

Report of an adverse drug reaction (ADR):

Swissmedic recommends using the reporting portal.

• Online reporting portal EIViS:

Direct-insert or by xml-files upload.

Details:

www.swissmedic.ch/elvis

Content

Editorial	1
Flash: Drug safety signals.....	3
• Toxic cerebellar syndrome due to methotrexate	3
• Direct oral anticoagulants (DOAC) – update	4
• Accidental overdoses of low-dose methotrexate	9
• Progressive multifocal leukoencephalopathy and medicinal products for treating multiple sclerosis – update.....	11
• Differing regulatory assessment of liver injury in hepatitis C patients	12
Regulatory	14
• Medical assessment of individual case reports	14
• FAQ Enhanced Pharmacovigilance	14
Information on the Swissmedic website	16

Impressum

Editorial team

Martina Schäublin, Eva Eyal, Helena Bill, Joy Diggelmann

Authors

Beat Damke, Dirk Essers, Thomas Munz, Wolfgang Renftle, Thomas Schwartz, Rudolf Stoller

We want to thank all colleagues for their contribution to the realisation of this edition of Vigilance-News.

Contact

Please send your comments, questions or suggestions to the following address:

news.vigilance@swissmedic.ch

Editorial

Dear Reader

Before a medicinal product is newly authorised, the future marketing authorisation holder must submit a Risk Management Plan (RMP) to Swissmedic. This plan describes the identified and potential risks associated with the product's active ingredient and the measures the marketing authorisation holder intends to take to track and minimise these risks. In addition, once the medicinal product has been authorised, further as yet unavailable data – relating to specific patient groups or administration over a prolonged period, for example – also need to be obtained. This can be achieved through specific studies, but also by means of training materials and certain instructions for use. The risk-benefit ratio stated at the time of authorisation can change constantly as a result of such new findings.

In the interests of transparency, Swissmedic decided to publish «RMP Summaries», concise descriptions of the most important known and suspected risks of medicinal products, including measures for preventing or minimising them, on the Swissmedic website:

<https://www.swissmedic.ch/marktueberwachung/00135/00165/03153/index.html?lang=en>

These «RMP Summaries» are provided in English by the marketing authorisation holders, who are also responsible for the accuracy of their content. However, the medicinal product information texts approved by Swissmedic (Information for healthcare professionals and Patient Information) published on www.swissmedicinfo.ch remain the binding reference documents for their use. The published RMP Summaries are referenced in this medicinal products information system.

Another measure for reducing the risks associated with new and known medicinal products is «enhanced pharmacovigilance», which goes beyond the routine pharmacovigilance measures of spontaneous reporting, signal detection and reviewing PSUR/PBRER (Periodic Safety Update Reports/ Periodic Benefit-Risk Evaluation Reports). Enhanced pharmacovigilance is the targeted, structured collection of data on specific safety issues associated with a medicinal product following market authorisation. It comes into effect when the data situation indicates that further information needs to be collected. The focus is on certain adverse drug reactions (ADR) arising from an active ingredient and/or a safety signal.

Examples include monitoring or reporting progressive multifocal leukoencephalopathy (PML) associated with medicinal products for multiple sclerosis, or observing accidental overdoses with methotrexate. Coordinated cooperation between the marketing authorisation holder and Swissmedic is extremely important in evaluating these cases, e.g. by means of specific questionnaires and/or hearings, so that the risk-benefit ratio can be continually reassessed as reliably as possible and corresponding measures initiated if applicable.

We hope you find this edition of Vigilance-News an interesting read and look forward to receiving your feedback at news.vigilance@swissmedic.ch.

The Editors

Flash: Drug safety signals

The interesting case: toxic cerebellar syndrome due to methotrexate

The following literature report was submitted to us by several pharmaceutical companies that market medicinal products containing methotrexate in Switzerland. Like traditional spontaneous reports, Swissmedic continuously assesses literature reports and reviews them in particular for their signal impact.

A study group at Berne's *Inselhospital* describes the case of a 62-year-old woman who was admitted to the emergency department after falling down stairs (1). The patient had fallen frequently in recent weeks and was also developing dysarthria and dysphagia. For the past 4.5 years she had been receiving treatment for rheumatoid arthritis in the form of 25 mg subcutaneous methotrexate per week and 5 mg folic acid per day. She was also taking quetiapine, lamotrigine and aripiprazole as concomitant medication for a bipolar disorder.

Physical examination revealed signs of a cerebellar syndrome, including gaze-evoked nystagmus, hypermetric saccades, inability to suppress vestibular nystagmus with visual fixation and dysarthria. Her gait was also ataxic and her stance during Romberg's test was unsteady. Blood tests and cerebrospinal fluid analysis were normal. MRI scans and a subsequent differential diagnosis procedure suggested the diagnosis of toxic cerebellar syndrome due to methotrexate. Methotrexate was discontinued, and six months later the clinical symptoms and examination findings had improved significantly.

This patient developed a partially reversible cerebellar syndrome caused by the toxic effects of subcutaneous treatment with methotrexate for several years. Leukoencephalopathy is a rare side effect of methotrexate that is described in both the Information for healthcare professionals

of drugs containing methotrexate and in the literature (2–5). The risk appears to be higher after intrathecal or high-dose intravenous administration than after low-dose oral or subcutaneous administration. The severity can vary widely, ranging from minimal encephalopathy that can only be detected in specific neurological examinations to substantial functional disorders and deficits involving cognitive impairment, psychoses, motor disorders, tremor, convulsions, visual disturbances, dementia and loss of consciousness.

Our Swiss drug safety database documents 13 further individual case reports of encephalopathy associated with methotrexate. 11 cases were reported by healthcare professionals to a Regional Pharmacovigilance Centre, while two reports were received from pharmaceutical companies.

Conclusion

We agree with the authors that the possibility of toxic cerebellar syndrome should be considered in any patient presenting with cerebellar dysfunction while taking methotrexate. Detection is crucially important because early discontinuation of methotrexate can greatly improve the symptoms and examination findings.

References

- 1) Kinzel O et al., Toxic cerebellar syndrome due to methotrexate, *Prac Neurol* 2015; 15: 214-215
- 2) Aradillas E et al., Methotrexate-induced posterior reversible encephalopathy syndrome, *J Clin Pharm Ther* 2011; 36: 529-536
- 3) Raghavendra S et al., Disseminated necrotizing leukoencephalopathy following low-dose oral methotrexate, *Eur J Neurol* 2007; 14: 309-314
- 4) Gowan GM et al., Methotrexate-induced toxic leukoencephalopathy, *Pharmacotherapy* 2002; 22: 1183-1187
- 5) Ferhanoglu B et al., Intrathecal methotrexate-induced acute cerebellar syndrome, *Ann Hematol* 2003; 82: 241-243

Direct oral anticoagulants (DOAC) – Update

In this update we provide details of a factor Xa inhibitor recently authorised in Switzerland, the first antidote for a DOAC substance to be authorised worldwide, and also about the development of ADR associated with DOAC in Switzerland.

Authorisation of Lixiana®

- On **31 March 2015**, **Lixiana®** (active ingredient: edoxaban) **was authorised in Switzerland**, marking the arrival of a third factor Xa inhibitor for anticoagulant treatment.
- Lixiana® had previously shown safety-related superiority over warfarin in the authorisation studies described below (1, 2).

Engage AF-TIMI 48

21,105 patients with documented atrial fibrillation in the last 12 months and a mean CHADS2 score of 2.8 were enrolled in this randomised, double-blind study. The patients were treated with either 60 or 30 mg edoxaban or, in the control group, with warfarin. The edoxaban dose was halved if one or more of the following clinical factors were present: moderate renal impairment (CrCl 30–50 ml/min), low body weight (< 60 kg) or concomitant use of specific P-gp inhibitors (verapamil, quinidine or dronedarone). The median treatment period was 907 days. The median follow-up period was 2.8 years.

The **primary efficacy endpoint** was the composite of stroke and systemic embolic events (SEE).

During the treatment period, the primary endpoint occurred in 232 patients in the warfarin control group (1.50 % per year), compared to 182 patients in the high-dose edoxaban group (1.18 % per year; hazard ratio vs. warfarin, 0.79; $p < 0.001$ for non-inferiority). In the low-dose edoxaban group the primary endpoint was

reached by 253 patients (1.61 % per year; hazard ratio vs. warfarin 1.07; $p = 0.005$ for non-inferiority). Thus, non-inferiority in relation to the primary efficacy endpoint was demonstrated for edoxaban compared to warfarin for both of the dosages investigated in this study.

The **secondary efficacy endpoint** was the composite of:

- stroke, systemic embolic event or cardiovascular death
- myocardial infarction, stroke, SEE or cardiovascular death
- stroke, SEE or death from any cause.

The patients in the high-dose edoxaban group reached these endpoints significantly less frequently than those patients in the warfarin group. There were no significant differences between the low-dose edoxaban group and the warfarin group as regards the occurrence of this composite endpoint.

The **primary safety endpoint** was major bleeding.

This was observed in 524 of the patients treated with warfarin (3.43 % per year) and in 418 of the patients (2.75 % per year) who received 60 mg edoxaban (hazard ratio 0.80; $p < 0.001$). Major bleeding also occurred in 254 of the patients treated with 30 mg edoxaban (1.61 % per year, hazard ratio 0.47; $p < 0.001$). Thus there were significantly fewer bleeding effects for both edoxaban dosages than for warfarin.

The number of adverse events (AE) and serious adverse events (SAE) was roughly the same in the three groups.

Hokusai-VTE

In this study, 8,292 randomised patients with acute venous thromboembolism (VTE) received initial treatment with heparin for at least 5 days, followed by 60 mg of edoxaban once daily. Patients with moderate renal impairment (CrCl 30–50 ml/min) or with a body weight of less than 60 kg were prescribed a reduced edoxaban dose

of 30 mg. Patients in the control arm received initial treatment with heparin and concurrent warfarin, titrated to a target INR of 2.0 to 3.0, followed by warfarin alone.

The treatment period ranged from 3 to 12 months and was determined by the investigator according to the patients' clinical features and preferences.

Recurrent thromboses were defined as the **primary efficacy endpoint**. These occurred in 130 patients in the edoxaban group (3.2 %) and 146 patients in the warfarin group (3.5 %) (hazard ratio 0.89; $p < 0.001$ for non-inferiority). Thus, non-inferiority was shown for edoxaban compared to warfarin in respect of the primary efficacy endpoint.

The **primary safety endpoint** was major or clinically relevant non-major bleeding. This occurred in 349 patients in the edoxaban group (8.5 %) and in 423 patients in the warfarin group (10.3 %) (hazard ratio 0.81; $p < 0.004$ for superiority). The rates for other adverse events were similar in both groups. Thus, safety-related superiority was demonstrated for edoxaban.

- The **indications** are both therapeutic and prophylactic:
 - Treatment of adult patients with venous thromboembolism, including deep vein thrombosis and pulmonary embolism, **after prior treatment with fractionated or unfractionated heparin for 5 days** and prevention of recurrent venous thromboembolism.
 - Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation.
- **Dosage**
The recommended dosage for patients weighing over 60 kg is 60 mg Lixiana[®] once daily.

- **Special patient groups**

- Renal impairment
Lixiana[®] is not recommended for use in patients with terminal renal failure ($\text{CrCl} < 15$ ml/min) or dialysis patients.
- Hepatic impairment
Lixiana[®] is not recommended for use in patients with severe hepatic impairment.
- Body weight
The recommended dosage for patients weighing less than 60 kg is 30 mg once daily.

- **Interactions**

- In volunteers with normal renal function, less than 10% of an orally administered edoxaban dose is metabolised via CYP3A4. No interaction with CYP3A4 inhibitors or inducers should therefore be expected. Patients who are taking CYP inhibitors or inducers do not require dose adjustment.
- Edoxaban is a substrate for the efflux transporter P-gp. Since concomitant administration with the P-gp inhibitors ciclosporin, dronedarone, erythromycin, ketoconazole, quinidine or verapamil can lead to increased plasma concentrations of edoxaban, the Lixiana[®] dose should be reduced to 30 mg in such cases. Although the P-gp inducer rifampicin reduced the area under the concentration-time curve (AUC) of edoxaban in the blood, it appeared to have no effect on the maximum concentration (C_{max}) of edoxaban in the blood. Consequently, no dose adjustment is required.

For further details of Lixiana[®], please refer to the Information for healthcare professionals, which can be viewed at

<http://www.swissmedicinfo.ch>.

Development of antidotes for the DOAC substance class

First antidote approved by the FDA

Life-threatening bleeding is a possibility with all DOAC in a worst-case scenario. It may also occur that a patient treated with a DOAC has to undergo emergency surgery. These are both important reasons why healthcare professionals have long been calling for an effective antidote for direct oral anticoagulants.

On 16 October 2015, the FDA approved the first **antidote** for the factor IIa inhibitor **Pradaxa**[®] (3). The preparation in question is **Praxbind**[®] (active ingredient: idarucizumab), which has been developed by Boehringer Ingelheim. The **REVERSE AD** authorisation study was conducted in order to investigate the efficacy and safety of Praxbind[®] in patients treated with Pradaxa[®] (4).

Between June 2014 and February 2015, 90 patients were enrolled in this prospective two-arm cohort study. More than 90 % of patients were anticoagulated with dabigatran for stroke prophylaxis with pre-existing atrial fibrillation. Group A consisted of 51 patients with serious bleeding events. On admission to the study, 16 of these patients were haemodynamically unstable due to persistent blood loss. 18 of the patients in Group A had intracranial haemorrhage, 20 gastrointestinal bleeding, and 9 trauma-induced bleeding. No details of the bleed type were available for 11 cases. Group B consisted of 39 patients who required an urgent surgical procedure. The median interval since the last dabigatran dose was 15.4 hours. The median age of the patients was 76.5 years.

The administration of 5 mg Praxbind[®] successfully reversed the anticoagulant effect of dabigatran within minutes in 88 to 98 % of the patients enrolled in the study.

18 deaths occurred, nine in each of the two groups. 10 of these deaths had a cardiovascular cause, and five patients died of bleeding events.

All the fatalities that occurred within the 96 hours following the administration of the medication were attributed to the following SAE: Septic shock in two cases, intracranial haemorrhage in three cases; multiorgan failure, haemodynamic collapse, respiratory failure and heart failure each caused the death of one patient. In the investigators' view, all the deaths that occurred after this point in time were associated with the patients' pre-existing conditions.

Thrombotic events were divided into «early events», which occurred up to 72 hours after Praxbind[®] administration, and «late events», which occurred more than 72 hours after administration, and were observed in five patients:

- One patient suffered deep-vein thrombosis and pulmonary embolism after two days
- One patient experienced deep-vein thrombosis, pulmonary embolism and left atrial thrombus after 9 days
- Deep-vein thrombosis was diagnosed in one patient after nine days
- One patient developed non-ST-segment elevation myocardial infarction (NSTEMI) after 13 days
- One patient suffered a stroke after 26 days.

None of these five patients received anticoagulant treatment when the above-mentioned thrombotic events occurred.

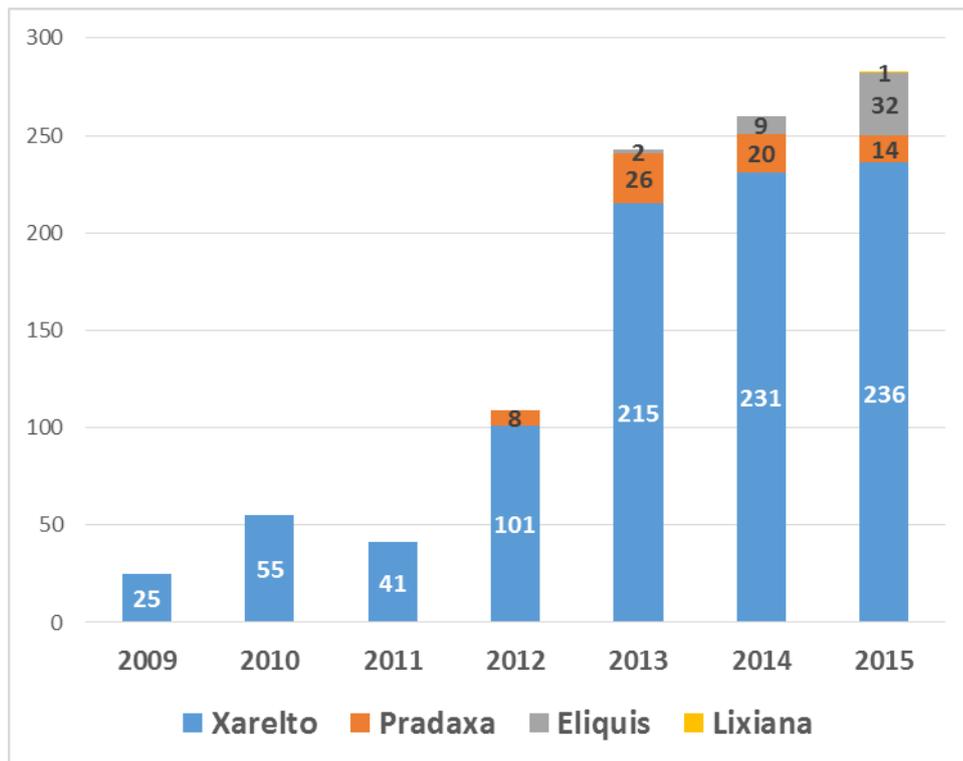
A total of 21 patients experienced serious adverse events while taking part in the study. In addition to the serious events already mentioned, these included gastrointestinal haemorrhage in two patients and postoperative wound infection, delirium, right ventricular failure and pulmonary oedema in one patient in each case.

Antidotes in clinical testing (5)

- Andexanet (currently in phase III): Antidote for all Xa inhibitors
- Ciraparantag (currently in phase II): Antidote for IIa inhibitors, Xa inhibitors and all heparins

ADR trends

The following diagram provides an overview of the chronological trend in reports of **adverse drug reactions (ADR) associated with DOAC medication in Switzerland up to 31 December 2015:**



The ADR reports associated with **Xarelto®** medication in Switzerland have more than doubled each year between 2009 and 2013, apart from 2011 when there was a reduction in the number of reports compared to the previous year. In Switzerland, ADR associated with Xarelto® that were reported to Swissmedic seem to have plateaued as of 2013. **Pradaxa®** was authorised in Switzerland in mid-2012, a fact that should be taken into account when considering the eight cases reported this year. The 26 ADR reported in 2013 were not exceeded either in the following year or in 2015. Despite being authorised in Swit-

zerland back in August 2011, no ADR were reported for **Elixia®** either that year or the following year. However, from 2014 there was a distinct (relative) increase in the number of reports. Following the authorisation of **Lixiana®** on 31 March 2015, Swissmedic received one report of an adverse drug reaction for this product in 2015.

The table below provides an overview of how many of the aforementioned reports were classified as medically serious. It also shows the number of cases with a fatal outcome.

ADR reports associated with DOAC medication, divided into serious (S) and non-serious (NS) cases, received by Swissmedic in the period up to 31 December 2015

	Xarelto®	Pradaxa®	Eliquis®	Lixiana®
Total	904	68	43	1
NS	113	15	15	1
S	791	53	28	0
Fatal	54	11	2	0

Of the 904 ADR reported to Swissmedic up to the end of 2015 for **Xarelto®**, 791 were classified as serious. 54 cases proved fatal. 29 patients died of intracranial haemorrhage, 11 of gastrointestinal bleeding and 4 patients of other uncontrollable bleeds. Ten patients died of a non-haemorrhagic event: Two patients died of ischaemic stroke, while pulmonary embolism, paralytic ileus and pericarditis each caused the death of one patient. The cause of death remained unclear in three patients.

Of the 68 ADR reported for **Pradaxa®**, 53 were classified as serious. 11 of these serious cases proved fatal. They included two intracranial haemorrhages, one gastrointestinal bleed and three other haemorrhagic events. One patient died of an ischaemic stroke, while the cause of death remained unclear in a further four patients.

By the end of 2015, Swissmedic had received 43 reports relating to **Eliquis®**. 28 ADR were classified as serious. Two of these cases proved fatal. One patient died of unspecified bleeding, while the cause of death remained unclear in one other patient.

In 2015 Swissmedic received one non-serious ADR report for **Lixiana®**.

Discussion

The risk of bleeding obviously represents a critical risk factor for the whole oral anticoagulants class (direct OAC and vitamin K antagonists). Although spontaneous reports provide important clues to the risks in everyday practice, they do not permit a reliable comparison between the individual medicinal products. This requires clinical and epidemiological studies. As far as pharmacovigilance data is concerned, Swissmedic would reiterate the following:

- These are spontaneous reports: Swissmedic collects and interprets the incoming spontaneous reports to obtain safety signals, i.e. new risks or new aspects of known drug risks. Since Swissmedic only receives information about a limited number of ADR, it is not possible to calculate an incidence rate or provide a reliable evaluation of the frequency of ADR.
- The reporting rate varies, being higher for newly authorised medicinal products than for older ones.
- There is only the suspicion of an ADR: A report is submitted as soon as a medicinal product is suspected of having triggered an ADR.
- Absolute figures for spontaneous reports should be viewed in relation to the exposure, including the date of first authorisation.
- The time at which the ADR occurred: The date stated in the report is often the date of the actual report rather than the date on which the

ADR occurred, and this naturally affects the incidence.

Other important parameters have to be taken into account when interpreting spontaneous reports:

- Medicinal products are normally prescribed for various indications and for various patient groups to patients of differing ages and with differing risk factors.
- Other medicinal products or non-medical factors can act as triggers (interaction).
- The seriousness of the complications/ADR must be weighed against the benefit of the medicinal product (e.g. prevention of serious complications, as in the case of strokes).

Consequently, spontaneous reports do not provide a suitable basis for comparing medicinal products or groups of medicinal products with each other. Such comparisons must be based on the results of clinical and epidemiological studies.

References

- 1) Gugliano RP et al. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2013; 369(22): 2093-104
- 2) Büller HR et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med.* 2013; 369(15):1406-15
- 3) http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/761025lbl.pdf
- 4) Pollack CV Jr et al. Idarucizumab for Dabigatran reversal. *N Engl J Med.* 2015; 373(6): 511-20
- 5) <https://clinicaltrials.gov/>

Accidental overdoses of low-dose methotrexate due to daily instead of once-weekly administration in patients with rheumatoid arthritis and psoriasis

The problem of daily instead of once-weekly administration of low-dose methotrexate in patients with rheumatoid arthritis and psoriasis has been known for years. Swissmedic first published a joint communication with the *Patient Safety Foundation* in Switzerland in November 2012. This contained a reminder of the appropriate precautions. However, since incidents involving erroneous daily administration are still repeatedly reported in Switzerland, Swissmedic has published another joint communication with the *Patient Safety Foundation*. This was published in the Swiss medical journal *Schweizerische Ärztezeitung* on 9 December 2015 and in *pharma-Journal* on 10 December 2015.

The mistakes occurred at all levels at the interfaces of the medication process: during medical prescription, administration by care-givers or relatives, dispensing in pharmacies or use by the patient and a lack of or poor communication. They are not restricted to the start of treatment, but have also occurred when therapy is well established. Any change plays a critical role, e.g. from s.c. pre-filled syringes to tablets, change in the institution or care-givers.

When it analyses case reports, Swissmedic notices that patients often feel that it is insufficient to take just one tablet once a week. This makes it all the more important for healthcare professionals to give patients extremely precise instructions and to monitor them.

From 1997 to mid-2015, Swissmedic received a total of 675 reports of adverse drug reactions (ADR) involving methotrexate.

- These included 18 accidental overdoses following daily instead of weekly administration – primarily orally but also subcutaneously in a few cases – four of which involved a fatal outcome (2000, 2009 (2) and 2014).

In the four fatal cases, daily administration had continued for 10, 12, 14 and 17 days respectively. Three of these four patients had concurrent renal insufficiency.

- In 14 reports, daily administration lasted for more than 10 days, and in four reports, for 6, 8, 8 and 9 days respectively.

In view of the continuing repeated occurrence of cases of daily instead of once-weekly administration of low-dose methotrexate involving serious side effects and occasional fatal outcomes, Swissmedic believes that information alone is no longer sufficient and that further action is required.

To discuss possible measures, all companies that market methotrexate for rheumatoid arthritis and psoriasis in Switzerland – regardless of the pharmaceutical forms involved (tablets, pre-filled syringes, concentrate for infusion) – were invited to a hearing in mid-January 2016.

Swissmedic presented the current situation and possible measures for improving safety. The objective was to find a common consensus and to promptly set in motion measures that could be rapidly implemented.

As regards tablets, the situation in Switzerland is unsatisfactory:

Tablets are only available in glass or plastic bottles; blister packs are not currently marketed.

Packs of 20 x 5 mg and 10 x 10 mg tablets are available, as are packs of 100 x 2.5 mg and 100 x 5 mg.

This situation shows that smaller pack sizes and additional dosage strengths are essential to avoid accidental overdoses.

It was decided to implement the following measures:

Short term: 3–6 months

- Adhesive label on the pack (German/French): For rheumatoid arthritis and psoriasis take/use once a week only
- Or direct fixed overprint on packs as a «boxed warning» and with place-holder where the drug dispensing outlet can insert the day on which administration is to take place (the label / overprint should be placed in a clearly visible position on the carton, possibly also with colour highlighting for easy recognition by the user).
- Adapted and restructured *Information for healthcare professionals* and *Patient Information*
- Leaflet / card for patients and relatives
- Joint DHPC (*Direct Healthcare Professional Communication*) issued by the affected authorisation holders reminding healthcare professionals about the risk and referring them to the above-mentioned measures and additional precautions. Swissmedic will provide an appropriate draft text. Examples of the leaflet / card are attached.
- The content of the DHPC will also be published in the *Ärztezeitung* and *pharmaJournal*, as well as in an appropriate publication aimed at the care-givers.

Long term: from 12 months

- Separate indications: Oncology / RA and psoriasis with corresponding dosage strengths and smaller pack sizes.
- Suffix added to the name of the medicinal product: e.g. *Methotrexate Onco*.
- Joint DHPC providing guidance on the new measures.

Progressive multifocal leukoencephalopathy and medicinal products for treating multiple sclerosis – update

The last article to appear in Vigilance-News on the subject of progressive multifocal leukoencephalopathy (PML) was published at the end of 2011. This update concerns the risk associated with MS products. On the one hand, advances in diagnosis have resulted in new recommendations, particularly for natalizumab (Tysabri®). In the meantime, however, there have also been isolated reports of PML disorders with dimethyl fumarate (Tecfidera®), which has been authorised in Switzerland since 2014, and with fingolimod (Gilenya®). Both act on the lymphocytes and require systematic monitoring of the lymphocyte count in order to prevent opportunistic infections.

PML results from infection of the central nervous system by the John Cunningham (JC) virus. Although this virus is widespread in the general population, it only causes PML in patients whose immune system has been considerably weakened for a prolonged period, for example due to leukaemia, AIDS or also immunosuppressant agents.

New approaches to detecting PML by means of MRI give grounds for hope that the disease can be identified at an early stage, i.e. before it has caused symptoms, and – by discontinuing the triggering medicinal product – halted more effectively. For years, the standard way of testing whether patients have come into contact with the JC virus has been to determine antibodies in their serum. The JC antibody index has recently been developed for this purpose. **In patients who have not been previously treated with immunosuppressants, this index correlates with the risk of contracting PML.** An index of less than 0.9 indicates a low risk, while a value higher than 1.5 is associated with a substantially elevated risk.

Important factors that increase the risk of developing PML include the duration of treatment with natalizumab and previous treatment with immunosuppressant agents.

Natalizumab (Tysabri®)

The new information outlined above primarily entails consequences for patients taking natalizumab (Tysabri®), who need to be systematically monitored in respect of their risk of contracting PML. The most important new recommendations issued by the EMA in February 2016 are listed below – these will now also be implemented in Switzerland:

- More frequent MRI scans, e.g. every 3 to 6 months for patients with a higher risk of PML, using a shorter protocol and primarily without the administration of contrast agents.
- Continuing annual MRI scans for lower-risk patients.
- Continuing 6-monthly determination of the JC antibody index in lower-risk patients.

There is still an elevated risk of PML for up to 6 months after natalizumab has been discontinued. Swissmedic intends to recommend an MRI scan at this point in time as well.

Dimethyl fumarate (Tecfidera®)

In August 2014 Tecfidera® (dimethyl fumarate) was authorised in Switzerland for the indication of MS. Prior to authorisation, preparations containing other fumaric acid derivatives had been on the market for the treatment of psoriasis in other countries for many years. A reduction in lymphocyte count occurs in around 30 % of patients who take such medication. A drop in lymphocyte count to less than 0.5 G/l is the most important risk factor for PML (or other opportunistic infections) with dimethyl fumarate. Swissmedic therefore requested a corresponding warning and contraindication during the authorisation process for Tecfidera®. Following a report of PML with a fatal outcome in association with Tecfidera®, a DHPC was issued at the end of 2014. Further isolated cases of PML have since

been reported. Here too, the patients concerned had long-standing lymphocytopenia and had been treated for at least several months.

The following should be observed:

- The risk of PML should be taken into account and the patient monitored for corresponding symptoms.
- A complete blood count is required before the start of treatment with dimethyl fumarate, at regular short intervals thereafter and as clinically indicated (see Information for healthcare professionals).
- If the lymphocyte count falls below 0.5 G/l or the leukocyte count falls below 3.0 G/l, dimethyl fumarate should be discontinued. Resumption may be considered only after these counts have completely returned to normal.

Fingolimod (Gilenya®)

This medicinal product was authorised in Switzerland for the indication of MS at the start of 2011. Isolated cases of PML have also been reported for fingolimod. These were not associated with lymphocytopenia below the limit.

Nevertheless, monitoring of the lymphocyte count is required in view of the risk of other opportunistic infections. As a result of its mechanism of action, fingolimod leads to sequestration of the lymphocytes in lymphatic tissue and to the lymphocyte count in the blood falling to 20–30 %. If it drops below 0.1 G/l, opportunistic infections, particularly cryptococcal infections, can occur.

Conclusions:

- The risk of PML should be taken into account and the patient monitored for corresponding symptoms.
- Check the patient's lymphocyte count (complete blood count) before the start of treatment, after 3 months and at least yearly thereafter.
- If a total lymphocyte count of < 0.1 G/l is confirmed, fingolimod should be suspended until recovery occurs. If the total lymphocyte count is < 0.2 G/l, a complete blood count should be evaluated at short intervals, at least every 3 months.

Differing regulatory assessment of liver injury in hepatitis C patients

Following reported adverse drug reactions, changes have been made internationally to the product information texts of the film-coated tablets **Viekirax**® (ombitasvir, paritaprevir, ritonavir) and **Exviera**® (dasabuvir). These trade names are identical in Switzerland and Europe in the area of the EMA. The corresponding combination preparations in the USA are Viekira Pak™ (ombitasvir, paritaprevir, ritonavir, dasabuvir) and Technivie™ (ombitasvir, paritaprevir, ritonavir), where Technivie™ has to be used only in combination with ribavirin.

In Switzerland, the indication for Viekirax® is as follows (www.swissmedicinfo.ch):

Viekirax is indicated in combination with Exviera or Exviera with ribavirin for the treatment of adults with chronic hepatitis C (CHC) genotype 1 (see «Dosage/Administration», «Warnings and precautions» and «Properties/Effects»).

In Switzerland, the indication for Exviera® is as follows (www.swissmedicinfo.ch):

Exviera is indicated in combination with Viekirax or Viekirax with ribavirin for the treatment of adults with chronic hepatitis C (CHC) genotype 1 (see «Dosage/Administration», «Warnings and precautions» and «Properties/Effects»).

In August 2015, Swissmedic started a signal assessment of reports of severe liver injury associated with Viekirax®, some of which required liver transplantation and some of which had fatal outcomes. Effective and appropriate measures for risk minimisation are product information amendments, particularly the Information for healthcare professionals and Direct Healthcare Professional Communications (DHPC). The DHPC is usually published on the website of the authority and the letter mailed directly to the relevant target group. Advertisements in selected professional journals are also used in Switzerland as a measure to raise risk awareness. The marketing authorisation holder can suggest suitable target groups. Swissmedic often has to consider

whether general practitioners, as the largest group of physicians, should be included. If in doubt, Swissmedic regularly opts for the greatest possible risk minimisation, i.e. for the largest possible target group.

A new contraindication had to be included in view of the severity and number of reports of liver injury and a certain level of causality. In this context, the question of the extent to which patients with advanced or decompensated liver cirrhosis before the start of drug treatment influenced the causality assessment is not to be discussed. Since the potential risk cannot be ruled out, the issue was not one of a «whether» for the contraindication, but of the inclusion of patients with narrowly or broadly assessed hepatic impairment.

Internationally, hepatic impairment is subdivided into three stages or classes – A, B or C – using the *Child-Pugh score*. The score takes account of the following parameters: total serum bilirubin, serum albumin, prothrombin time, ascites detected per ultrasound scan and hepatic encephalopathy. The resulting scores for classes A, B, or C provide a percentage indication of the survival rate after 1 year, 5 years and 10 years and of the perioperative mortality.

Following the signal assessment, it emerged that the two largest regulatory and pharmacovigilance authorities (EMA and FDA) had in part decided differently. Swissmedic and the Japanese authority PMDA took their decisions at a later date, after having made their own assessments and weighed up risk minimisation measures for their own populations.

Authority	CI Child-Pugh «B»	CI Child-Pugh «C»
FDA, USA	YES	YES
EMA, Europe	NO*	YES
Swissmedic	YES	YES
PMDA, Japan	YES	YES
Health Canada	NO	YES

CI = Contraindications

* = Administration «is not recommended», i.e. is strongly discouraged, but this is not a comprehensive CI with corresponding legal implications for the physician.

Why does Swissmedic's decision differ from the EMA's (EU)?

- Same assessment within the preparation group (ATC code) / within the indication
- Therapeutic alternatives are available
- In view of the risk situation, physicians should be given unambiguous instructions by the authority and not be obliged to bear the liability

risk associated with vaguer wording if they deviate from the recommendation and the serious adverse reaction then occurs.

Regulatory

PV responsibility of industry: Medical assessment of individual case reports

Medical assessment of individual case reports improves report quality and is an important tool in the early detection of signals. Swissmedic therefore expects all individual case reports submitted by pharmaceutical companies to include a medical assessment containing the following information:

Level of awareness of the ADR

Details relating to the labelledness in the Swiss Information for healthcare professionals or, if the adverse drug reaction is not described in the Information for healthcare professionals, additional details of the listedness in the Core Company Data Sheet (CCDS), findings from the literature, class effects, similar cases in the database, etc.

Assessment of causality

This should take into account factors such as chronological correlation, information on *dechallenge* and *rechallenge* and alternative causes. An assessment of *unrelated* or *not assessable* is only justified if a plausible and verifiable explanation can be provided (e.g. *unrelated* if the adverse event occurred before the suspected medicinal product was administered). An inadequate data situation or alternative explanations are unsuitable explanations because a causal relationship with the suspected medicinal product cannot be ruled out with sufficient certainty. *Implied causality* should instead be assumed for spontaneous reports, and causality should consequently be rated as *related* or *possible*.

Need for risk minimising measures (including signal evaluation)

Swissmedic recommends entering this information in the «Sender's comment» field.

References

TPO Art. 35 para 2, Art. 39, para 1
International Guidelines on Good Case Management Practice (EMA Module VI, CIOMS V, ICH E2D)

FAQ Enhanced Pharmacovigilance

Link: <https://www.swissmedic.ch/marktueberwachung/00135/00160/00163/03220/index.html?lang=en>

What is enhanced pharmacovigilance and what is it used for?

Enhanced pharmacovigilance (*enhanced PV*) is the targeted, structured collection of data on specific safety issues associated with a medicinal product following market authorisation. It comes into effect when the data situation indicates that further information needs to be collected.

Usually this involves obtaining follow-up information on specific spontaneous cases from the reporting source using customised questionnaires containing specific relevant questions. For example, all case reports of encephalopathy associated with a particular medicinal product could be followed up as a way of generating additional data on their outcome.

Who arranges enhanced PV measures?

Enhanced PV measures can be ordered as part of a Risk Management Plan (RMP) or initiated separately by Swissmedic independently of an RMP if specific information is required to minimise the risk associated with a safety signal. Marketing authorisation holders can also initiate enhanced PV measures themselves.

What must MAH need to know about enhanced PV measures in Switzerland?

Early coordination and planning with Swissmedic is required if the Regional Pharmacovigilance Centres (RPVC) are to be involved in data collection activities. Swissmedic and the marketing authorisation holder define the scope and organisational procedure for collecting the data. The envisaged procedure, including the expected time frame, is then agreed in writing with Swissmedic.

What documents need to be submitted for enhanced PV measures?

The following documents should be submitted to Swissmedic:

- Description of the planned measures, e.g. RMP or another relevant document.
- Specific description of how the measures will be implemented in Switzerland.
- Materials for recording the data (e.g. questionnaires) in all the languages used.

Will enhanced PV measures involve costs for marketing authorisation holders?

The collection of additional information from the primary reporting source by the RPVC will involve extra costs resulting from additional contact with the primary reporter and the extra work involved in entering and processing the case. Swissmedic will charge the marketing authorisation holder for the time involved in this extra work by.

Who is Swissmedic's contact for enhanced PV?

Questions relating to enhanced PV should be sent to the Risk Management unit (Safety of Medicines Department) at:

riskmanagement@swissmedic.ch.

Information on the Swissmedic website

(Most of the links are available in German/French only)

Communications regarding the safety of medicines

- 18.05.2016
New findings on the risks of the antiepileptic agent pregabalin in pregnancy
 A new international study conducted under the auspices of Lausanne University Hospital (CHUV) has shown an increased risk of birth defects following the administration of the active pharmaceutical ingredient pregabalin during pregnancy.
- 11.05.2016
DHPC – Invokana® (Canagliflozin) und Vokanamet® (Canagliflozin/Metformin)
 Risiko einer Amputation an den unteren Gliedmassen (in erster Linie der Zehen)
- 03.05.2016
DHPC – Wichtige Mitteilung zur sicheren Anwendung von Peyona® (Coffeincitrat)
 20mg/ml Infusionslösung und Lösung zum Einnehmen
- 18.04.2016
DHPC - Locabiotal® (Fusafungin)
 Widerruf der Zulassung und Marktrücknahme
- 13.04.2016
HPC - Misodel® Vaginal-Insert (Misoprostol)
 Polysystolien (verstärkte Wehentätigkeit)
- 08.04.2016
DHPC Viekirax® (Ombitasvir, Paritaprevir, Ritonavir) und Exviera® (Dasabuvir)
 Neue Kontraindikation und Empfehlungen
- 31.03.2016
DHPC – Dancor® (Nicorandil)
 Kein Einsatz als First-Line-Therapie für Angina pectoris; Risiko von Ulzerationen und Fortschreiten zu Komplikationen – Therapie mit Nicorandil muss bei Auftreten von Ulzerationen abgebrochen werden.
- 22.03.2016
Patentblau V Guerbet
 Die Zulassungsinhaberin Guerbet AG informiert über einen möglicherweise irreführenden Hinweis auf dem Primär- respektive Sekundärpackmitteln.
- 21.03.2016
DHPC – Zydelig® (Idelalisib)
 Einschränkungen für die Anwendung
- 15.03.2016
DHPC - Levonorgestrel-haltige Intrauterinsysteme und kupferhaltige Intrauterine Devices
 Aktualisierte Information zum Risiko einer Uterusperforation

- 04.03.2016
DHPC Xalkori®
Neuer Warnhinweis zu Herzinsuffizienz und Aufnahme von Herzinsuffizienz als unerwünschte Wirkung in die Arzneimittelinformation
- 01.03.2016
Sistierung der Zulassung von InductOs 1.5 mg/ml, Pulver, Lösungsmittel und Matrix zur Herstellung einer Matrix zur Implantation
Bei einer behördlichen GMP-Inspektion des Herstellers der in InductOs verwendeten resorbierbaren Kollagenmatrix wurden Abweichungen von den EU-Vorgaben der Guten Herstellungspraxis (GMP, Good Manufacturing Practice) festgestellt.
- 19.02.2016
DHPC CellCept® - Teratogenes Risiko von Mycophenolat Mofetil
Neue Kontraindikationen und wichtige neue Hinweise zu Schwangerschaftstests sowie zur Schwangerschaftsverhütung bei Frauen und Männern für CellCept® und für mycophenolat mofetil-haltige Arzneimittel der Zulassungskategorie „Bekannter Wirkstoff“ (früher „Generika“).
- 29.12.2015
Dafalgan Kindersirup 30 mg / ml zum Einnehmen für Kinder
Zusatzinformation zum Chargenrückruf
- 22.12.2015
DHPC - Genotropin, Injektionspräparat im vorgefüllten Pen GoQuick (Somatropin)
Die Pfizer AG informiert über einen Defekt im Dosierungsmechanismus von Genotropin® GoQuick zur Administration von Genotropin (Somatropin).
- 22.12.2015
DHPC - Falsche Dosierungsangaben und fehlende Angabe zu Maximaldosierung von Methotrexat
im Hinblick auf die intrathekale Prophylaxe bei akuter lymphatischer Leukämie und Therapie der Meningeosis leucaemica in den Fachinformationen von Cytosar® und Solu-Cortef® SAB
- 09.12.2015
Akzidentelle Überdosierungen von Low Dose Methotrexat
Gemeinsame Mitteilung der Swissmedic und der Stiftung für Patientensicherheit (SPS)
- 08.12.2015
DHPC – Potenzierung der Strahlentoxizität in Zusammenhang mit Zelboraf®
- 07.12.2015
Information zu Laboratoire Stallergenes
Auslieferungsstopp für allergologische Arzneimittel der Firma Laboratoire STALLERGENES Greer SAS, F-Antony Cedex, Frankreich

Communications

- 10.05.2016
Fragen und Antworten zur Umsetzung der per 01. Januar 2013 revidierten Arzneimittelzulassungsverordnung (AMZV; SR 812.212.22): neue Anforderungen zu Angaben und Texten auf Behälter und Packungsmaterial
Die Antwort zu Frage 33 wurde bezüglich Vorgehen bei Änderungen der Packungselemente und bei Verzicht auf Musterpackungen ergänzt.
- 03.05.2016
Anpassung der Merkblätter Erläuterungen zur Patienteninformation / Fachinformation
Die neuen Versionen der Merkblätter treten per sofort in Kraft.

- 08.04.2016
Announcement "Warning concerning Harvoni® packs with counterfeit contents": correction
 In the original version of the announcement, the colour of genuine tablets was incorrect. Swissmedic regrets and apologises for this error.
- 01.04.2016
Nachtrag 8.7 der Europäischen Pharmakopöe in Kraft
 Der Institutsrat hat den Nachtrag 8.7 der Europäischen Pharmakopöe auf den 1. April 2016 in Kraft gesetzt.
- 01.04.2016
Änderung im Pflichthinweis für Arzneimittelwerbung ab 1. April 2016 - Inkrafttreten der Teilrevision der Arzneimittel-Werbeverordnung (AWV)
 Am 1. April 2016 tritt eine Teilrevision der Arzneimittel-Werbeverordnung in Kraft, mit der insbesondere die folgenden Artikel der AWV geändert oder neu aufgenommen werden: Art. 16 Abs. 5 Bst. c, Art. 17 und Art. 17a (neu).
- 04.03.2016
Hepatitis medicines: Warning concerning Harvoni® packs with counterfeit contents
 Counterfeit packs of the preparation Harvoni® have been discovered in Israel. The Swiss Agency for Therapeutic Products Swissmedic is working with other European authorities to establish whether Harvoni® packs with counterfeit contents have also been imported into other countries.
- 25.02.2016
Illicit trade in medicines: Fewer slimming products, more sleeping tablets and tranquillisers
 In 2015, Swiss customs reported 1,134 cases of illegally imported medicinal products to Swissmedic, the Swiss Agency for Therapeutic Products.
- 11.02.2016
Zika Virus Press Release of the International Coalition of Medicines Regulatory Authorities, ICMRA
 Global medicines regulators pledge support to tackle Zika virus disease
- 01.01.2016
Nachtrag 8.6 der Europäischen Pharmakopöe in Kraft
 Der Institutsrat hat den Nachtrag 8.6 der Europäischen Pharmakopöe auf den 1. Januar 2016 in Kraft gesetzt.
- 16.12.2015
Neuerungen zu den elektronischen Meldungen in der Pharmacovigilance
- 15.12.2015
Der Kampf gegen Designerdrogen geht weiter
 Um den Kampf gegen neue Designerdrogen erfolgreich führen zu können, verbietet die Schweiz weitere 21 Einzelsubstanzen.
- 10.12.2015
Public invitation to tender of a computerized Adverse Event Reporting System (AERS)

Please find the complete list at the following web address: www.swissmedic.ch/updates.