialist Group": centre of expertise and coordination office for nitrosamine issues

23.06.2023
Meeting of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)
New Areas of Harmonisation adopted alongside Significant Advancement of Ongoing Activities in Vancouver, Canada

22.06.2023
Changes to the guidance document on biosimilars
Update of section 5.10 on interchangeability

21.06.2023

Medicinal products with a medical device component (combination products)

Implementation of the transitional provisions for medical devices

15.06.2023

Modification of the Guidance document Authorisation of homeopathics, anthroposophics and other complementary medicinal products

Content-related clarifications and additions to the guidance document, including on the declaration, on packaging texts and on details in the patient information

13.06.2023

Swissmedic publishes its Annual Report for 2022

On 9 June 2023 the Federal Council approved Swissmedic's Annual Report for 2022

01.06.2023

Delayed implementation time limits for replacement changes

Changes to the guidance documents Variations and Extensions HMP and Variations VMP

01.06.2023

Changes to guidance document Fast-track authorisation procedure and guidance document Temporary authorisation for human medicinal products

Exchange of documentation for the AAA now possible via the eGov portal

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

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Istituto svizzero per gli agenti terapeutici
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