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In this edition

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Editorial

Dear Reader

In medicinal product safety, it is essential to respond to the latest scientific findings and pharmacovigilance trends. One very topical example is the discussion on Janus kinase inhibitors (JAKi). An increased risk of severe infections, major adverse cardiovascular events (MACE), malignant diseases, thromboses and overall mortality have been observed with JAKis. An article in this edition looks at risk minimisation and communication measures for JAKis by the US FDA, EMA and Swissmedic, while a second covers the dose-response relationship of JAKis.

New data on the risk profile of a medicinal product can be collected and evaluated by analysing spontaneous case reports. The possible association between ibrutinib or venetoclax and progressive multifocal leukoencephalopathy is elucidated in one article, while another outlines a university hospital's experience of using remdesivir in myasthenia gravis.

In exposed groups such as pregnant women in particular, current findings play an important role. Spontaneous reports on exposure to immune checkpoint inhibitors in the perinatal period and the possible occurrence of pregnancy-related outcomes were evaluated.

Regarding vaccines, adverse events following immunization (AEFI) with COVID-19 vaccines continue to be monitored even after the large-scale vaccination campaigns. Swissmedic evaluated reports of myocarditis and pericarditis following COVID-19 vaccination in elderly patients as well as reports of suspected AEFI following vaccination with a bivalent COVID-19 vaccine. One article also focuses on AEFI reports after monkeypox vaccination in Switzerland.

In haemovigilance, both incorrect blood component transfused (IBCT) incidents and near-misses (errors discovered before transfusion) are reported and analysed to improve transfusion safety. This approach is described in the second part of our haemovigilance series.

In order to continue to receive up-to-date information on the safety of medicinal products, we ask you to submit adverse drug reaction (ADR), AEFI and haemovigilance reports to Swissmedic. You can find all information on submitting reports at www.swissmedic.ch.

With the present 30th edition of Swissmedic Vigilance News, we have also decided to refresh the layout according to contemporary criteria.

We hope you enjoy reading our "relaunched" publication.

Eva Eyal

Pharmacist and editor of Swissmedic Vigilance News
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Safety of medicines and case reports

An analysis of pregnancy-related outcomes with immune checkpoint inhibitors in VigiBase®

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Introduction

Immune checkpoints are involved in the maintenance of maternal immune tolerance to the developing foetus (1, 2). Therefore, blockade of the immune checkpoints programmed cell death-1 protein (PD-1), its ligands (programmed cell death-ligand 1 and 2, PD-L1 and PD-L2) and cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) could provoke an immune response against the foetus (3). Preclinical studies showed that using ICIs in pregnancy increases the risk of foetal death (4). Accordingly, ICIs are not recommended in pregnant women and women of childbearing potential (if not using effective contraception) (5). However, some clinical cases of ICI exposure before, at or after conception have been reported showing favourable foetal outcomes without developmental abnormalities (6–17).

Considering the inherent challenges and limitations of pregnancy research, including ethical issues regarding inclusion in clinical trials, large-scale spontaneous reporting systems represent a privileged source of real-world data to investigate drug safety in pregnancy.

To gain further insight into ICI safety in pregnancy, Noseda R et al. (18) queried VigiBase®, the World Health Organization's (WHO) global pharmacovigilance database, and described the largest series of spontaneous safety reports from clinical practice to date referring to ICI exposure during the peri-pregnancy period and the possible occurrence of pregnancy-related outcomes.

Methods

This study used disproportionality analysis alongside a case-by-case evaluation using de-duplicated safety reports gathered in the VigiBase® database from its inception until 30 April 2022. This complementary design was implemented to provide an exhaustive pharmacovigilance perspective. Drugs of interest were ICIs reported as suspected and selected as active ingredients among ipilimumab, nivolumab, pembrolizumab, atezolizumab, avelumab, durvalumab, cemiplimab and dostarlimab. Events of interest were pregnancy-related outcomes retrieved using the standardised query "pregnancy and neonatal topics" available through the Medical Dictionary for Regulatory Activities (MedDRA®), on which VigiBase® relies. After selection, safety reports were manually revised to ascertain ICI exposure during the peri-pregnancy period and/or the reporting of specific pregnancy-related outcomes. Safety reports included in the study cohort were described in terms of demographic and clinical characteristics. Pregnancy-related outcomes were classified into maternal and foetal/neonatal. To detect potential safety signals, disproportionality analyses (raw and on the subgroup of safety reports concerning women aged 20–44 years – based on the characteristics of the study cohort) were performed for pregnancy-related outcomes reported in at least five of the included safety reports. The reporting odds ratio (ROR) was computed and considered to be significant when the lower limit of its 95% confidence interval (CI) was > 1. Three groups of safety reports were used as comparators: (i) the entire database, (ii) only safety reports suspecting antineoplastic agents other than ICIs to control confounding by indication, and (iii) only safety reports suspecting antineoplastic agents other than ICIs and submitted after 2011 (when the first-in-class ICI ipilimumab received marketing authorisation from the US Food and Drug Administration).

Results

As of 30 April 2022, 103 out of 123,289 safety reports with ICIs as suspected drugs were included in the study cohort. 65 (63.1%) safety reports came from the United States of America, 2 (1.9%) came from Switzerland. In 86 (83.5%) safety reports, the reporter was a healthcare professional whilst in 15 (14.6%) it was the patient/consumer. The median age was 32 years (ranging from 20 to 44 years, n = 45), maternal exposure to ICIs occurred more frequently during pregnancy (n = 77, 74.8%), the PD-1/PD-L1 pathway was the target of ICI treatment in most of the safety reports (n = 76, 73.8%) and malignant melanoma was the most common underlying cancer type, affecting 28 (27.2%) patients from the study cohort.

Table 1. Pregnancy-related outcomes reported on immune checkpoint inhibitors in VigiBase® as of 30 April 2022

Pregnancy-related outcomes	n (%), N=56
Maternal outcomes	
Specific pregnancy complications	
Pre-eclampsia	1 (1.8)
HELLP syndrome	1 (1.8)
Placental disorder	1 (1.8)
Placental infarction	1 (1.8)
More general outcomes	
Diarrhoea	3 (5.4)
Nausea	2 (3.6)
Fatigue	2 (3.6)
Abdominal pain	2 (3.6)
Pruritus	2 (3.6)
Chest pain	2 (3.6)
Diabetes mellitus	1 (1.8)
Hypophysitis	1 (1.8)
Arthralgia	1 (1.8)
Hypophagia	1 (1.8)
Starvation	1 (1.8)
Ketoacidosis	1 (1.8)
Urinary tract infection	1 (1.8)
Neutropenia	1 (1.8)
Lung disorder	1 (1.8)
Iron deficiency anaemia	1 (1.8)
Antiphospholipid syndrome	1 (1.8)
Abdominal distension	1 (1.8)
Autoimmune disorder	1 (1.8)
Anxiety	1 (1.8)
Cardiac disorder	1 (1.8)
Tri-iodothyronine increased	1 (1.8)
Insomnia	1 (1.8)
Dyspnoea	1 (1.8)
Foetal / neonatal outcomes	
Normal newborn	4 (7.1)
Live birth	1 (1.8)
Foetal death	1 (1.8)
Stillbirth	1 (1.8)
Spontaneous abortion	12 (21.4)
Abortion induced	7 (12.5)
Spontaneous abortion incomplete	1 (1.8)
Foetal growth restriction	6 (10.7)
Foetal distress syndrome	1 (1.8)
Small for gestational age	1 (1.8)
Umbilical cord compression	1 (1.8)
Prematurity	18 (32.1)
Neonatal respiratory distress syndrome	2 (3.6)
Hypoxia	1 (1.8)
Lung disorder	1 (1.8)
C-reactive protein increased	1 (1.8)
White blood cell count increased	1 (1.8)
Retinopathy of prematurity	1 (1.8)
Neonatal intraventricular haemorrhage	1 (1.8)
Motor developmental delay	1 (1.8)
Neonatal type 1 diabetes mellitus	1 (1.8)
Birth defects	
Congenital hand malformation	1 (1.8)
Congenital pulmonary valve disorder	1 (1.8)
Congenital hypothyroidism	1 (1.8)
Hypospadias	1 (1.8)

Characterisation of pregnancy-related outcomes

Out of 103 safety reports, 47 (45.6%) reported only exposure to ICIs during the peri-pregnancy period, while 56 (54.4%) also reported 104 pregnancy-related outcomes (more than one outcome was recorded in some safety reports). Of these, 36 were maternal and 68 foetal/neonatal (Table 1). Specific maternal pregnancy complications occurred in three cases and included pre-eclampsia, HELLP syndrome (haemolysis, elevated liver enzymes and low platelet count) with a placental disorder, and a case of placental infarction. Among 32 more general maternal outcomes, no specific toxicity patterns were observed. Regarding foetal/neonatal pregnancy-related outcomes, five safety reports reported a normal new-born/live birth, while fatal events occurred in two safety reports. No patterns of major birth defects or of specific foetal/neonatal immune-related adverse events were found.

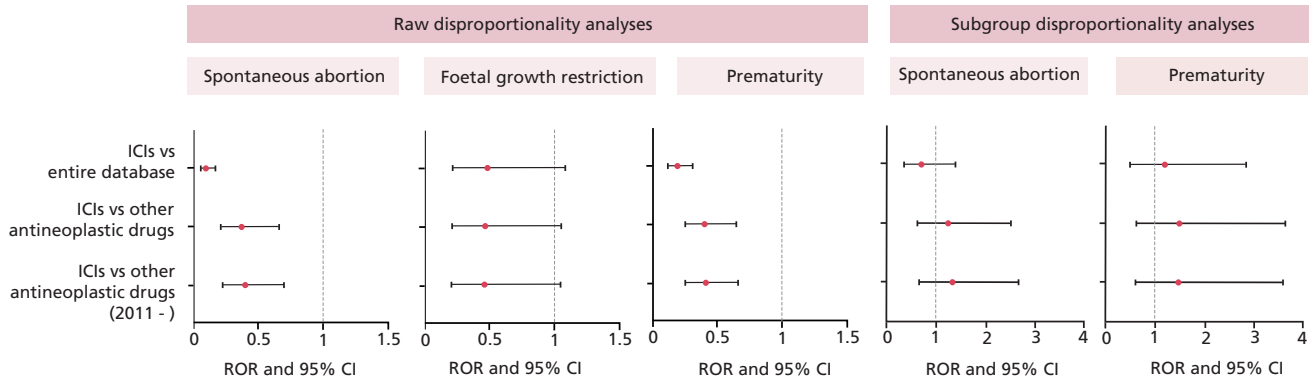

Figure 1. Raw and subgroup (by sex and age, females aged 20-44 years) disproportionality analyses between immune checkpoint inhibitors and the entire database, other antineoplastic agents and other antineoplastic agents since 2011, to compare the reporting of spontaneous abortion, foetal growth restriction and prematurity.
Forest plots represent reporting odds ratios along with 95% confidence intervals.
Abbreviations: ICI = immune checkpoint inhibitor; ROR = reporting odds ratio; CI = confidence interval.

Disproportionality analyses

In raw disproportionality analyses for spontaneous abortion, foetal growth restriction and prematurity, there were no signals of disproportionate reporting with ICIs for any of the three predefined comparator groups (Figure 1). In subgroup disproportionality analyses in women aged 20–44 years, no safety signals were found for either spontaneous abortion or prematurity, regardless of the comparator group used (Figure 1).

Discussion

This pharmacovigilance study in VigiBase® provided the largest series of cases to date referring to ICI exposure during the peri-pregnancy period and reporting pregnancy-related outcomes. In line with previously published single clinical cases (6–17), it found no specific patterns of maternal, foetal, or neonatal toxicity. No signal of disproportionate reporting was detected for spontaneous abortion, foetal growth restriction or prematurity with ICIs.
Notably, most of the safety reports included in the present study were from healthcare professionals, suggesting a growing awareness of the potential negative effects of ICI use in pregnant women or those of childbearing age. Moreover, slightly less than half of the safety reports referred to ICI exposure during the peri-pregnancy period without mentioning any type of pregnancy-related outcomes. This finding might further support the fact that among healthcare professionals, the use of ICIs during the peri-pregnancy period, whenever chosen, remains questionable and prompts them to spontaneously report their off-label use, even in the absence of pregnancy complications.

VigiBase® as a data source allowed identification and description of 56 patients who reported a

total of 104 pregnancy-related outcomes, a far greater number than that of clinical cases published to date concerning exposure to ICIs in pregnancy (6–17). Despite a lack of clinical details important for the comprehensive characterisation of ICI toxicity in pregnancy, VigiBase® collects a high number of safety reports that can be exploited for data mining. Indeed, nowadays, pharmacovigilance studies using spontaneous reporting databases to investigate drug safety in pregnancy by means of disproportionality approaches are increasing. However, VigiBase® suffers from the main drawbacks of spontaneous reporting systems, including over- and under-reporting, partial and missing information, the impossibility of firmly inferring causality, a lack of information on differential diagnoses and, as far as the aim of this specific study is concerned, a lack of information on the follow-up of children.

Considering the increasing use of ICIs, not least in pregnant women and women of childbearing potential, continuous surveillance by clinicians and pharmacovigilance experts of large-scale spontaneous reporting systems is warranted. As disproportionality analyses rely on the number of safety reports gathered in the spontaneous reporting system, the results from these analyses for the pregnancy-related outcome(s) of interest might change over time, thus making reassessment of the ICI safety profile in the peri-pregnancy period of the utmost importance. Moreover, pharmacoepidemiological studies on different sources of real-world evidence, such as birth records, are needed to precisely assess the exact timing of exposure to ICIs during the peri-pregnancy period and to further characterise relevant outcomes.

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Ibrutinib and venetoclax associated with progressive multifocal leukoencephalopathy

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Introduction

Progressive multifocal leukoencephalopathy (PML) is an opportunistic infection of the central nervous system (CNS) caused by the JC polyomavirus (1). The majority of PML cases occur in patients co-infected with HIV. Other risk factors include haematological malignancies, autoimmune diseases (e.g. multiple sclerosis, sarcoidosis, rheumatoid arthritis) or immunosuppression following solid organ transplantation. Some medications have been associated with an increased risk of PML, such as B-cell depleting agents (rituximab) and VLA4-integrin antagonists (natalizumab). For other drugs, the association with PML is not clearly established (1–4). Cases of drug-induced PML most often manifest with motor and/or cognitive deficits with radiological lesions predominantly in the frontal and parietal regions (5). In oncological settings, drug-induced PML occurs on average 14 months after the introduction of the offending drug (5). We report on a patient who developed PML with likely involvement of ibrutinib and venetoclax in the context of chronic lymphocytic leukaemia (CLL).

Case report

A patient in his seventies with CLL diagnosed in 2014 was considered in remission after 15 cycles of rituximab and bendamustine (last administration in September 2019). Due to haematological relapse, venetoclax (Venclyxto®) 400 mg 1x/d and ibrutinib (Imbruvica®) 280 mg 1x/d were started in January 2022. The standard ibrutinib dosage was 420 mg 1x/d, but the patient received a lower dose due to a drug-drug interaction between ibrutinib and CYP3A4 inhibitors (i.e. amiodarone and diltiazem for atrial flutter). Other prescribed drugs were apixaban, olmesartan and cholecalciferol/calcium. In December 2022, a rapid onset of cognitive impairment with memory loss and executive dysfunction was reported. In mid-February, the patient was admitted for investigation of an acute motor and hemineglect syndrome. Vital parameters upon admission: blood pressure 140/73 mmHg, heart rate 67 bpm, ambient O2 saturation 95%, body temperature 36.8°C. During the neurological examination, the patient was disoriented with right multimodal hemineglect, labial ptosis, right limb droop and Babinski sign on the right foot. Laboratory tests showed stable renal function with a creatinine level of 136 µmol/l (N 62-106 µmol/l) and liver parameters, including transaminases, within normal limits. A complete blood count showed no abnormalities associated with neutrophils. Regarding lymphocyte count: B cells were at 8 cells/mm^3 (N 80-490 cells/mm^3), CD4+ T cells at 359 cells/mm^3 (N 490-1640 cells/mm^3) and CD8+ T cells at 1709 cells/mm^3 (N 170-880 cells/mm^3). HIV serology was negative. Cerebral MRI findings were consistent with PML features: multifocal periventricular and subcortical areas with T2 hypersignal predominating in the bilateral fronto-parieto-occipital regions were reported. A lumbar puncture revealed elevated proteins at 707 mg/l (N 150-460 mg/l) but glucose and lactates remained in the normal range. There were no tumour cells identified on cytology and the cellularity was normal. CSF microbiology was positive for JC polyomavirus (PCR with 900 copies/mL). Reactivation of the JC virus was attributed to the immunosuppression associated with CLL and to the treatment with venetoclax and ibrutinib (both of which were stopped). The disease course was unfavourable and palliative care was initiated. The patient died four weeks after admission.

Discussion

The patient developed PML in the context of CLL one year after starting treatment with venetoclax and ibrutinib.

Venetoclax, as navitoclax, is a selective inhibitor of the anti-apoptotic protein BCL-2 (B-Cell Lymphoma): it inhibits the BCL-2 protein, resulting in mitochondrial cell apoptosis by activation of caspases, a family of protease enzymes playing essential roles in programmed cell death. The immunosuppressive effect of venetoclax is ultimately due to the protracted cytopenias (6). Neutropenia and lymphopenia with respiratory and urinary tract infections are common adverse events. However, opportunistic infections (such as reactivation of JC virus) are not reported as adverse drug effects, even in the long term. In the European Medicines Agency database, there are five cases of PML in association with venetoclax. According to a review by the European Society of Infectious Diseases, 3.6% of patients taking venetoclax develop opportunistic infections (including aspergillosis, pneumocystis, nocardiosis, toxoplasmosis). Yet the authors do not report an association between venetoclax and PML (7). To our knowledge, there is no case report describing an association between venetoclax and PML. By contrast, one case report mentioned a patient with CLL who survived PML. Approximately seven years after the diagnosis of PML, he presented with a recurrence of his malignancy. Treatment with venetoclax was introduced without reactivation of JC virus (8).

Ibrutinib is an inhibitor of Bruton's tyrosine kinase (BTK) which interferes in the pathogenesis of several B-cell malignancies. BTK plays a role in the proliferation, survival and differentiation of B cells. The occurrence of PML during ibrutinib treatment is labelled in the product information. In the European Medicines Agency database, there are currently 31 cases of PML in association with ibrutinib. In the literature, ibrutinib has been associated with an increased risk of PML. A study based on FDA post-marketing data observed the occurrence of PML with different biological agents and cancer treatments. For ibrutinib, they identified 10 cases of PML (9). One case series described five patients with CLL who died of PML after receiving ibrutinib (n = 1), ibrutinib + rituximab (n = 3), or ibrutinib + rituximab + bendamustine (n = 1). The median duration of ibrutinib treatment was 11 months (range: 1.5–24 months), and PML developed on average eight years after the diagnosis of CLL (range: 3–17 years) (10). The mechanism suggested to explain the association between PML and ibrutinib is the inhibition of B-cell proliferation by ibrutinib. B cells and the humoral immune response are thought to play a crucial role in the control of JC virus replication (interaction between B and T cells for the antiviral response) (5, 11).

In the present case, the last administration of rituximab and bendamustine was in September 2019. Their involvement in the occurrence of PML seems unlikely. The majority of PML cases with rituximab develop within two years of starting the treatment (12). The association between bendamustine and PML has not been established in the literature, and the long delay since the last administration makes this drug causality very unlikely (13–14).

About 10–20% of PML cases occurred in patients with haematological malignancies, most commonly non-Hodgkin lymphoma and CLL (1, 3). The treatments administered are often confounding factors in explaining the occurrence of PML in haematological malignancy. However, a case report described a case of a patient who was diagnosed with CLL and PML simultaneously, i.e. neither with prior chemotherapy nor immunosuppressive therapy (15).

Conclusion

PML is a rare disease occurring mainly in the context of specific immunosuppressive conditions, such as HIV or with VLA4-integrin antagonists. In this case presentation, venetoclax and ibrutinib, which are reported only in a few case reports, could be suspected as causative agents. As PML is a very rare event, hindsight is still too limited to exclude or infer a formal causal relationship for either drug (ibrutinib approved by the FDA since 2013 and venetoclax approved by the FDA since 2016). Nonetheless, the increasingly common combination of a selective BCL-2 inhibitor and a BTK inhibitor should make us vigilant about their contributory role in the occurrence of PML.

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Safety of remdesivir in the presence of myasthenia gravis; the experience of a university hospital

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Introduction

Remdesivir (Veklury®) is a prodrug, a nucleotide analogue inhibitor of viral RNA polymerases (1) that is administered intravenously. It is authorised for the treatment of coronavirus disease 2019 (COVID-19), specifically in those patients with pneumonia requiring supplemental oxygen, or in those patients who do not require supplemental oxygen but who are at increased risk of progressing to a severe form of the disease, for example when nirmatrelvir/ritonavir (Paxlovid®) is contraindicated due to major drug interactions. For patients with severe COVID-19, the World Health Organization (WHO) has issued a conditional recommendation in favour of the administration of remdesivir, since it may reduce mortality and probably reduces the need for non-invasive mechanical ventilation. In the clinical trials, remdesivir was well tolerated and adverse events were rare. In patients with non-severe COVID-19 but who are at high risk of hospitalisation, the WHO has likewise issued a conditional recommendation in favour of remdesivir (2).

Since it was only recently launched on the market, limited experience is available to date concerning its safety profile in certain subpopulations, for example in pregnant women, children or adults suffering from certain comorbidities: end-stage renal disease with or without dialysis, myasthenia gravis. In this context, post-marketing surveillance can provide data concerning possible risks. The aim of this article is to report our clinical experience on the use of remdesivir in adult patients suffering from myasthenia gravis (MG).

Methodology

We reviewed the medical records of all patients with known MG whose cases were submitted to the Clinical Pharmacology and Toxicology Division for an opinion concerning the introduction of remdesivir.

Results

We were asked for our opinion concerning the introduction of remdesivir for a total of six patients. One of the patients was excluded from our analysis because she had not received remdesivir due to low kidney function. Moreover, MG was merely suspected and not confirmed in this patient. Finally, five patients (four men, one woman) with known MG aged between 27 and 84 had received remdesivir. The duration of treatment was from 3 to 5 days depending on the indication. All had also received a corticosteroid. None of these five patients experienced a deterioration in their MG after taking the remdesivir.

Discussion

MG is an autoimmune disease in which antibodies bind to acetylcholine receptors or to functionally related molecules in the postsynaptic membrane of the neuromuscular junction, causing the skeletal muscles to weaken. This weakness may be generalised or localised and almost always affects the ocular muscles, with diplopia and ptosis. The prevalence of MG is 150 to 250 cases per million persons (3).

Certain drugs may have an adverse impact, either by triggering or by exacerbating MG. Those that cause MG de novo produce an autoimmune reaction against the neuromuscular junction and primarily include checkpoint inhibitors and tyrosine

kinase inhibitors. Drugs that alter neuromuscular transmission can aggravate the symptoms of the disease and primarily include certain antibiotics (macrolides, aminoglycosides, fluoroquinolones, penicillins), curare and class IA antiarrhythmic agents. Cases of aggravation of MG have been reported for numerous other drugs in the form of case reports, and those particularly implicated are statins, beta blockers, calcium antagonists and lithium (4).

We report our clinical experience with the use of remdesivir in five patients with MG without any worsening of their underlying disease. MG is not mentioned in the contraindications listed in the Information for healthcare professionals for remdesivir (5, 6). Although experience is still limited concerning this recent drug, its mechanism of action does not suggest that it affects acetylcholine and its receptors (7). The literature reports five cases of MG patients in whom remdesivir was used (7–9). The first series describes the use of remdesivir in three patients without any resulting deterioration in their myasthenia (7). One case report describes a patient admitted for SARS-Cov2 infection with a simultaneous exacerbation of his MG. He was treated with dexamethasone and remdesivir, supplemented by plasmapheresis, with a positive clinical outcome (8). The last case describes a young female patient admitted with a diagnosis of MG, who was subsequently found to have SARS-Cov2 infection, requiring the administration of dexamethasone and remdesivir, with a good clinical response (9).

In a cohort of 93 patients with MG and infected with SARS-CoV-2, 72 were treated with an acetylcholinesterase inhibitor and a corticosteroid, 44 with an immunosuppressant (azathioprine, mycophenolate mofetil, cyclosporine or tacrolimus) and six with a biological agent, including four who received rituximab. Only 14 (15%) of the patients experienced a worsening of their MG following the infection with SARS-CoV-2 (three of these patients died and all three had received rituximab). The treatments of remdesivir, favipiravir and convalescent plasma taken for the infection were not associated with an exacerbation of the MG (10).

In a review of the literature on COVID-19 treatments administered to patients with MG, remdesivir was considered to be safe in the absence of any evidence of adverse effects on the MG (11).

According to the health authorities in the United Kingdom (NHS – National Health Service), remdesivir may be prescribed for patients with a neurological disorder such as MG (12).

The WHO global database of adverse drug reactions does not report any cases of a deterioration of MG for remdesivir. Two cases of myasthenia crisis have been reported (probably the same patient and therefore a duplicate entry), out of a total of 10,706 reported potential side effects of this drug. No further details are available since this was a spontaneous report without any clinical details.

Conclusion

When remdesivir was launched on the market, the experience with its use in certain subpopulations, including MG patients, was still lacking. In our hospital, this drug has been used in five patients known to have MG without any mention in their medical records of a subsequent deterioration of the underlying disease. Therefore, our clinical experience and the literature data are reassuring concerning the possibility of using this drug in patients with MG when there is a proven indication.

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swissmedic

JAK inhibitors: need for dosage individualisation?

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Janus kinases (JAK) are multi-domain non-receptor tyrosine kinases with pivotal functions in cellular signal transduction and provide unique opportunities in the modulation and long-term control of pathogenic immune response in multiple disease states (1). JAK inhibitors (JAKi) are used for multiple inflammatory and oncological disorders, such as inflammatory bowel diseases, rheumatoid arthritis, immune-mediated arthropathies (e.g. spondyloarthritis), multiple immune-driven dermatological diseases, myeloproliferative neoplasms, polycythaemia vera, essential thrombocythaemia, and more recently graft versus host disease (GvHD). In Switzerland, the first JAKi to be approved were ruxolitinib (Jakavi®, 2012) and tofacitinib (Xeljanz®, 2013).

The type of JAKi affinity to the receptor plays a key role in the drug properties and disease targets in these highly selective medications. All JAKi for chronic inflammatory diseases inhibit, at least partly, the JAK1 isoform: this specific inhibition could be associated with a class effect with respect to their safety (1).

The rapid rate of resynthesis (2–4h) for the isoforms JAK1, JAK2, and TYK2 impacts the spectrum of JAKi characteristics and their duration of action (2). Inhibition of one or more JAK isomers results in a wide range of biological responses (i.e., desired and untoward effects).

The pharmacokinetics of JAKi, such as the biological half-life, peak concentrations, the time to reach the maximum concentration at the target site, and the elimination pathways, as well as the binding type and the affinity to the four isomers, affect their pharmacodynamics. JAKi represent a chemically heterogenous group of medications with various pharmacokinetic and pharmacodynamic patterns of physiological actions: concentration-effect and concentration-adverse drug reaction (ADR) relationships are substance-specific. Efficacy and ADR depend essentially on the concentration-response relationship to adjust the drug dosage and drive concentrations close to target within therapeutic ranges. For instance, an association between plasma exposures and efficacy was observed in ulcerative colitis and rheumatoid arthritis patients treated with upadacitinib. Similar relationships were seen for serious infections, liver transaminase or CPK elevation, lymphopenia, and decrease in haemoglobin (3–5).

Novel mechanisms of immunosuppression inevitably entail a risk of either insufficient efficacy or toxic effects, raising dosage optimisation concerns for a large array of non-standard patients. Safety issues of JAKi (e.g. increase in cardiovascular events, cancers, opportunistic infections, reactivation of herpes zoster, chronic viral hepatitis infections, and latent tuberculosis) are discussed in a separate article in the newsletter.

Formatted standard-of-care to patients with straightforward oral administration is the rule to streamline immunosuppressive treatments, regardless of age, gender, pharmacogenetic profile, drug-drug interactions or disease-induced metabolic phenoconversion (6). Pharmacokinetic characteristics of JAKi and drug-drug interactions may affect the effectiveness and tolerability. In particular, the cytochromes P450 (CYP), whose activity is strongly influenced by genetic polymorphism and drug-drug interactions (induction or inhibition), play a critical role in the biotransformation of JAKi to active metabolites considered as active compounds. Pharmacokinetic characteristics of JAKi are summarised in Table 1.

Table 1. Pharmacological descriptions of the main JAKi available in Switzerland

Molecule	Drug name	Indications	Half-life	Dosage	Pharmacokinetic / DDIs
Abrocitinib	Cibinqo®	• AD • **Clinical studies**: Prurigo nodularis, chronic pruritus, plaque psoriasis	3–5 h	100–200 mg QD	• Elimination: mainly hepatic (<1% renal in unchanged form) • Substrate: CYP2C19 (major), CYP2C9 (major) • Active metabolites (renal elimination)
Baricitinib	Olumiant®	• RA, AD • **Swissmedic, FDA**: COVID-19 • **FDA, EMA**: alopecia areata • **Clinical studies**: SLE, lupus nephritis, type I diabetes, giant cell arteritis, PJIA, Sjögren's syndrome, pyoderma gangrenosum, HIV, dermatomyositis, …	12–16 h	2–4 mg QD	• Elimination: mainly renal (69% renal in unchanged form) • Substrate: CYP3A4, P-gp (minor)
Fedratinib	Inrebic®	• MF • **Clinical studies**: chronic neutrophilic leukaemia, acute myeloid leukaemia, essential thrombocythaemia, chronic beryllium disease	41 h	Depends on the platelet count and adverse effects: • Platelets ≥50 x 109/l :400 mg QD	• Elimination: mainly hepatic (3% renal in unchanged form) • Substrate: CYP3A4 (major) and FMO3. • Inhibits: CYP2C19 (moderate), CYP3A4 (moderate).
Ruxolitinib	Jakavi®	• MF, PV, aGvHD • **EMA, FDA**: cGvHD • **Clinical studies**: AD, vitiligo, CAR-T cell therapy-related cytokine release syndrome, COVID-19, breast cancer, acute lymphoblastic leukaemia, chronic myeloid leukaemia …	3h–5.8h	Depends on the platelet count: • Platelets > 200,000/mm³: ・MF: 20 mg BID ・PV: 10 mg BID • Platelets 100,000-200,000/ mm³ ・MF: 15 mg BID ・PV: 10 mg BID • Platelets 50,000-100,000/mm³ ・MF: max. 10 mg BID ・PV: 5 mg BID	• Elimination: mainly hepatic (<1% renal in unchanged form) • Substrate: CYP3A4 (major) • Active metabolites (renal elimination)

Molecule	Drug name	Indications	Half-life	Dosage	Pharmacokinetic / DDIs
Tofacitinib	Xeljanz®	• RA, PsA, UC • **EMA, FDA**: AS, UC, PJIA • **Clinical studies**: COVID-19, systemic sclerosis, Crohn's disease, alopecia areata, dermatomyositis, psoriasis, SLE, AD, AS, uveitis, sarcoidosis …	3 h	5–10 mg BID	• Elimination: mainly hepatic – 70% (30% renal in unchanged form) • Substrate: CYP3A4 (major)
Upadacitinib	Rinvoq®	• RA, PsA, AS, AD • **EMA, FDA**: UC • **Clinical studies**: Crohn's disease, PJIA, hidradenitis suppurativa, vitiligo, SLE, giant cell arteritis, Takayasu's arteritis	9–14 h	15–45 mg QD	• Elimination: mainly hepatic (24% renal in unchanged form) • Substrate: CYP3A4 (major)

AD, atopic dermatitis; aGvHD, acute graft versus host disease; AS, ankylosing spondylitis; BID, twice a day; CES, carboxylesterase; cGvHD, chronic graft versus host disease; CYP, cytochrome P450; DVT, deep vein thrombosis; FMO, Flavin-containing monooxygenase; GI, gastrointestinal; MACE, major adverse cardiovascular events; MF, myelofibrosis; PE, pulmonary embolism; P-gp, P glycoprotein; PJIA, polyarticular juvenile idiopathic arthritis; PV, polycythaemia vera; PsA, psoriatic arthritis; QD, once a day; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; UC, ulcerative colitis. **Table adapted from Tachet Revue Médicale Suisse, 2022** (7).

The drug actionability is enhanced by using different doses for different indications in a wide range of diseases in rheumatology, dermatology, haematology, infectiology, and immunology (Table 1). Recently, tofacitinib, filgotinib or upadacitinib indications have been extended to include gastroenterology for inflammatory bowel diseases. In clinical trials, Crohn's disease patients treated with upadacitinib were within off-label indications, with a tripling of the dose for the induction phase (45 mg/d) and a doubling of the dose for the maintenance phase (30 mg/d) compared to the dose administered for e.g. rheumatoid arthritis or atopic dermatitis (15 mg/d) (8, 9). However, tofacitinib and filgotinib (approved in the EU but not in Switzerland) dosages were not sufficiently high and failed in pivotal clinical trials for the treatment of Crohn's disease (phase 3), in contrast to ulcerative colitis, which requires lower doses (10 mg BID and 200 mg/day, respectively, in induction therapy) (10, 11). The difference in optimal doses between these patient populations with IBD is related to the difference in the exposure-response relationship and the expected risk-benefit trade-off (5).

Considering the inhomogeneous pharmacokinetic characteristics and the variations in dosage that significantly impact biological effects, JAKi are drug candidates that would require individual dose adjustment to optimise their effectiveness and safety profiles. Thus, dose-dependent efficacy and tolerability issues could be addressed by treatment individualisation approaches, such as therapeutic drug monitoring (TDM), using blood concentration as a marker for drug exposure-response optimisation (12).

In summary, JAKi are subject to a wide range of intrinsic and extrinsic factors (e.g. drug-drug interactions, patient characteristics, including pharmacogenetic profile) that influence their disease-specific efficacy and tolerability. Recently, clinical trials have provided new relevant information on

the crucial role of concentration-response relationships to balance the expected risk-benefit ratios. Using therapeutic drug monitoring for treatment individualisation, concentration-effect and concentration-tolerability relationships could constitute a new clinical marker to gain insight into the effectiveness and safety issues of JAKi.

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Increased risk of serious infections, major adverse cardiovascular events (MACE), malignancies, thrombosis, and all-cause mortality with Janus kinase inhibitors (JAKi) for chronic inflammatory diseases

Risk minimisation measures and risk communication by the FDA, EMA and Swissmedic

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Key messages

1. There is an increased risk of serious infections, MACE, malignancies, thrombosis and all-cause mortality with JAKi for chronic inflammatory diseases compared to TNFi (1).
2. The above AESIs are considered a class effect of JAKi for chronic inflammatory diseases (2).
3. JAKi have a dose-dependent toxicity (1).
4. There was no dose-dependent difference in the clinical efficacy of tofacitinib in RA (1). For safety, the lowest licensed/effective dose of JAKi for the indication should be used.
5. The efficacy of TNFi was similar to that of JAKi (1). Individual risk factors should be considered before starting treatment with JAKi.
6. JAKi, unlike TNFi, are administered orally, which might be relevant for the treatment of advanced RA.
7. The risk minimisation measures and risk communication by the FDA, EMA and Swissmedic for JAKi for chronic inflammatory diseases were similar, with the exception of restriction of the indication to post-TNFi and dose adaptation for certain patient groups with risk factors.

Introduction

The subject of this review is the Janus kinase inhibitors (JAKi) Cibinqo® (abrocitinib), Olumiant® (baricitinib), Rinvoq® (upadacitinib) and Xeljanz® (tofacitinib), which are licensed in Switzerland for the treatment of several chronic inflammatory conditions, including rheumatoid arthritis (RA), psoriatic arthritis, ankylosing spondylitis, ulcerative colitis and atopic dermatitis. The approved indications vary depending on the medicinal product as described in the respective information for healthcare professionals.

Two other JAKi, Jakavi® (ruxolitinib) and Inrebic® (fedratinib), are licensed for the treatment of myeloproliferative disorders and are not the subject of this review.

Cytokines are key drivers of inflammation in RA and other chronic inflammatory diseases. JAKi target and block cytokine signalling mediated by the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway, thereby regulating the immune response and cell growth (3). JAKi inhibit the four JAK isoforms (JAK1, JAK2, JAK3 and TYK2) with different selectivity (4):

- tofacitinib (JAK3 >JAK2 >JAK1)
- baricitinib (JAK1 and JAK2, and moderate activity against TYK2)
- upadacitinib (JAK1 >JAK2 and JAK3)
- abrocitinib (JAK1)

However, all JAKi that are the subject of this review inhibit JAK1, which is presumed to be a key target for RA and other inflammatory diseases since it associates with receptors for γ_c cytokines, interferons, type II cytokine receptors (e.g. IL-6) and other interleukins (5). The effects of the JAKi discussed on cytokine-receptor signalling are similar when compared at clinically effective doses for RA treatment (6, 7).

Increased cholesterol levels and malignancies in the clinical development programme with tofacitinib prompted the FDA to mandate a large, long-running post-approval randomised controlled study (A3921133; ORAL Surveillance) (1).

This study enrolled 4,362 patients with RA ≥50 years of age on MTX with at least one cardiovascular risk factor. Patients were randomised 1:1:1 to receive 5 or 10 mg tofacitinib BID or tumour necrosis factor inhibitor (TNFi). The FDA pre-specified ≥1,500 patients with a follow-up of 3 years, 103 MACE and 138 malignancies (excl. non-melanoma skin cancer (NMSC), incidence of which was already known to be increased with tofacitinib).

The study had the following endpoints:

1. Safety: MACE (fatal cardiovascular disease, non-fatal myocardial infarction or stroke) and cancers, excl. NMSC.
2. Efficacy: Simplified Disease Activity Index (SDAI) and Health Assessment Questionnaire–Disability Index (HAQ-DI).

The ORAL Surveillance revealed (8):

1. Safety

i. MACE (defined as cardiovascular death, myocardial infarction and stroke) and malignancies (including lymphomas and lung cancers) occurred more often with tofacitinib (5 and 10 mg) than with a TNFi. In this trial, the number needed to harm for tofacitinib at 5 mg BID relative to a TNFi was 567 patient-years for MACE and 276 patient-years for cancer. This means that 113 and 55 patients would need to be treated for 5 years with tofacitinib (rather than a TNFi) to result in one additional MACE and malignancy, respectively.

ii. In a prespecified subgroup analysis, differences in the risk of MACE and cancers between tofacitinib and a TNFi were more pronounced in patients ≥65 years of age than in younger patients.

iii. The risk for overall infections, including and excluding reactivation of herpes zoster, was significantly higher in patients treated with tofacitinib (5 or 10 mg) than with a TNFi.

iv. The incidences of death from any cause and of pulmonary embolism were significantly higher among patients treated with tofacitinib 10 mg (but not 5 mg) versus a TNFi.

v. Higher incidence of thrombosis (including pulmonary embolism, venous and arterial thrombosis) with tofacitinib versus a TNFi.

2. Efficacy

i. The efficacy of JAKi and TNFi was similar, assessed as improvements in SDAI and HAQ-DI scores.

3. Dosing

i. There was a dose-dependent significant difference in the frequency of serious infections, thrombosis (PE, VTE) and death from any cause. For MACE and malignancies the differences did not reach statistical significance.

ii. There was no dose-dependent difference in the clinical efficacy of tofacitinib (5 mg vs 10 mg) in RA.

Discussion

Spontaneous adverse drug reaction reporting shows several limitations, which are mainly related to under-reporting (9). Integrated clinical data sets might enhance sensitivity to detect adverse drug reactions when the duration of follow-up, size of treatment groups and chosen control are adequate. However, the ORAL Surveillance is by far the most thorough safety evaluation of a JAKi.

Despite differences in JAK-inhibition profiles, all JAKi share the same mechanism of action. In the absence of detailed safety data on non-tofacitinib JAKi, the FDA concluded that the identified risks observed with tofacitinib in RA apply to all JAKi approved for the treatment of chronic inflammatory diseases and extrapolated these data to all patients and all licensed indications (2). Swissmedic and the EMA adopted this approach (10, 11).

The FDA, EMA and Swissmedic mandated the following risk minimisation measures:

1. Update warnings

i. Based on the results of the ORAL Surveillance, all three national competent authorities required strengthening of the warnings on the label of the JAKi covered by this review regarding MACE, malignancies, thrombosis and increased all-cause mortality.

ii. In addition, the Swissmedic and EMA labels of the JAKi covered in this review state that JAKi should be used in the following patients only when no suitable treatment alternatives are available:

- Patients over 65 years of age,
- Patients who currently smoke or have previously smoked,
- Patients with other risk factors for malignant disease,
- Patients with other cardiovascular risk factors.

2. Boxed warning

The FDA, EMA and Swissmedic labels of the JAKi that are the subject of this review now include a boxed warning, the strictest and most serious type of warning.

The FDA updated the boxed warning at the beginning of the label, which now covers serious infections, higher rate of all-cause mortality, malignancies, MACE and thrombosis. Swissmedic added a similar boxed warning at the beginning of the label covering all these important AESIs.

The boxed warning in the EMA SmPC in section 4.4 "Special warnings and precautions for use" states that JAKi should be used only when there are no suitable alternatives available in patients ≥65 years, current or past smokers or those with risk factors for cardiovascular disease and cancer.

3. Limiting indication

The FDA limited the use of the JAKi covered in this review for all licensed indications to patients who have had an inadequate response or intolerance to one or more TNFi. The ORAL Surveillance revealed similar efficacy for tofacitinib and TNFi, with TNFi showing better safety. The results were extrapolated to all patient populations in all licensed indications.

4. Update of dose recommendations in patients with risk factors

The EMA revised the dosing recommendations for certain patient groups with risk factors and mandated a dose reduction to the next lowest licensed dose level for certain indications for patients at increased risk of VTE, MACE and malignancies, as well as for patients ≥65 years of age and for patients with a history of chronic or recurrent infections.

As stated above, the ORAL Surveillance revealed dose-dependent toxicity for tofacitinib, whereas the efficacy of tofacitinib was not dose-dependent.

5. DSC / DHPC

Based on the results of the ORAL Surveillance, the FDA, EMA and Swissmedic mandated drug safety communications in 2019 and 2021. In March 2023, the MAHs of the JAKi covered in this review circulated joint DHPCs mandated by Swissmedic and the EMA on the JAKi class effect.

In summary, the FDA mandated a large post-marketing safety study with a long follow-up on tofacitinib vs. TNFi in RA patients. This study revealed that tofacitinib had a higher risk for serious infections, MACE, malignancies, thrombosis and all-cause mortality compared to TNFi. In contrast to the safety profiles, the efficacy was similar/comparable in the three treatment arms.

In the absence of detailed safety data for non-tofacitinib JAKi, the FDA, EMA and Swissmedic considered these AESIs to be a class effect for all JAKi for chronic inflammatory diseases.

The risk minimisation measures and risk communication by the FDA, EMA and Swissmedic were similar, with the exception of restriction of the indication and dose adaptation for patients with risk factors (Table 1).

Table 1. Summary of risk communication on JAKi covered in this review

	FDA	EMA	SMC
Label update of **Warnings and Precautions**	✓	✓	✓
Boxed warning in label	✓	✓ (Last line treatment in patients with risk factors)	✓
Limiting indication to post-TNFi	✓	-	- (Further measures are under evaluation)
Update of dose recommendations in patients with increased risk for thrombosis, MACE and malignancies	-	✓	- (Further measures are under evaluation)
DSC / DHPC	✓ Link	✓ Link	✓ Link

Abbreviations

AESI	adverse event of special interest
BID	twice a day
DHPC	direct healthcare professional communication
DSC	drug safety communication
EMA	European Medicines Agency
FDA	Food and Drug Administration (USA)
HAQ-DI	Health Assessment Questionnaire–Disability Index
IL	interleukin
JAK	Janus kinase
JAKi	Janus kinase inhibitor
MACE	major adverse cardiovascular events
MAH	marketing authorisation holder
MTX	methotrexate
NMSC	non-melanoma skin cancers
PE	pulmonary embolism
RA	rheumatoid arthritis
SDAI	Simplified Disease Activity Index
SmPC	Summary of Product Characteristic
STAT	signal transducer and activator of transcription
TNFi	tumour necrosis factor inhibitor
VTE	venous thromboembolism

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Myocarditis and pericarditis following COVID-19 immunisation in elderly patients: evaluation of case reports received by Swissmedic

Valeriu Toma, MD; Irene Scholz, MD, MPH; Thomas Schwartz MD; Tugce Akyüz, Pharmacist; Thomas Stammschulte, MD

Safety of Medicines Division, Swissmedic

Introduction

Myocarditis and pericarditis became an important safety issue of the mRNA-based COVID-19 vaccines, with a primary focus on young male patients, who are predominantly affected (1). So far, little is known about similar cases following vaccination in elderly people, although suspected cases with fatal outcome were recently published (2). Therefore, Swissmedic Pharmacovigilance performed a careful examination of case reports received in this particular age group.

Methods

Evaluation with descriptive statistics of case reports from the Swiss pharmacovigilance database in elderly patients (≥ 65 years).

Results

By the end of 2022, Swissmedic had received 32 case reports of myocarditis (n=9), pericarditis (n=14) or perimyocarditis (n=9) in elderly patients. Of these, 20 cases were reported in association with the Moderna COVID-19 vaccine and 11 with the Pfizer-BioNTech vaccine. Based on criteria of the US CDC (3), the clinical diagnosis of myocarditis and/or pericarditis was mostly judged as "probable" (n=11) or "confirmed" (n=10). More cases of myocarditis (5/9) and perimyocarditis (4/9) remained clinically unconfirmed compared to cases of pericarditis (2/14).

The age of patients ranged between 65 and 88 years (mean=72 years) and more events were reported in men (n=21; 65.6%) than in women (n=9; 28%). Pre-existing cardiovascular diseases were recorded in 13 of the 32 patients. At the time of reporting, 22 cases were clinically recovered or recovering. However, 6 cases needed ICU-treatment and 1 case had a fatal outcome.

More cases were reported after the second vaccine dose (n=16; 50%) compared to the first (n=9; 28%) or the third dose (n=4; 12%). The time to onset (TTO) ranged from <1 to 327 days (median=14.5 days), with a faster onset of symptoms after the second (median TTO=11.5 days) or third vaccine dose (median TTO=12.5 days) compared to the first dose (median TTO=22 days). In most of the 32 cases (n=23; 72%) the TTO was shorter than 28 days.

Conclusions

These findings enhance the knowledge about cardiac adverse reactions to the mRNA vaccines against COVID-19 in the elderly population. Swissmedic received reports of confirmed myocarditis and/or pericarditis in temporal association with mRNA COVID-19 vaccines for this age group as well. Most cases had a favourable outcome, whereas some cases had a severe clinical course. Hence, these diagnostic entities should be considered and thoroughly clarified in elderly patients with suggestive cardiac symptoms following vaccination.

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Reports of suspected adverse reactions following vaccination with a bivalent COVID-19 vaccine

Irene Scholz, MD, MPH; Thomas Stammschulte, MD

Safety of Medicines Division, Swissmedic

Swissmedic approved Moderna's bivalent COVID-19 boosters in August 2022 (Spikevax bivalent Original/Omicron BA.1) and March 2023 (Spikevax bivalent Original/Omicron BA.4-5), and Pfizer's bivalent booster in October 2022. In addition to the original strain of SARS-CoV-2, these vaccines also cover the stated Omicron subvariants.

A total of 299 reports of side effects following vaccination with a bivalent vaccine were received up to 15 March 2023. In 127 further cases concerning a fourth or fifth vaccination, it remains unclear whether the bivalent vaccine was involved. These cases were excluded from this evaluation.

The 299 reports result in a reporting rate of 0.3 reports per 1,000 vaccine doses for the bivalent vaccines. The reporting rate is therefore lower than for the COVID-19 vaccines overall (1). The majority (n =166, 56%) of the reports came from medical professionals; in 44% (n =133) of cases, the reports were submitted by the person affected or a relative. Most of the reports (n =221, 74%) were classified as non-serious. 121 (40.5%) cases concerned women, 73 (24.4%) men; 105 (35.1%) reports did not specify gender. The median age of those affected was 56 (age range: 2–102).

In total, the reports included 980 reactions, i.e. an average of three reactions were listed per report. At the time the reports were submitted, the outcome of the adverse reaction was predominantly indicated as "unknown". The most frequent incidents given in the reports fall under the category "Product storage errors and issues in the product use system". These cases were not associated with an adverse drug reaction. The most commonly reported side effects in all reports included headache, fever, fatigue, urticaria and joint pain. Among the serious reports, headache, nausea, fatigue, fever and chills were the most common adverse reactions. The side effects profile is therefore similar to that of the monovalent vaccines (1). There is no evidence in the reports to indicate any hitherto unknown side effects of the vaccines. Evaluations of reports on Omicron-adapted bivalent COVID-19 vaccines by other regulatory authorities reach similar conclusions (2, 3).

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Reports of suspected adverse reactions following monkeypox vaccination in Switzerland

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Introduction

As of November 2022, the Bavarian Nordic smallpox vaccine, which is authorised in Europe and the USA, may be administered in Switzerland to high-risk individuals as a preventive measure against infection with the monkeypox virus. The cantons are responsible for the organisation and administration of the vaccinations and stipulate where people can be vaccinated. The Federal Office of Public Health (FOPH) has published comprehensive information on the ongoing vaccination campaign and treatment of monkeypox infections on its website (1).

The vaccination with Jynneos® is provisionally being administered in Switzerland on a no-label basis without authorisation. No-label means that, since Swissmedic has not authorised the product in Switzerland, the Jynneos® vaccine is administered without the information for healthcare professionals or patient information specific to Switzerland. At the end of 2022, the manufacturer Bavarian Nordic submitted an application to Swissmedic for the authorisation of the equivalent smallpox vaccine Imvanex®.

Swissmedic is responsible for the market surveillance of authorised medicinal products (MPs), MPs which are exempt from authorisation as well as MPs that are not authorised in Switzerland, but are imported into Switzerland (based on exemption provisions).

According to the Therapeutic Products Act, medical professionals must notify Swissmedic of any serious or previously unknown adverse reactions and medically significant incidents involving therapeutic products (Art. 59 para. 3 TPA).

The reporting of suspected adverse drug reactions by healthcare professionals is an important pillar of vaccine safety. Medical professionals can submit reports to Swissmedic directly via the ElViS reporting portal (2, 3).

Private individuals can also report suspected adverse reactions via a Swissmedic online portal (4, 5).

Results

By 5 March 2023, Swissmedic had reviewed 39 reports of suspected adverse drug reactions (ADRs) following vaccination with Jynneos®, as well as three case reports in association with the Imvanex® vaccine.

37 (88%) ADR reports after monkeypox vaccination were received from directly affected persons, i.e. the patients, or their relatives, and five (12%) reports were submitted by medical professionals. In 39 (92.9%) reports, the affected persons were men, who currently constitute the group of people at risk of contracting monkeypox.

All of those affected were aged between 18 and 64 years (39.8 years on average). 31% were over 44 years of age, while 69% were in the 18 to 44 age group.

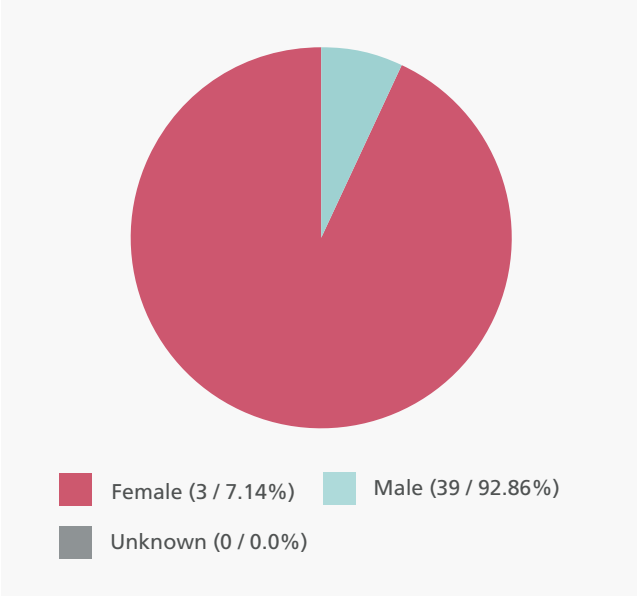

Figure 1. Sex distribution

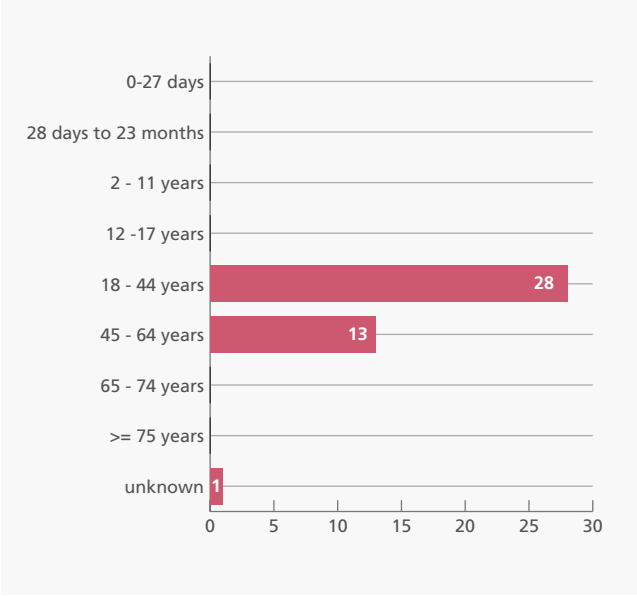

Figure 2. Age distribution

Of the 42 reports received, 40 (95.2%) were reported as "**non**-serious", while two of the suspected adverse reactions (4.8%) were classified as "serious" by the reporting individuals. Most of the reports involved more than one reaction. In total, 90 reactions were reported, corresponding to an average of 2.1 reactions per report.

The most commonly reported ADRs were local injection site reactions, headache, fatigue or fever (pyrexia).

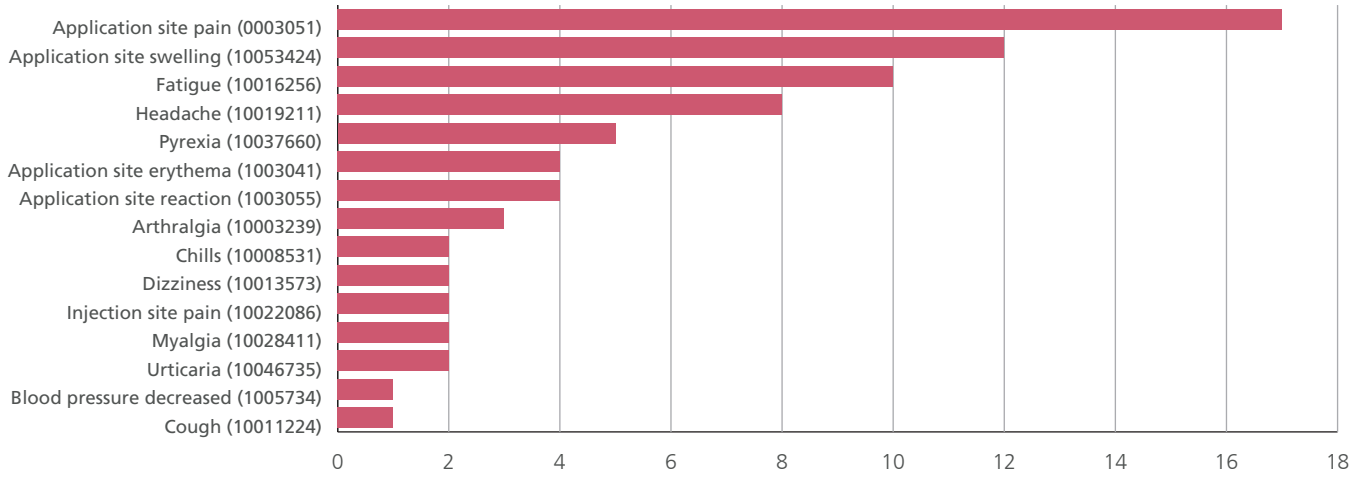

Figure 3. Top 15 preferred terms

Discussion

The reports of adverse reactions to the monkeypox vaccination received and reviewed to date in Switzerland were overwhelmingly non-serious and were in line with the known risk profile for the monkeypox vaccine used. There is no evidence in the reports to indicate any hitherto unknown risks of the vaccine. A review of 118 reports related to Imvanex® received by Lareb, the Dutch pharmacovigilance system, also did not indicate any new risk signals (6).

Reporting adverse reactions or suspected adverse reactions makes an important contribution to the safety of the vaccine against monkeypox. The links to the reporting portals are listed in the references.

References

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(6) Overview of reports after monkeypox vaccination (lareb.nl)

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Swiss Haemovigilance System

Incorrect Blood Component Transfused (IBCT) and Near Misses

Julia Engels, MD; Max Mendez Lopez, MD

Safety of Medicines Division, Haemovigilance, Swissmedic

Abstract

The reporting and processing of errors in the transfusion chain represent an opportunity to increase the safety of transfusions. These errors include transfusion errors ("incorrect blood component transfused", IBCT) and errors detected before a transfusion took place (Near Misses). The analysis of these errors plays a significant role in haemovigilance. In Switzerland, reporting of these events to Swissmedic is mandatory by federal law.

In 2021, 2,585 Near Misses and 49 IBCT were reported, including five cases of "wrong component transfused" (wrong patient / product, ABO-compatible by chance).

Introduction

Haemovigilance is a set of surveillance procedures that cover the entire blood transfusion chain, from the donation and processing of blood to the epidemiological follow-up of patients (1). In the previous edition of Vigilance News, we presented an overview of the regulatory aspects governing the haemovigilance system in Switzerland and focused on transfusion reactions reported to Swissmedic in 2021. Today, we turn our attention to the reporting of errors in the transfusion process in 2021.

Errors in the transfusion chain consist of transfusion errors, also known as IBCT (Incorrect blood component transfused), and errors that were detected before a transfusion took place – so-called "Near Misses" (NM) or "errors without harm".

Swissmedic is responsible for monitoring the safety of medicinal products according to Art. 58 TPA (Therapeutic Products Act, SR 812.21), including blood and blood products according to Art. 4 para. 1 TPA. Art. 59 para. 3 TPA requires serious or previously unknown adverse effects and incidents, observations of other serious or previously unknown facts and quality defects that are of significance for drug safety to be reported. Equally, reporting adverse events relating to medicinal products (including transfusion errors) to Swissmedic is mandatory according to Art. 63 of the TPO (Therapeutic Products Ordinance). The explanatory report on the TPO (published in September 2018) explicitly addresses Near Misses in this context.

Looked at more closely, IBCT are events where a blood component was transfused to a patient for whom it was not intended, where the transfusion was compatible by chance, was not suitable or not necessary, or where the transfusion was delayed for a significant amount of time (2). Depending on the kind of error, IBCT have a high potential to cause morbidity or death. Near Misses are "errors without harm" but involve incidents in which an intended process failed.

Thus, a structured analysis of these events helps to identify gaps in safety mechanisms, sources of errors, effective barriers and potential points for improvement and thereby increase transfusion safety.

Transfusion errors in 2021

Swissmedic classifies IBCT events following the criteria defined by SHOT (Serious Hazards of Transfusion), the haemovigilance scheme of the United Kingdom – seen in Table 1 (3). A transfusion error can originate from any point in the transfusion chain: ordering the blood product, taking the blood sample, laboratory analysis, releasing the product or the transfusion itself. In order to carry out an adequate analysis, error reports include the

cause and type of deviation (e.g. communication, documentation, technical error), as well as error discovery and measures taken on site.

In terms of severity, IBCT and NM events are classified according to their potential harm or – in the case of NM – risk of mix-up. For a detailed explanation of severity and for further examples, please refer to the "Annual Haemovigilance Report 2021" (Publications & Events, swissmedic.ch).

A total of 49 IBCT and 2,585 Near Misses were reported to Swissmedic in 2021, which corresponds to reporting rates (RR) of 0.18/1,000 (IBCT) and 9.1/1,000 (NM) transfusions. In the case of IBCT, the RR is slightly higher than that for 2020 (0.14/1,000), but remains within the 5-year average of 0.16/1,000 transfusions (Figure 1).

Table 1. IBCT classification

Wrong component transfused (WCT)
Cases in which a patient was transfused with a blood product different from the one prescribed (e.g. platelets instead of RBC), in which the blood product was of an incorrect blood group or was intended for another patient (and was ABO/RhD incompatible), or where the blood product was transfused to another patient and was compatible by chance.
Specific requirements not met (SRNM)
Cases in which the transfused blood component did not meet the required specifications because of an error (e.g. irradiated products or HLA-matched platelets when indicated). **If the deviation is the result of a deliberate clinical decision (e.g. because of an emergency situation) it is not considered an SRNM** (one exception here is the deliberate administration of Rhesus D-positive blood to Rhesus D-negative recipients in the context of a mass transfusion – this situation should be reported).
Handling and storage errors (HSE)
Cases in which a blood product is selected and tested correctly, but its quality or safety are compromised due to errors in handling or storage (e.g. interruption of the cold chain, incorrect thawing of plasma, shelf life exceeded).
Avoidable, delayed or under-/over-transfusion (ADU)
ADU is the term used to describe errors in the quantity and timing of transfusions: **Avoidable transfusions**: Transfusions in which the indication was incorrect, e.g. due to incorrect laboratory results (such as false low haemoglobin or platelet values), errors in transmitting results or incorrect clinical decisions. The term also covers the avoidable use of emergency products (0 RhD neg). **Delayed transfusions**: Clinically indicated transfusions, which were not given or were given with a relevant delay. These include, for example, the delayed provision of blood products in an emergency situation with relevant delays in patient care (e.g. rescheduling of surgery) **Over-/under-transfusion**: Transfusion of too large or too small a quantity of a product, e.g. due to incorrect prescription or the malfunction of an infusion pump.
Right blood, right patient (RBRP)
Incidents in which the transfusion was correct but there were relevant errors in identifying or prescribing the blood products. These include, for example, damaged or incomplete labelling, a missing patient ID bracelet, a missing official prescription or missing signatures.

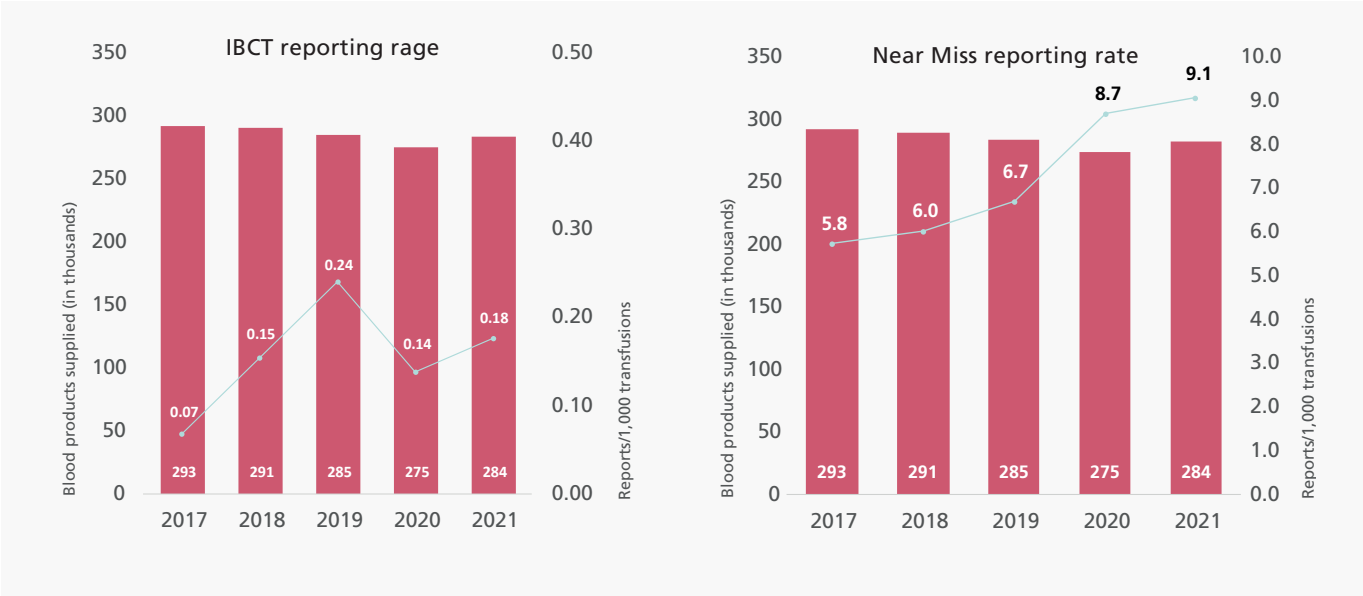

Figure 1. IBCT and Near Miss reporting rates

The reporting rate for IBCT in 2021 remains within the 5-year average of 0.16/1,000. The reporting rate for Near Misses rose in 2021 (9.1 reports per 1,000 transfusions in 2021 versus 8.7 in 2020).

The reporting rate for IBCT in 2021 remains within the 5-year average of 0.16/1,000. The reporting rate for Near Misses rose in 2021 (9.1 reports per 1,000 transfusions in 2021 versus 8.7 in 2020).

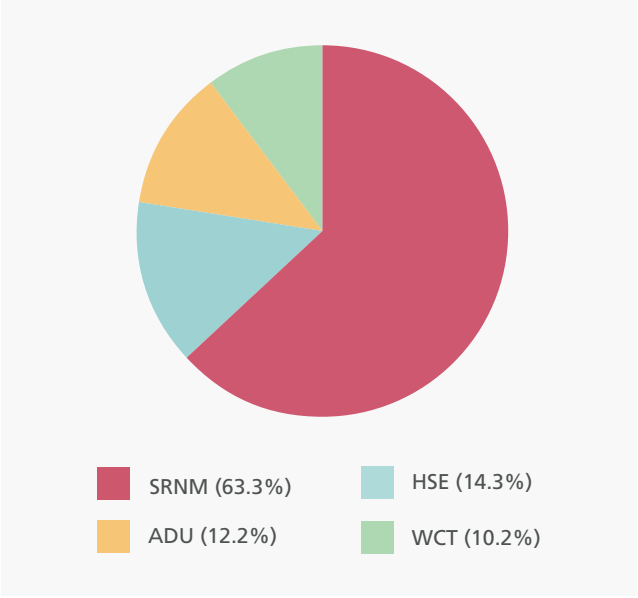

Figure 2. Transfusion errors/IBCT reported in 2021

SRNM represent the most commonly reported category of transfusion errors/IBCT

Within the IBCT subcategories, SRNM accounted for the majority of reports in 2021 (n=31; 63.3%), followed by HSE (n=7, 14.3%) (Figure 2). The majority of SRNM occurred at the step of "component selection" (n=26, 84%) and, in most cases, involved giving Rhesus D positive blood to Rhesus D negative patients (so called "Rhesus D conversion"; n=11, 35%). There were no ABO-incompatible transfusions reported in 2021, while three events were reported as ABO-compatible by chance (6%).

The cause of IBCT (all subclasses) was localised in the clinical area in 56% of cases - with a similar distribution in the subclasses of SRNM and ADU. HSE occurred predominantly in the clinical area, while the majority of WCT originated in the laboratory (Figure 3). The majority of near misses occurred in the clinical area (preparation and administration, 96% in total), with 89% of the grade 3 errors being localised in clinical preparation. Errors were mostly discovered in the laboratory (81% of the NM reports), which illustrates the importance of sequential control (and the possibility of discovering an error) at each step of the transfusion process.

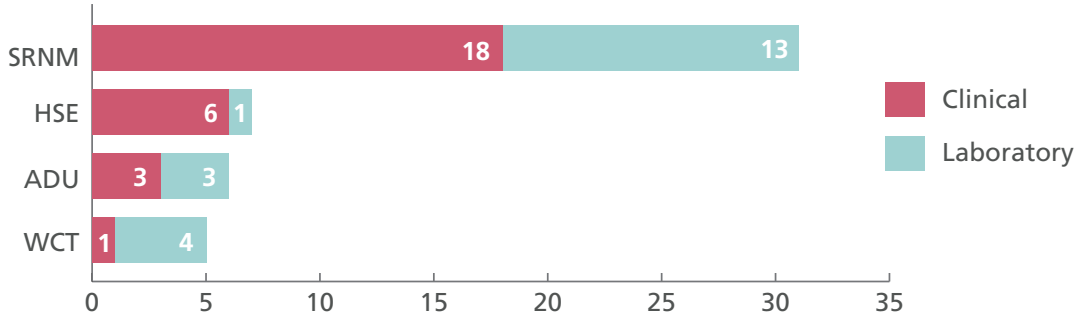

Figure 3. Localisation of error in ICBT (reported in 2021)
Localisation of error in IBCT events. The numbers represent the absolute amount of reports.

Different factors or situations contribute to the occurrence of transfusion errors. While half of the IBCT reported in 2021 were related to a human error (51 %), contributing factors and a lack of barriers exist in most situations. The following contributing factors were identified for the five cases of "wrong component transfused (WCT)": emergency situations with mix-ups due to temporary patient identification, mix-ups due to verbal prescriptions as well as the transfer of information (interface).

Conclusion

Improvement in transfusion safety is one of the main goals of haemovigilance, which proactively looks for safety gaps and sources of error so that actions can be taken to minimise risk. The structured analysis of IBCT and Near Misses aims to identify failed control mechanisms and points in the transfusion chain that can be improved. Furthermore, individual examples can be helpful in raising awareness of particularly critical processes. The processing and reporting of errors represent an opportunity to increase the safety of transfusions.

References

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Information on the Swissmedic website

Pharmacovigilance in the spotlight

Learning from adverse reaction reports – cases from pharmacovigilance

09.05.2023
Metamizole and agranulocytosis

11.04.2023
Loperamide and intentional overdose

08.02.2023
Drug-induced pancreatitis

26.11.2022
Fluoroquinolones and tendon inflammation/ruptures

21.11.2022
Amiodarone and hyperthyroidism

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

Side effects of COVID-19 vaccines in Switzerland

24.02.2023
Reports of suspected adverse reactions to COVID-19 vaccines
16,855 reports of suspected adverse vaccination reactions evaluated

You can access the complete overview at the following web address:
www.swissmedic.ch/covid-19-en

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Healthcare Professional Communication

Some links are available in German/French only

24.05.2023
DHPC – Simponi® (Golimumab)
Wichtige Änderungen der Hinweise zur Handhabung des Fertigpens

05.05.2023
HPC – Becetamol (Propylene glycol)
The propylene glycol concentration following the administration of Becetamol Drops at the recommended dosage exceeds the defined thresholds for propylene glycol in neonates and children under 5 years

13.04.2023
DHPC – Simulect (basiliximabum)
Important information on Simulect preparation for injection 10 mg and 20 mg

01.03.2023
DHPC – Januskinase (JAK)-Inhibitoren / Cibinqo® (Abrocitinib), Olumiant® (Baricitinib), Rinvoq® (Upadacitinib) und Xeljanz® (Tofacitinib)
Erhöhtes Risiko für Malignome, schwerwiegende kardiovaskuläre Ereignisse (MACE), schwerwiegende Infektionen, Thrombosen und Gesamtmortalität

09.12.2022
DHPC – Mitem 20 mg, Pulver zur Herstellung einer Injektions- bzw. Infusionslösung oder zur Herstellung einer Lösung zur intravesikalen Anwendung
Aufhebung der Vorsichtsmassnahme der zusätzlichen Filtration vor Anwendung

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Announcements

17.05.2023
Establishment licence for Dr. Heinz Welti AG: Suspension of establishment licence at Gebenstorf site lifted
Manufacturing and distribution activities at the Bubendorf site still suspended

11.05.2023
Establishment licence of Amino AG: Manufacture of non-sterile medicinal products permitted again at the Gebenstorf site
Manufacturing and distribution activities at the Belp site still suspended

01.05.2023
Changes to the guidance document GMP compliance by foreign manufacturers and the form Declaration by the Responsible Person for foreign manufacturers
Clarification of the requirements for the submission of audit reports

01.05.2023
Changes to the forms for new authorisations of and variations to human and veterinary medicinal products)
Information on study design and data sources of RWE in application forms

21.04.202
Swissmedic issues warning about erectile stimulants from online sources
Man hospitalised after taking illegal erectile stimulants – Swissmedic issues warning about erectile stimulants from Internet sources

11.04.2023
Swissmedic approves bivalent Pfizer Ltd. COVID-19 Original / Omicron BA 4-5 booster dose for adults aged 12 and over
Bivalent Original / Omicron BA.4-5 mRNA vaccine (tozinameran / famtozinameran) approved

04.04.2023
Update – Warning about supposedly herbal products
Swissmedic is issuing an urgent warning regarding slimming products and other supposedly natural products

27.03.2023
Comirnaty® COVID-19 vaccines from Pfizer AG: authorisation without special conditions approved
Three formulations (authorisation nos. 68225 and 68710, with 30 and 10 µg/dose) authorised for five years

17.03.2023
eCTD v4.0 Implementation Guide published
Swissmedic has published the Implementation Guide for eCTD v4.0. The package is now available for download

15.03.2023
Adaptations of the templates Patient information for herbal medicinal products and Patient information for homeopathic and anthroposophic medicinal products
Templates have been updated and better structured

08.03.2023
Swissmedic issues unlimited authorisation for booster dose of Moderna's bivalent COVID-19 Original / Omicron BA.4-5 vaccine
Spikevax bivalent Original / Omicron BA.4-5 mRNA vaccine authorised for people aged 18 and over

03.03.2023
Authorisations of complementary and herbal medicinal products in 2022
This report provides, among other things, an overview of the number of authorisations of complementary and herbal medicines with indication and complementary medicines without indication in 2022.

02.03.2023
Authorisations of human medicinal products with a new active substance and additional indications 2022
47 human medicinal products with new active substances authorised

01.03.2023
Changes to the guidance document Product information for human medicinal products
The detailed Information for healthcare professionals and Patient information templates are being withdrawn

01.03.2023
New Mobile technologies guidance document for human and veterinary medicinal products
Regulations on the use of QR codes on packaging and in medicinal product information

15.02.2023
Modifications to guidance document "Formal requirements"
Clarification of documentation to be submitted for co-marketing medicinal products; conditions can be the subject of collective applications

13.02.2023
Public consultation on ICH Guideline M13 "Bioequivalence for Immediate-Release Solid Oral Dosage Forms" launched in Switzerland
Swissmedic launches the public consultation on Guideline M13 of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH Guidelines), with a deadline of 26 May 2023 for comments

13.02.2023
Applications for clinical trials with medicinal products and ATMPs (advanced therapy medicinal products)
can be submitted via portal from early summer 2023

10.02.2023
Illegal imports 2022: many confiscated shipments contained erectile stimulants
Number of illegally imported therapeutic products has decreased

01.02.2023
Efficacy of monoclonal antibodies against SARS-CoV-2 variants

23.01.2023
Validity of GMP certificates during the COVID-19 pandemic
Update of the validity period of EMA GMP certificates

20.01.2023
Strategic objectives 2023–2026
The strategy for 2023-2026 was developed with recognised strategy development methods that have demonstrated their usefulness in practice.

17.01.2023
Authorities clearly work together
There are products and substances that are difficult to classify – for example, is a product containing hemp or hemp extracts (e.g. a CBD oil) a foodstuff, a therapeutic product, a cosmetic or a chemical? Depending on the answer, different legislation applies and different authorities are responsible. A cross-agency committee of experts with representatives from various cantonal authorities regularly advises on these types of delimitation questions.

15.01.2023
Changes to the guidance document Authorisation of human medicinal products under Art. 13 TPA
Application of Art. 13 TPA possible for temporary additional indications

15.01.2023
Changes to the Guidance documents Fast-track authorisation procedure and Temporary authorisation for human medicinal products
Extension of the time limit for finalising the decision minutes. Exchange of documentation for the AAA now possible via the eGov portal

10.01.2023
Illegal imports of medicines: Swissmedic warns against the risk of dependence associated with the long-term use of nasal sprays and laxatives
Increase in illegal imports of nasal sprays and laxatives

01.01.2023
Changes to SwissPAR HMV4 guidance document
Section 5, Clinical Assessment, of the Public Assessment Report is not part of the SwissPAR

15.12.2022
Clarification of terminology for combination products (medicinal products with a medical device component)
Current status and revision of specification documents

13.12.2022
Reporting suspected adverse reactions following vaccination against mpox (monkeypox)
Suspected adverse reactions can be reported electronically

02.12.2022
Reports of adverse reactions to veterinary medicinal products 2021
Vigilance for veterinary medicinal products Annual report 2021

01.12.2022
Expansion of scope of temporary authorisations
Temporary additional indications will also be possible from 1 January 2023

30.11.2022
Meeting of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)
Excellent Progress by ICH Expert Working Groups in Incheon, Republic of Korea

28.11.2022
Public consultation on ICH Guideline M11 "Clinical electronic Structured Harmonised Protocol (CeSHarP)" launched in Switzerland

28.11.2022
Public consultation on ICH Guideline Q5A(R2) "Viral safety evaluation of biotechnology products derived from cell lines of human or animal origin" launched in Switzerland

21.11.2022
Access Consortium Statement on Good Manufacturing Practice (GMP) Inspections Reliance and Recognition
Access Consortium commits to demonstrate greater inspection reliance and accept GMP inspection outcomes held amongst their members

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

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