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Vigilance News

Edition 33 – November 2024

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We would like to thank all colleagues who contributed to this issue of Swissmedic Vigilance News, and particularly all those involved for their support with the translations.

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In this edition

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Editorial

Dear reader

In each autumn issue of Vigilance News, Swissmedic publishes the annual statistics for individual case safety reports of adverse drug reactions (ADR) and adverse events following immunization (AEFI) for vaccines. At Swissmedic the data from individual case safety reports from healthcare professionals, patients/caregivers and users (for veterinary medicinal products) as well as those from pharmaceutical companies are recorded and evaluated. In this issue, you will also now find a comprehensive statistical overview of reports on other medicinal products used in humans – in addition to vaccines.

In individual case safety reports (ICSRs) regarding adverse drug reactions, a "case narrative" is an important element enabling better interpretation of the reports. The case narrative describes the key details of a case in free text form. Swissmedic has developed a "narrative" that "semi-automatically" generates easily readable free text from the structured data in a report. This newly developed free text is introduced in an article.

Sex-specific differences in the efficacy and safety of medicinal products have been a topic of discussion for many years. An article looks at sex-specific differences in reactions to medicinal treatments, primarily regarding pharmacokinetics and pharmacodynamics.

Medicinal products and pregnant women is also a subject of particular interest. The Geneva Regional pharmacovigilance centre (RPVC) recorded and assessed data on lithium exposure during pregnancy.

While the importance of pharmacovigilance is often stressed for newly authorised medicinal products, it is also of interest for medicinal products that have been in use for a long time and seemingly have a known safety profile. The warnings against excessive use of SABA (short-acting β2-agonists), such as salbutamol, fenoterol and terbutaline, in asthma were strengthened recently.

Another article deals with the risk of Brugada syndrome, which has occurred when taking bupropion, an active substance that is indicated for the treatment of depressive episodes and nicotine dependency.

Despite warnings and risk-minimising measures such as Direct Healthcare Professional Communications (DHPCs), medication errors unfortunately keep occurring. Swissmedic has analysed and discussed the data from spontaneous reports regarding low-dose methotrexate.

Swissmedic encourages you to continue submitting reports of ADR and AEFI. 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.

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Safety of medicines and case reports

Impact of sex on pharmacokinetics and pharmacodynamics

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Introduction

The influence of sex and gender in the field of medicine, particularly in drug therapy, is a highly topical issue. This article focuses mainly on sex-related differences in the response to medicines.

The origins of sexual dimorphism can be traced back to conception, with the development of an embryo carrying XX or XY chromosomes. In medicine, this dimorphism is associated with differences in the frequency and severity of certain pathologies: for example, autoimmune diseases are more common in women and gout is more common in men. Morbidity and mortality linked to COVID-19 is significantly higher in men, partly explained by biological differences between the sexes (modulation of the immune system and expression of ACE2 receptors to which SARS-CoV-2 binds via sex hormones) (1). As regards drug treatments, sex can also have an impact on pharmacokinetics (PK) and pharmacodynamics (PD).

Sex-related pharmacokinetic differences

Numerous anatomical, physiological and biological differences between men and women can affect PK (table 1). The impact of sex on different PK parameters is substance-specific and depends on the physicochemical characteristics and elimination routes of the drug. The net impact is the result of the effect of sex on the phases of absorption, distribution, metabolism and excretion of the drug. Since gastrointestinal transit is slower in women, the absorption of certain drugs may be delayed, e.g. ketoprofen, an NSAID (2). The amount absorbed can also vary according to sex: in preadolescent girls and boys, with no differences in iron stores or haemoglobin levels, the absorption of iron administered orally was significantly higher in the girls (3).

Compared to men, women's body composition is characterised by a higher percentage of fat and a lower percentage of water. By accumulating in body fat, which acts as a reservoir, lipophilic drugs can have a prolonged elimination half-life in women, and consequently the time taken to reach steady state is also longer. The peak concentration of hydrophilic drugs may be higher in women, because these drugs are distributed in a smaller volume than in men. However, the effect of sex on distribution is limited, less than that of obesity on the distribution of lipophilic drugs or the effect of lean body weight on the distribution of hydrophilic drugs.

Clearance (metabolic and/or by excretion) is the PK parameter most significantly affected by sex. Men generally have a higher drug clearance than women due to larger organs of elimination (liver, kidneys) and, overall, a higher enzyme activity irrespective of organ size. Since dosing recommendations are the same for both sexes, based until recently on PK studies conducted in men, women tend to be systematically overexposed (4). This overexposure is generally moderate, with concentrations on average 20% higher than those of men, which is less than an interindividual PK variability considered moderate (~30%) (5). Zolpidem is an exception: an exposure ranging from 40–50% higher in women prompted the FDA and Health Canada in 2013 to reduce the recommended dosage for women by half (6, 7). This recommendation has not been adopted by other regulatory authorities, including Swissmedic. Moreover, the relevance of this exceptional decision by the FDA and Health Canada has since been called into question (8).

Table 1: Anatomical, physiological and biological differences between men and women

Anatomy	Physiology	Biology
weight*	gastric pH**	alfa-1 glycoprotein acid*
height*	gastric acid output*	CYP1A2*, 2D6*, 2E1* ; 2C8* ; 2C9* ; 2C19 *
intestinal length**	gastro-intestinal transit time*	CYP3A4**
organ size*	cardiac output*	TPMT*, UGT*, DPD*, COMT*
muscle mass*	glomerular filtration rate*	p-glycoprotein*
body fat**	sex hormones***	alcohol dehydrogenase*

*higher in men; **higher in women; *** hormone-specific difference

CYP: cytochromes P-450; TPMT: thiopurine methyltransferase; UGT: UDP-glucuronosyltransferases; DPD: dihydropyrimidine dehydrogenase; COMT: catechol-O-methyltransferase

Sex-related pharmacodynamic differences

Pharmacodynamic differences also exist between the sexes, although these are less well documented than the PK differences, since they are probably more difficult to study. In one study, the maximum efficacy of vasopressin, also known as antidiuretic hormone, was observed at lower concentrations in women than in men, and hyponatraemia was more common in women (9). Cortisol secretion was suppressed at lower concentrations of methylprednisolone in women than in men (10). In healthy volunteers, at equivalent concentrations, quinidine caused a more pronounced QT prolongation in women than in men (11).

Summary

Sex therefore does affect the body's response to drugs, although it is only one of several factors of variability. The PK variability in a population of the same sex is indeed greater than the PK variability between the sexes. Many factors are responsible for interindividual PK variability, primarily renal and hepatic function, and these should routinely be taken into account when drugs are prescribed.

Nevertheless, women do tend to be exposed to higher concentrations of drugs than men. Although this overexposure is moderate overall, its systematic nature is problematic at the population level, accounting for some of the significant excess of adverse drug reactions observed in women, all of which are, to varying degrees, concentration-dependent. One study investigating the safety of new drugs showed a 60% excess of adverse drug reactions in women compared with men (12). In a study of different classes of cancer treatments, an excess of 34% of serious adverse events was observed in women, rising to 49% when the treatments included immunotherapies (13). Finally, between 1997 and 2000, the FDA withdrew 10 drugs from the market for safety reasons, and 8 of these 10 drugs had been associated with significantly higher risks in women (14). Apart from overexposure, other factors, including some that are likely gender-related, may contribute to the excess of adverse reactions observed in women. These factors include differences in sensitivity to adverse reactions (PD differences), exposure to a higher number of drugs and a greater propensity to report adverse reactions in women compared to men (15, 16, 17).

For a long time, drug development, particularly in the early phases, was conducted with male subjects, mainly due to fear of teratogenic effects. Although female participation in clinical trials has steadily increased over the last two decades, women are still in the minority in phases I and II. The same applies to preclinical studies, which are still predominantly conducted with male animals (5). Better representation throughout drug development and data analysis in subgroups according to sex should make it possible to better characterise the PK/PD of drugs in women, particularly to reduce bias when determining the dose, and thus lead to the launch of new drugs that are better adapted and safer for all women.

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Sex and gender considerations must continue to be taken into account after market launch, particularly in phase IV studies and pharmacovigilance activities, but also in routine clinical practice.

References

1
Ya'qoub L, Elgendy IY, Pepine CJ. Sex and gender differences in COVID-19: More to be learned! Am Heart J Plus 2021;3:100011. doi: 10.1016/j.ahjo.2021.100011.

2
Magallanes L, Lorier M, Ibarra M, et al. Sex and food influence on intestinal absorption of ketoprofen gastroresistant formulation. Clin Pharmacol Drug Dev 2016;5(3):196-200. doi: 10.1002/cpdd.208.

3
Woodhead JC, Drulis JM, Nelson SE, et al. Gender-related differences in iron absorption by preadolescent children. Pediatr Res 1991;29(5):435-9. doi: 10.1203/00006450-199105010-00005.

4
Stader F, Marzolini C. Sex-related pharmacokinetic differences with aging. Eur Geriatr Med 2022;13(3):559-565. doi: 10.1007/s41999-021-00587-0.

5
Dekker MJHJ, de Vries ST, Versantvoort CHM, et al. Sex proportionality in pre-clinical and clinical trials: an evaluation of 22 marketing authorization application dossiers submitted to the European Medicines Agency. Front Med (Lausanne). 2021 Mar 11;8:643028. doi: 10.3389/fmed.2021.643028.

6
Greenblatt DJ, Harmatz JS, Singh NN, et al. Gender differences in pharmacokinetics and pharmacodynamics of zolpidem following sublingual administration. J Clin Pharmacol 2014;54(3):282-90. doi: 10.1002/jcph.220.

7
https://www.fda.gov/files/drugs/published/Drug-Safety-Communication--Risk-of-next-morning-impairment-after-use-of-insomnia-drugs--FDA-requires-lower-recommended-doses-for-certain-drugs-containing-zolpidem-%28Ambien--Ambien-CR--Edluar--and-Zolpimist%29.pdf (viewed on 4 September 2024).

8
Greenblatt DJ, Harmatz JS, Roth T. Zolpidem and gender: are women really at risk? J Clin Psychopharmacol 2019;39(3):189-199. doi: 10.1097/JCP.0000000000001026.

9
Juul KV, Klein BM, Sandström R, et al. Gender difference in antidiuretic response to desmopressin. Am J Physiol Renal Physiol 2011;300(5):F1116-22. doi: 10.1152/ajprenal.00741.2010.

10
Lew KH, Ludwig EA, Milad MA, et al. Gender-based effects on methylprednisolone pharmacokinetics and pharmacodynamics. Clin Pharmacol Ther 1993;54(4):402-14. doi: 10.1038/clpt.1993.167.

11
El-Eraky H, Thomas SH. Effects of sex on the pharmacokinetic and pharmacodynamic properties of quinidine. Br J Clin Pharmacol 2003;56(2):198-204. doi: 10.1046/j.1365-2125.2003.01865.x.

12
Martin RM, Biswas PN, Freemantle SN, et al. Age and sex distribution of suspected adverse drug reactions to newly marketed drugs in general practice in England: analysis of 48 cohort studies. Br J Clin Pharmacol 1998;46(5):505-11. doi: 10.1046/j.1365-2125.1998.00817.x.

13
Unger JM, Vaidya R, Albain KS, et al. Sex differences in risk of severe adverse events in patients receiving immunotherapy, targeted therapy, or chemotherapy in cancer clinical trials. J Clin Oncol 2022 May 1;40(13):1474-1486. doi: 10.1200/JCO.21.02377.

14
Heinrich J. Drug safety : most drugs withdrawn in recent years had greater health risks for women. United States general accounting office 2001. https://digital.library.unt.edu/ark:/67531/metadc297960/m1/3/ (viewed on 4 September 2024).

15
Sportiello L, Capuano A. Sex and gender differences and pharmacovigilance: a knot still to be untied. Front Pharmacol 2024;15:1397291. doi: 10.3389/fphar.2024.1397291.

16
Holm L, Ekman E, Jorsäter Blomgren K. Influence of age, sex and seriousness on reporting of adverse drug reactions in Sweden. Pharmacoepidemiol Drug Saf 2017;26(3):335-343. doi: 10.1002/pds.4155. Epub 2017 Jan 10. PMID: 28071845.

17
Watson S, Caster O, Rochon PA, et al. Reported adverse drug reactions in women and men: Aggregated evidence from globally collected individual case reports during half a century. EClinicalMedicine 2019;17:100188. doi: 10.1016/j.eclinm.2019.10.001.

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Exposure to lithium during pregnancy – experience of a regional pharmacovigilance centre

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Introduction

According to some professional organisations, lithium is the agent of choice for the long-term treatment of bipolar disorder (1–3). However, its use during pregnancy (particularly during the first trimester) is not recommended by the manufacturer (4), since exposure to lithium during pregnancy correlates with an increased risk of malformations and neonatal complications (a risk correlated with the newborn's blood lithium level according to certain findings) (5) as well as hospitalisation in a neonatal unit (6).

In general, as with other mood stabilisers, the discontinuation of lithium before or during pregnancy is associated with an increased risk of relapse in patients with bipolar disorder (7–9). The relapse rate for bipolar disorder during pregnancy is estimated at between 23% and 71% depending on the author (10). Consequently, discontinuation and switching to another mood stabiliser is not always recommended in clinical practice.

The aim of this article is to present the data collected over the past 10 years by our regional centre on the use of lithium during pregnancy and to review the scientific literature on this subject.

Results

Between 2014 and 2024, a relatively small number of cases of lithium exposure during pregnancy have been reported to our centre (table 1). The causal relationship between adverse reactions and lithium is difficult to evaluate, particularly if concomitant treatments are also involved.

One of these reports, case 2023-1, which occurred when the woman was being treated solely with lithium, is interesting because of several serious adverse reactions (particularly malformations), including some that have not previously been described in association with lithium.

Case report 2023-1

The report concerns a 36-year-old woman with a psychiatric history of bipolar disorder who was stabilised on lithium (Lithiofor®). She was referred to our division at 4 weeks and 6 days of gestation. Since the patient needed a mood stabiliser (several relapses in the past) and was responding well to lithium, the drug was continued with appropriate monitoring.

Treatment with lithium was therefore administered throughout the pregnancy, initially at a dose of 660 mg twice daily, reduced to 990 mg once daily, then to 660 mg once daily from the 6th week of gestation until delivery. An ultrasound scan at 34 weeks and 5 days of gestation revealed polyhydramnios, which had increased two weeks later.

The woman gave birth to a boy weighing 2710 g (7th percentile) by vaginal delivery at 38 weeks and 2 days of gestation following cervical ripening/provocation due to polyhydramnios. Symmetrical intrauterine growth retardation was attributed to a placental origin. The newborn showed good neonatal adaptation, with an Apgar score of 9/9/10 at 1/5/10 minutes, but, after 5 minutes of life, he developed a respiratory distress syndrome and hypersalivation requiring suctioning. A radiograph showed coiling of the orogastric tube, prompting the diagnosis of type III oesophageal atresia.

The newborn underwent surgery at 1 day old with no major postoperative complications.

Echocardiography carried out as part of the malformation assessment at 1 day old revealed a wide patent ductus arteriosus with a L-R shunt, isosystemic pulmonary pressures, a patent foramen ovale (vs. atrial septal defect), mild mitral insufficiency, slight dilatation of the left atrium and good biventricular function. Cerebral, spinal and abdominal ultrasound scans on the same day revealed no abnormalities apart from a partial non-occlusive thrombosis of the proximal left portal vein.

Since the mother was taking lithium, the baby's thyroid status was assessed at 1 day and 10 days old and revealed normal values for his age.

The cardiac assessment at 1 month old showed a favourable outcome, with closure of the ductus arteriosus and the persistence of a tiny patent foramen ovale. At 4 months old, the cardiac check-up was completely normal. An abdominal ultrasound at 3 months old revealed that the previously visualised, partially occlusive thrombus in the proximal part of the left portal branch had disappeared. The abdominal ultrasound scan at 6 months was perfectly normal, with disappearance of the portal vein thrombosis.

Discussion

Lithium crosses the placenta, and the neonatal and maternal concentrations are equivalent (11).

The risk of major malformations (MMs) associated with lithium exposure during the first trimester of pregnancy is a subject of debate. In the 1970s, lithium was associated with an increased risk of cardiovascular malformations, particularly Ebstein's anomaly, whose frequency among infants born to mothers who had taken lithium during the course of the 1st trimester of pregnancy was estimated to be up to 400 times higher than that expected in the general population, which is around 1 in 20,000 (12–14). These frequencies, which are based on data collected in a register of voluntarily reported cases, have since been reviewed downwards (15–19). A dose-dependent relationship has been described (15). Under similar conditions, prospective studies have shown contradictory results: the first, published in 1992, showed no increase in the risk of MMs (17). Another, more recent study, concluded that there was an increased risk of cardiac MMs (estimated risk of Ebstein's anomaly: 0.8%) (20). In two case-control studies, the first including 59 infants with an Ebstein's anomaly (16) and the second 25 infants with an Ebstein's anomaly and 44 with tricuspid atresia (21), none of the mothers had taken lithium during pregnancy. These studies cannot rule out an association between the drug and the actual anomaly even in the presence of 0 lithium exposures. However, these results indicate that drugs are not major contributory factors to tricuspid valve malformation, supporting the hypothesis that the connection between Ebstein's anomaly and lithium is weak. A meta-analysis in 2012 concluded that there was no evidence of a teratogenic risk associated with lithium (22). However, a large international multicentre meta-analysis involving 6 cohorts (22,124 pregnancies in patients with mood disorders, including 727 with lithium exposure) and collecting better-quality data, concluded that there was an increased risk of MMs in the event of exposure during the first trimester (7.4% versus 4.3% in unexposed women; pooled OR 1.71, 95% CI: 1.07–2.72), although this was not statistically significant for major cardiac malformations (6).

Maternal treatment with lithium until delivery has been associated with a higher risk of premature birth and macrosomia (23), pre-eclampsia and polyhydramnios (24). Symptoms of neonatal toxicity include lethargy, hypotonia and cyanosis (floppy infant/baby syndrome), respiratory disorders, hypoglycaemia, reduced sucking reflex and Moro reflex, thyroid disorders and nephrogenic diabetes insipidus (5, 25, 26). These problems are transient and usually disappear without sequelae within 1 to 2 weeks of birth (in line with the elimination of lithium, which is slower in neonates than in adults), with the exception of nephrogenic diabetes insipidus, which can persist for up to 2 months (27). The use of lithium during pregnancy may also increase the risk of

miscarriage (28). In one small study, the rate of low birth weight newborns was higher in the group heavily exposed to lithium than in the group lightly exposed to lithium, but the differences only approached the threshold of significance (11).

Therefore, if pregnancy occurs during lithium treatment, the lowest effective dose should be chosen and blood lithium levels should be monitored regularly, because of the changes in renal function that accompany pregnancy and childbirth, in order to avoid foetal toxicity and ensure mood stability in the mother (4). Some sources recommend checking lithium levels once a month and then weekly during the last month of pregnancy (29, 30). To avoid intoxication in the mother and the newborn, the lithium should be stopped 7 to 10 days before the expected term (4). If, however, the delivery takes place while the mother is still taking lithium, the maternity team must be informed so that the arrival of the newborn can be adapted accordingly. Immediately after delivery, the lithium should be resumed at the dose prescribed before pregnancy (11, 29).

No case of oesophageal atresia associated with lithium has been described in the literature. Only one case of portal vein thrombosis has been reported in connection with lithium in the VigiBase (the WHO pharmacovigilance database). Since our report in March 2024, a further case of oesophageal atresia was reported in July 2024 in VigiBase, in a newborn whose mother was taking lithium and quetiapine during pregnancy (31).

Oesophageal atresia is a congenital malformation that affects approximately 1 in 3,500 newborns (32). The oesophageal continuity is interrupted, resulting in a blind termination that may be associated with an oesophagotracheal fistula. The atresia is usually diagnosed shortly after birth, often following the introduction of a nasogastric tube that fails to reach the stomach because of the interrupted oesophagus. The primary treatment is surgery, with the aim of closing the tracheo-oesophageal fistula and reconnecting the two segments of the oesophagus. Survival rates after surgery have increased considerably over the decades, currently reaching as high as 90% (33). The aetiology of oesophageal atresia has not yet been clarified, and the contribution of genetic and environmental factors may differ between subtypes of oesophageal atresia (34). Oesophageal atresia appears to be one of the malformations associated with methimazole (carbimazole) embryopathy (35, 36).

Portal vein thrombosis (PVT) in newborns has been described as a rare but increasingly recognised event. Estimates range from 1 in 100,000 live births (37) to 36 per 1,000 admissions to neonatal intensive care units (38). PVT may be congenital or acquired secondary to inflammation and/or infection, trauma, systemic disorders or iatrogenic causes (39). In approximately 50% of children with PVT, no underlying aetiology is identified, and the patients are generally asymptomatic in the neonatal period. The PVT is diagnosed by Doppler ultrasound. The thrombus resolves within a few days or months in 30–70% of cases (40).

Conclusion

When a woman treated with lithium plans to become pregnant, it is essential to schedule a preconception consultation in order to reassess the therapeutic strategy and discuss the possibility of switching to a different mood stabiliser. Despite the opinion of some experts who consider lithium to be the drug of choice for treating bipolar disorder during pregnancy (10, 41), according to its product information lithium should not be administered during pregnancy (particularly during the first trimester). Some sources mention antipsychotics such as quetiapine as possible mood regulators during pregnancy (29, 42). If, after a specialist consultation, it proves impossible to discontinue the lithium because of the risks to maternal stability, the treatment should be continued at the minimum effective dose, with appropriate prenatal monitoring, including regular monitoring of blood lithium levels (4).

This caution is justified because an increased risk of MMs associated with lithium has been observed even in recent studies. The patient must be informed of these risks and the potential complications for the newborn.

Table 1: Individual case safety reports of pregnancy during lithium treatment (n=10) processed by Geneva Regional Pharmacovigilance Center (RPVC) between 2014 and 2024.

Year	Case	Trimester(s) with exposure to lithium	Concomitant treatment	Outcome
2024	2024-1	1st	Aripiprazole; lorazepam; alprazolam; quetiapine	Anembryonic gestation
2023	2023-1	1st, 2nd, 3rd	None	Polyhydramnios, Intrauterine growth retardation, Neonatal respiratory distress, Hypersalivation, Oesophageal atresia, Patent ductus arteriosus, Patent foramen ovale, Mitral regurgitation, Portal vein thrombosis
	2023-2	3rd, stop 48h before cesarean section	Quetiapine; lamotrigine; lorazepam	Polyhydramnios, Macrosomia
2020	2020-1	1st, 2nd, 3rd	None or not reported	Normal newborn
	2020-2	1st	None or not reported	Normal newborn
	2020-3	1st, unknown thereafter	Aripiprazole; diazepam; zopiclone	Lost to follow-up
2017	2017-1	1st, 2nd, 3rd	None or not reported	Intrauterine growth retardation, Neonatal hypotonia
	2017-2	1st	Levothyroxine; hydroxyzine; melatonin; zopiclone	Spontaneous abortion
2014	2014-1	1st	Biperiden	Normal newborn
	2014-2	1st	Citalopram; clonazepam; quetiapine; zolpidem	Premature baby

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References

1
Goodwin GM, Haddad PM, Ferrier IN, Aronson JK, Barnes TRH, Cipriani A, et al. Evidence-based guidelines for treating bipolar disorder: revised third edition Recommendations from the British Association for Psychopharmacology. J Psychopharmacol. June 2016;30(6):495-553.

2
Malhi GS, Bassett D, Boyce P, Bryant R, Fitzgerald PB, Fritz K, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. Aust N Z J Psychiatry. 1 Dec 2015;49(12):1087-206.

3
Vieta E, Nolen WA, Grunze H, Licht RW, Goodwin G. A European perspective on the Canadian guidelines for bipolar disorder. Bipolar Disord. 2005;7 Suppl 3:73-6.

4
Swissmedic. SwissmedicInfo. [accessed on 11 September 2023]. AIPS - Individual search. Available at: https://www.swissmedicinfo.ch/ViewMonographie

5
Poels EMP, Bijma HH, Galbally M, Bergink V. Lithium during pregnancy and after delivery: a review. Int J Bipolar Disord. 2 Dec 2018;6:26.

6
Munk-Olsen T, Liu X, Viktorin A, Brown HK, Di Florio A, D'Onofrio BM, et al. Maternal and infant outcomes associated with lithium use in pregnancy: an international collaborative meta-analysis of six cohort studies. Lancet Psychiatry. Aug 2018;5(8):644-52.

7
Newport DJ, Stowe ZN, Viguera AC, Calamaras MR, Juric S, Knight B, et al. Lamotrigine in bipolar disorder: efficacy during pregnancy. Bipolar Disorders. 2008;10(3):432-6.

8
Deiana V, Chillotti C, Manchia M, Carta P, Bocchetta A, Ardau R, et al. Continuation Versus Discontinuation of Lithium During Pregnancy: A Retrospective Case Series. Journal of Clinical Psychopharmacology. June 2014;34(3):407.

9
Viguera AC, Nonacs R, Cohen LS, Tondo L, Murray A, Baldessarini RJ. Risk of Recurrence of Bipolar Disorder in Pregnant and Nonpregnant Women After Discontinuing Lithium Maintenance. AJP. Feb 2000;157(2):179-84.

10
Graham RK, Tavella G, Parker GB. Is there consensus across international evidence-based guidelines for the psychotropic drug management of bipolar disorder during the perinatal period? J Affect Disord. 1 March 2018;228:216-21.

11
Newport DJ, Viguera AC, Beach AJ, Ritchie JC, Cohen LS, Stowe ZN. Lithium placental passage and obstetrical outcome: implications for clinical management during late pregnancy. Am J Psychiatry. Nov 2005;162(11):2162-70.

12
Nora JJ, Nora AH, Toews WH. Letter: Lithium, Ebstein's anomaly, and other congenital heart defects. Lancet. 7 Sep 1974;2(7880):594-5.

13
Weinstein MR, Goldfield M. Cardiovascular malformations with lithium use during pregnancy. Am J Psychiatry. May 1975;132(5):529-31.

14
Schou M, Goldfield MD, Weinstein MR, Villeneuve A. Lithium and Pregnancy—I, Report from the Register of Lithium Babies. Br Med J. 21 April 1973;2(5859):135-6.

15
Patorno E, Huybrechts KF, Bateman BT, Cohen JM, Desai RJ, Mogun H, et al. Lithium Use in Pregnancy and the Risk of Cardiac Malformations. N Engl J Med. 8 June 2017;376(23):2245-54.

16
Zalzstein E, Koren G, Einarson T, Freedom RM. A case-control study on the association between first trimester exposure to lithium and Ebstein's anomaly. Am J Cardiol. 15 March 1990;65(11):817-8.

17
Jacobson SJ, Jones K, Johnson K, Ceolin L, Kaur P, Sahn D, et al. Prospective multicentre study of pregnancy outcome after lithium exposure during first trimester. Lancet. 29 Feb 1992;339(8792):530-3.

18
Reis M, Källén B. Maternal use of antipsychotics in early pregnancy and delivery outcome. J Clin Psychopharmacol. June 2008;28(3):279-88.

19
Källén B, Tandberg A. Lithium and pregnancy. A cohort study on manic-depressive women. Acta Psychiatr Scand. Aug 1983;68(2):134-9.

20
Diav-Citrin O, Shechtman S, Tahover E, Finkel-Pekarsky V, Arnon J, Kennedy D, et al. Pregnancy outcome following in utero exposure to lithium: a prospective, comparative, observational study. Am J Psychiatry. July 2014;171(7):785-94.

21
Källén B. Comments on teratogen update: Lithium. Teratology. Dec 1988;38(6):597-597.

22
McKnight RF, Adida M, Budge K, Stockton S, Goodwin GM, Geddes JR. Lithium toxicity profile: a systematic review and meta-analysis. Lancet. 25 Feb 2012;379(9817):721-8.

23
Hastie R, Tong S, Hiscock R, Lindquist A, Lindström L, Wikström AK, et al. Maternal lithium use and the risk of adverse pregnancy and neonatal outcomes: a Swedish population-based cohort study. BMC Med. 2 Dec 2021;19:291.

24
Oyebode F, Rastogi A, Berrisford G, Coccia F. Psychotropics in pregnancy: safety and other considerations. Pharmacol Ther. July 2012;135(1):71-7.

25
Pinelli JM, Symington AJ, Cunningham KA, Paes BA. Case report and review of the perinatal implications of maternal lithium use. Am J Obstet Gynecol. July 2002;187(1):245-9.

26
Kozma C. Neonatal toxicity and transient neurodevelopmental deficits following prenatal exposure to lithium: Another clinical report and a review of the literature. Am J Med Genet A. 1 Feb 2005;132A(4):441-4.

27
Mizrahi EM, Hobbs JF, Goldsmith DI. Nephrogenic diabetes insipidus in transplacental lithium intoxication. The Journal of Pediatrics. 1 March 1979;94(3):493-5.

28
Poels EMP, Kamperman AM, Vreeker A, Gilden J, Boks MP, Kahn RS, et al. Lithium Use during Pregnancy and the Risk of Miscarriage. J Clin Med. 11 June 2020;9(6):1819.

29
Le CRAT [Internet]. [accessed on 2 September 2024]. Available at: https://www.lecrat.fr/

30
NICE [Internet]. NICE; 2014 [accessed on 23 September 2024]. Recommendations | CG192 | Indicators. Available at: https://www.nice.org.uk/guidance/cg192/chapter/recommendations

31
VigiBase [Internet]. [accessed on 2 September 2024]. Available at: https://vigilyze.who-umc.org/

32
Sfeir R, Michaud L, Salleron J, Gottrand F. Epidemiology of esophageal atresia. Dis Esophagus. 2013;26(4):354-5.

33
Sfeir R, Bonnard A, Khen-Dunlop N, Auber F, Gelas T, Michaud L, et al. Esophageal atresia: data from a national cohort. J Pediatr Surg. Aug 2013;48(8):1664-9.

34
Felix JF, de Jong EM, Torfs CP, de Klein A, Rottier RJ, Tibboel D. Genetic and environmental factors in the etiology of esophageal atresia and/or tracheoesophageal fistula: an overview of the current concepts. Birth Defects Res A Clin Mol Teratol. Sep 2009;85(9):747-54.

35
Clementi M, Di Gianantonio E, Pelo E, Mammi I, Basile RT, Tenconi R. Methimazole embryopathy: delineation of the phenotype. Am J Med Genet. 5 March 1999;83(1):43-6.

36
Di Gianantonio E, Schaefer C, Mastroiacovo PP, Cournot MP, Benedicenti F, Reuvers M, et al. Adverse effects of prenatal methimazole exposure. Teratology. Nov 2001;64(5):262-6.

37
Heller C, Schobess R, Kurnik K, Junker R, Günther G, Kreuz W, et al. Abdominal venous thrombosis in neonates and infants: role of prothrombotic risk factors – a multicentre case–control study. British Journal of Haematology. 2000;111(2):534-9.

38
Morag I, Epelman M, Daneman A, Moineddin R, Parvez B, Shechter T, et al. Portal vein thrombosis in the neonate: Risk factors, course, and outcome. The Journal of Pediatrics. June 2006;148(6):735-9.

39
Albers BK, Khanna G. Vascular Anomalies of the Pediatric Liver. RadioGraphics. May 2019;39(3):842-56.

40
Williams S, Chan AKC. Neonatal portal vein thrombosis: Diagnosis and management. Seminars in Fetal and Neonatal Medicine. 1 Dec 2011;16(6):329-39.

41
Gentile S. Lithium in pregnancy: the need to treat, the duty to ensure safety. Expert Opinion on Drug Safety. 1 May 2012;11(3):425-37.

42
Embryotox - lithium salts [Internet]. [accessed on 26 September 2024]. Available at: https://www.embryotox.de/arzneimittel/details/ansicht/medikament/lithiumsalze

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Brugada syndrome and bupropion

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Brugada syndrome is a rare cardiac repolarisation disorder characterised by specific abnormalities on the electrocardiogram (ECG), including a characteristic ST segment elevation in the right precordial leads, associated with a pattern of right bundle branch block, in the absence of structural cardiac abnormalities, electrolyte disorders, or myocardial ischaemia. Patients suffering from this syndrome are at high risk of polymorphic ventricular tachycardia and ventricular fibrillation, potentially leading to syncope and, occasionally, sudden death. Its prevalence in the general population is difficult to estimate. The clinical symptoms are highly variable and difficult to identify, particularly as these arrhythmias tend to occur at rest or during sleep, rather than during physical exertion. The age of onset of the first symptoms varies considerably, ranging from 2 to 84 years, with an average age of around 40. The condition affects more men than women. Diagnosis of Brugada syndrome is based primarily on the appearance of characteristic electrocardiographic changes. In some cases, a challenge test with the administration of sodium channel blockers such as flecainide may be needed to unmask the typical electrocardiographic phenotype and confirm the diagnosis (1, 2).

Brugada syndrome can result from several causes. It is primarily a hereditary disorder with varying penetrance. Variants in some 20 different genes have been associated with the syndrome, and most cases (between 15 and 25%) are attributed to mutations in the SCN5A gene, which encodes a subunit of the cardiac sodium channel. Although direct causality is often not demonstrated in the literature, a link between a growing number of drugs and the induction or unmasking of electrocardiographic and arrhythmic manifestations of Brugada syndrome has been suggested. Among these drugs, certain antiarrhythmic agents, particularly those that block sodium channels, are often cited as having the ability to exacerbate the characteristic ECG abnormalities of this syndrome. While the underlying mechanisms responsible are still unclear, the vast majority of these suspected drugs have the capacity to block cardiac sodium channels (INa). This blockade could be a key factor in the onset of the ECG abnormalities observed in patients with individual susceptibility, possibly due to latent ion channel dysfunction similar to what is observed in drug-induced long QT syndrome. Drug withdrawal is an effective management strategy in most cases of drug-induced Brugada syndrome (3–6).

Swissmedic ensures regular updates of the information for healthcare professionals on medicines when it needs to be revised based on data from the literature and pharmacovigilance reports. Recently, new findings have been reported concerning bupropion in particular.

Bupropion is a selective inhibitor of the neuronal reuptake of catecholamines, norepinephrine and dopamine, with a minimal effect on the reuptake of serotonin. Its precise mechanism of action in helping people stop smoking has not been fully elucidated. In Switzerland, bupropion is indicated for the treatment of depressive episodes (Wellbutrin XR®) and the treatment of nicotine dependence (Zyban®). Recent cases of bupropion-induced Brugada syndrome, including several with positive dechallenges, have been reported in the literature and pharmacovigilance databases, suggesting a causal link (7–9). Furthermore, although the electrophysiological mechanism has not been defined, and since bupropion has been associated with effects on the cardiac sodium channels (INa), the hypothesis of the induction/unmasking of Brugada syndrome via the blockade of these channels has been suggested (10). These findings have prompted several competent authorities, including Swissmedic and the EMA, to request a product information update (information for

healthcare professionals and patient information) in order to inform caregivers and patients. The EMA and Swissmedic have included this information in the "Warnings and precautions" section, while the FDA has done the same in its "Adverse reactions" section.

This update is effective in the latest updated versions of the product information texts (information for healthcare professionals and patient information) for Zyban® and Wellbutrin®, available at swissmedicinfo.ch

It is imperative that patients with Brugada syndrome report this condition prior to any medication prescription. Moreover, it is also essential that healthcare professionals have access to regularly updated information, not only to withdraw any suspected medication in the event of a Brugada syndrome onset, but also to avoid prescribing potentially harmful drugs to these patients and to consider appropriate alternative therapeutic options where possible.

This regular updating of product information not only optimises the safety of patients with Brugada syndrome, it also improves the overall effectiveness of their medical management.

Reporting adverse drug reactions

The reporting of suspected adverse drug reactions is one of the key pillars of drug safety. These reports play a vital role in the detection of potential drug risks at an early stage and the continuous monitoring of the benefit/risk profile of all available medicines.

Healthcare professionals are encouraged to report serious and/or previously unknown side effects to Swissmedic via the electronic vigilance and reporting portal ElViS.

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References

1
Brugada J, Campuzano O, Arbelo E, Sarquella-Brugada G, Brugada R. Present Status of Brugada Syndrome: JACC State-of-the-Art Review. J Am Coll Cardiol. 2018 Aug 28;72(9):1046-1059. doi: 10.1016/j.jacc.2018.06.037. PMID: 30139433.

2
Alings M, Wilde A. "Brugada" syndrome: clinical data and suggested pathophysiological mechanism. Circulation. 1999 Feb 9;99(5):666-73. doi: 10.1161/01.cir.99.5.666. PMID: 9950665.

3
Sieira J, Ciconte G, Conte G, de Asmundis C, Chierchia GB, Baltogiannis G, Di Giovanni G, Saitoh Y, Casado-Arroyo R, Juliá J, La Meir M, Wellens F, Wauters K, Pappaert G, Brugada P. Long-term prognosis of drug-induced Brugada syndrome. Heart Rhythm. 2017 Oct;14(10): 1427-1433. doi: 10.1016/j.hrthm.2017.04.044. Epub 2017 May 4. PMID: 28479512.

4
Shimizu W. Acquired forms of the Brugada syndrome. J Electrocardiol. 2005 Oct; 38(4 Suppl):22-5. doi: 10.1016/j.jelectrocard.2005.06.005. PMID: 16226070.

5
Konigstein M, Rosso R, Topaz G, Postema PG, Friedensohn L, Heller K, Zeltser D, Belhassen B, Adler A, Viskin S. Drug-induced Brugada syndrome: Clinical characteristics and risk factors. Heart Rhythm. 2016 May;13(5):1083-1087. doi: 10.1016/j.hrthm.2016.03.016. PMID: 27131070.

6
Yap YG, Behr ER, Camm AJ. Drug-induced Brugada syndrome. Europace. 2009 Aug;11(8):989-94. doi: 10.1093/europace/eup114. Epub 2009 May 29. PMID: 19482855.

7
Alampay MM, Haigney MC, Flanagan MC, Perito RM, Love KM, Grammer GG. Transcranial magnetic stimulation as an antidepressant alternative in a patient with Brugada syndrome and recurrent syncope. Mayo Clin Proc. 2014 Nov;89(11):1584-7. doi: 0.1016/j.mayocp.2014.08.010. Epub 2014 Nov 3. PMID: 25444490.

8
Ketenci M, Way H, Estep Z, Ehinmisan A, Homayounrooz F, Kathryn Mitra K, Lader J. Abstract 15984: Toxic Twist: A Case of Bupropion Induced Brugada Syndrome. Circulation. 2023;148:A15984

9
Reactions Weekly. "Bupropion may unmask Brugada syndrome and lead to sudden death." Reactions Weekly, vol. 1959, 2023, p. 3, doi:10.1007/s40278-023-40175-0.

10
Caillier B, Pilote S, Castonguay A, Patoine D, Ménard-Desrosiers V, Vigneault P, Hreiche R, Turgeon J, Daleau P, De Koninck Y, Simard C, Drolet B. QRS widening and QT prolongation under bupropion: a unique cardiac electrophysiological profile. Fundam Clin Pharmacol. 2012 Oct;26(5):599-608. doi: 10.1111/j.1472-8206.2011.00953.x. Epub 2011 May 30. PMID: 21623902.

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Stronger warnings about the risks associated with overuse of SABAs

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Asthma is a chronic disease characterised by inflammation, hyperresponsiveness and airway obstruction, leading to recurrent episodes of respiratory symptoms. Depending on the country, asthma affects between 1% and 29% of the population, i.e. around 300 million people worldwide (1). In Switzerland, the prevalence of asthma is around 7% (2), making it one of the most common chronic diseases.

The management of asthma aims to control symptoms, prevent exacerbations and improve the patients' quality of life. It is primarily based on an assessment and classification of the severity of the disease, thereby enabling treatment to be adapted appropriately to the individual. From a pharmacological point of view, treatment includes background medication aiming to control the disease in the long term and prevent attacks, combined with rescue (or "as needed") treatments during exacerbations. The pharmacological treatment of asthma is based mainly on two major therapeutic classes: corticosteroids, usually inhaled (ICS), intended to reduce inflammation of the airways and their sensitivity to irritants, and β2-agonists, which act as bronchodilators. Two main types of β2-agonists are used in asthma: long-acting β2-agonists (LABAs), such as formoterol and salmeterol, and short-acting β2-agonists (SABAs), such as salbutamol, fenoterol and terbutaline, which are effective in providing rapid relief of acute symptoms.

These treatments are complemented by the use of several other drug classes: anticholinergic agents, which are likewise used for their bronchodilator properties; leukotriene receptor antagonists, which help to reduce inflammation; mast cell stabilisers, whose role is to prevent inflammatory reactions; and finally, methylxanthines and immunomodulators for cases of severe asthma that are refractory to conventional therapies.

The management recommendations are regularly updated by specialist organisations, including the Global Initiative for Asthma (GINA), in order to incorporate new scientific evidence and improve the diagnosis and management of asthma.

For many years, the use of SABAs alone was a common practice in the treatment of asthma, based on the rationale that SABAs offer rapid relief of asthma symptoms. The efficacy of SABAs led to a mistaken perception of safety and the underuse of anti-inflammatory maintenance therapy in favour of SABAs.

However, although SABAs provide rapid symptomatic relief, they do not treat the underlying inflammation of the asthma. Rather, there is a risk of masking this inflammation and delaying the initiation of appropriate treatment. In addition, overuse of SABAs may not only cause side effects such as tremor, palpitations and tachycardia, but also, according to several studies, particularly the worldwide retrospective SABINA (SABA Use In Asthma) study, be associated with reduced β2-receptor expression, an increased risk of poor symptom control, exacerbation of the asthma and death, in both children (5) and adults (6–11). Since overuse of SABAs may be a sign of poor asthma control, the background treatment should be reassessed by a physician. The use of the combination of ICS and formoterol "on demand" is supported by data from several randomised controlled trials, a systematic review and a meta-analysis (12–15).

In their recent updates, specialist organisations such as GINA have incorporated several changes in the management of asthma, particularly in terms of medication, by no longer recommending the use of SABAs alone as rescue therapy (3, 4). Swissmedic, similarly to the European Medicines Agency (EMA), has required an update of the product information (information for healthcare professionals and patient information) of SABA-containing products to inform patients and healthcare professionals about the potential risks of SABA overuse. As the risks are already described in the product information for terbutaline, a recent update was necessary for inhaled salbutamol preparations. Henceforth, the product information for all mono-preparations of inhaled SABAs authorised in Switzerland for the treatment of asthma will include a warning about

- the risks of severe exacerbation and death associated with the excessive use of SABA monotherapy,
- the need to continue regular anti-inflammatory treatment (for example inhaled corticosteroids),
- the fact that the need to increase the use of SABAs may be an indicator of sub-optimal treatment or a deterioration in the asthma, and requires a medical consultation in order, in particular, to reassess the therapeutic regimen.

Regular updates of drug information based on the latest evidence are essential to help healthcare professionals and patients to make more informed treatment decisions and ensure appropriate medical follow-up, thereby optimising disease management.

Reporting adverse drug reactions

The reporting of suspected adverse drug reactions is one of the key pillars of drug safety. These reports play a vital role in the detection of potential drug risks at an early stage and in the continuous monitoring of the benefit/risk profile of all available medicines.

Healthcare professionals are encouraged to report serious and/or previously unknown adverse reactions to Swissmedic. Reports can be submitted via the electronic vigilance and reporting portal ElViS.

Glossar

EMA	European Medicines Agency
GINA	Global Initiative for Asthma
ICS	inhaled corticosteroids
LABA	long-acting β2-agonist
SABA	short-acting β2-agonist
SABINA	SABA Use In Asthma

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References

1
Global Initiative for Asthma GINA. Global Strategy for Asthma Management and Prevention, Update 2024, available on https://ginasthma.org/2024-report/

2
Masoli M, Fabian D, et al., for the Global Initiative for Asthma (GINA) Program. The global burden of asthma: executive summary of the GINA Dissemination Committee report. Allergy. 2004 May;59(5):469-78. doi: 10.1111/j.1398-9995.2004.00526.x.

3
Global Initiative for Asthma GINA. Global Strategy for Asthma Management and Prevention, 2019, available on https://ginasthma.org/archived-reports/

4
Global Initiative for Asthma GINA. Global Strategy for Asthma Management and Prevention, 2022, available on https://ginasthma.org/archived-reports/

5
Melén E, Nwaru BI, et al. Short-acting β2 -agonist use and asthma exacerbations in Swedish children: A SABINA Junior study. Pediatr Allergy Immunol. 2022 Nov;33(11):e13885. doi: 10.1111/pai.13885.

6
Bloom CI, Cabrera C, et al. Asthma-Related Health Outcomes Associated with Short-Acting β2-Agonist Inhaler Use: An Observational UK Study as Part of the SABINA Global Program. Adv Ther. 2020 Oct;37(10):4190-4208. doi: 10.1007/s12325-020-01444-5. Epub 2020 Jul 27.

7
Nwaru BI, Ekström M, et al. Overuse of short-acting β2-agonists in asthma is associated with increased risk of exacerbation and mortality: a nationwide cohort study of the global SABINA programme. Eur Respir J. 2020 Apr 16;55(4):1901872. doi: 10.1183/13993003.01872-2019.

8
Noorduyn SG, Qian C, et al. SABA use as an indicator for asthma exacerbation risk: an observational cohort study (SABINA Canada). ERJ Open Res. 2022 Sep 26;8(3):00140-2022. doi: 10.1183/23120541.00140-2022.

9
Quint JK, Arnetorp S, et al., SABINA North American and European Study contributors. Short-Acting Beta-2-Agonist Exposure and Severe Asthma Exacerbations: SABINA Findings From Europe and North America. J Allergy Clin Immunol Pract. 2022 Sep;10(9):2297-2309.e10. doi: 10.1016/j.jaip.2022.02.047. Epub 2022 Mar 29.

10
Bateman ED, Price DB, et al. Short-acting β2-agonist prescriptions are associated with poor clinical outcomes of asthma: the multi-country, cross-sectional SABINA III study. Eur Respir J. 2022 May 5;59(5):2101402. doi: 10.1183/13993003.01402-2021.

11
Stanford RH, Shah MB, et al. Short-acting β-agonist use and its ability to predict future asthma-related outcomes. Ann Allergy Asthma Immunol. 2012 Dec;109(6):403-7. doi: 10.1016/j.anai.2012.08.014. Epub 2012 Oct 1.

12
Crossingham I, Turner S, et al. Combination fixed-dose β agonist and steroid inhaler as required for adults or children with mild asthma: a Cochrane systematic review. BMJ Evid Based Med. 2022 Jun;27(3):178-184. doi: 10.1136/bmjebm-2021-111764. Epub 2021 Jul 19.

13
O'Byrne PM, FitzGerald JM, et al. Inhaled Combined Budesonide-Formoterol as Needed in Mild Asthma. N Engl J Med. 2018 May 17;378(20):1865-1876. doi: 10.1056/NEJMoa1715274.

14
Bateman ED, Reddel HK, et al. As-Needed Budesonide-Formoterol versus Maintenance Budesonide in Mild Asthma. N Engl J Med. 2018 May 17;378(20):1877-1887. doi: 10.1056/NEJMoa1715275.

15
Hardy J, Baggott C, et al., PRACTICAL study team. Budesonide-formoterol reliever therapy versus maintenance budesonide plus terbutaline reliever therapy in adults with mild to moderate asthma (PRACTICAL): a 52-week, open-label, multicentre, superiority, randomised controlled trial. Lancet. 2019 Sep 14;394(10202):919-928. doi: 10.1016/S0140-6736(19)31948-8. Epub 2019 Aug 23. Erratum in: Lancet. 2020 May 2;395(10234):1422. doi: 10.1016/S0140-6736(20)30982-X.

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Medication errors associated with low-dose methotrexate: An analysis of spontaneous reports following the Direct Healthcare Professional Communication in 2016

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Despite previous warnings in the product information (1) and several publications (2, 3, 4), medication errors such as accidental overdose continued to occur with low-dose methotrexate (Mtx). Therefore, enhanced risk minimisation measures (RMMs) were introduced in 2016 in Switzerland and published in a Direct Healthcare Professional Communication (DHPC) (5). These included patient cards, a sticker or a fixed overprint on the outer packages and boxed warnings in the Information for healthcare professionals and patient information leaflets. Furthermore, hospitals and care institutions were advised to appoint a professional to assume responsibility for checking all prescriptions of low-dose methotrexate before they are released. Additionally, the four-eyes principle was recommended. Acknowledging the importance of measuring the impact of risk minimisation measures, our study aimed to identify and analyse instances of medication errors reported after the implementation of these enhanced measures.

We evaluated individual case safety seports (ICSRs) from the Swissmedic database in which Mtx was a suspected and/or interacting product. We included reports up to 31 December 2023, focusing on reports submitted after the issuance of the DHPC in July 2016. ICSRs containing at least one medication error among the coded adverse events/adverse drug reactions (AEs/ADRs) (standardised MedDRA query "medication errors", narrow search) were further analysed.

In the period after July 2016, Swissmedic received a total of 807 reports involving low-dose Mtx. Following de-duplication, 179 (22.2%) cases involving a medication error were identified. Most cases were reported by healthcare professionals (n= 160, 89%). The patients were female in 52.2% (n= 94) and male in 33.3% (n= 60) of the ICSRs (unknown in 25 ICSRs, 14.0%). The ages ranged from 14 to 90 years (median 52). Half of the ICSRs were categorised as serious (n= 90). A fatal outcome was reported in twelve cases (6.7%). In about 58% (n= 104) of the cases, at least one ADR was reported in addition to a medication error.

The 179 reports contained a total of 559 ADRs. The most common reactions are displayed in Figure 1. Most reported medication errors occurred in an outpatient environment (n= 151, 84.4%), while 25 (13.9%) were recorded in an inpatient setting, including rehabilitation centres and retirement homes (circumstances unclear in three reports).

One third of the errors (n= 61, 34%) were related to the handling of Mtx injections leading to underdosage. In 41% (n= 74) an overdose occurred as a result of a prescribing error, patient's misunderstanding regarding the intake interval, drug-drug interaction or omitted dosage adaptation in reduced kidney function (Table 1).

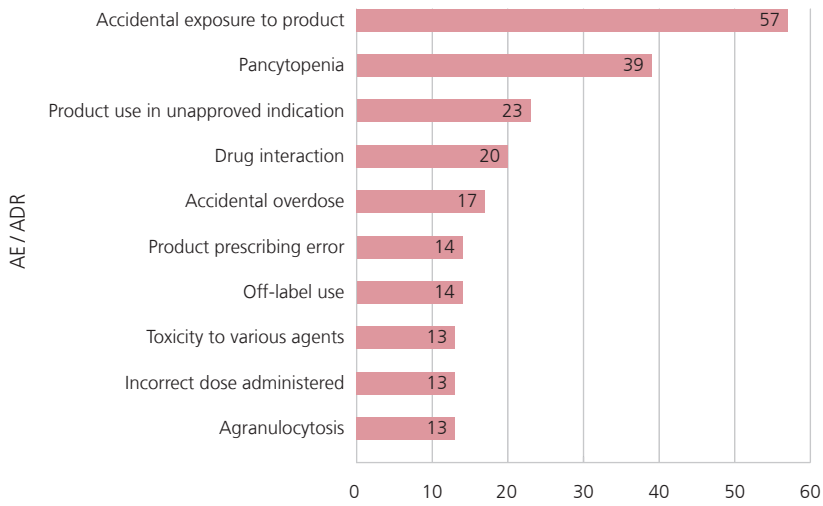

Figure 1: Ranking of the most common AEs/ADRs in ICSRs with medication errors and methotrexate (total number of AEs/ADRs n= 559)

Table 1: Type of medication errors by outpatient and inpatient settings

Outpatient (n=151)	n	Inpatient (n=25)	n
Accidental exposure through handling error by patient (injection)	61	Prescribing error in hospital	20
Unapproved indication	26	Prescribing error in retirement home/rehabilitation centre	4
Drug-drug interaction by adding a new medication	22	Drug-drug interaction by adding a new medication	1
Prescribing error (physician)	14		
Accidental overdose by patient (intake)	13		
No adaptation to reduced kidney function	8		
Wrong technique in usage process	7		

Since 1993, Swissmedic has received 1,702 reports related to Mtx, including 118 cases with a fatal outcome, regardless of whether a medication error was reported (Figure 2).

The tendency towards a higher number of annual reports after 2016 may be an indication of greater awareness. The most commonly reported reactions of fatal cases were pancytopenia, sepsis and agranulocytosis (Figure 3).

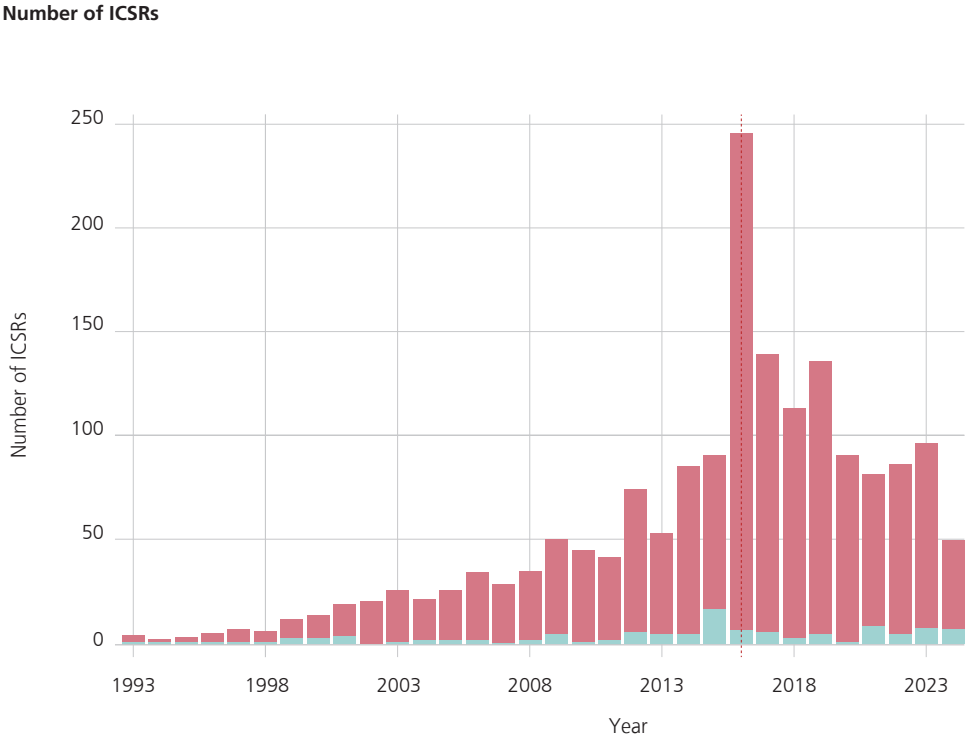

Figure 2: Number of ICSRs related to Mtx since 1993. The blue portion of the columns represents fatal cases. The red line indicates the issuance of the DHPC in 2016

Despite several additional risk minimisation measures, including a DHPC, a concerning number of medication errors in association with Mtx have been reported to Swissmedic since 2016. Our findings show that errors occur in both outpatient and inpatient settings and can affect all steps of the medication process.

Our results are consistent with a survey conducted in five EU countries, which revealed that risk minimisation measures related to low-dose Mtx are not effective across outcomes of awareness, knowledge, and self-declared behaviour in prescribers, pharmacists, and patients (6).
Swissmedic published a reminder on the risks of Mtx in April 2024 (7). However, in light of the results of the investigations into the effectiveness of the extensive measures to date, the need for further measures and how such measures could be designed should be reviewed.

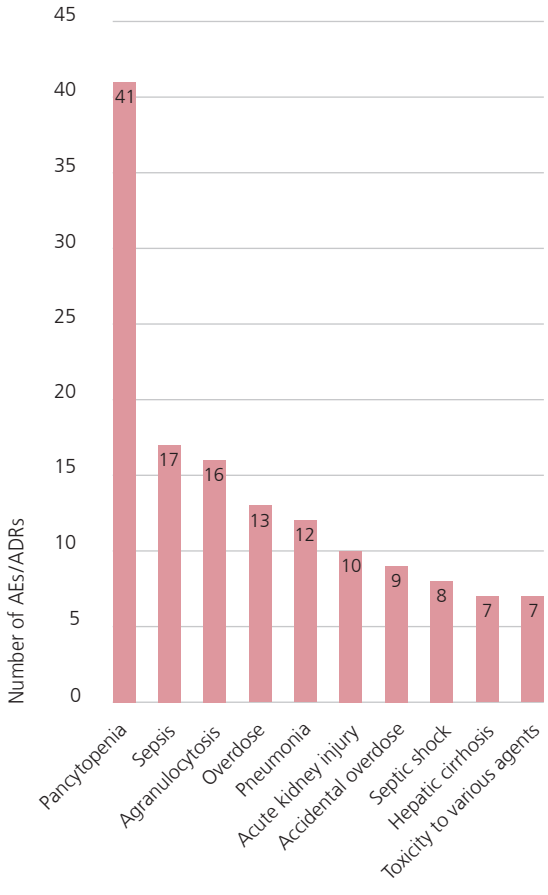

Figure 3: Ranking of the most commonly reported reactions in fatal reports related to low-dose Mtx

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References

1
www.swissmedicinfo.ch
Medicinal product information (human medicinal product)

2
Hirsch, Stefanie; Ahrenstorf, Gerrit; Schmidt, Reinhold E.; Klintschar, Michael. Methotrexat: Todesfälle durch falsche Dosis, Dtsch Arztebl 2020; 117(3): A-76 / B-68 / C-64

3
Grissinger M. Severe Harm and Death Associated With Errors and Drug Interactions Involving Low-Dose Methotrexate. P T. 2018 Apr;43(4):191-248. PMID: 29622936; PMCID: PMC5871236.

4
Moore TJ, Walsh CS, Cohen MR. Reported medication errors associated with methotrexate. Am J Health Syst Pharm. 2004 Jul 1;61(13):1380-4. doi: 10.1093/ajhp/61.13.1380. PMID: 15287234.

5
DHPC low-dose methotrexate, available under https://www.swissmedic.ch/swissmedic/en/home/humanarzneimittel/market-surveillance/health-professional-communication--hpc-/archive/dh-pc-_-low-dose-methotrexate-in-rheumatoid-arthritis-and-psorias.html

6
Lysen T, Karimi L, Wang M, Singh S, Toussi M. Impact of European Union label changes to avoid inadvertent use of medicinal products containing methotrexate for once-weekly administration: A survey amongst prescribers, pharmacists and patients on awareness, knowledge, and behaviour. Pharmacoepidemiol Drug Saf. 2024; 33(1):e5692.

7
https://www.swissmedic.ch/swissmedic/en/home/humanarzneimittel/market-surveillance/pharmacovigilance/vigilance-news/ueberdosierung-methotrexat.html

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Regulatory

The revised auto-narrative in the Swissmedic PV Database

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Introduction

The case narrative is an essential component of an individual case safety report (ICSR). It should serve as a comprehensive, stand-alone summary of all relevant clinical and related information, i.e. patient characteristics, therapy details, medical history, clinical course of events, diagnosis, and adverse drug reactions including the outcome, laboratory evidence (with normal ranges), and any other information that supports or refutes an adverse drug reaction (1).

ICH Guideline E2B(R3) specifies the structure of a case report for electronic messaging. Terms such as adverse drug reactions, indication, and medical conditions in the narrative should be accurately reflected in the appropriate ICH E2B data elements (1).

In this article, we introduce the auto-narrative we developed for post-marketing case reports in the Swissmedic Pharmacovigilance unit in collaboration with the software provider of our database system. We explain our main focus and underscore the importance of a sufficiently detailed, and at the same time easy-to-read, case narrative. The auto-narrative is currently used for case reports directly submitted to Swissmedic by healthcare professionals or patients. Case reports from marketing authorisation holders already contain case narratives that have been prepared by the respective senders.

Case narrative

The ICH E2B(R3) standard adopted by the ICH for the electronic transmission of ICSRs made provisions for transmission of a full free-text case summary narrative. The case narrative field (H.1) calls for a focused, factual and clear description of the case in up to 100,000 characters.

The case narrative is an essential tool in pharmacovigilance because it serves as a brief summary of an ICSR and can play a crucial role in signal processes. A well-written and comprehensive narrative is necessary for a valid and time-saving evaluation of an individual case. While line-listing data also provide quantitatively analysable information about case reports, a case narrative offers more in-depth information about the single case and contextualises the coded terms. For the same reason, reviewing a group of narratives during the signal detection process can be a helpful addition to evaluating line-listed information, as the narrative can clarify diagnoses, associations with different drugs, and identify or delineate risk factors and risk groups.

A case narrative should, therefore, contain at least the following information (2):

- Source of the report and patient information
- The suspected drug(s) and timing of the reaction(s)
- The progression of the event(s) and its (their) outcome in the patient
- If outcome is fatal, relevant details (timing, autopsy)
- Medical drug history
- Relevant investigations

Automation of case narratives

The commonly used auto-narrative function of current safety databases populates a narrative template with E2B data elements from a specific case.

This facilitates the quick creation of a case narrative with a standardised structure containing information consistent with other data in the case. The automation of case narratives significantly reduces the time and effort required to complete this task manually and produces less error-prone narratives.

However, a common limitation of auto-narratives is that they can be very difficult to read. One reason for restricted readability can be that the narrative template is not adaptable enough to produce an easy-to-read narrative for all possible entries in a specific E2B data element. Another reason may be that missing data in E2B data elements results in a narrative with "unknown" appearing too frequently, affecting readability.

The Swissmedic Auto-Narrative

The revised auto-narrative developed in the Swissmedic PV database aimed to create an improved narrative where the template adjusts to the data elements as much as possible. Another main objective was to provide a short summary within the case narrative, i.e. a first sentence that summarises the main information in the case.

Table 1 shows the general structure of the auto-narrative and an example of the Swissmedic auto-narrative including the insertion of free text and the content of E2B data elements in bold.

The narrative template was intentionally designed with the flexibility to include additional important information through free-text sections (e.g. for a more detailed reaction description). The generated case narrative must be reviewed by a PV assessor and potentially edited to address specific preferred terms, such as special situations (e.g. pregnancy, overdose) or parent-child cases.

Conclusion

The narrative is a crucial component of ICSRs, as it provides a brief summary of all relevant clinical information that supports or refutes an adverse drug reaction. High-quality, readable narratives contextualise reported adverse events, which in turn enables a thorough assessment of the safety profile of the suspected drug. While the automation of narrative writing is an effective method for generating standardised and less error-prone narratives, it significantly reduces the time required for processing ICSRs. In our article we present an automated narrative we developed to improve and facilitate the evaluation of case reports processed in the Swissmedic Pharmacovigilance unit. Nonetheless, auto-narratives still require review and input from PV personnel to ensure accuracy and completeness.

Table 1: Structure and example of the Swissmedic auto-narrative with the insertion of free text; content of E2B data elements in bold.

Structure of the auto-narrative	Example
Short summary	This spontaneous report from a **physician** describes a **female** patient, **114 year(s)** old at time of onset of reaction (date of birth: **1910**) who developed **toxic epidermal necrolysis** in association with suspected drugs: **Ibuprofen Fiktiva*** (**Ibuprofen sodium**), **Acetylsalicylic acid 500 Akuto*** (**Acetylsalicylic acid**). This case is considered **serious** (**Results in Death, Caused / Prolonged Hospitalisation**).
Suspect / interacting drug(s)	The reporter suspected the adverse reaction(s) to be related to the following drugs: • **Ibuprofen Fiktiva***, indication: **headache**, administration from **unknown date** to **2024-08-14**, action taken with drug: **drug withdrawn**. • **Acetylsalicylic acid 500 Akuto***, indication: **unknown**, administration from **2024-06** to **2024-08-14**, action taken with drug: **drug withdrawn**.
Information on ADR(s)	The patient experienced the following adverse reaction(s): • **Toxic epidermal necrolysis**, start date **2024-08-14** (**serious**), outcome **fatal**. Treatment of the ADR: **medical treatment**. The patient died on **2024-08-22**. Autopsy was performed: **yes**.
Free text	The patient developed toxic epidermal necrolysis most likely after taking ibuprofen or acetylsalicylic acid. Initially, 30% of the body surface area was affected. After 2 days, the affected body surface area was found to be 95%. In addition to the skin, the conjunctiva, liver, and kidneys were also affected. There were further complications as the disease progressed. The patient ultimately died in the ICU.
Relevant investigations	The most relevant investigation results with regard to the patient's adverse reaction(s) were as follows: • **2024-08-15**, **Histology**, **acute multiforme reaction**, **compatible with diagnosis of toxic epidermal necrolysis**.
Medical history	The patient's medical history includes **coronary heart disease**, **hip osteoarthritis**, **chronic obstruct airways disease**.
Concomitant drug(s)	The patient received the following concomitant medication: **Bisoprololfumarat** (**Bisoprolol fumarate**), **Vitamin B12** (**Cobalamin**).

*fictitious drug

References

1
European Medicines Agency. (2004). ICH Topic E 2 D. Post Approval Safety Data

2
Council for International Organizations of Medical Sciences. (2001). CIOMS current challenges in pharmacovigilance: pragmatic approaches. Report of CIOMS working group V.

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Statistical review 2023

Pharmacovigilance: Human medicinal products

Reports of suspected adverse drug reactions

Irene Scholz, Thomas Stammschulte

Safety of Medicines Division, Swissmedic, Bern, Switzerland

Introduction and comments on the interpretation of the data

This report provides a statistical summary of adverse drug reactions reported to Swissmedic in 2023. Due to legal requirements, Swissmedic receives reports of suspected adverse drug reactions from various sources: reports come from healthcare professionals or directly from patients; a large portion of the reports is submitted via pharmaceutical companies. Reports may concern cases that have occurred in medical or clinical practice, cases that have occurred in studies or trials or during systematic observation, or even cases published in journals.

The first thing to note when interpreting data from the spontaneous reporting system is that the cases reported involved suspected adverse reactions. This means that there is no definite causal relationship between the medicine or vaccine that has been administered and the reaction that has occurred. Furthermore, and despite legal obligations, only a small portion of adverse drug reactions that occur are actually reported.

Despite these limitations, spontaneous reports remain one of the fundamental components of medicinal product safety. The majority of rare and as yet unknown side effects are first discovered through the system and then confirmed with the aid of other data.

Moreover, it should be borne in mind, when interpreting the data from the Swiss spontaneous reporting system shown here, that the figures for reports can change over time. This may be due to information that supplements the initial report but changes the data being received in due course, for example. For this reason, there may be discrepancies in report-related figures in Swissmedic publications at different points in time.

Total number of reports received

15,319 reports were received in 2023, of which 8,950 were initial reports (i.e. this figure is the number of suspected reactions reported) and 6,369 were follow-up reports (reports containing supplementary information). These figures for reports received are largely back to the levels seen in the years leading up to the COVID vaccination campaign see Figure 1. Around 54% of the initial reports involved serious reactions; however, the legal reporting obligation means that a higher percentage of reports of serious reactions can always be expected.

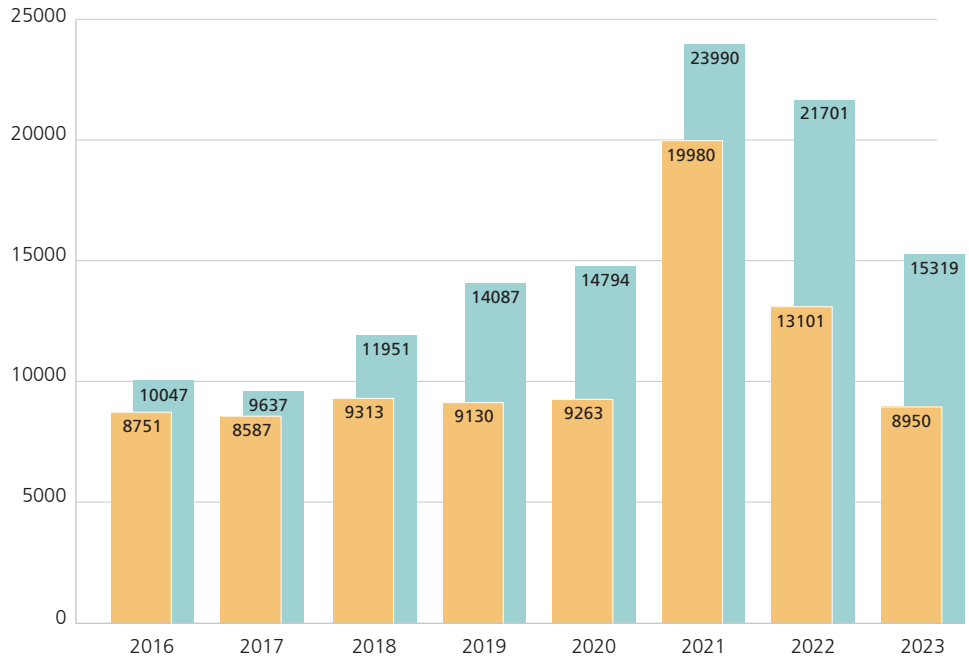

Figure 1: Number of reports received between 2016 and 2023. Yellow columns: Initial reports. Blue columns: Initial and follow-up reports combined.

Information on reporters and sources

81% of primary reporters of suspected reactions (n=7,239) were healthcare professionals such as doctors or pharmacists, while 19% (n=1,711) were patients or other non-healthcare professionals. Around one-third (n=540) of reports from non-healthcare professionals were submitted using the reporting tool on Swissmedic's website or to a lesser extent (n=54) by e-mail. Around 65% of non-healthcare professional reports were submitted to Swissmedic by pharmaceutical companies.

Of the total 8,950 initial reports received, 6,394 (71.4%) were submitted to Swissmedic by the pharmaceutical companies (marketing authorisation holders, MAHs), and 2,556 (28.6%) were submitted directly to Swissmedic. 70.4% of reports from pharmaceutical companies were spontaneous (n=4,501), 29.6% were from studies or other post-market surveillance programmes.

Among the reports submitted directly to Swissmedic, 1,109 (43%) came from healthcare professionals (primarily via the ElViS reporting tool), 540 (21.1%) via the reporting tool for patients (see above) and 822 (32.2%) from the regional pharmacovigilance centres (85 reports were generated by the database system due to technical reasons); see Figure 2.

Swissmedic works closely with five regional pharmacovigilance centres in Basel, Geneva, Lausanne, Lugano and Zurich to assess case reports. The regional centres analysed some 1,914 reports in greater depth in 2023.

Reports received by source

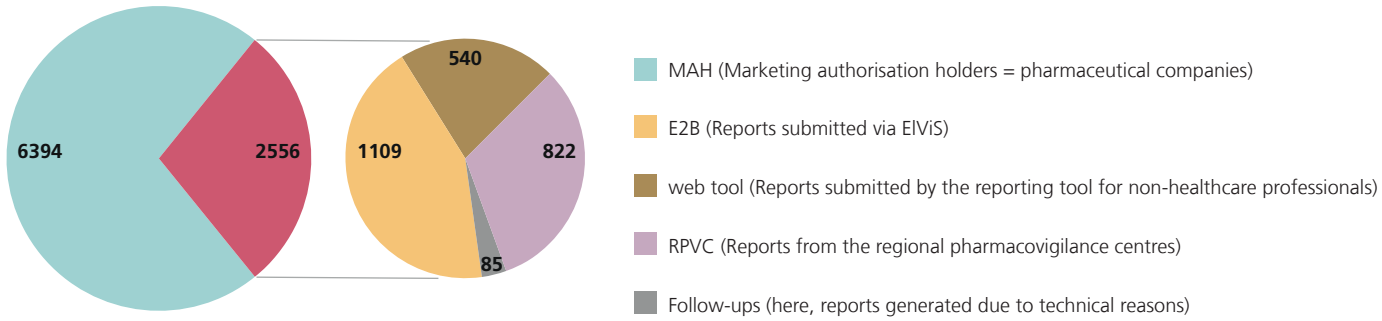

Figure 2: Reports received by source.

Information on affected patients

For the following information, a dataset was used in which suspected duplicate reports were no longer included. This results in a total of 8,815 reports.

The age of the people affected by reported suspected adverse reactions ranged from 0 to 102. The median age was 55. For the number of reports by age group and sex, see Figure 3 and Figure 4.

Number of reports by age group

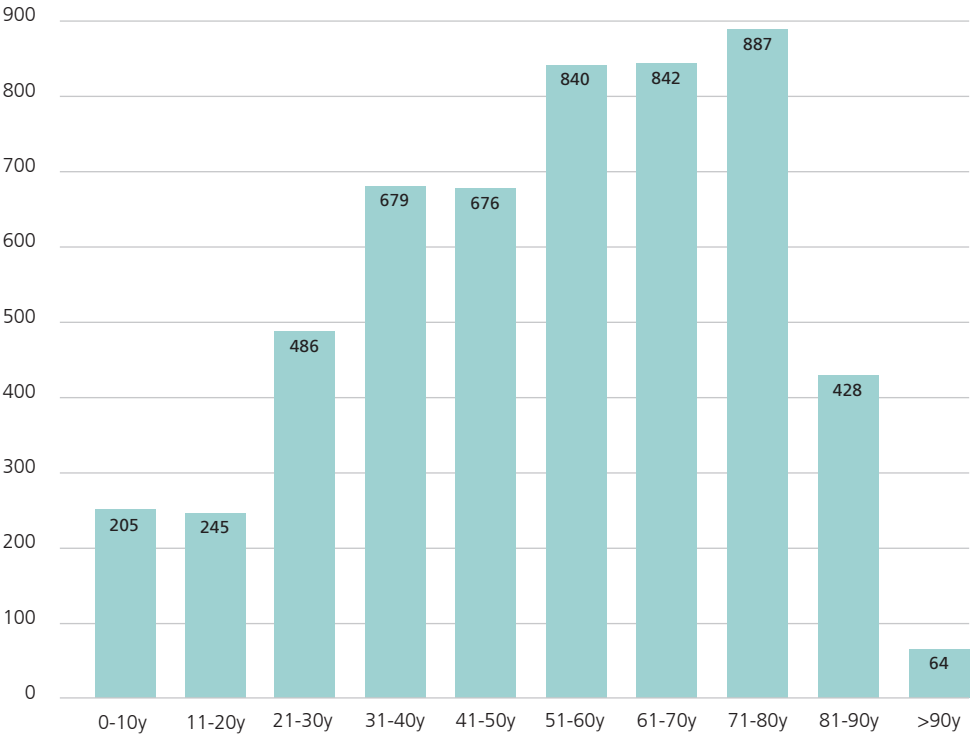

Figure 3: : Reports by affected patients' age group.

Sex distribution

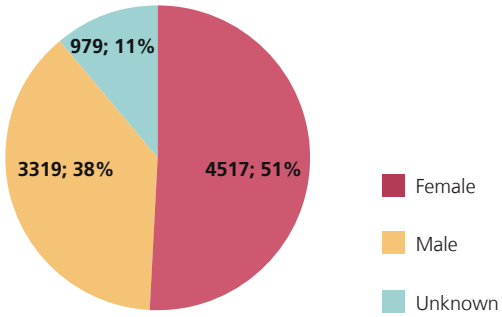

Figure 4: : Reports by affected patients' sex.

Information on suspected and interacting medicinal products

Reports of suspected adverse drug reactions always list one or more medicinal products that are suspected of having caused the reaction or being implicated in it by interaction.

Table 1 shows the medicinal products that were most frequently reported as "suspected" or "interacting" in 2023. The 20 most frequently mentioned medicinal products are listed by chemical, therapeutic or pharmacological category using the ATC classification system.

Table 1: Ranking list of the 20 medicinal products most frequently mentioned as "suspected" or "interacting" by chemical, therapeutic or pharmacological category using the ATC classification system.

ATC code	Designation	Number
J07BX	COVID-19 vaccines	777
L01XC	Monoclonal antibodies for cancer treatment	708
L04AA	Selective immunosuppressants	588
L01XE	Protein kinase inhibitors	413
J05AR	Antiviral agents for HIV treatment	324
L04AC	Interleukin inhibitors	256
H02AB	Glucocorticoids	231
L04AB	TNF inhibitors	227
L01XX	Other antineoplastic agents	211
L04AX	Other immunosuppressants	208
N03AX	Other antiepileptic agents	155
B03AC	Iron, parenteral preparations	154
N06AX	Other antidepressants	153
J01CR	Penicillin combinations incl. beta lactamase inhibitors	150
L01BC	Pyrimidine analogues (antineoplastic agents)	147
N05AX	Other antipsychotics	140
N05BA	Benzodiazepine derivatives	132
N02BE	Anilides (primarily paracetamol)	130
N02BB	Pyrazalone (primarily metamizole)	128
M05BX	Other agents that affect bone structure and mineralisation	126

Information on reported reactions

The reactions detailed in a suspected adverse drug reaction report are classified according to an international system (Medical Dictionary for Regulatory Activities, MedDRA) that can be used to assign all reactions to particular organ systems.

Overall, the reports in 2023 contained about 22,500 reactions, equivalent to approximately 2.6 reactions per report. Figure 5 shows the number of reported reactions by MedDRA organ system.

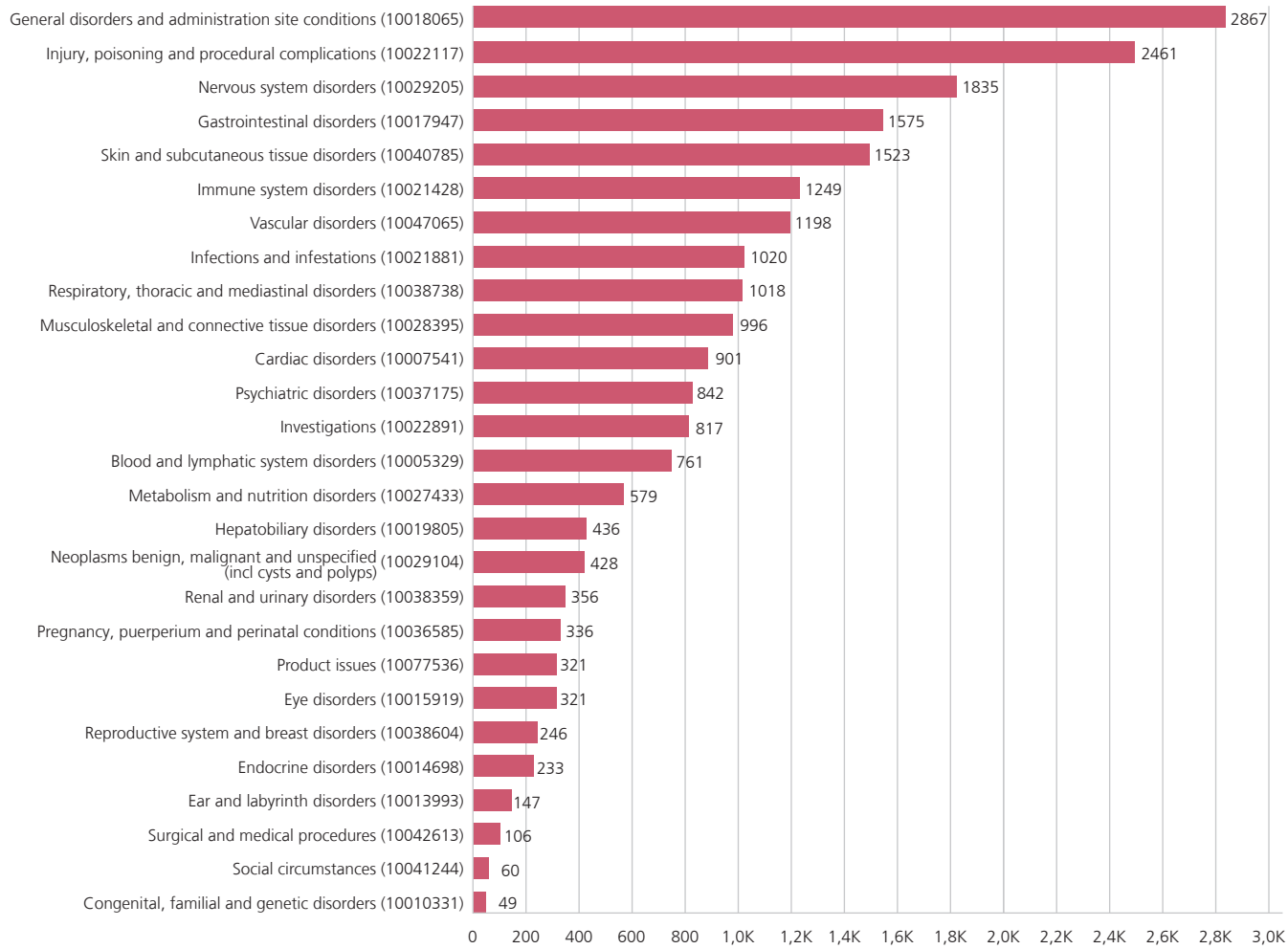

Figure 5: Number of reported reactions by affected organ system (System Organ Classes, SOC, in MedDRA)

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Vaccinovigilance

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Complete report:

Vaccinovigilance – Annual report 2023

Summary of adverse events following immunization reported in Switzerland during 2023

During 2023, the Pharmacovigilance Unit of Swissmedic received a considerable number of case reports of suspected "adverse events following immunization (AEFIs)" from Switzerland. Although lower in number than in 2022, the majority of these reports (>700 cases) were still submitted in relation to COVID-19 vaccines. Overall, these figures are a consequence of continuing COVID-19 vaccination in Switzerland and most of these reports describe well-known reactions following COVID-19 immunisation such as fever, chills or administration site reactions. In addition, 264 AEFI reports were submitted in Switzerland for **non**-COVID vaccines during 2023, which is a higher number compared with 2022 (217 reports) and 2021 (159 reports). The main focus of this summary report is on **non**-COVID vaccine AEFIs, since COVID-19 vaccine safety reports have been published as **cumulative** updates on Swissmedic's website. Nevertheless, a brief summary of COVID-19 AEFI reports received during 2023 is presented in the final section of this document.

AEFI reports submitted during 2023 were recorded, assessed and analysed in the pharmacovigilance database of Swissmedic. As previously, Swissmedic is encouraging spontaneous reporting of AEFIs in high quality, which enables early detection of new safety signals. Important safety issues concerning vaccines are 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.

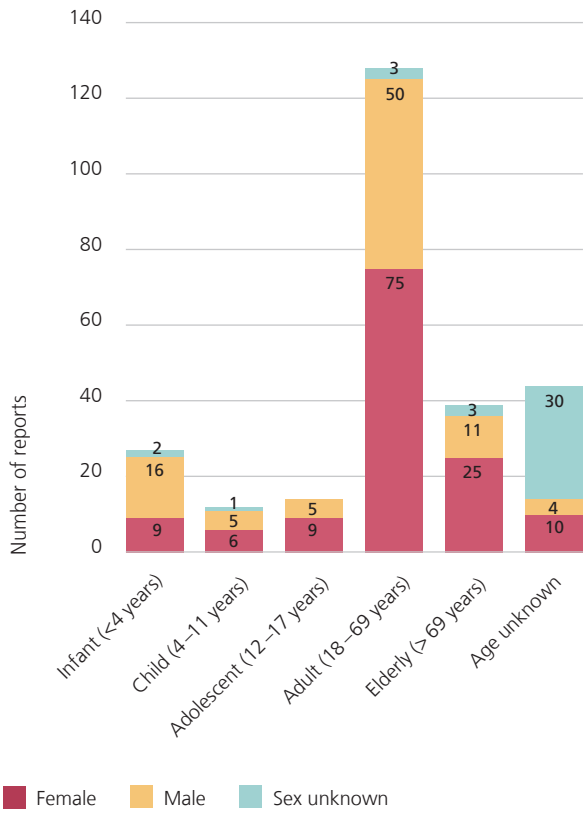

Figure 1: Number of AEFI reports by age group and sex, 2023

Figure 1 compares the number of reports by age group and sex. The largest number of AEFI reports involved adults (128 reports), followed by the elderly (39 reports), infants (27 reports), adolescents (14 reports) and children (12 reports). Throughout 2023, the number of reports concerning females (134 reports; 50.8%)

exceeded those concerning males (91 reports; 34.4%). In 39 AEFI reports (14.8%), the sex of the persons remained unknown. In 44 case reports (16.6%), the age group of the patients was not recorded.

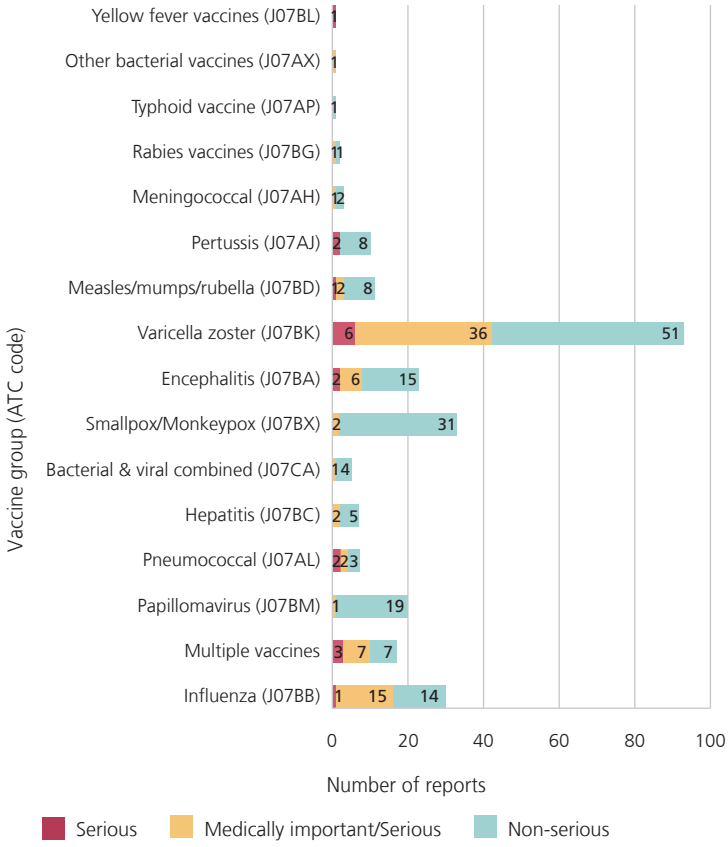

Figure 2: Number of reports by vaccine group (ATC code) and seriousness, 2023

Figure 2 shows the number of spontaneous AEFI reports by vaccine group (ATC code) and seriousness. Generally, a safety report is assessed as "serious" if it involves an adverse event leading to death, hospitalisation or prolongation of an existing hospitalisation, if it was life-threatening or 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 264 spontaneous reports received in 2023, 169 (64%) were "non-serious", 77 (29.2%) included only medically important events and 18 (6.8%) of the reports involved AEFIs with serious consequences.
Generally, by considering all vaccines in 2023, the relative frequency (percentage) of "serious" including "medically important" cases taken together (95 reports; 36%) was quite similar to 2022 (37.3%) and higher than in 2021 (32.1%).

Case reports where several (n >1) different vaccines were administered and were reported relating to suspected AEFIs are shown in Figure 2 as "Multiple vaccines".

Similarly to 2022, during 2023 a higher number of cases was submitted relating to the herpes zoster vaccination, which are shown in Figure 2 as ATC code "Varicella zoster (J07BK)", and to the new monkeypox vaccination, shown in Figure 2 as "Smallpox/Monkeypox (J07BX)". The majority of these case reports were assessed as "non-serious" for the herpes zoster vaccines (51 of 93 cases; 54.8%), and almost all reports relating to smallpox/monkeypox vaccination (31 of 33 cases in 2023) included only "non-serious" AEFIs.

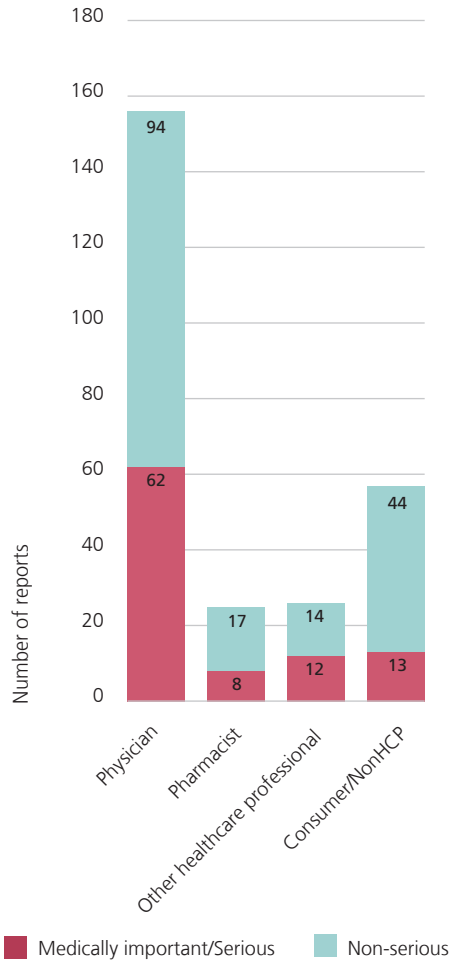

Figure 3: Number of AEFI reports by reporter qualification and seriousness, 2023

Figure 3 shows the number of Swiss AEFI reports in 2023 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 number of AEFI reports (156 of 264), including a higher number of reports assessed as "serious" or "medically important" (62 of 156 reports). Notably, consumers/patients submitted the second-highest number (57) of non-COVID AEFI reports to Swissmedic during 2023.

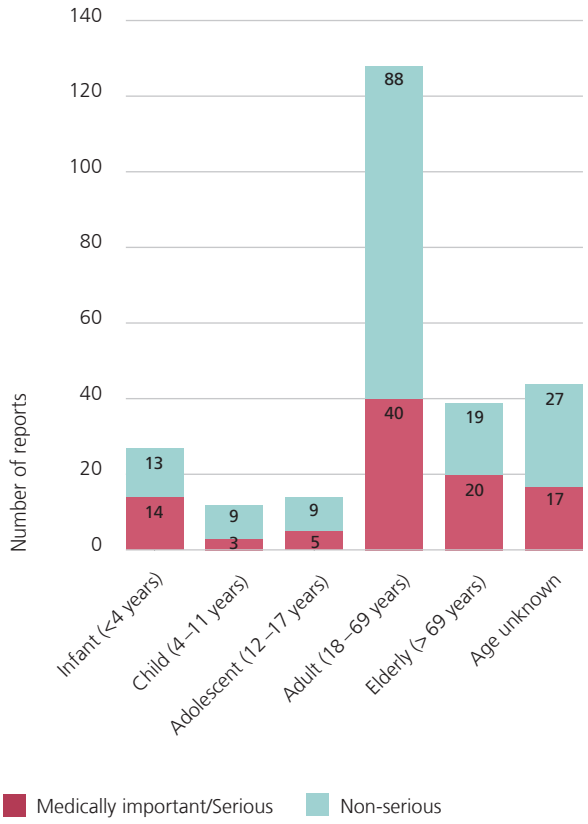

Figure 4: Number of AEFI reports by age group and seriousness, 2023

Figure 4 shows the number of spontaneous AEFI reports by age group and seriousness. It is evident that the highest number of "serious" or "medically important" cases (40 of 128 AEFI reports in total) were recorded in the "adults" age group, followed by the elderly (20 of 39 reports), infants (14 of 27 reports), adolescents (5 of 14 reports) and children (3 of 12 reports).

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AEFI reports received by Swissmedic in 2023 following COVID-19 vaccinations

In Switzerland, the COVID-19 vaccine rollout continued during 2023; however, Swissmedic received far fewer reports of suspected adverse reactions in this year (727 cases) compared to the first two years of the immunisation campaign.

On 24 February 2023, Swissmedic published a new "**Update Report of suspected adverse reactions to COVID-19 vaccines in Switzerland**", ("Update 29"); (1). Similarly to previous editions, this report 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.

This Update Report includes statistical data (overall figures), the presentation and ranking of suspected reactions by individual vaccines and by vaccination doses, as well as updated information from Swissmedic on particular safety aspects of COVID-19 vaccines (1).

Altogether, the reports of adverse reactions received and analysed 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, published Swiss product information texts (2).

The most recent (additional) cumulative safety update on COVID-19 vaccines was published online by Swissmedic on 5 July 2024 (3). Among other topics, cases of longer-lasting symptoms with a temporal relationship to a vaccination against COVID-19 are addressed in this report. Swissmedic evaluates such reports thoroughly, continually reviews the latest drug safety findings, follows the scientific literature and works in close contact with international regulatory authorities.

References

1
Reports of suspected adverse reactions to COVID-19 vaccines in Switzerland – Update 29; Swissmedic Website, 24.02.2023

2
AIPS (www.swissmedicinfo.ch)

3
Reports of suspected adverse reactions to the COVID-19 vaccines in Switzerland; Swissmedic Website, 05.07.2024

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Vigilance for veterinary medicinal products

Cedric R. Müntener

Veterinary Medicines Division, Swissmedic, Bern, Switzerland

Complete report:

Vigilance for veterinary medicinal products – Annual report 2023

Adverse reactions reported in 2023
A summary of the main points

- 462 reports, increase compared with 2022: 9.5%
- Most frequently affected species: 273 dogs, 115 cats, 41 cattle, 14 horses
- Most frequent medicinal product types: antiparasitics (142 reports), immunological veterinary medicinal products (111), hormone products (82), products to modulate the nervous system (38), anti-infectives (12)
- 125 cases of suspected lack of efficacy, largely for antiparasitics and hormone products
- 54 cases passed on by Tox Info Suisse
- 32 cases of accidental ingestion of flavoured tablets by dogs/cats
- 104 cases of human exposure to veterinary medicinal products
- 10 signal procedures initiated

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Information on the Swissmedic website

Pharmacovigilance in the spotlight

Learning from adverse reaction reports – cases from pharmacovigilance

22.11.2024
Risk of product mix-up with various insulin products

22.07.2024
Isotretinoin and teratogenicity

01.11.2024
Microscopic colitis associated with sertraline and duloxetine

28.05.2024
Daptomycin and eosinophilic pneumonia

23.09.2024
SonoVue® (sulphur hexafluoride) and anaphylactic reactions

03.05.2024
Medicinal product interactions of Paxlovid (nirmatrelvir/ritonavir) with certain immunosuppressants

30.08.2024
Drug-induced suicidality

22.04.2024
Oral methotrexate and risk of unintentional overdose due to medication errors

Reporting of ADRs by healthcare professionals

Explainer video

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Healthcare Professional Communication

Some links are available in German/French only

22.11.2024
DHPC – Eylea® (aflibercept)
Information zum Füllvolumen von Eylea® 8 mg/0.07 ml, Injektionslösung in Durchstechflasche

14.11.2024
DHPC – Rhophylac® (immunoglobulinum humanum anti-D)
Wichtige Mitteilung

15.10.2024
DHPC – Comirnaty® JN.1 (bretovameranum)
Wichtige Mitteilung zu Auslieferung von aufgetauter Ware

10.10.2024
DHPC – Vincristin-Teva® (vincristini sulfas)
Vorübergehender Lieferengpass von Vincristin-Teva

24.09.2024
DHPC – Spikevax JN.1 (mRNA-1273.167), Dispersion zur Injektion
Versand von aufgetauter Ware

17.09.2024
DHPC – Glatirameracetat (Copaxone®, Glatiramyl®)
Anaphylaktische Reaktionen können Monate bis Jahre nach Beginn der Behandlung auftreten

16.09.2024
DHPC – Ceprotin 1000 IE, Pulver und Lösungsmittel zur Herstellung einer Injektionslösung
Veraltete Versionen der Packmaterialien und der Fachinformation bei mehreren Chargen

12.09.2024
DHPC – Mögliche Beeinträchtigung der Sterilität der beiliegenden Nadelpakete
Sicherheitsrelevante Informationen

26.08.2024
DHPC – Zemplar (paricalcitolum)
Translation error in the French text of the package leaflet

16.08.2024
DHPC – Measures to minimise risks from solutions for infusion containing hydroxyethyl starch (HES)
Important information on the revised information for healthcare professionals for Voluven 6% balanced, solution for infusion, and the revised training material as part of the controlled access programme (CAP)

13.08.2024
DHPC – Rabipur (virus rabiei inactivatus)
Berichte über Partikel nach der Rekonstitution - Empfehlungen zur Minimierung des Risikos für Partikel

19.07.2024
DHPC – Nuwiq (simoctocogum alfa)
Wichtige Information: Packungsbeilage entspricht nicht der aktuellen Version

16.07.2024
DHPC – Privigen, Infusionslösung (immunoglobulinum humanum normale)
Bei einer Stabilitätsprüfung von Privigen® 50 mL, wurde festgestellt, dass vereinzelte Chargen des Produkts Flocken zeigten

27.06.2024
DHPC – Vabysmo® (Faricimab)
Riss in der Verpackung der Transferfilterkanüle, die dem Vabysmo Kit beigelegt ist

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Announcements

13.11.2024
Swissmedic warns: Illegal "Slimming preparations" and "detox products" can make you ill
Illegal slimming tablets or teas and detox products can contain undeclared harmful pharmaceutical substances such as sibutramine

11.11.2024
Swissmedic podcast – focus on therapeutic products
Alex Josty im Interview mit Ruth Mosimann, Einheitsleiterin Kontrolle illegale Arzneimittel

05.11.2024
Combating designer drugs: Further psychoactive substances prohibited
Health risks of designer drugs: new psychoactive substances added to Narcotics List

01.11.2024
Clinical trials: Revised implementing regulations of the Human Research Act
The amended ordinances relating to the Human Research Act enter into force today

17.10.2024
Delivery of medicinal products to conflict areas
Exports of medicinal products to conflict regions should be organised by established aid organisations

15.10.2024
Changes to the guidance documents Fast-track authorisation procedure and Temporary authorisation for human medicinal products
Optimisation of the application procedure for the implementation of a fast-track authorisation procedure and the implementation of temporary authorisation

07.10.2024
Swissmedic inspections: Potential for improvement in hospitals
Annual report

01.10.2024
The "Public Summary SwissPAR" is now called the "Summary report on authorisation"
Swissmedic is changing the name of the "Public Summary SwissPAR" to the "Summary report on authorisation"

20.09.2024
Unvollständige Angaben auf perforierten Blistern
Überprüfung der Druckvorlagen von perforierten Blistern

17.09.2024
International meeting of the Permanent Forum on International Pharmaceutical Crime
International trends were discussed and the collaboration was strengthened

16.09.2024
New implementing regulations apply as of 1 November 2024
Swissmedic publishes instructions on the procedure for submitting applications

13.09.2024
Bluetongue: no authorised vaccines against serotype 3 in Europe
Swissmedic has not received any relevant applications. The assessment of such applications will be given top priority

03.09.2024
Haemovigilance annual report 2023
Evaluation of haemovigilance reports in 2023

01.09.2024

Electronic data sets from pivotal bioequivalence studies

From 1 September 2024, Swissmedic is accepting electronic data sets from pivotal bioequivalence studies for applications for new authorisation of human medicinal products with known active substances without innovation

01.09.2024

Mobile technologies – Submission of films as additional information regarding the safety, efficacy and quality of medicinal products

From 1 September 2024, Swissmedic will be accepting the submission of films as part of the authorisation of QR codes

01.09.2024

SEND data sets for new authorisation applications for human medicinal products with new active substances

From 1 September 2024, Swissmedic is accepting SEND data sets for applications for new authorisation for human medicinal products with new active substances

01.09.2024

Combined studies

New forms and a new information sheet for submissions to Swissmedic

01.09.2024

Submission of accompanying documentation for applications for authorisation and variation for human medicinal products

Additional accompanying documentation for applications for authorisation and variation for medicinal products can now be submitted directly via the eGov portal with immediate effect

01.09.2024

Changes to the guidance document Time limits for authorisation applications

To standardise practice, written notification regarding the "Doc. OK" milestone will in future no longer be sent following a formal objection

28.08.2024

Update – Warning about supposedly herbal products

Swissmedic is issuing an urgent warning regarding slimming products and other supposedly natural products

14.08.2024

Update of information sheet on non-standardised medicinal products and on the list of non-standardised medicinal products and medicinal product groups with a manufacturing process subject to mandatory authorisation according to Annex 3 TPLO

The revised information sheet is valid with effect from 01 July 2024

02.08.2024

Swissmedic authorises dengue fever vaccine

Qdenga (powder and solvent for solution for injection in a pre-filled syringe) can be placed on the market in Switzerland

24.07.2024

Benchmarking study 2023

International comparison of Swiss authorisation times

12.07.2024

Public consultation for ICH Guideline M14 launched in Switzerland

Swissmedic launches the public consultation on Guideline M14 "Bioequivalence for Immediate-Release Solid Oral Dosage Forms General principles on plan, design, and analysis of pharmacoepidemiological studies that utilize real-world data for safety assessment of medicines" of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), with a deadline of 30 August 2024 for comments

05.07.2024

Reports of suspected adverse reactions to the COVID-19 vaccines in Switzerland

COVID-19 vaccinovigilance reports up to the end of June 2024

02.07.2024

Update to the forms New authorisation of human medicinal products and Variations and authorisation extensions HAM

Swissmedic clarifies in the authorisation forms how to describe the indication of the medicinal product and simplifies the standardised consents for sharing information with partner authorities

01.07.2024

TPLRO, TPLO: Update of annexes

Nachführung der Anhänge AMZV und VAZV

01.07.2024

Ordinance 3 on Measures to Combat the Coronavirus (COVID-19) ceases to apply as of 30 June 2024

As there will no longer be any legal basis for doing so, Swissmedic will cease granting exceptions with regard to the authorisation and importing of medicinal products for the treatment or prevention of COVID-19

01.07.2024

Expiry of COVID-19 Ordinance 3

Dispensing of coronavirus self-tests still possible from 1 July 2024

01.07.2024

Standardisation of practice on publication of indications in Swiss Public Assessment Report

The new practice and the revised Guidance document SwissPAR come into effect on 1 July 2024

19.06.2024

Meeting of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)

Continued advancement of ICH's global harmonisation efforts in Fukuoka, Japan

17.06.2024

Changes to declaration of goods for the export of medicinal products (including clinical trials) and narcotics made to the Federal Office for Customs and Border Security FOCBS

Changes to the declaration of medicinal products and narcotics

15.06.2024

Simplification of requirements for renewed authorisation of medicinal products

Swissmedic has simplified the requirements for renewed authorisation of medicinal products

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