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Vigilance News

Edition 27 – November 2021

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

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Since 1 July 2021 only electronic reports are accepted.

Report of an adverse drug reaction (ADR)

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

Online reporting portal ElViS

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Editorial

Dear Reader

As already noted in the previous issue of Swissmedic Vigilance News, vigilance with regard to COVID-19 vaccines remains a focal area for drug safety. The COVID-19 vaccines currently authorised in Switzerland are Comirnaty® (tozinameran, authorisation holder Pfizer AG, Zurich), Spikevax® (COVID-19 mRNA vaccine (nucleoside modified), authorisation holder Moderna Switzerland GmbH, Basel) and COVID-19 Vaccine Janssen (COVID-19 vaccine (Ad26.COV2-S [recombinant]), authorisation holder Janssen-Cilag AG, Zug).

Adverse events following immunization (AEFI) are being closely monitored, both in Switzerland and internationally. The article "COVID-19 pandemic: International cooperation in the area of pharmacovigilance" explains how exchange and discussion between the drug regulatory authorities works.

AEFI are recorded in the national vigilance systems and evaluated so that potential risks can be identified in good time and possible risk-minimising measures introduced.

Continuous analysis of the reports submitted with AEFI is particularly important in long-term data and in the case of previously unknown, rare or severe AEFI. Swiss case reports on "Myocarditis/pericarditis in association with COVID-19 immunisation" are presented in an article by way of an example.

AEFI are reported by both healthcare professionals and patients. As Swissmedic received reports of possible menstrual disorders following COVID-19 vaccination in connection with the COVID-19 vaccine reports, we asked Prof. Michael von Wolff (Consultant in the Department of Gynaecological Endocrinology and Reproductive Medicine, University Women's Hospital, Inselspital Bern) to write a guest article on this issue. He elucidates, among other things, that COVID-19 vaccination has no demonstrable effects on fertility.

The effects of COVID-19 infection and vaccination on pregnant women are explained in another article: "SARS-CoV-2: Recent study findings and recommendations for vaccination of pregnant women".

To obtain current findings on the COVID-19 vaccines on an ongoing basis, we are continuing to encourage healthcare professionals to be vigilant and report AEFI (via the Electronic Vigilance System, ElViS).

You can find a summary of the reports submitted and evaluated in 2020 in the statistical analyses for pharmacovigilance (human medicinal products), vaccinovigilance (vaccines), haemovigilance (blood transfusions) and monitoring of veterinary medicines.

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

Eva Eyal

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Please send any suggestions or feedback on this issue of Swissmedic Vigilance News to:
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Drug safety and signals

SARS-CoV-2: Recent study findings and recommendations for vaccination of pregnant women

For reasons of safety, pregnant women were not permitted to take part in clinical trials investigating the efficacy and safety of the vaccines against COVID-19.

7,809 pregnant women and 2,886 non-pregnant women (the control group) were enrolled in a major prospective cohort study in the USA (1). More than 99% of the subjects were given the Pfizer/BioNTech BNT162b2 vaccine or the Moderna mRNA-1273 vaccine. Tolerance of the two mRNA vaccines was good in the pregnant group and comparable to that in the non-pregnant group, thus confirming the results of a previous study (2).

An analysis performed by the largest health insurance provider in Israel showed that the mRNA vaccine BNT162b2 (Comirnaty® from Pfizer/BioNTech) used in that country had a protective effect of 96% in pregnant women (3). The protective effect is therefore at a level similar to that in other groups within the population.

In Israel, 38,836 pregnant women insured by Clalit Health Services (CHS), the country's largest health insurance provider, had been vaccinated with BNT162b2 by 3 June 2021. A team of researchers from the Clalit Research Institute in Tel Aviv compared 10,861 vaccinated pregnant women with the same number of unvaccinated pregnant women.

They calculated a protective effect of 96% (95% confidence interval: 89–100%) from the 28th day (7 days after the second dose). The frequency of symptomatic infections was reduced by 97% (91–100%). The rate of hospitalisation was 89% lower (43–100%). No deaths occurred. The results refer to the Alpha variant of SARS-CoV-2, the dominant infectious strain in Israel while the study was being carried out.

When weighing the arguments for and against vaccination, the main factor to consider is that the risks associated with severe COVID illness during pregnancy are far greater than those associated with vaccination. This is demonstrated impressively by a recent study undertaken by a research team at the University of California (4). Of 869,079 women who gave birth in 499 medical centres in the USA, 18,715 (2.2%) had COVID-19 and 850,364 (97.8%) did not.

The likelihood of premature birth was greater in women with COVID-19 (3,072 [16.4%] versus 97,967 [11.5%]; $P < 0.001$). Women who gave birth with COVID-19 were significantly more likely to be admitted to an intensive care unit than women who did not have COVID-19 (977 [5.2%] versus 7,943 [0.9%]; odds ratio [OR] 5.84 [95% CI, 5.46-6.25]; $P < 0.001$), were more likely to require intubation and mechanical ventilation (275 [1.5%] versus 884 [0.1%]; OR 14.33 [95% CI, 12.50-16.42]; $P < 0.001$) and were more likely to die in hospital (24 [0.1%] versus 71 [<0.01%]; OR 15.38 [95% CI, 9.68-24.43]; $P < 0.001$).

In summary, pregnant women who have COVID-19 when they give birth have a 10-fold greater risk of dying in the perinatal period than healthy pregnant women, they require intensive care nearly six times more frequently and their risk of being intubated and ventilated is 15 times greater.

Since pregnant women have a substantially greater risk of severe illness with COVID-19, COVID-19 vaccination with the authorised

mRNA vaccines is advised in the Swiss vaccination recommendations for all women before and during pregnancy (from the second trimester) and while breastfeeding. A growing body of evidence shows that the benefit of COVID-19 vaccination during pregnancy substantially outweighs the possible risks (5). Similar recommendations also exist in other countries (6, 7).

References

(1) Alisa Kachikis, MD, MS; Janet A. Englund, MD; Michael Singleton, PhD et al., Short-term Reactions Among Pregnant and Lactating Individuals in the First Wave of the COVID-19 Vaccine Rollout, JAMA Network Open. 2021;4(8); DOI: 10.1001/jamanetworkopen.2021.21310

(2) Tom T. Shimabukuro, M.D., Shin Y. Kim, M.P.H., Tanya R. Myers, Ph.D. et al., Preliminary Findings of mRNA Covid-19 Vaccine Safety in Pregnant Persons, N Engl J Med 2021; 384:2273-2282; DOI: 10.1056/NEJMoa2104983

(3) Effectiveness of the BNT162b2 mRNA COVID-19 vaccine in pregnancy, Noa Dagan, Noam Barda, Tal Biron-Shental et al., Nature Medicine 07.09.2021 (Effectiveness of the BNT162b2 mRNA COVID-19 vaccine in pregnancy | Nature Medicine)

(4) Characteristics and Outcomes of Women With COVID-19 Giving Birth at US Academic Centers During the COVID-19 Pandemic, Justine Chinn, Shaina Sedighim, Katharine A. Kirby et al., JAMA Netw Open 11.08.2021 (Characteristics and Outcomes of Women With COVID-19 Giving Birth at US Academic Centers During the COVID-19 Pandemic | Pediatrics | JAMA Network Open | JAMA Network)

(5) Impfempfehlung für mRNA-Impfstoffe gegen Covid-19 (Stand 14.09.21) Bundesamt für Gesundheit (BAG) und Eidgenössische Kommission für Impffragen (EKIF)

(6) New CDC Data: COVID-19 Vaccination Safe for Pregnant PeopleMedia Statement, 11.08.2021 (New CDC Data: COVID-19 Vaccination Safe for Pregnant People | CDC Online Newsroom | CDC)

(7) Pressemitteilung der STIKO zur Aktualisierung der COVID-19-Impfempfehlung für Schwangere und Stillende (10.09.2021) (RKI - Empfehlungen der STIKO - Pressemitteilung der STIKO zur Aktualisierung der COVID-19-Impfempfehlung für Schwangere und Stillende (10.9.2021)

Thomas Schwartz, MD

Safety of Medicines division, Swissmedic

Myocarditis/pericarditis in association with COVID-19 immunisation: Case reports received by Swissmedic

The vaccines being used against the SARS-CoV-2 virus include the first mRNA-based vaccines approved for use in humans (Pfizer/BioNTech and Moderna), and continuous evaluation of their safety is critical. By the end of March 2021 Swissmedic received the first report of suspected myocarditis in temporal association with a vaccination in a 35-year-old male. Following several cases reported in Israel (1), these possible reactions following COVID-19 immunisation became an emerging safety issue in international pharmacovigilance. In Switzerland, healthcare professionals were notified initially on 4 June 2021 about the suspicion and the ongoing evaluation of a potential association between mRNA vaccines and cases of myocarditis (2). For this article, an assessment of the case reports in the Swiss national pharmacovigilance database regarding myocarditis following administration of one of the COVID-19 vaccines was performed.

As of 13 August 2021, there were 95 cases reporting the MedDRA Preferred Term (PT) "Myocarditis" (n=73) or "Pericarditis" (n=22) for all COVID-19 vaccines and these were included in the analysis. Notably, in some (n=5) of the cases with PT "Myocarditis", pericardial involvement was also recorded (PT: "Pericardial effusion"). Of all cases, 81 were reported in association with the COVID-19 vaccine from Moderna and 13 cases following immunisation with the Pfizer/BioNTech vaccine. In one case report, the manufacturer of the vaccine was not specified.

For both COVID-19 vaccine reports taken together, there was a statistically significant increase in observed reports of myocarditis/pericarditis in younger males compared to the calculated expected number of such reports, taking into account the background incidence (4). Furthermore, the observed/expected ratio was consistently higher in several age groups of male patients below 40 years: 10-19 years, 20-29 years and 30-39 years.

In our case series, the diagnosis of myocarditis/pericarditis – weighed by criteria of the US CDC (Table 1); (3) – was assessed in the vast majority of cases (n= 90, 94.7%) either as "probable" (n=57), or as "confirmed" (n=33). In most of these case reports, typical clinical symptoms as well as test results specific for myocarditis (such as chest pain, dyspnoea, palpitations, elevated troponin, consistent MRI-findings) and/or pericarditis (such as abnormal ECG findings, pericardial effusion on echocardiogram or MRI) were recorded.

Table 1. Diagnosis of myocarditis/pericarditis in the reviewed case series

	Total cases	Confirmed cases	Probable cases
Myocarditis (PT)	73	27	43
Pericarditis (PT)	22	6	14
All cases	95	33	57

All cases were reported as serious (n=95, 100%). In 86 cases (89.5%), the symptoms led to hospitalisation and seven cases (7.4%) were assessed as "life threatening". In one single case report, the outcome of myocarditis was reported as fatal.

Based on all cases of myocarditis/pericarditis examined, the ages of patients ranged between 16 and 88 years (mean=39 years). The fraction of patients which were hospitalised was between 18 and 73 years old (mean=44 years).

In line with the known disease epidemiology of myocarditis in the general population (4), the events occurred more frequently in

males (n=79, 83%) and in younger adults, with 60 (63% of total) reports in patients between 18 and 44 years old. Three (3%) cases occurred in adolescent males between 16 and 17 years old.

According to the information reported, there were more cases after the second vaccine dose (n=51, 54%) as compared to the first dose administered (n=33, 35%). The mean time-to-onset (TTO) was 6.7 days (ranging from < 1 day to 26 days) and there seemed to be a more rapid onset of symptoms after the second dose (mean TTO=3.7 days) as compared with the first dose (mean TTO=11.3 days).

The clinical course of myocarditis/pericarditis was mostly mild to moderate following medical treatment, as patients were discharged after a few days of hospitalisation. With the exception of the fatal case mentioned below, none of the cases clearly mentions intensive care treatments; however, this information is not systematically recorded in the case reporting forms. The outcome was reported as "recovered/resolved" (n= 23, 24%) or "recovering/resolving" (n=39, 41%). In 19 (20%) cases, the outcome was "not recovered" at the time of reporting, and in 13 cases (13.7%) the outcome of the pericarditis/myocarditis remained "unknown".

The only report with a "fatal" outcome concerned an older male patient with serious renal and cardiac underlying diseases. He developed severe cardiac failure 26 days after the first dose of COVID vaccine. The clinical course was unfavourable, with cardiogenic shock leading to death despite all intensive therapeutic measures applied in the hospital. The autopsy report contains several findings confirming recent myocarditis, most probably of viral origin.

Generally, the underlying pathomechanism of any possible causal association between COVID-19 immunisation and myocarditis is currently unclear. It could theoretically include an interaction of the spike protein produced by the vaccine with myocardial cells, and/or the inflammatory response to the vaccine (5).

Despite uncertainties about the mechanism, the globally available evidence of a causal association between rare cases of myocarditis and the mRNA vaccines is currently accumulating. Consequently, this possible risk has recently been included in the product information and healthcare professionals have been notified via a Healthcare Professional Communication (HPC) (6).

As our local case numbers are still rather low, it is not possible to estimate accurately the incidence of myocarditis from this case series. We received more reports of myocarditis in association with Spikevax® than with Comirnaty®. However, we believe that comparisons of the two vaccines based only on spontaneous reports are methodogically questionable and we cannot exclude that this difference derives from the higher usage of Spikevax® in Switzerland. Therefore, possible differences in the risk of myocarditis should be investigated further on the basis of data from other studies in larger populations. Furthermore, regarding the later clinical evolution and outcome of such cases, longer-term investigations including well-designed clinical studies are of high impact.

References

(1) Abu Mouch S, Roguin A, Hellou E, Ishai A, Shoshan U, Mahamid L, Zoabi M, Aisman M, Goldschmid N, Berar Yanay N. Myocarditis following COVID-19 mRNA vaccination. Vaccine. 2021 Jun 29;39(29):3790-3793. doi: 10.1016/j.vaccine.2021.05.087. Epub 2021 May 28. PMID: 34092429; PMCID: PMC8162819

(2) Investigation of reports of myocarditis in connection with COVID-19 mRNA vaccines

(3) CDC-Overview of Myocarditis and Pericarditis: www.cdc.gov/vaccines/acip/meetings/downloads/slides-2021-06/02-COVID-Oster-508.pdf

(4) Kang M, An J. Viral Myocarditis. In: StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2021, StatPearls Publishing LLC.; 2021.

(5) Talotta R. Do COVID-19 RNA-based vaccines put at risk of immune-mediated diseases? In reply to "Potential antigenic cross-reactivity between SARS-CoV-2 and human tissue with a possible link to an increase in autoimmune diseases" Clin Immunol. 2021;224.

(6) DHPC – mRNA-Impfstoffe gegen COVID-19 (COVID-19 Vaccine Moderna und Comirnaty) (swissmedic.ch)

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Menstrual disorders after COVID-19 vaccination – facts, possible causes, unanswered questions

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The media are reporting widely on menstrual disorders in women who have been vaccinated against COVID-19. With this in mind, this article seeks to address the facts, the possible causes and the unanswered questions.

The facts

Regulation of menstruation

Menstruation is a unique process in which every four weeks a complex tissue, the endometrium, is built up over an approximately two-week period under the influence of oestrogens, then transformed by progesterone and finally, if pregnancy does not occur, shed in response to a drop in the levels of both hormones. Oestrogens and progesterone are formed mainly in the ovaries under the influence of hormones released by the pituitary gland.

The endometrium consists of a large number of different cells, including various immune cells. Both the implantation of the embryo and menstrual bleeding display immunological parallels to the cellular processes involved in an infection. The entire hormonal system that regulates the ovaries and the endometrium is sensitive and can be disrupted by many factors such as infections, stress and changes in the diurnal rhythm (e.g. jet lag).

Definition, causes and frequency of menstrual disorders

Normal is defined as follows: (1)

- menstruation that occurs every 24–38 days,
- a cycle length that varies by 2-20 days,
- bleeding that lasts between 4.5 and 8 days,
- a volume of menstrual blood between 5 and 80 ml,
- spotting and light bleeding around the time of ovulation.

In other words, it is normal for the bleeding pattern and intensity to vary.

Deviations from these normal values, i.e. menstrual disorders, are defined, for example, as oligomenorrhoea (bleeding that occurs rarely), amenorrhoea (absence of menstruation for three months), hypermenorrhoea (increased blood volume), etc.

Menstrual disorders, also referred to as abnormal uterine bleeding, are relatively common and can be caused by dozens of different factors (1). It is not possible to generalise about the frequency of these disorders since there are so many different causes and because it is difficult to distinguish them from normal fluctuations in bleeding patterns.

Effects of COVID-19 vaccination on fertility

Several publications have shown that COVID-19 vaccination has no demonstrable effect on fertility (2–5). This is significant in itself but also because pregnancy (and the menstrual cycle itself) requires undisrupted regulation of the ovaries and the endometrium.

Reports of menstrual disorders

By mid-October 2021, the British spontaneous reporting system had received some 40,000 reports of suspected adverse reactions that were classified as "menstrual disorders (period problems) and unexpected vaginal bleeding" (6).

By the start of October, Swissmedic had received 301 reports of menstrual disorders. Most of these reports concerned the Spikevax® vaccine from Moderna (230 of 310

reports, 74%) which, however, is used much more widely in Switzerland than Comirnaty® from Pfizer/BioNTech. The reports were submitted largely by the affected women (275 of 310 reports, 89%), with only a relatively small number submitted by doctors and pharmacists. The median age of the women was 37 years. Their ages ranged from 18–57 years, so post-menopausal bleeding was also documented.

The majority of the cases reported were classified as "not serious", and in no case was treatment in hospital required as a result of the reaction. The most commonly reported events were heavier and more frequent bleeding, intermenstrual bleeding and pain, followed by less frequent menstruation and absence of menstruation.

From a gynaecological and endocrinological point of view, it is difficult to evaluate many of the reports in qualitative terms. In many cases it is not clear whether the changes observed and reported by the women concerned were within the normal variability of their bleeding pattern and intensity. Since menstrual disorders are in any case so common, and in the absence of a comparator group for the spontaneous reports, it is also difficult to provide a quantitative assessment.

The outcome of the reactions was reported as "recovered" in 136 of 310 cases (43.9%), as "not recovered" at the time the report was submitted in 89 cases (29%) and as "unknown" in 76 cases (24.5%). 27 cases (8.7%) were reported as "recovering" and 1 as "recovered with sequelae". In the majority of the reports, other reactions to the vaccination, most commonly fever, headache, fatigue, chills and nausea, were mentioned in addition to menstrual disorders.

Possible causes

If COVID-19 vaccines are indeed capable of inducing menstrual disorders, the following are the most likely causes:

1. Short-term stress-related changes in the hormonal regulation of the ovaries,
2. Short-term effects on the immune system of the endometrium.

Re. 1., a Turkish cross-sectional study (7) investigated 952 women whose menstruation was regular prior to the pandemic. During the pandemic nearly 30 per cent of them developed an irregular menstrual cycle. The likelihood of an irregular cycle developing was statistically associated with the pandemic-related intensity of anxiety, stress and depressive symptoms.

Although this study does not permit any conclusions to be drawn about COVID-19 vaccination as such, it does illustrate the great susceptibility of the menstrual cycle to stress, here specifically during the pandemic. It is therefore conceivable that vaccination is an additional stress factor that destabilises menstruation.

Re. 2., COVID-19 infection is associated with powerful stimulation of the immune system. By definition, COVID-19 vaccination also stimulates the immune system. It is therefore conceivable that the sensitive immune system of the endometrium is briefly modified by vaccination, thus potentially leading to menstrual disorders. However, no systematic investigations of the effect of COVID-19 vaccination on endometrial function have been carried out to date. A study designed specifically to investigate this relationship is currently ongoing at the Johns Hopkins Department of Gynecology and Obstetrics in the USA (9).

Basically, however, it can be assumed that the potential effect of a vaccine can only be very small since COVID-19 vaccination is not

associated with reduced fertility (2–5). Relevant functional impairment of the ovaries and endometrium is not compatible with pregnancy.

Unanswered questions

The spontaneous reports submitted to date do not permit a valid qualitative and quantitative assessment of the effect of the various COVID-19 vaccines on the development of menstrual disorders.

The following aspects of COVID-19-induced menstrual disorders are therefore still unanswered and require further investigation:

- Frequency
- Intensity
- Duration
- Causes

Although it has not yet been demonstrated scientifically that COVID-19 vaccines per se cause menstrual disorders, the large number of documented reports suggests that this type of effect may occur in some women. From an immunological and clinical standpoint, however, it can be assumed that disorders of this kind, when they do occur, are only transient and in the vast majority of cases are of no clinical relevance.

Since menstrual disorders, no matter what their cause, can nonetheless be clinically relevant in isolated cases and may be symptomatic of other diseases, women with new, severe or persistent menstrual disorders or post-menopausal bleeding should consult their doctor.

References

(1) Gynäkologische Endokrinologie und Reproduktionsmedizin, Hrsg.: M. von Wolff & P. Stute, Schattauer-Verlag, 2013.

(2) Morris RS. SARS-CoV-2 spike protein seropositivity from vaccination or infection does not cause sterility. F S Rep. 2021;2:253-255.

(3) Orvieto R, Noach-Hirsh M, Segev-Zahav A, Haas J, Nahum R, Aizer A. Does mRNA SARS-CoV-2 vaccine influence patients' performance during IVF-ET cycle? Reprod Biol Endocrinol 2021;19:69.

(4) Bentov Y, Beharier O, Moav-Zafrir A, et al. Ovarian follicular function is not altered by SARS-Cov-2 infection or BNT162b2 mRNA Covid-19 vaccination. medRxiv 2021:2021.04.09.21255195. [Preprint.]

(5) Safrai M, Rottenstreich A, Herzberg S, Imbar T, Reubinoff B, Ben-Meir A. Stopping the misinformation: BNT162b2 COVID-19 vaccine has no negative effect on women's fertility. medRxiv 2021:2021.05.30.21258079. [Preprint.]

(6) https://www.gov.uk/government/publications/coronavirus-covid-19-vaccine-adverse-reactions/coronavirus-vaccine-summary-of-yellow-card-reporting

(7) Takmaz T, Gundogmus I, Okten SB, Gunduz A. The impact of COVID-19-related mental health issues on menstrual cycle characteristics of female healthcare providers. J Obstet Gynaecol Res. 2021;47:3241-3249.

(8) Grigoryan L, Pulendran B. The immunology of SARS-CoV-2 infections and vaccines. Semin Immunol. 2020;50:101422.

(9) https://www.hopkinsmedicine.org/news/newsroom/news-releases/covid-19-news-study-to-investigate-impacts-of-covid-vaccines-on-menstruation.

Regulatory

COVID-19 pandemic: International cooperation in the area of pharmacovigilance

Swissmedic has been committed to international cooperation for many years. Research and development in the health sector are constantly producing new findings that need to be incorporated into the regulatory environment. Both bilaterally and multilaterally, Swissmedic is therefore committed to harmonising or aligning the requirements for the regulation of therapeutic products, thereby contributing both to faster access to new, innovative medicinal products and to more efficient market surveillance for improved patient safety.

The COVID-19 pandemic strengthened cooperation between authorisation and supervisory authorities and international organisations working with medicinal products and medical devices in many ways. In this article, three collaborations will be highlighted: the International Coalition of Medicines Regulatory Authorities (ICMRA) on Heads of Agency level, the Access Consortium, as well as the European Medicines Agency (EMA) "OPEN" initiative.

The International Coalition of Medicines Regulatory Authorities

The International Coalition of Medicines Regulatory Authorities (ICMRA) is an initiative of more than 30 regulators from all over the world and the World Health Organization (WHO) as an observer. ICMRA promotes cooperation between medicinal product regulatory authorities and, in particular, coordinated responses to crisis in the interests of safeguarding public health. From the onset of the pandemic, ICMRA held regular calls and organised workshops on specific regulatory issues, including topics on pharmacovigilance. The ICMRA COVID-19 Vaccines Pharmacovigilance Network was initiated, a platform used to discuss, amongst other issues, adverse events related to vaccines and medicines and to share information about emerging safety issues, in order to take quick action to mitigate risks. ICMRA gave Swissmedic experts the possibility to exchange views with regulators from countries where vaccination campaigns were well advanced. Communication on adverse events to the public, anaphylaxis or myocarditis after vaccination with mRNA vaccines, vaccination in children and young adults or now extra doses or booster vaccines are amongst the topics that were discussed.

COVID-19 | International Coalition of Medicines Regulatory Authorities (ICMRA)

Access Consortium

The Access Consortium is a collaborative initiative of five authorities that regulate human medicines and other health products: Therapeutic Goods Administration (TGA), Australia, Health Canada, Health Sciences Authority (HSA) Singapore, Swissmedic and since January 2021, the UK Medicines and Healthcare products Regulatory Agency (MHRA). According to the Access Strategic Plan 2021-2024, the Access Consortium is committed to maximising collaboration by aligning regulatory and policy approaches, reducing duplication and facilitating our populations' access to high-quality, safe and effective health products.

During the pandemic, intensive dialogue on COVID-19 vaccines and treatments was established at management and expert levels. A subgroup of the New Active Substance (NAS) Working Group was launched: the COVID-19 Vaccines and Therapeutics Working Group,

dedicated to the discussion of regulatory requirements specific to the regulation of COVID-19 vaccines and therapeutics, for work-sharing and information-sharing on COVID-19 therapeutics and vaccines as well to enable an exchange on safety-related issues. With the consent of marketing authorisation holders, Swissmedic and its partner agencies held in-depth technical discussions on submitted dossiers as well as on labelling changes or planned Healthcare Professional Communications (HPC).

Information on the Access Consortium as well as on its statements related to the COVID-19 pandemic can be found at the following link: Access Consortium (swissmedic.ch).

Collaboration with the European Medicines Agency

Swissmedic also has the possibility of collaborating with the European Medicines Agency (EMA) in the "OPEN" initiative. The collaboration allows the involved regulators to share scientific expertise during the assessment of specific COVID-19 vaccine and therapeutic applications by having discussions on specific technical issues or by contributing to the work of EMA's human medicines committee (CHMP) and the COVID-19 EMA pandemic Task Force (COVID-ETF).

EMA COVID-19 assessments 'OPEN' to non-EU regulators | European Medicines Agency (europa.eu)

In addition, Swissmedic has the opportunity to attend the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) meetings as an observer where e.g. COVID-19 vaccine-related safety issues such thrombosis with thrombocytopenia syndrome (TTS) after vaccination with Vaxzevria® (formerly COVID-19 Vaccine AstraZeneca, not authorised in Switzerland) have been discussed extensively.

Concluding remarks

Taking into account assessments that have been performed by partner authorities and work-sharing are explicitly mentioned in Swissmedic's Strategic Objectives.

Swissmedic used both reliance and work-sharing in collaboration with partner agencies during the COVID-19 pandemic, taking independent decisions on approvals to conclude the assessment procedure as well as on any measures taken due to safety issues.

International collaboration was considered as highly valuable: just one day after the first COVID-19 vaccine was placed on the market, regulators got together to discuss adverse events that occurred.

The exchange with ICMRA and the WHO to discuss the regulatory framework, policies and pathways as well as deep dives that were organised and collaboration with the Access Consortium or the EMA were considered as most useful.

Dr Gabriela Zenhäusern

Management Services and International Affairs, Stakeholder Engagement

Statistical Review 2020

Pharmacovigilance: human medicines

Swissmedic records safety signals associated with medicinal products and vaccines on the basis of reports of suspected adverse drug reactions (ADR) from within Switzerland. If investigation confirms a new risk, Swissmedic initiates the necessary actions following international consultation. Within the pharmacovigilance network, direct reports of ADR from healthcare professionals and patients are evaluated by Swissmedic in cooperation with the six regional pharmacovigilance centres (RPVC) and recorded in the national database. Pharmaceutical companies also submit reports on adverse reactions from within Switzerland to Swissmedic.

Activities

The Vigilance One Ultimate database for adverse drug reactions from within Switzerland was upgraded so that it is possible to carry out specialised data analyses. The systems for processing COVID vaccination notifications were also optimised.

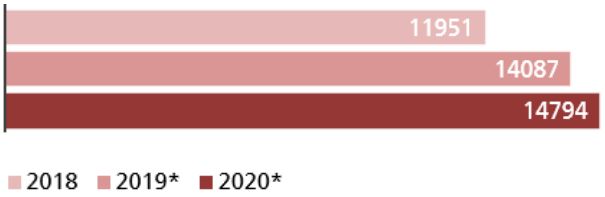
The collaboration with other countries' authorities and in multinational specialist organisations was intensified, for example as part of regular dialogue on safety signals with consortium partners or as part of ICH and WHO activities.

Processes and systems underwent extensive modification in anticipation of all ADR reports being submitted directly to Swissmedic from 2021. This move will leverage the expertise of the RPVC even more effectively and further improve detection of new safety risks.

ADR reports from RPVC

ADR reports from pharmaceutical companies

Total ADR reports



* The 2019 and 2020 figures also include follow-up reports and are therefore not directly comparable with the previous years' figures.

Safety of Medicines division, Swissmedic

Vaccinovigilance

Complete report – link:

Adverse events following immunization - annual report 2020

Summary of adverse events following immunization reported in Switzerland during 2020

During 2020, the Pharmacovigilance Unit of Swissmedic received 271 new case reports of suspected adverse events following immunization (AEFI) from Switzerland. This is quite a stable reporting level as compared to the number of case reports submitted in 2019 (273 reports) and higher compared to 2018 (223 reports).

Notably, as the COVID-19 vaccination campaign was starting in Switzerland in late December, only isolated AEFI cases were reported in 2020 for the new COVID vaccines. Similar to the previous year, AEFI reports submitted during 2020 were recorded, assessed and analysed in the pharmacovigilance database of Swissmedic. However, no accurate data was available regarding the number of doses administered in Switzerland during 2020 for different vaccine groups or products, and therefore a straightforward conclusion regarding AEFI reporting rates cannot be drawn.

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 being evaluated in international collaboration with other foreign agencies and/or with the participation of the Human Medicines Expert Committee (HMEC) of Swissmedic, if necessary. An increased AEFI reporting rate within the Swiss database followed by an assessment of relevant cases can lead to risk minimisation measures in order to ensure vaccine safety.

Figure 1: Number of AEFI reports by age group and gender, 2020

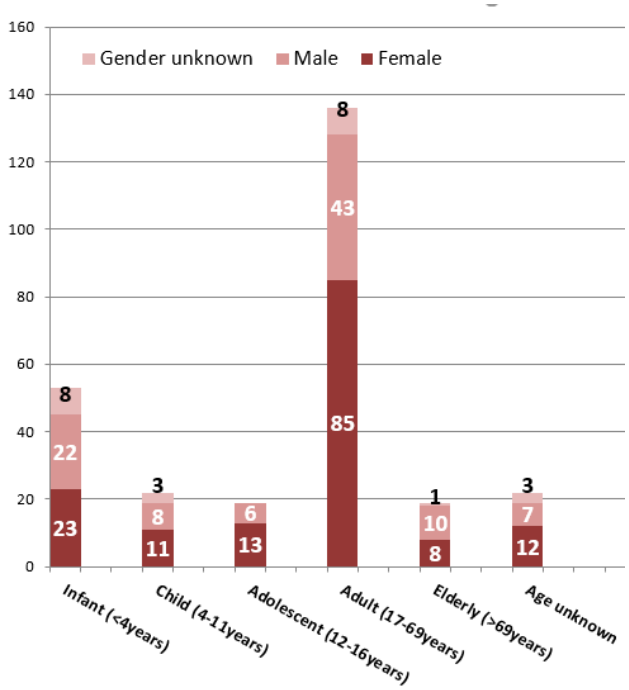


Figure 1 compares the number of reports by age group and gender. The largest number of AEFI reports involved adults (136 reports), followed by infants (53 reports), children (22 reports), the elderly (19 reports) and adolescents (19 reports).

Throughout 2020, the number of reports concerning females (152 reports; 56.1%) exceeded the number of reports concerning males (96 reports; 35.4%). In 23 AEFI reports (8.5%), the gender of the persons remained unknown. In 22 case reports (8.1%), the age-group of the patients was not recorded.

Figure 2: Number of reports by vaccine group (ATC code) and seriousness, 2020

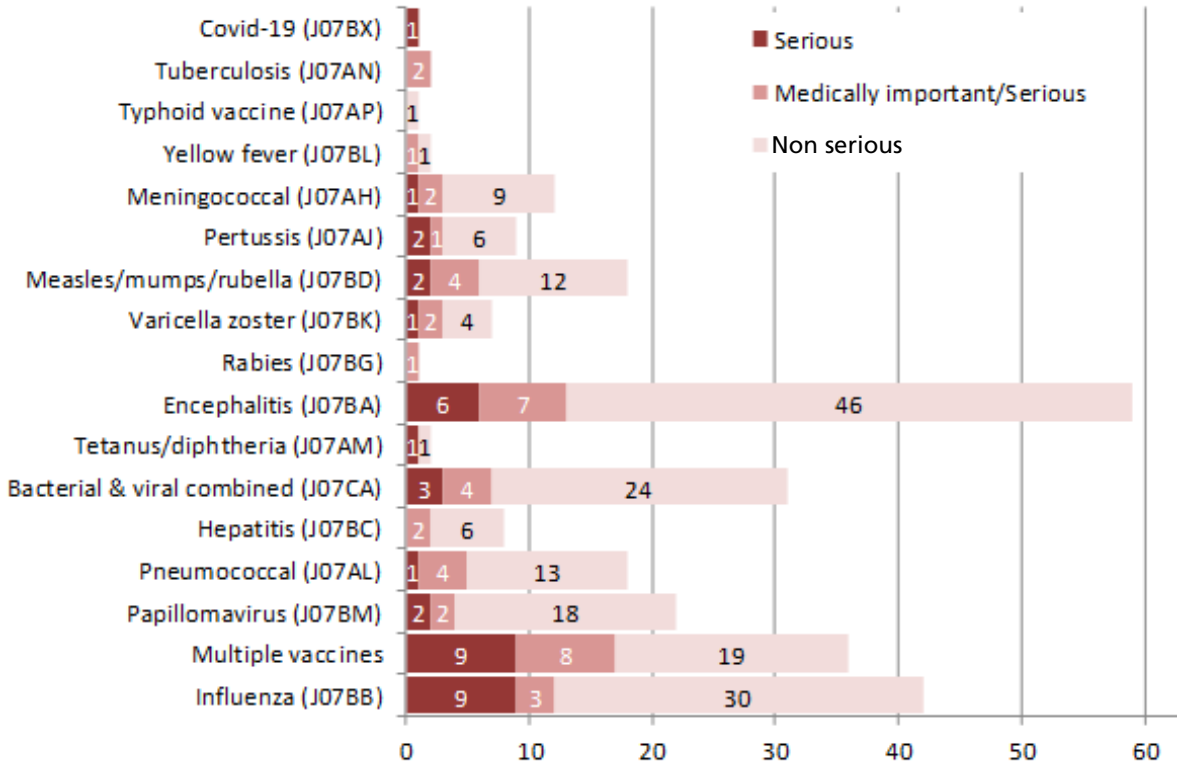


Figure 2 shows the number of spontaneous AEFI reports grouped by vaccine group (ATC code) and seriousness. There is no accurate data available to Swissmedic regarding the number of doses administered in each particular vaccine group in 2020, and therefore this figure does not indicate which vaccine group had a higher AEFI rate (e.g. as number per 100,000 doses). Generally, a safety report is assessed as "serious" if it involves an adverse event leading to death, hospitalisation or prolongation of an existing hospitalisation, if it was life threatening or 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 it involves an event considered to be significant by medical judgement. All other reports are assessed as "not serious" (e.g. self-limiting adverse events with good recovery). Of the 271 spontaneous reports received in 2020, 190 (70.1%) were not-serious, 43 (15.9%) included only medically important events and 38 (14%) of the reports involved AEFIs with serious consequences.

Generally, by considering all vaccines in 2020, the relative frequency (percentage) of "serious" and "medically important" cases taken together (29.9%) declined slightly as compared to those recorded in the previous year 2019 (35.2%).

During 2020, a higher number of cases was submitted in relation with the tick-borne encephalitis vaccine. However, the majority of these case reports were assessed as "non-serious", whereas the number of "serious" and/or "medically important" cases regarding encephalitis vaccines (n=13) was comparable with those received for other vaccine groups. Among the serious/medically important reports, a few cases of "vaccination failure" and subsequent "tick-borne viral encephalitis" were received for this vaccine-group.

Figure 3: Number of AEFI reports by reporter qualification and seriousness, 2020

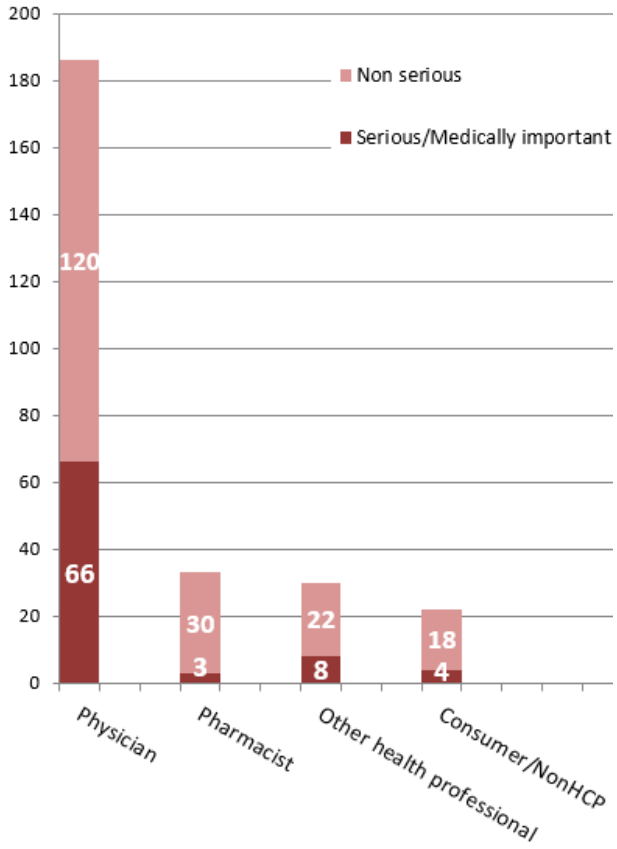


Figure 3 shows the number of Swiss AEFI reports in 2020 grouped by primary reporter and seriousness. Healthcare professionals – generally providing medically confirmed data and good quality of individual AEFI reports – were primary reporters in the vast majority of cases. Physicians reported the largest group of AEFI reports (186 of 271), also comprising a higher number of reports assessed as serious or medically important (66 of 186 reports).

Figure 4: Number of AEFI reports by age group and seriousness, 2020

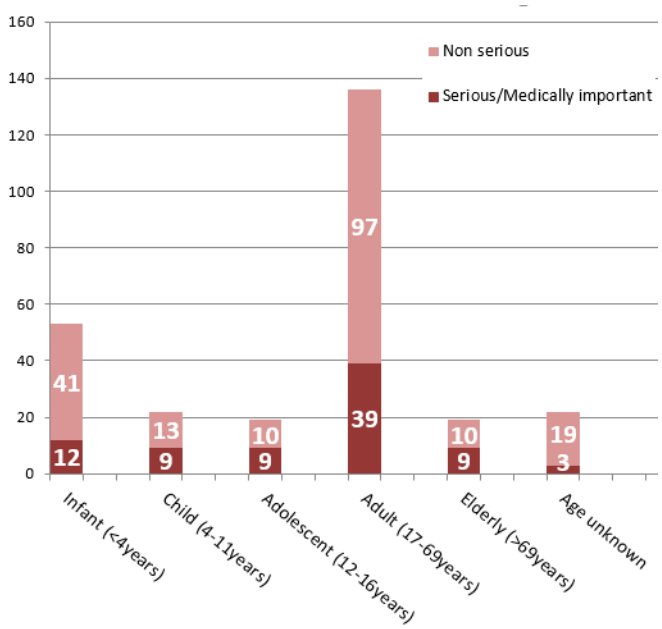


Figure 4 shows the number of spontaneous AEFI reports grouped by age group and seriousness. It becomes apparent that the highest number of "serious" or "medically important" cases (39 AEFI reports in total) were recorded in the age group "adults".

However, during 2020 the age groups "elderly" as well as "adolescents" together totalled the highest percentage of "serious" or "medically important" cases (9 of 19 reports or 47.4% each) as compared with the other age groups specifically recorded: "children" (9 of 22 reports, 40.9%), "adults" (39 of 136 reports, 28.7%), and "infants" (12 of 53 reports, 22.6%).

Valeriu Toma, MD

Safety of Medicines division, Swissmedic

Haemovigilance

Haemovigilance is the monitoring system employed for blood and blood products. It covers the entire transfusion chain from the donor through processing and transport to administration to the patient. The purpose of a haemovigilance system is to minimise transfusion risks and dangers associated with donated blood and the transfusion of blood and blood products.

Activities

The number of reports declined by just under 12% year-on-year.

The look-back procedure was redefined and approved in partnership with various stakeholders during 2020.

Complete report – link:

Haemovigilance Annual Report 2020

Vigilance for veterinary medicinal products: Adverse reactions reported in 2020

A total of 365 reports of adverse reactions to veterinary medicinal products were received during 2020 – a slight decrease of 1.6% compared to 2019.

As in previous years, the most frequently reported reactions were in small animals (216 in dogs and 92 in cats), as well as in cattle (37 reports). In common with previous years, most of the reported reactions were linked to the use of antiparasitics (173 reports), hormone products (21 reports), products to modulate the nervous system (21 reports) and anti-infectives (20 reports).

32 of the 365 reports were passed on by Tox Info Suisse. Half of these cases involved the excessive ingestion of flavoured veterinary medicinal products, with some use of products under the cascade regulation (applied to a species other than that authorised). Tox Info Suisse also reported 110 cases of human exposure to veterinary medicinal products.

Three signals were identified from the reports and periodic safety update reports, resulting in revisions of the product information in the sections addressing adverse reactions, precautions and indications.

A summary of the main points:

- Slight increase in reports received (up 1.6%)
- Most frequently affected species: 216 dogs, 92 cats, 37 head of cattle
- Most frequent medicinal product types: antiparasitics (173), hormone products (82), products to modulate the nervous system (21), anti-infectives (20)
- 151 cases of suspected lack of efficacy, largely for antiparasitics and hormone products
- 32 cases passed on by Tox Info Suisse
- 16 cases of accidental ingestion of flavoured tablets by dogs/cats
- 110 cases of human exposure to veterinary medicinal products
- 3 signal procedures concluded

Cedric R. Müntener, D.V.M.

Veterinary Medicines department, Swissmedic

Complete report 2020 (available in German):

Vigilance Tierarzneimittel: Gemeldete unerwünschte Wirkungen 2020

Information on the Swissmedic website

Side effects of COVID-19 vaccines in Switzerland

26.11.2021
Reports of suspected adverse reactions to COVID-19 vaccines
10,386 reports of suspected adverse vaccination reactions evaluated

05.11.2021
Reports of suspected adverse reactions to COVID-19 vaccines
9,834 reports of suspected adverse vaccination reactions evaluated

15.10.2021
Reports of suspected adverse reactions to COVID-19 vaccines
8,757 reports of suspected adverse vaccination reactions (ADR) evaluated – the overall positive benefit-risk ratio of the vaccines remains

24.09.2021
Reports of suspected adverse reactions to COVID-19 vaccines
7,571 reports evaluated – the overall positive benefit-risk ratio of the vaccines remains

03.09.2021
Reports of suspected adverse reactions to COVID-19 vaccines
6,603 reports evaluated – the overall positive benefit-risk ratio of the vaccines remains

13.08.2021
Reports of suspected adverse reactions to COVID-19 vaccines in Switzerland – update
5,304 reports evaluated – the overall positive benefit-risk ratio of the vaccines remains

23.07.2021
Reports of suspected adverse reactions to COVID-19 vaccines in Switzerland – update
4,319 reports evaluated – the overall positive benefit-risk ratio of the vaccines remains

02.07.2021
Reports of suspected adverse reactions to COVID-19 vaccines in Switzerland – update
3,419 reports evaluated – the overall positive benefit-risk ratio of the vaccines remains

In focus

20.09.2021

Coronavirus disease (COVID-19) Pandemic

Information on the new coronavirus (SARS-CoV-2)

Healthcare Professional Communication

Some of the links are available in German/French only

27.09.2021
DHPC – Glatirameracetat
Seltene Fälle schwerer Leberschäden

15.09.2021
DHPC - XELJANZ® (Tofacitinib)
Erhöhtes Risiko für schwerwiegende unerwünschte kardiovaskuläre Ereignisse und maligne Erkrankungen bei Anwendung von Tofacitinib im Vergleich zu TNF-alpha-Inhibitoren

23.08.2021
DHPC – Beovu® (Brolucizumab)
Erste Ergebnisse einer klinischen Studie deuten auf eine erhöhte Inzidenz intraokularer Entzündungen (IOI) einschliesslich retinaler Vaskulitis (RV) und retinalem Gefässverschluss (RO) bei einer Dosierung von Brolucizumab alle 4 Wochen über die ersten drei Dosen hinaus („Aufsättigungsphase“) im Vergleich zu Aflibercept hin

13.08.2021
DHPC – mRNA-Impfstoffe gegen COVID-19 (COVID-19 Vaccine Moderna und Comirnaty)
Risiko für Myokarditis und Perikarditis

16.07.2021
DHPC – Hycamtin, Lyophilisat / Hycamtin, Kapseln
Wichtiger sicherheitsrelevanter Hinweis

Announcements

Some of the links are available in German/French only

26.11.2021
Swissmedic approves booster dose of the Moderna COVID-19 vaccine for adults aged 18 and over
Indication extension for booster with Spikevax® approved from 18 years

23.11.2021
COVID-19 vaccine from Pfizer/BioNTech: Swissmedic approves the extension of the booster dose to everyone aged 16 years and over
Booster with Comirnaty® approved for the population aged 16 years and over

19.11.2021
Pfizer applies for indication extension of COVID-19 vaccine to children aged 5 to 11
Swissmedic reviews Pfizer Schweiz AG application for Comirnaty®

18.11.2021
Visible 4/21
Das ist bereits die 4. Ausgabe des Swissmedic Magazin «Visible». Themenschwerpunkt in dieser Ausgabe: Wie Swissmedic mit Veränderungen umgeht. Wir wünschen Ihnen eine interessante Lektüre.

18.11.2021
COVID-19 vaccine for children aged 6 to 11: Moderna submits application for indication extension
Swissmedic reviews Moderna Switzerland GmbH application for Spikevax®

15.11.2021
Update of the information sheet Procurement of medical devices in health institutions
Additional information on the import of medical devices by healthcare professionals and health institutions

11.11.2021
HPC – Dectomax ad us. vet., Injektionslösung
Neue Wartezeit für essbare Gewebe

09.11.2021
Adverse events following immunization – annual Vaccinovigilance report
Summary of adverse events following immunization reported in Switzerland during 2020

04.11.2021
AstraZeneca withdraws authorisation application for COVID-19 vaccine in Switzerland
COVID-19 Vaccine AstraZeneca (previously AZD1222) no longer in review procedure

02.11.2021
Swissmedic warns against purchasing medications to treat or prevent COVID-19 infections online
COVID-19: increase in illegally imported medicinal products

01.11.2021
Position paper on decentralized clinical trials (DCTs) with medicinal products
Swissmedic and swissethics summarise the main current challenges of DCTs with medicinal products and show under which conditions such clinical trials could be conducted in Switzerland.

01.11.2021
New guidance document: Involvement of patient organisation in assessment of patient information HMV4
The new guidance document is valid with effect from 1 November 2021.

26.10.2021
COVID-19 vaccines from Moderna and Pfizer/BioNTech: Swissmedic approves third vaccination for certain population groups
Booster vaccination with third dose for high-risk individuals and third dose of vaccine for people with weakened immune system

22.10.2021
50 Jahre – 300 Sitzungen
Ein beeindruckendes Jubiläum der deutschsprachigen Ausgabe der Europäischen Pharmakopöe

19.10.2021
CureVac withdraws authorisation application for COVID-19 vaccine
Vaccine candidate CVnCoV no longer in rolling review procedure

15.10.2021
Wichtige Mitteilung - Paclitaxel Sandoz 100 mg/16.7 ml, Konzentrat zur Herstellung einer Infusionslösung
Fehlerhafte Beschriftung

05.10.2021
Anpassung der Praxis bezüglich Arzneimittelinformation
Präzisierung der Publikation vom 08.10.2019

01.10.2021
COVID-19 vaccine from Johnson & Johnson expected to be available from the middle of next week
Vector vaccine as an alternative to mRNA vaccines

28.09.2021
Vigilance for veterinary medicinal products: Adverse reactions reported in 2020
Report on adverse drug reactions (ADR) after use of veterinary medicinal products (VMP) in Switzerland

27.09.2021
Changes to the guidance document Formal requirements HMV4 and the form Import of a medicinal product according to Art. 14 (2) TPA (parallel import) HMV4
ZL_00_020e_WL / ZL106_00_002e_FO

27.09.2021
Frequently Asked Questions on medical devices – FAQ MD
Updates to the frequently asked questions (FAQ) on medical devices

23.09.2021
HPC – Endex 19,5% ad us. vet., orale Suspension für Rinder und Endex 8.75% ad us. vet., orale Suspension für Schafe
Anpassung der Wartezeit für die Milch (Streichung)

23.09.2021
COVID-19 pandemic – Reports concerning Sars-CoV-2 rapid tests
Swissmedic takes action against dispensing of non-compliant rapid tests by Swiss online shops

21.09.2021
Important information – Comirnaty concentrate for the manufacture of a dispersion for injection
Extension of the shelf-life at ultralow temperature

21.09.2021
Practical interpretation – Swiss authorised representative (CH-REP) for combination products
(Medicinal products with a medical device component)

16.09.2021
Swissmedic is reviewing the authorisation extension for a third dose of the COVID-19 vaccines from Pfizer/Biontech and Moderna
Pfizer Schweiz AG and Moderna Switzerland GmbH have submitted applications for a third vaccine dose (booster)

15.09.2021
HPC – Dinolytic 5 mg/ml ad us. vet., Injektionslösung für Pferd, Rind und Schwein
Neue Wartezeit für essbare Gewebe beim Rind

15.09.2021
Access Consortium: Alignment with ICMRA consensus on immunobridging for authorizing new COVID-19 vaccines
Access Consortium members agree that well-justified and appropriately designed immunobridging studies are an acceptable approach for authorizing COVID-19 vaccines.

07.09.2021
More than 1,600 participants at the information event on the new medical devices regulation
Successful Swissmedic online event on 2 September 2021

02.09.2021
FAQ on the COVID-19 vaccines
On this page you'll find answers to frequently asked questions about mRNA vaccines.

02.09.2021
New VO form and new format for authorisation applications plus changes/notifications/reports regarding clinical trials with medicinal products
as of 13 September 2021

01.09.2021
Changes to the guidance document Project Orbis HMV4
ZL000_00_048e_WL

01.09.2021
Update to the forms New authorisation of human medicinal products HMV4 and Variations and authorisation extensions HMV4
Consent to exchange of information for applications in collaboration with Access Consortium and Project Orbis

01.09.2021
Guidance document Authorisation according to Art. 14 para. 1 abis-quater TPA HMV4 updated
ZL000_00_022e_WL

30.08.2021
COVID-19 rapid self-tests
Federal Office of Public Health (FOPH) lists the certified self-tests

27.08.2021
HPC – Sedanol 40 mg/ml ad us. vet., Injektionslösung für Schweine
Neue Wartezeiten für essbares Gewebe und Einschränkung des Injektionsvolumens

11.08.2021
New Work Sharing Initiative from the Access Consortium for assessment of Biosimilar applications
Biosimilar Working Group (BSWG)

11.08.2021
Haemovigilance Annual report 2020
Evaluation of haemovigilance reports in 2020

09.08.2021
Swissmedic approves indication extension for Spikevax vaccine for 12- to 17-year-olds
previously COVID-19 Vaccine Moderna

06.08.2021
Empfehlung bezüglich COVID-19 für die autologe Blutstammzellspende
Beschluss Vorschriften SBSC – Blutstammzellspende

04.08.2021
Executive Summary - Benchmarking 2021
Comparison of Swiss approval times for human medicines with the EU and the USA

28.07.2021
HPC – Valbazen ad us. vet., Suspension für Rinder
Neue Wartezeiten für Milch und essbares Gewebe

20.07.2021
HPC – Stresnil ad us. vet., Injektionslösung
Neue Absetzfristen für essbare Gewebe

16.07.2021
Update to Field Safety Notice from Philips Respironics regarding specific ventilators, sleep apnoea and respiratory care devices – recommendations from professional associations
Recommendations of the professional societies SGP and SSSSC published

15.07.2021
Swissmedic publishes public data on the Swiss administration's Open Government Data (OGD) portal
On the first working day of each month, data relating to authorised human and veterinary medicines are generated in XML files and made available by interested users.

14.07.2021
HPC – Tylan 200 ad us. vet., Injektionslösung
Neue Absetzfristen/Wartezeiten bei Rindern und Schweinen

13.07.2021
HPC – Betamox LA ad us. vet., Injektionssuspension / Duphamox L.A. ad us. vet., Injektionssuspension / Longamox ad us. vet., Injektionssuspension
Neue Absetzfristen für essbares Gewebe und Milch bei Rindern, Schweinen und Schafen

08.07.2021
Meetings of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and of the International Pharmaceutical Regulators Programme (IPRP)
ICH – Continuous growth and development

06.07.2021
Swissmedic is monitoring the situation – we remain vigilant
Swissmedic performs regular and targeted checks on advertisements that promote medicines in print media, TV spots and electronic media

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