Vigilance – News

December 2011

In this issue:

I: Editorial

Pharmacovigilance – Cooperation inside and outside Swissmedic

Dear Reader,

Medicines are not only monitored by the Safety of Medicines Division; other sectors are also involved, and there are various connection points and areas of cooperation both inside and outside Swissmedic.

Our overview of the responsibilities of the Clinical Trials Division in processing SUSARs (see definition in article) shows to what extent the various Swissmedic divisions are complementary to each other. So we would like to thank all the colleagues who support the Pharmacovigilance sector in their day-to-day work.

Those working at the regional pharmacovigilance centres in the various university hospitals and the regional hospital in Ticino make a vital contribution to this work. They also deserve our thanks.

There was also important and fruitful cooperation at the first joint conference involving the SRC Blood Transfusion Service, the Swiss Association for Transfusion Medicine (SVTM/ASMT) and Swissmedic in Fribourg, Switzerland, on 8 & 9 September, 2011.

In terms of international cooperation, not only is the availability of the broad database at the Uppsala Monitoring Centre (UMC) important but so too is our collaboration and information exchange

Swissmedic • Hallerstrasse 7 • Postfach • CH-3000 Bern 9 • www.swissmedic.ch • Tel. +41 31 322 02 11 • Fax +41 31 322 02 12

with other medicines authorities, such as our MoU partners[1] and whenever possible with the EMA (European Medicines Agency). This proved its value recently in particular in respect of nimesulide preparations and in the progressive multifocal leukoencephalopathy (PML) cases with natalizumab.

Swissmedic is currently working on an important project aimed at the electronic exchange of standardized pharmacovigilance reports in E2B format between the marketing authorization holders and Swissmedic. The key element of this project is the development and implementation of a gateway for the electronic exchange of reports of adverse drug reactions (ADRs) between Swissmedic and pharmaceutical companies and the mutual confirmation that the report has been received. This will optimize the reporting procedure for ADRs and bring us into line with international standards.

The pharmacovigilance gateway is an essential first step towards the introduction of an electronic data exchange between Swissmedic and its external partners. This project supports Swissmedic's strategic objective regarding communication with its stakeholders.

In the spirit of maintaining a dialogue with our readers, we look forward to receiving your feedback about this issue of Vigilance-News at vigilance@swissmedic.ch.

The Editors

[1] *MoU: Memorandum of Understanding as the basis of the information exchange between the medicines authorities in Canada, Australia, New Zealand, Japan, Singapore, Ireland and the US FDA (Food & Drug Administration)*

Swissmedic • Hallerstrasse 7 • Postfach • CH-3000 Bern 9 • www.swissmedic.ch • Tel. +41 31 322 02 11 • Fax +41 31 322 02 12

II: Flash: Signals relating to the safety of medicines from the Swiss database of the Vigilance Unit

Update: Adverse drug reactions to oral isotretinoin

Swissmedic provides an updated overview of ADR reports for oral isotretinoin that were entered in the national database between 1 October 2010 and 30 September 2011, focusing on severe skin and liver reactions, mental disorders and drug exposure during pregnancy.

Oral isotretinoin preparations are authorized in Switzerland for the treatment of severe forms of acne (such as acne nodularis, acne conglobata or acne with the risk of permanent scarring) that have proved resistant to appropriate standard treatment regimes with systemic antibiotics and topical therapies.

Owing to the high teratogenic potential of the substance, these preparations may only be prescribed to women of childbearing age when specific precautionary measures are taken as described in the product information.

The good level of efficacy is nevertheless associated with a serious potential for side-effects, therefore the isotretinoin must be restrictively prescribed and the precautionary measures mentioned in the product information must be strictly adhered to. Risk minimizing measures have been taken regularly since oral isotretinoin was first authorized in 1983. The product information was updated most recently in 2010 mentioning the potential for severe skin reactions and a corresponding Health Professional Communication was published[1].

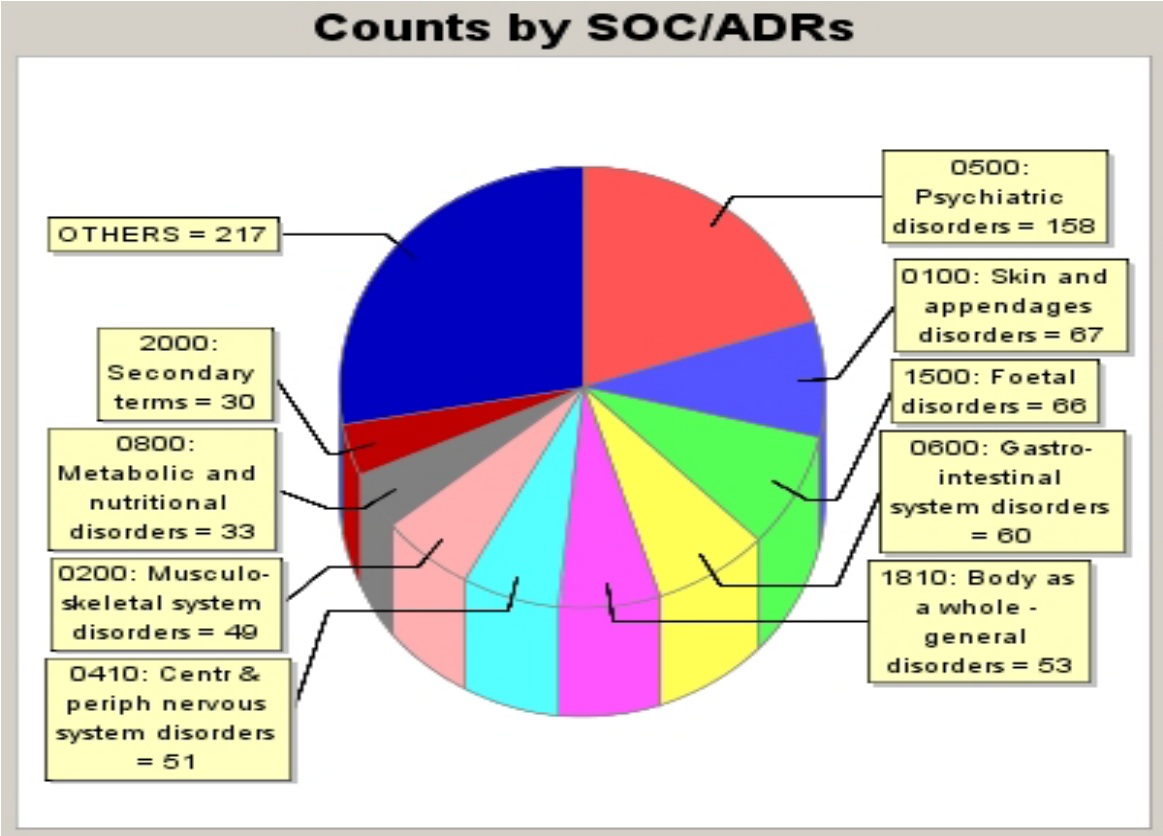
Pharmacovigilance of isotretinoin focuses on severe skin and liver reactions, as well as psychiatric ADRs and exposures during pregnancy.

The overall profile of the ADRs to isotretinoin reported in Switzerland has not changed since the last Swissmedic publication in December 2010[2]: Between 1 October 2010 and 30 September 2011 further 26 ADR reports were entered in the national database, bringing the number of registered reports to a total of 525. The distribution among the various system organ classes (SOC) can be seen in the following chart.

1 http://www.swissmedic.ch/marktueberwachung/00091/00092/01209/index.html?lang=de *(no English version available)*

2 http://www.swissmedic.ch/marktueberwachung/00091/00136/00137/01176/index.html?lang=de *(no English version available)*

Swissmedic • Hallerstrasse 7 • Postfach • CH-3000 Bern 9 • www.swissmedic.ch • Tel. +41 31 322 02 11 • Fax +41 31 322 02 12



Mental disorders

About 30 % of the total of 525 reports concern psychiatric symptoms.

In the period from October 2010 to September 2011 two attempted suicides and one completed suicide were reported, which leads to a total of 11 reports of attempted suicide and 21 of completed suicides. The three new reports are unfortunately not very well documented: one report mentions concomitant multiple-drug addiction, while the other dates back several years and it cannot be excluded that the case is a duplicate. In all three cases there is a temporal association with isotretinoin intake; however, owing to the rudimentary information available, it is not possible to assess causality. Another four reports mention depressive states.

Spontaneous reports do not allow to determine the frequency of psychiatric ADRs and cannot definitely prove causality between psychiatric symptoms and treatment with isotretinoin. So far, the available epidemiological data do not confirm any connection with psychiatric disorders. However, the high number of spontaneous reports of psychiatric symptoms reported over the years merit our attention and justify the recommended precautions: patients, their families and the health care professionals involved are called upon to immediately report any changes in the mental state and to take appropriate measures (see below).

Rare serious skin reactions

The database contains 67 case reports of skin reactions (13 %). These include two reports of erythema nodosum and one report of severe skin reaction (erythroderma) that required hospitalization. Although Stevens-Johnson syndrome and TEN (toxic epidermal necrolysis, aka Lyell's syndrome) have been

Swissmedic • Hallerstrasse 7 • Postfach • CH-3000 Bern 9 • www.swissmedic.ch • Tel. +41 31 322 02 11 • Fax +41 31 322 02 12

reported in other countries, to date no such reports have appeared in the Swissmedic database.

In the period under review a total of six reports of skin reactions were received: none of these reports concern serious reactions.

Hepatic ADRs

With a total of 20 reports, hepatic reactions were less than 4 % of the total number. More than half of the hepatic ADRs in these reports were not serious. A handful led to hospitalization and there was one case of liver failure with a fatal outcome. However, the person concerned had taken isotretinoin along with another potentially hepatotoxic drug.

In the period under review only one report of hepatic ADRs was received. The report states that the patient was affected by liver dysfunction that was considered not serious.

Exposure during pregnancy

Although isotretinoin should only be dispensed for one month at a time, a negative pregnancy test no more than 7 days old is required and a reliable contraceptive must be prescribed, every year Swissmedic receives reports of exposure during pregnancy.

There are a total of 66 reports of exposure during pregnancy in our database, often followed by an induced abortion. Four reports concern newborn babies whose mothers were under treatment with isotretinoin: these children were born with defects affecting the heart, ear and face.

In the period from October 2010 to September 2011, five cases of exposure during pregnancy were reported. In three cases the pregnancy was terminated and in the two other reports the outcome is unknown. No reports were received about teratogenic defects in children born in this period, which is not surprising as from experience we know that in such situations the pregnancy is rarely taken to full term. It can only exceptionally be concluded from the information given in the reports which precautionary measures failed and for what reason.

Conclusion

Swissmedic once again reminds healthcare professionals and public that oral isotretinoin preparations may only be prescribed by doctors who are familiar with the use of systemic retinoids in the treatment of severe acne and who have full knowledge of the risks of isotretinoin treatment and the necessary precautionary measures, or under their supervision.

It remains important to inform patients and their families of the risk of mood swings or even depression and that this must be reported without delay to their healthcare professional. The prescribing doctor must also pay careful attention to any signs of depression and/or any similar symptoms to ensure an early diagnosis, particularly in patients who have already suffered from psychiatric disorders in the past. Discontinuing isotretinoin alone might not be sufficient to alleviate the symptoms and psychiatric or psychological measures might be required without delay.

In the light of the high teratogenic potential of isotretinoin, it is essential to adhere to the precautionary measures in women of childbearing age.

Detailed information about the warnings, precautionary measures (teratogenicity) and adverse reactions can be found in the product information for isotretinoin preparations (www.kompendium.ch). The following oral isotretinoin products are currently authorized in Switzerland: Roaccutan®, Curakne®, Tretinac®, Isotretinoin-Teva® and Isotretinoin Mepha®.

Oral isotretinoin preparations are under continuous intensive monitoring. Information on the safety profile of isotretinoin is published periodically.

Nimesulide[1] for oral administration

Medicines containing nimesulide for oral administration are non-steroidal anti-inflammatory drugs (NSAIDS) that are only available on prescription and have been authorized in Switzerland for more than 20 years.

Over the past 10 years or so, a greater risk of hepatic toxicity during treatment with nimesulide by oral administration, in comparison with other non-steroidal anti-inflammatory drugs, has made it a subject of controversy.

Restrictive measures were taken in Switzerland in the past to improve the safety and reduce the risks of liver damage in patients treated with oral nimesulide. There were therefore only few indications for such drugs, i.e. as a second-line treatment with the minimum effective dose (maximum dosage: one tablet or one sachet containing 100 mg of nimesulide twice daily) for the shortest period possible, and a maximum treatment length of 15 days, along with new warnings with a special mention of liver damage, additional contraindications such as severe liver function disorders (cirrhosis of the liver and ascites) and treatment in conjunction with other potentially hepatotoxic substances.

In the course of a reevaluation procedure of oral nimesulide products Swissmedic decided to maintain the indications for the symptomatic treatment of acute pain and primary dysmenorrhoea. However, they are no longer authorized for the symptomatic treatment of localized osteoarthritis in the major joints (knees, hips).

Moreover, in June last year the Committee for Medicinal Products for Human Use of the EMA (European Medicines Agency) also confirmed that the risk–benefit ratio remained positive in the short-term treatment of acute pain and primary dysmenorrhoea[2] (see decision of the EU Commission to be published soon).

Recently an HPC[3] (Health Professional Communication) was sent out to health professionals by the marketing authorization holders of Aulin® 100 and Nisulid® 100 (tablets and granules), in agreement with Swissmedic, to remind them of the authorized indications, warnings and precautions, and adverse effects on liver function. The communication is also published in the *Schweizerische Ärztezeitung/Bulletin des médecins suisses* and the *PharmaJournal*.

[1] *Medicines authorized in Switzerland: Aulin® 100 tablets and sachets (granules) and Nisulid® 100 tablets and sachets (granules). See the Swiss Compendium: http://www.kompendium.ch/*

[2] *http://www.swissmedic.ch/marktueberwachung/00091/00092/01712/index.html?lang=fr (no English version)*

[3] *http://www.swissmedic.ch/marktueberwachung/00091/00092/01805/index.html?lang=fr (no English version)*

Schweizerisches Heilmittelinstitut
Institut suisse des produits thérapeutiques
Istituto svizzero per gli agenti terapeutici
Swiss Agency for Therapeutic Products

Swissmedic • Hallerstrasse 7 • Postfach • CH-3000 Bern 9 • www.swissmedic.ch • Tel. +41 31 322 02 11 • Fax +41 31 322 02 12

Multaq® (dronedarone): reevaluation of the benefit-risk balance following liver, heart and lung safety issues

Since late 2010 reports about liver, heart and lung adverse events arising under treatment with dronedarone have led to an overall reevaluation of the benefit-risk balance in Switzerland and in the European Union and to a series of risk minimisation measures. The conclusions of the Swiss evaluation concur with those of the EU experts and point out that the benefit-risk balance remains favourable for a limited group of patients with non-permanent atrial fibrillation and no associated comorbidities such as heart failure, a well established contraindication.

Dronedarone has been authorized as an anti-arrhythmic drug in Switzerland since 2009 for the treatment of atrial fibrillation. This is the most common type of sustained heart rhythm disorder, in particular in the elderly. The risk of atrial fibrillation increases with age and various associated heart conditions. Less than 0.5 % of the population presents with atrial fibrillation between the ages of 40 and 50, whereas 5–15 % are affected at 80 years [1]. The classification distinguishes between paroxysmal forms (lasting less than 7 days with a spontaneous return to sinus rhythm, usually after 24–48 hours), persistent (lasting more than 7 days and requiring electrical or pharmacological cardioversion) and permanent (unsuccessful or unlikely cardioversion).

Efficacy and safety at the time of approval

Several studies have confirmed the effectiveness of dronedarone in preventing the recurrence of atrial fibrillation and the slowing of the heart rate. In a comparative study, however, dronedarone proved less effective in maintaining the sinus rhythm than amiodarone, yet with a favourable safety profile in particular with regard to thyroid and neurological adverse events [2]. On the other hand, dronedarone has no place in pharmacological cardioversion [3].

Liver damage

Available data were reevaluated following reports, in late 2010, of acute liver failure requiring urgent liver transplants in two patients taking dronedarone for 5–6 months. The experimental and clinical studies that preceded the marketing authorization had not brought any liver problems to light. The small proportion of subjects presenting with an increase in transaminases was similar in the placebo group and the group treated with dronedarone. The drug information did not therefore mention either any liver side-effects or warnings or precautions for use in this regard. The analysis of the spontaneous reports of liver injury after dronedarone was approved revealed that a drug induced liver injury was possible or probable in a few cases. Although the mechanism has not been established, an idiosyncratic reaction is suspected.

The unpredictable nature of these reactions lessens the effectiveness of risk-reduction measures, but a series of standard precautions were added to the drug information and announced on the Swissmedic website and in a Health Professional Communication (HPC) in January 2011.

Cardiovascular events

In July 2011, the PALLAS study involving patients with permanent atrial fibrillation lasting at least 6 months had to be stopped when it was observed that there was a significant increase in unplanned hospitalisations for cardiovascular causes (HR: 1.97; 95 % CI: 1.44–2.7), heart failure episodes or hospitalisations (HR: 2.16; 95 % CI: 1.57–2.98), strokes (HR: 2.32; 95 % CI: 1.11-4.88) and deaths from cardiovascular cause (HR: 2.11; 95 % CI 1.00-4.49) [4].

Swissmedic immediately announced a series of precautionary measures via its website and informed all Swiss physicians by a direct e-mailing through the Swiss Medical Association (FMH). It recommended in particular to

Swissmedic • Hallerstrasse 7 • Postfach • CH-3000 Bern 9 • www.swissmedic.ch • Tel. +41 31 322 02 11 • Fax +41 31 322 02 12

stop dronedarone in patients with permanent atrial fibrillation and not to start any new treatment in patients diagnosed with this disorder. A careful evaluation of the heart function was also recommended before starting or continuing treatment with dronedarone in patients with non-permanent atrial fibrillation. Physicians were moreover required to closely monitor the clinical signs of heart failure (weight gain, oedema, shortness of breath) and to inform their patients to report immediately any such signs or symptoms [5]. Information from the company followed in late July 2011 with a Health Professional Communication [6].

At the same time, Swissmedic launched a reevaluation of the benefit-risk balance based on the latest data available including the risk of liver, cardiovascular and lung adverse events (see "Discussion and conclusion"). In the European Union, the evaluation procedure launched in January 2011 following the reports of liver injury was extended to include the new data on the risk of injury to the cardiovascular system and the lung.

Lung damage

The pulmonary toxicity of amiodarone is well known. In contrast to amiodarone, pulmonary toxicity has not been observed in animal experiment data for dronedarone. However, since the approval of dronedarone few cases of interstitial lung injury have been reported. In half of those cases, the patients had previously been exposed to amiodarone. In the others, the involvement of dronedarone was considered to be possible in some cases while a clear causal relationship could not be established yet. However, precautionary measures have to be added to the product information. Treatment with dronedarone is now contraindicated in patients with interstitial lung disease including pulmonary fibrosis and after treatment with amiodarone resulting in lung toxicity. In other words, dronedarone can no longer be considered as an alternative to amiodarone in the event of lung damage prior to the treatment.

Summary of risk minimisation measures

The following measures should be added to the product information:

Restriction of indication

- Maintenance of sinus rhythm after a successful cardioversion in clinically stable adult patients with paroxysmal or persistent atrial fibrillation
- Prescription only, once alternative treatments have been considered

Contraindications

- Permanent atrial fibrillation
- Unstable haemodynamic status
- History of heart failure, current heart failure or left ventricular systolic dysfunction
- Hepatic or pulmonary toxicity owing to prior use of amiodarone.

Monitoring

- Close, regular monitoring of heart, liver and lung function throughout the treatment with dronedarone
- Stop treatment with dronedarone if a patient develops any conditions that would lead to a contraindication. In the event of recurrent episodes of atrial fibrillation during treatment, ceasing dronedarone should be considered
- Regular reevaluation of the treatment during consultations.

Discussion and conclusion

The dronedarone case is a good example of the respective contributions of various components to a well-performing pharmacovigilance system. First of all, the relevance of the spontaneous reporting system was confirmed once again by its ability to identify rapidly after the drug approval two cases of very severe liver damage, a rare but life-threatening adverse event almost impossible to detect in clinical trials prior to marketing authorization. This prompted a safety review and the implementation of risk minimisation measures with a warning being added in the product information.

Swissmedic • Hallerstrasse 7 • Postfach • CH-3000 Bern 9 • www.swissmedic.ch • Tel. +41 31 322 02 11 • Fax +41 31 322 02 12

New safety measures have also been issued following an analysis of data from spontaneous reports of lung injury. Even though these data almost never enable a causal relationship to be clearly established, they are crucial for detecting unknown adverse reactions, formulating hypotheses and introducing measures to improve the safety of the drug.

Clinical studies after the product authorization are another essential element of the pharmacovigilance system. The PALLAS study aimed to establish the efficacy and safety of the drug in the treatment of permanent atrial fibrillation, an indication not currently approved in most countries. The significant increase in cardiovascular events observed in the interim analysis resulted in the study termination and led to the changes of the recommendations for use.

Speed of reaction, additional studies and analyses, open communication and good coordination of the various partners in the system enabled the quick dissemination of the essential safety measures restricting the indication to those patients who can continue to benefit from a treatment for a difficult condition such as atrial fibrillation.

References

1. *Camm A.J. et al., Guidelines for the management of atrial fibrillation - The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J, 2010. 31(19): p. 2369-2429.*
2. *Le Heuzey, J.Y., et al., A short-term, randomized, double-blind, parallel-group study to evaluate the efficacy and safety of dronedarone versus amiodarone in patients with persistent atrial fibrillation: the DIONYSOS study. J Cardiovasc Electrophysiol, 2010. 21(6): p. 597-605.*
3. *Touboul, P., et al., Dronedarone for prevention of atrial fibrillation: a dose-ranging study. Eur Heart J, 2003. 24(16): p. 1481-7.*
4. *Connolly, S.J., et al., (2011) Dronedarone in High-Risk Permanent Atrial Fibrillation. N Engl J Med, DOI: 10.1056/NEJMoa1109867.*
5. *Swissmedic. Multaq® (dronédarone) - Risque d'accidents cardio-vasculaires chez les patients avec fibrillation auriculaire permanente Multaq® (Dronedaron) – Risiko kardiovaskulärer Ereignisse bei Patienten mit permanentem Vorhofflimmern. 2011. Available from: http://www.swissmedic.ch/marktueberwachung/00091/00092/01481/index.html?lang=de http://www.swissmedic.ch/marktueberwachung/00091/00092/01481/index.html?lang=fr.*
6. *Swissmedic. MULTAQ® (dronédarone): Risque d'évènements cardiovasculaires chez les patients présentant une fibrillation auriculaire permanente MULTAQ® (Dronedaron): Risiko kardiovaskulärer Ereignisse bei Patienten mit permanentem Vorhofflimmern. 2011. Available from: http://www.swissmedic.ch/marktueberwachung/00091/00092/01749/index.html?lang=de http://www.swissmedic.ch/marktueberwachung/00091/00092/01749/index.html?lang=fr.*

PML: Is forewarned forearmed?

Progressive multifocal leukoencephalopathy is a demyelinating disease of the central nervous system that in the majority of cases results in permanent injury or death. The pathogen is the JC virus, a DNA virus that belongs to the polyomavirus family. First described in the late 1950s in patients with tumours of the lymph system and leukaemias, in the 1980s this opportunistic infection was one of the AIDS-defining diseases and is nowadays often an adverse effect of new potent medicines with an immunosuppressive effect, either in patients undergoing an organ transplant, those with severe immune diseases or with cancer. A major cause is natalizumab (Tysabri®) which is approved in Switzerland as a reserve drug – under strict precautionary measures – in cases of severe multiple sclerosis (high level of disease activity despite treatment with interferon beta) and in patients with rapidly evolving relapsing–remitting MS.

A significant number of cases arise under treatment with rituximab (MabThera®) which is authorized for prescription in cases of non-Hodgkin's lymphoma but also for therapy-resistant rheumatoid arthritis.

We can now report on the first concrete progress made since our report in Vigilance Newsletter No. 5 of June 2010, along with ongoing work to improve knowledge of PML in general and in connection with natalizumab in particular.

Swissmedic • Hallerstrasse 7 • Postfach • CH-3000 Bern 9 • www.swissmedic.ch • Tel. +41 31 322 02 11 • Fax +41 31 322 02 12

Transatlantic workshop: drug-related progressive multifocal leukoencephalopathy

PML is difficult to research. There is no adequate animal model available. The disease is – fortunately – rare. Nevertheless, in order to make progress the research efforts (of neurologists, neuropathologists, infectiologists, virologists, immunologists, pharmacologists, etc.) must be combined and coordinated, but also with the support of the pharmaceutical industry, the medicines control agencies and the health authorities. The European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) therefore organized a joint two-day workshop in London on 25 & 26 July 2011 at which all stakeholders could exchange experiences and information with experts from the various fields. More than 150 representatives attended the workshop: researchers, clinical doctors, industry, regulatory authorities and patient advocates. After the first part about the state of the art, the second part of the workshop was dedicated to funding, future planning and coordination.

Eight topical sessions were organized:

- PML as an adverse event of immunobiologicals
- The regulatory role – a collaborative approach
- Treatment of drug-induced PML
- Ongoing research in PML
- Research agendas
- Building collaboration
- Funding of research
- Keeping abreast of progress for the benefits of public health

In the service of public health, the EMA and the FDA therefore chose the target-oriented approach, broke new ground and dared to do something unusual. The immediate success of the workshop proves them right. For the patients' sake it is to be hoped that it will bear fruit over the long term and lead to more concrete results in pursuit of the objectives: “predict, prevent, treat”.

Predict/prevent – Test to detect virus carriers

The priority is on developing prevention strategies and surrogate markers for PML. A distinction must be made between virological and immunological markers. In the case of virological markers, there are published studies with a single-step and a two-step ELISA (enzyme-linked immunosorbent assay) as proof of anti-JCV antibodies in the blood.

In the near future we can expect that more than just a few reference laboratories in the world will be able to analyse samples, but also that this will be available more or less worldwide and so hopefully this will bring down prices.

Testing for anti-JCV antibodies in the blood is already routinely performed before starting treatment with natalizumab, then repeated every year after that. If the test is negative, the risk of developing PML when being treated with natalizumab is very small. If it is positive and the patient has other risk factors – previous immunosuppressive therapy or more than two years on natalizumab – the risk rises sharply and if all three factors are present it reaches the percentage range.

In the meantime PML will be suspected and diagnosed earlier.

Treat – treatment options currently restricted to IRIS (immune reconstitution inflammatory syndrome)

There is currently no specific therapy for JC virus infection.

However, the early administration of high doses of steroids to prevent and treat the severe immune reconstitution inflammatory syndrome (IRIS) – together with the earlier diagnosis of PML – has improved the prognosis of PML in patients on Tysabri.

Compiling patient registries

In Europe there are five countries with registries of patients on natalizumab (patient

Swissmedic • Hallerstrasse 7 • Postfach • CH-3000 Bern 9 • www.swissmedic.ch • Tel. +41 31 322 02 11 • Fax +41 31 322 02 12

numbers in brackets): Sweden (1481), Denmark (828), France (approx. 3000), Italy (4927), Austria (811). It should be the aim of each registry to collect as much information as possible about patients according to a particular main criterion and to monitor them. No existing (PML) registry has managed to reach anywhere near a 100 % registration rate. Every country has its specificities and legal obstacles.

In Switzerland we are striving to systematically register all patients being treated with natalizumab.

Conclusion

The most important of the risk-reducing measures is the introduction of blood antibody detection. Progress has also been made in identifying risk factors, the early diagnosis of PML and the prevention and treatment of IRIS.

The answer to the initial question is therefore: the aim of significantly reducing the individual risk of PML is now closer than ever before.

Swissmedic • Hallerstrasse 7 • Postfach • CH-3000 Bern 9 • www.swissmedic.ch • Tel. +41 31 322 02 11 • Fax +41 31 322 02 12

III: Drug safety / Vigilance and the Clinical Trials Division

In which aspects do the Safety of Medicines Division, the Vigilance Unit and the Clinical Trials Division closely work together?

SUSARs (suspected unexpected serious adverse reactions), similar to reports of adverse drug reactions to authorized medicines, must be reported by the sponsors to the Vigilance Unit of the Safety of Medicines Division at Swissmedic. There they are recorded in a table and forwarded to the Clinical Trials Division. This unit assesses the SUSARs and decides whether further measures should be taken, such as a protocol amendment.

Which SUSARs must be reported?

This can be understood from a full definition of reportable SUSARs: a serious unexpected event that was probably caused by the substance administered as part of a clinical trial.

Here is an *example*: If a pulmonary embolism were to occur in a tumour patient during treatment with lenalidomide, this would indeed be a serious event probably even caused by the drug, yet it would not be unexpected because both thromboses and pulmonary embolisms are listed in the range of side-effects described in the product information for lenalidomide. However, this type of thrombogenic event must always be expected in tumour patients as they have other thrombogenic factors such as the primary illness and immobility.

So, this case is not a SUSAR that needs to be reported.

Herein lies the difference between the reporting system for the Clinical Trials Division and the Vigilance Unit. In case of the Vigilance Unit spontaneous reports must additionally be submitted for serious expected events and non-serious unexpected events.

On the other hand, if this pulmonary embolism should occur after taking the substance rivaroxaban and the principal investigator were to consider that this event was caused by the drug, this would be a SUSAR because, although thrombocytosis is listed in the product information as a possible adverse side-effect, an event of the severity of a pulmonary embolism would still be unexpected.

Another important factor is the country the SUSAR occurred in. SUSARs should only be reported to the Vigilance Unit if they have occurred in Switzerland.

Are periodical reports also required?

In Switzerland (as described in VKlin Article 23, point 4) the sponsor must submit a list of all serious adverse events (SAEs) and SUSARs to Swissmedic every year. These data are compiled into a so-called ASR (annual safety report) or DSUR (development safety update report). These reports enable the sponsor to evaluate the risk-benefit profile of the substances at regular intervals. Those documents can be submitted as paper version or on CD. The cover letter must clearly state what has been reported in Switzerland over the past year along with any measures the sponsor has taken when indicated.

Swissmedic • Hallerstrasse 7 • Postfach • CH-3000 Bern 9 • www.swissmedic.ch • Tel. +41 31 322 02 11 • Fax +41 31 322 02 12

IV: Conferences

Swisstransfusion 2011 – Synergic Effects of a Joint Conference 8 & 9 September 2011 in Fribourg

The first joint conference of the **SRC Blood Transfusion Service**, the **Swiss Association for Transfusion Medicine** (SVTM/ASMT) and **Swissmedic** was held in Fribourg, Switzerland, on 8 & 9 September 2011. All three institutions expect their joint efforts presented at this conference to lead to further improvements in transfusion safety.

In their introductory remarks, Paul Pugin, the chairman of the conference and Director-General of the Fribourg Regional Blood Transfusion Service, Annemarie Huber-Hotz, President of the Swiss Red Cross, Eduard Belser, the chairman of the board of the SRC Blood Transfusion Service, Rudolf Schwabe, Director-General of the SRC Blood Transfusion Service, Behrouz Mansouri, President of the SVTM/ASMT, and Jürg Schnetzer, Director-General of Swissmedic, emphasised the importance of cooperation between the three institutions involved.

The SRC Blood Transfusion Service ensures the continuous supply of labile blood products to the health services in Switzerland in all circumstances. The SVTM/ASMT promotes science, collaboration and networking with other specialised institutions working in the domain of transfusion medicine. Swissmedic ensures that therapeutic products in Switzerland meet high standards for safety, quality, and efficacy. Swissmedic also supervises the manufacture and the safe use of blood components. With the haemovigilance reporting system more than 1,000 reports of adverse events connected to blood transfusions are registered each year. The reports are then analysed and measures taken as required.

This first joint conference shows how successful cooperation can help to ensure and improve the safety of both blood donors and patients.

The first day of the conference included presentations of current issues in transfusion medicine along with national and international projects. Behrouz Mansouri provided a comprehensive overview of the introduction of pathogen inactivation for platelet concentrates in Switzerland, in which he presented the risk–benefit assessment in the context of national and international scientific data. Other speakers addressed issues relating to donations of blood and stem cells, including donor motivation and ethical and legal aspects of donor care.

The morning of the second day was organised by the Swissmedic Haemovigilance Team which described the current status of haemovigilance, with statistics, interactive case studies, and an exchange of experiences with analyses and feedback on near-miss events. The presentation of innovative therapeutic strategies, the basis for developing transfusion guidelines and experiences with systematic donor-vigilance provided insight into future developments and tasks of haemovigilance.

The conference also featured a large number of presentations on current research projects in transfusion medicine in Switzerland. The three institutions involved have agreed on continuing this joint approach in coming years.

Swissmedic • Hallerstrasse 7 • Postfach • CH-3000 Bern 9 • www.swissmedic.ch • Tel. +41 31 322 02 11 • Fax +41 31 322 02 12

Post-Approval-Summit

21 & 22 September 2011 in Zurich

This seminar has been held in the USA and in Europe every year for some time. The organizer, Outcome (www.outcome.com), is a commercial provider of information on all aspects of post-approval studies on pharmaceuticals and medical devices, founded in 1998 as a spin-off company by the Harvard Medical School in Boston.

Post-approval studies are becoming increasingly significant, particularly within the context of risk management, for the continuous evaluation of safety and in relation to the cost-reimbursement issue for the comparative evaluation of effectiveness (in contrast to 'efficacy'). One sector of development where progress was necessary and has been achieved in recent times is that of increased quality and the setting of compulsory standards for these studies. This type of study may be in a range of designs, including the whole spectrum of pharmacoepidemiology, and has the advantage over randomized controlled trials (RCT) of providing considerably better insight into the conditions of day-to-day clinical practice. Depending on the objectives, this real-world perspective can make up for or even outweigh the disadvantages in comparison with the gold standard RCT, the typical design for authorization studies. For example, there is the balance between the two main problems in the different study types, the stringent exclusion and inclusion criteria in RCTs and the confounding factors with the large range of potential for bias in all other studies. Finally, RCTs often cannot be carried out after approval to clarify specific issues, e.g. because of the overall cost and problems recruiting trial subjects, or even from an ethical point of view.

The speakers were from industry, EU institutions and universities. Here are a few brief highlights of some of the presentations.

Lode Dewulf, MD, UCB Pharma

He gave an excellent overview of a company's management perspective that was in many respects applicable to various professional sectors or organizations. Particularly interesting aspects were:

- the description of the dwindling influence of the 'key opinion leaders' (KOL) since the 1980s and the reasons for this, such as the increased government regulation with regard to licensing requirements, reimbursement of costs and conflicts of interests, together with the advent of the internet and social media;
- the RACI model as a basis for successful teamwork: **R**esponsible are those who execute, **A**ccountable is the one (!) in charge who makes it happen, **C**onsulted by those who provide input, **I**nformed all who need to be informed.

Richard Gliklich, MD, Summit Chairperson, Professor Harvard Medical School, President Outcome

He talked in detail about patient registries, including definitions, issues in planning and design, data management and evaluation.
Particularly noteworthy aspects were:

- The definition of a patient registry: "an organized system that uses observational study methods to collect uniform data (clinical or other), that evaluates specific outcomes for a population de-

Swissmedic • Hallerstrasse 7 • Postfach • CH-3000 Bern 9 • www.swissmedic.ch • Tel. +41 31 322 02 11 • Fax +41 31 322 02 12

fined by a particular disease, condition or exposure, and that serves a predetermined scientific, clinical or policy purpose."

- The presentation of the second edition of the US Department of Health & Human Services publication *Registries for Evaluating Patient Outcomes: A User's Guide*, a comprehensive book with articles from industry, universities, medical associations, insurance companies, and government departments. The book is more than 300 pages long and contains case studies, and can also be downloaded free of charge as a PDF document.

Jérôme Boehm, Health & Consumers Directorate, EU Commission

He discussed the problems and solutions for international registries which are not at all easy even within the EU. Examples given were registries for carcinomas and for rare diseases. The main obstacles are the differences between national data protection laws, how developed the electronic health records (EHR) are, and the requirements in terms of participating doctors and ethics committees. At the same time there is a growing need for international registries, for medical, political and financial reasons. Registries for example for rare diseases only make sense if they are multinational. There is a need for action by the legislators.

Nancy Dreyer, PhD, MPH, Senior Vice-President Outcome

Her topic was Comparative Effectiveness Research (CER). As this was not actually a pharmacovigilance topic, there are no particular comments about this except for the important fact that this can remind us that even RCTs are not totally free of bias. Potential bias may originate, for example, from the choice of population, choice of end point and the measurement methods, or in selective publication.

Stella Blackburn, MA, MSc, European Medicines Agency (EMA)

She gave a clearly structured presentation of the changes to the EMA Risk Management Guidelines and quality standards for epidemiological studies. This is a huge project with the most significant changes in pharmacovigilance since the EMA was founded, which are to come into force along with the new PV legislation in the EU in July 2012. Taking account of the benefit and improved transparency are the two most important terms for this undertaking.
Points worth noting are:

- Regarding methodology standards, the 'hallmark' of the European Network of Centres for Pharmacoepidemiology & Pharmacovigilance (ENCePP) should guarantee the best possible neutrality and scientific quality in order to regain or enhance public confidence.
- A risk management plan (RMP) is compulsory for all new applications for authorizations of medicines. It is divided into seven sections and has a modular structure, to provide greater flexibility and interaction with the PSUR, while at the same time avoiding duplication of the workload for both industry and the regulatory authorities. The sections summarizing efficacy (on one page!) and the planning of effectiveness and long-term efficacy studies, in particular, are new.
- A summary of the RMP will be published. The companies must write this public section, which will then be checked and edited by the EMA as necessary. This summary must be written in layman's language and explain both the risks and the benefits of the product.
- The current Volume 9A of the EMA Guidelines is to be replaced by a good vigilance practice document (GVP, in the style of the ICH standards GCP, GMP, etc.). The next large-scale consultation on the drafts will be in January 2012.
- A public electronic registry for safety studies will be introduced, in particular for all studies belonging to a PV plan. This registry should be open to all, though studies from ENCePP centres will be marked with an appropriate certificate.

Swissmedic • Hallerstrasse 7 • Postfach • CH-3000 Bern 9 • www.swissmedic.ch • Tel. +41 31 322 02 11 • Fax +41 31 322 02 12

Miriam Sturkenboom, PhD, Professor of Pharmacoepidemiology, Erasmus University, NL

Her presentation described the problems and positive future prospects for post-approval risk management.

Her key messages were:

- Risk-reducing measures must be carefully considered, because simply increasing the number of them causes doctors and patients to ignore them.
- One outstanding issue is still how to evaluate the effectiveness of such measures.
- Join forces instead of conducting meta-analyses of many different fragmented studies. This means setting up networks of databases, such as what has already been started in the PROTECT and SENTINEL projects.
- In future a database of electronic medical files from approximately 30 million patients will facilitate research into drug safety in the EU.

The outstandingly high level – both in terms of content and presentation – of almost all the speakers at this Post-Approval Summit was impressive in comparison to many other seminars. (There is no connection between the author of this report and the organizer, Outcome.)

Excerpt from the most important internet sources:

- *Registries for Evaluating Patient Outcomes: A User's Guide*
  http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=531&pageaction=displayproduct

- *Homepage ENCePP: http://www.encepp.eu/*

- *New EU pharmacovigilance directive: http://www.ec.europa.eu/health/human-use/pharmacovigilance/index_en.htm*
  Other important topics, e.g. medical devices, health technology assessment (HTA) and cooperation on rare diseases can also be found on the EU website http://www.ec.europa.eu/health/.

Swissmedic • Hallerstrasse 7 • Postfach • CH-3000 Bern 9 • www.swissmedic.ch • Tel. +41 31 322 02 11 • Fax +41 31 322 02 12

Annual conference of the International Society of Pharmacovigilance (ISoP) 25–28 October 2011 in Istanbul

The International Society of Pharmacovigilance held its 11th annual conference in Istanbul from 25 to 28 October 2011. The following are a few personal impressions:

True to the WHO's definition of pharmacovigilance – *"the science and activities relating to the detection, understanding and prevention of adverse effects and any other drug related problem*[1]*"* – the ISoP addresses a broad spectrum of issues concerning the safety of medicines and all the steps from primary reports to risk minimizing measures. This is in contrast to the International Society for Pharmacoepidemiology (ISPE) which focuses on pharmacoepidemiological studies.

Spontaneous reporting

Spontaneous reporting has been around, at least in pioneer countries such as Britain, for almost half a century. That's a good reason to think about the future. A report from the USA[2] that was recently published on the internet identifies persistent major obstacles regarding methodology, responsible persons, the inclination of potential reporters and above all mutual understanding. More work must be done in mutual communication and in the training of reporters as well as in technology and management, e.g. online reporting, as was done successfully in Switzerland for the pandemic vaccines. All these items are also on agenda at Swissmedic.

A short Swissmedic presentation tried to correct a widespread misconception – the idea that pharmacovigilance primarily deals with new risks such as, for example, the discovery of nephrogenic systemic fibrosis after the use of gadolinium contrast agents in patients with renal insufficiency several years ago.

However, on a day-to-day basis pharmacovigilance signals mostly concern new aspects of known risks, as we showed through an analysis of the spontaneous reports of venous thromboembolisms (VTE) in patients taking hormonal contraceptives. There is a broad range of issues, so-called risk factors for ADRs – more than a third of women with VTE present with one or more risk factors, and 6 of the 11 fatalities do so. Either the signal involves characteristics of adverse reactions (e.g. onset latency, severity, symptoms, etc.) or else the problems arise from prescribing and use. We would liked to have found out more from the reports: how the user was informed, and whether she understood and complied with the warning in the patient information but unfortunately this kind of information was only available in a few cases. One unusual yet important signal in the case of contraceptives was the diagnosis of the adverse effect. To diagnose suspected pulmonary embolism is a challenge for the physician – more than five days elapsed between the initial symptoms and the diagnosis of pulmonary embolism in 55 of the documented reports of this condition. VTEs are rare in young women who are not on hormonal contraceptives. According to a new Danish study[3], the incidence is 2.1/10,000 per year in 20–24 year-olds. In the 40–44 age range the rate more than doubles (4.8/10,000 per year) and is just as high in 20–24 year-olds who are on a combined hor-

[1] *WHO Technical Report No 498 (1972)*
[2] *Berniker Jessamin S., Spontaneous reporting Systems: Achieving Less Spontaneity and more reporting available from Leda at Harvard Law School. http://leda.law.harvard.edu/leda/data/363/Berniker.html*
[3] *Lidegaard et al., Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses: Danish cohort study, 2001-9. BMJ 2011;343:d6423 doi: 10.1136 (online publication)*

Swissmedic • Hallerstrasse 7 • Postfach • CH-3000 Bern 9 • www.swissmedic.ch • Tel. +41 31 322 02 11 • Fax +41 31 322 02 12

monal contraceptive. This means that although the physician may have a 20-something woman in front of him/her, she carries the VTE risk of a woman in her forties. It is essential for patients who consult the doctor for health issues to inform him/her that they are on the pill – and that the physician asks them. Finally, in women between 40 and 44 years old who are taking a combined hormonal contraceptive the incidence of VTE increases to 15.2/10,000 a year.

Spontaneous reporting was also the primary tool for monitoring the vaccination campaign during the pandemic influenza (H1N1) 2009. Jerry Labadie, Senior Safety Specialist at the Uppsala Monitoring Centre, who is in charge of Vaccine Pharmacovigilance, provided an overview of the safety problems and the lessons learned from the campaign. The risk of narcolepsy that was noted in children and adolescents after the end of the national vaccination campaigns is evidence that we need to conduct specific monitoring whenever medicines for which there is only a limited amount of experience of use generally or in sub-groups, are used for a short time to combat pandemics in large sectors of the population or the population as a whole.

Women's health

Valerie Beral, Director of the Cancer Epidemiology Unit at Oxford University and author of the famous WHI study, gave a presentation of the long-term effects of frequently used 'women's medicines' from an epidemiological viewpoint. She started with the first contraceptive pills, most of whose users nowadays live in developing countries, then hormone-replacement therapy, which was taken by 30–40% of women in industrialized countries in the 1990s but whose use has stopped sharply since the WHI study was published in 2002, and then the bisphosphonates which are increasingly used by women over the age of 60 as prophylaxis against osteoporosis.

Short presentations on the risks of various hormonal contraceptives and the regulatory consequences – are measures taken early enough, do they go far enough? - gave rise to a lively discussion.

Registries are increasingly used and for a greater range of pharmacovigilance issues, not just to monitor the effects and risks of orphan drugs (defined as important pharmaceuticals for rare diseases)[4]. The term is used broadly for the compilation of data about a defined cohort of people (e.g. users of medicines, patients with specific diagnoses, pregnant women, customers of an insurance company, etc.). Nancy Dreyer gave a presentation about the opportunities and restrictions for using such data in pharmacoepidemiology. The quality of the data and the question of whether the actual parameters collected are of interest are the crucial issues. The "relevant outcomes during the time period of interest" must be compiled and it must be possible to identify major subgroups and potential bias, especially 'bias by indication'. A recent comprehensive paper on these issues, in which the speaker was the co-editor, is available on the internet[5].

Demet Aydinkarahaliloglu, Director of the Turkish Pharmacovigilance Centre, presented an interesting system that enables the exposed population and the ADRs to be constantly monitored. It was used for new medicines (including rivaroxaban and fingolimod). Physicians fill in a web-based prescription and receive on the homepage important information and guidance for prescribing. The relevant details are then reported to the authorities and the marketing authorization holders. The

[4] *In accordance with Article 4 of the Ordinance on the simplified licensing of pharmaceuticals and the authorization of medicines in the reporting procedure (VAZV) dated June 2006*

[5] *Gliklich RE, Dreyer NA, editors., Registries for Evaluating Patient Outcomes: A User's Guide. 2nd edition, Rockville (MD): Agency for Healthcare Research and Quality (US); 2010 Sep*
http://www.effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=531&pageaction=displayproduct

Swissmedic • Hallerstrasse 7 • Postfach • CH-3000 Bern 9 • www.swissmedic.ch • Tel. +41 31 322 02 11 • Fax +41 31 322 02 12

same website can be used to report adverse drug reactions, which must of course be done as systematically as possible.
Other fundamental topics were also covered, such as the definition of 'preventability' of ADRs and related assessment criteria. Reference to the authors' publications can be found here [6; 7].

[6] *Ferner RE et al., EIDOS A mechanistic classification of adverse drug effects. Drug Safety 2010;33(1):13-23*
[7] *Aronson JK et al., Joining the DOTS. New approach to classifying adverse drug reactions. BMJ 2003;327:1222-5*

Swissmedic • Hallerstrasse 7 • Postfach • CH-3000 Bern 9 • www.swissmedic.ch • Tel. +41 31 322 02 11 • Fax +41 31 322 02 12

V: Information on the safety of medicines – published on the Swissmedic website

Caelyx, Infusionskonzentrat
08.12.2011 *

Noratak – Aktualisierung der Nutzen-Risiko Beurteilung und Marktrückzug
08.12.2011 *

Wichtiger Schritt im Kampf gegen Designer-Drogen
06.12.2011 *

Neue Studien zum Risiko von Venenthrombosen und Lungenembolien unter hormonalen Verhütungsmitteln* – Empfehlungen Swissmedic
05.12.2011 *

HPC - Revatio (Sildenafil) - Erhöhtes Mortalitätsrisiko von pädiatrischen Patienten mit pulmonaler arterieller Hypertonie (PAH) bei der Verwendung höherer Dosen von Revatio
01.12.2011 *

HPC – 58'245 STRATTERA (Atomoxetin)
30.11.2011 *

Primperan (Metoclopramid) – Kontraindikation für Kinder unter 1 Jahr und Marktrückzug der rein pädiatrischen Formulierungen
23.11.2011 *

International Conference on Harmonisation (ICH) Meeting in Sevilla, Spanien
21.11.2011

Methergin, Tropflösung 0,25 mg/ml: Lieferstopp wegen Medikationsfehlern / Injektionslösung 0,2 mg/ml: wichtige Sicherheitsinformationen in Zusammenhang mit der intramuskulären/intravenösen Anwendung
17.11.2011 *

Xigris (rekombinantes humanes Aktiviertes Protein C [Drotrecogin alfa]) – Information zu Marktrückzug wegen ungenügender Wirksamkeit
11.11.2011 *

Vorkommnisse mit Medizinprodukten melden – Sicherheit verbessern (Schweizerische Ärztezeitung 2011;92:45, Seiten 1732-1733)
10.11.2011 *

Aktueller Stand bei Zulassungen von homöopathischen und anthroposophischen Arzneimitteln ohne Indikation
31.10.2011 *

Fragen/Antworten zu „Zulassungsanforderungen an Generika und Arzneimittel mit bekanntem Wirkstoff“
31.10.2011 *

Anpassung des Formulars Zulassung Musterpackungen im Meldeverfahren
31.10.2011 *

Electronic exchange of ICSRs
27.10.2011

Switzerland and Ireland work together in the therapeutic products sector
27.10.2011

Xigris (rekombinantes humanes Aktiviertes Protein C [rhAPC]) – Information zu Marktrückzug wegen ungenügender Wirksamkeit
25.10.2011 *

Gemeinsam gegen Medikamente mit schmutziger Vergangenheit
25.10.2011 *

Einschränkung der Indikationen für AULIN® 100 und NISULID® 100 (Tabletten und Granulat) zur Erhöhung der Sicherheit
17.10.2011 *

Week of action against medicines that can kill
29.09.2011

Swissmedic • Hallerstrasse 7 • Postfach • CH-3000 Bern 9 • www.swissmedic.ch • Tel. +41 31 322 02 11 • Fax +41 31 322 02 12

Fewer antibiotics in veterinary medicine
20.09.2011

Serotonin-Syndrom als Folge der Interaktion von intravenös verabreichtem Methylenblau (MB) mit Serotonin-Wiederaufnahme-Hemmern
29.07.2011 *

Ten-year summary on reports of suspected adverse events following immunisation in Switzerland, 2001-2010
29.06.2011

Please find the complete list at the following web address:
http://www.swissmedic.ch/aktuell/00003/index.html?lang=en

*** *in German and/or French only***

Report of a suspected adverse drug reaction (ADR)

► The ADR reporting form can be filled in electronically:

MU101_20_001d_FO Meldung einer vermuteten unerwünschten Arzneimittelwirkung (UAW) [in German]
MU101_20_001f_FO Annonce d'effets indésirables suspectés d'un médicament (EI) [in French]

Contacts

Please do not hesitate to send your comments, questions or suggestions relating to this publication to the following addresses: eva.eyal@swissmedic.ch and/or helena.bill@swissmedic.ch.

Editorial team:
Eva Eyal, Thomas Munz, Helena Bill

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

Swissmedic • Hallerstrasse 7 • Postfach • CH-3000 Bern 9 • www.swissmedic.ch • Tel. +41 31 322 02 11 • Fax +41 31 322 02 12