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## **Statin-associated immune-mediated necrotising myopathy (IMNM)**

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# Vigilance-News

Edition 18 – May 2017

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## In this edition

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- Cockayne syndrome and metronidazole for systemic use: risk of severe hepatotoxicity
- Statin-associated immune-mediated necrotising myopathy (IMNM)
- «Big Data» in Pharmacovigilance
- Back reporting of Swissmedic reports

## Report of an adverse drug reaction (ADR)

Swissmedic recommends using the reporting portal (direct-insert or by XML file upload)

Online reporting portal ELViS:  
[www.swissmedic.ch/elvis](http://www.swissmedic.ch/elvis)

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## Impressum

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## Editorial

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Dear Reader

This 18th issue of Swissmedic Vigilance News has been given a new layout: The document structure has been simplified, and more contrast has been added. These typographical and structural changes make the publication more accessible and are a further step towards barrier-free communication on drug risks.

Freedom from barriers is something that helps both people with disabilities (e.g. visually or hearing-impaired people or those with motor or cognitive disabilities) and older people with age-related impairments to receive information through the internet without additional help.

Where the use of medicinal products is concerned, it is especially important that both medical professionals and patients are able to make immediate use of information about the relative risks and benefits of, and potential adverse reactions to, the medicines in question – regardless of any disability they may have. Swissmedic will continue to work on making access to websites and electronic documents barrier-free.

The importance of wide-ranging pharmacovigilance data has been demonstrated time and again. The article on “Big Data in Pharmacovigilance” summarises this situation.

In our “Signal-Flash”, moreover, we report on the systemic use of metronidazole in patients with Cockayne syndrome, on new contraindications for codeine- or dihydrocodeine-containing medicinal products, and on statin-associated immune-mediated necrotising myopathy.

Please send any suggestions or feedback on this issue of Vigilance News to [news.vigilance@swissmedic.ch](mailto:news.vigilance@swissmedic.ch).

The Editors

## Flash: Drug safety signals

### Cockayne syndrome and metronidazole for systemic use: risk of severe hepatotoxicity

Swissmedic is taking the opportunity of this communication to inform the healthcare professionals concerned about the risks of severe hepatotoxicity with rapid onset after the start of treatment with metronidazole for systemic use in patients with Cockayne syndrome. It is important to specify that metronidazole should be used in these patients after a careful benefit-risk assessment and only if no alternative treatment is available.

#### Cockayne syndrome (CS): prevalence, aetiology, clinical presentation, prognosis, treatment

Cockayne syndrome (CS) is a rare disease with an estimated prevalence in Europe of around 1 case per 200,000 births.

CS is a genetic disorder caused by a mutation of one of the genes ERCC6 (located on chromosome 10) or ERCC8 (located on chromosome 5) and which leads to abnormalities in the repair and “decoding” of DNA information (transcription). It is associated with autosomal recessive transmission. The disease can occur equally in boys and girls.

Cockayne syndrome is clinically characterised by growth problems, intellectual impairment of varying severity, motor difficulties (neurological disorders) and impaired vision and hearing. Children have a prematurely aged face and are extremely thin (cachexia).

The signs and symptoms are highly variable in terms of severity and age of onset.

The most common form of CS, known as classical CS (type I) manifests itself during the first year of life as delayed growth and neurological disorders, followed by a decline in vision and hearing. Cases involving an earlier onset

and with more severe symptoms (type II) such as ocular abnormalities and neurological disorders from birth have been described. Finally, cases with a later onset and more moderate symptoms (type III) have also been reported.

The cerebro-oculo-facio-skeletal (COFS) syndrome corresponds to the extreme prenatal form of the clinical spectrum of CS and is characterised by very severe malformations of the brain (microcephaly), eyes (microphthalmia and cataract) and joints (arthrogryposis).

Another form of the illness known as Cockayne syndrome also exists – xeroderma pigmentosum, which combines all the clinical manifestations of Cockayne syndrome with an extreme sensitivity of the skin and eyes to ultraviolet light (UV), leading to major lesions of the skin and an increased risk of skin cancer.

The prognosis varies according to the type of CS. Life expectancy is limited, and few people suffering from the classical form of the syndrome (type I) reach the age of twenty. The prognosis is even worse in children with type II. By contrast, individuals suffering from type III live to adulthood.

Unfortunately, no treatment capable of curing patients is available to date. The condition is managed symptomatically.

#### Metronidazole for systemic use

Metronidazole, a synthetic nitroimidazole derivative, is active against most strictly anaerobic bacteria and also against protozoa. The antibacterial and antiparasitic activity of metronidazole is based on the inhibition of the synthesis of the nucleic acids of sensitive bacteria and protozoa.

Metronidazole for systemic use is indicated for the treatment of infections where the

presence of anaerobic bacteria is proven or suspected, taking account of metronidazole's spectrum of activity.

Metronidazole can be used in cases of amoebiasis (intestinal or hepatic), urogenital trichomoniasis, Gardnerella vaginalis infections and giardiasis.

### Risk of severe hepatotoxicity

It is important to note that cases of severe hepatotoxicity / acute hepatic failure, including cases with a fatal outcome, with rapid onset after treatment initiation have been reported in patients with Cockayne syndrome taking products containing metronidazole for systemic use. In this population metronidazole should be used after a careful benefit-risk assessment and only if no alternative treatment is available. Liver function tests must be performed prior to the start of therapy, throughout and after the end of treatment until liver function is within normal ranges, or until the target values are reached. If the liver function test results become markedly elevated during treatment, the drug should be discontinued.

Patients with Cockayne syndrome should be advised to immediately report any symptoms of potential liver injury to their physician, including abdominal pain, anorexia, nausea, vomiting, fever, malaise, fatigue, jaundice, dark urine, mastic coloured stools or itching, and discontinue their metronidazole treatment.

In contrast, liver injuries have only been described very rarely in patients with metronidazole treatment, but without Cockayne syndrome.

### Conclusion

Swissmedic would like to alert healthcare professionals who treat patients with Cockayne syndrome to the increased risk of severe hepatotoxicity after the initiation of metronidazole for systemic use. It is important to specify that metronidazole should be used in these patients after a careful benefit-risk assessment and only if no alternative treatment is available.

Furthermore, the "Warnings and precautions" section of the product information for drugs based on metronidazole for systemic use are to be amended to reflect the risk of hepatotoxicity described above.

### Reporting suspected adverse drug reactions

Swissmedic recommends that healthcare professionals use its dedicated portal to report adverse drug reactions (ADR). This portal, which is known as the Electronic Vigilance System (EIViS) can be used to directly submit ADR.

All necessary information can be found at [www.swissmedic.ch](http://www.swissmedic.ch) > Market surveillance > Pharmacovigilance. Reporting undesirable side-effects.

The latest information about medicinal products can be found on the Swissmedic website: [www.swissmedicin.ch](http://www.swissmedicin.ch).

### Literature

- (1) B. T. Wilson et al., Metronidazole Toxicity in Cockayne Syndrome: A Case Series, Pediatrics Volume 136, number 3, September 2015
- (2) B. T. Wilson et al., The Cockayne Syndrome natural History (CoSyNH) study: clinical findings in 102 individuals and recommendations for care, Genetics in medicine, Volume 13, Number 5, May 2016

## Statin-associated immune-mediated necrotising myopathy (IMNM)

### General

The great medical value of statin therapy is clear. In their guidelines, the international societies recommend this substance class as highly effective first-line drugs for primary and secondary prevention of cardiovascular diseases (1).

**Table 1** provides an overview of the statins authorised in Switzerland. Use of statins may be associated with adverse effects that may necessitate discontinuation of the substance concerned. The major concern here is a broad spectrum of potential adverse drug effects involving the muscles that are associated with this substance class.

They range from mild muscle pain, with or without changes in laboratory parameters, to serious complications such as the development of rhabdomyolysis with acute renal failure. In most cases, a statin-associated myopathy is self-limiting and ceases when the medication is discontinued (2). However, an estimated 2 to 3 patients per 100,000 of those treated with statins develop a so-called immune-mediated necrotising myopathy (IMNM) (3).

### Epidemiology of immune-mediated necrotising myopathy (IMNM)

The statin “exposure time” required for IMNM to develop is stated in the literature as an average of 2–3 years (4), although this may vary greatly from one individual to the next. Together with polymyositis, dermatomyositis, inclusion body myositis and antisynthetase syndrome, IMNM belongs to a subgroup of idiopathic inflammatory myopathies (IIM) (5). Although there are a few cases of IMNM in children, the disease mainly affects adults. It is estimated that women are twice as likely as

men to develop an IIM, although this does not apply to statin-associated IMNM. Up to the age of 50, women are slightly more at risk than men to develop this condition. Above this age, there are no gender-specific differences in its prevalence (6, 7).

### Autoantibodies in IMNM

Two-thirds of patients with IMNM have specific autoantibodies (8). Antibodies against the signal recognition particle (SRP) were identified in this context a long time ago (9). The existence of autoantibodies against 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMGCR) that are usually, but not necessarily, found in patients with statin-associated IMNM was not discovered until considerably later. It is assumed that up to 30 or 40 % of IMNM patients have no autoantibodies (8).

### Pathophysiology of IMNM

The pathophysiology of statin-associated IMNM has not definitely been elucidated. Anti-HMGCR autoantibodies are directed at the catalytic domain of HMGCR, a protein found in the membrane of the endoplasmic reticulum. Remarkably, HMGCR is involved in the biosynthesis of cholesterol and is inhibited by statins (10). It is assumed that statins can trigger the development of IMNM by up-regulating HMGCR expression, hereby triggering an autoimmune response determined by certain immunogenetic factors.

The class II HLA allele DRB1\*11:01, present in just 10 % of the normal population, has been found in 70 % of patients. Regenerating muscle fibres express large quantities of HMGCR. This situation, in combination with exposure to a statin, ensures a persistently high concentration of this protein and disrupts the balance between cell decay and repair. Vitamin D deficiency is under discussion as a further predisposing factor for IMNM (11).

**Table 1: Statins authorised in Switzerland (1)**

ACTIVE SUBSTANCE/ Proprietary names in Switzerland (selection)	Oral daily dose (mg)	Mode of administration	Bioavailability (%)	EHL (h)	Av. LDL ↓ (%) at max. daily dose / potency	Metabolism	Property: lipophilic (L) / hydrophilic (H)	Contraindication
<b>ATORVASTATIN</b> Sortis® Atorvastax®	10–80	any time, independently of food	12	14	61 high	CYP3A4	L	<ul style="list-style-type: none"> <li>Active liver disease or unexplained persistent elevation of transaminases</li> <li>Cholestasis</li> <li>Myopathies</li> <li>Pregnancy/breastfeeding</li> </ul>
<b>FLUVASTATIN</b> Lescol®	20–80	<b>prolonged-release form:</b> any time, independently of food <b>non-prolonged release form:</b> evening, independently of food	20–30	<3	34 (after 24 wk) moderate	CYP2C9	H	<ul style="list-style-type: none"> <li>Active liver disease or unexplained persistent elevation of transaminases</li> <li>Pregnancy/breastfeeding</li> </ul>
<b>ROSUVASTATIN</b> Crestor® Crestastatin®	5–40	any time, independently of food g	20	19	63 (after 4 wk) high	only 10 % usually into N-Desmethyl derivative	H	<ul style="list-style-type: none"> <li>Active liver disease or unexplained persistent elevation of transaminases</li> <li>Severe renal impairment (&lt;30 ml/min)</li> <li>Myopathies</li> <li>Concomitant administration of ciclosporin</li> <li>Pregnancy/breastfeeding</li> </ul>
<b>PRAVASTATIN</b> Mevalotin® Pravastax® Selipran®	10–40	any time, independently of food	17	3	34 (after 8 wk) low		H	<ul style="list-style-type: none"> <li>Active liver disease or unexplained persistent elevation of transaminases</li> <li>Pregnancy/breastfeeding</li> </ul>
<b>SIMVASTATIN</b> Zocor® Sicora® Simvasin®	20–80	evening, independently of food	<5	1.5	53 moderate	CYP3A4	L Prodrug	<ul style="list-style-type: none"> <li>Active liver disease or unexplained persistent elevation of transaminases</li> <li>Concomitant administration of potent CYP3A4 inhibitors, gemfibrozil, ciclosporin or danazol</li> <li>Pregnancy/breastfeeding</li> </ul>
<b>PITAVASTATIN</b> Livazo®	2–4	any time, independently of food	51	12	46.5 (after 12 wk) moderate	UGT1A3 UGT2B7	L	<ul style="list-style-type: none"> <li>Active liver disease or unexplained persistent elevation of transaminases</li> <li>Myopathy</li> <li>Concomitant admin. of ciclosporin</li> <li>Pregnancy/breastfeeding</li> </ul>

**Key:** **low** = less than 30 % LDL cholesterol reduction; **moderate** = 30–49 % LDL cholesterol reduction; **high** = 50 % or more LDL cholesterol reduction; **wk** = weeks

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### Histological diagnosis of IMNM

IMNM is characterised histologically by pronounced muscle fibre necrosis with simultaneous muscle fibre regeneration.

There are only weak, if any, histological signs of inflammation (12). Moreover, increased expression of MHC I on necrotic and non-necrotic muscle fibres and abnormal capillary morphology have been found during muscle biopsies (13). Clinical studies have shown macrophages that infiltrate the muscle at the histological level to be the dominant type of inflammatory cell in anti-HMGCR-positive patients.

Moreover, a few CD4- and CD8-positive cells and plasmacytoid dendritic cells may sometimes be found in perivascular and endomysial tissue. In contrast, perifascicular atrophy and a strikingly large number of B cells – of the type generally found in dermatomyositis – are completely absent in this case (6). Compared with other muscle disorders, autoantibodies against HMG-CoA reductase are predominantly found in biopsy material from patients with IMNM.

### Clinical features of IMNM

IMNM manifests clinically as symmetrical proximal muscle weakness of the arms and legs, indicative of muscle atrophy/myopathy. Disease activity correlates with the measurable and objective muscle strength of the individual patient. The onset of the disease may be acute (days to weeks) or subacute (months). Laboratory testing can show creatine kinase (CK) levels raised many fold up to 13,000 U/l (normal values: up to 170 in women and 190 in men, depending on the laboratory method used) (14).

CK may be (substantially) elevated many months previously without the patient experiencing subjective muscle problems (15). To this extent, CK is only of limited use as a parameter of the course of the disease since a correlation with muscle strength in the context of IMNM has not yet been demonstrated (15). Electromyography (EMG) of affected patients shows spontaneous electrical discharges (fibrillation potential) and sharply rising waves (13). MRI imaging shows muscle oedema of the thigh reminiscent of marked, active inflammation – a finding that is sometimes at odds with the biopsy (8, 16).

It is not always only the skeletal muscles of the extremities that are affected by IMNM. Isolated cases of dyspnoea as a result of restriction of the respiratory muscles have been described (17). In addition, there have been reports of patients with bulbar muscle weakness and symptomatic dysphagia (18).

### Complications of IMNM

There are indications that statin-associated IMNM may be associated with an elevated risk of malignant disease (13). Initial studies of this aspect have been performed in a number of countries. A study in France also compared the risk of malignancy in patients with an anti-HMGCR-positive myopathy with the risk in patients who had an anti-SRP-positive myopathy.

There was a trend towards IMNM patients having a higher risk of developing cancer. This seems to apply above all to patients in whom HMGCR autoantibodies were found (23).

**Table 2: Medical Dictionary for Regulatory Activities (MedDRA) System Organ Classes (SOC)**

**High Level Term (HLT) “muscular autoimmune disorders” with the corresponding Preferred Terms (PT) and Lowest Level Terms (LLT)**

<b>Muscular autoimmune disorders (HLT)</b>
» <b>Immune-mediated necrotizing myopathy (PT)</b>
» <b>Immune-mediated necrotising myopathy (LLT)</b>
» <b>Immune-mediated necrotizing myopathy (LLT)</b>
» Inclusion body myositis (PT)
» Inclusion body myositis (LLT)
» Sporadic inclusion body myositis (LLT)
» Juvenile Polymyositis (PT)
» Juvenile polymyositis (LLT)
» Morvan syndrome (PT)
» Morvan syndrome (LLT)
» Morvan's fibrillary chorea (LLT)
» Myasthenia gravis (PT)
» Myasthenia gravis (LLT)
» Myasthenia gravis aggravated (LLT)
» Myasthenia gravis paralytica (LLT)
» Myasthenia gravis crisis (PT)
» Myasthenia gravis Krise (LLT)
» Myasthenia gravis neonatal (PT)
» Myasthenia gravis neonatal (LLT)
» Neonatal myasthenia gravis (LLT)
» Myasthenic syndrome (PT)
» Drug induced myasthenic syndrome (LLT)
» Eaton-Lambert syndrome (LLT)
» Lambert-Eaton myasthenic syndrome (LLT)
» Myasthenia gravis-like paralysis (LLT)
» Myasthenia gravis-like reaction (LLT)
» Myasthenia gravis-like syndrome (LLT)
» Myasthenic syndrome (LLT)
» Reaction myasthenia gravis-like (LLT)
» Neuromyotonia (PT)
» Isaac's syndrome (LLT)
» Isaacs Syndrom (LLT)
» Neuromyotonia (LLT)
» Ocular myasthenia (PT)
» Okulare Myasthenie (LLT)
» Ocular myasthenia (LLT)
» Polymyalgia Rheumatica (PT)
» Polymyalgia rheumatica aggravated (LLT)
» Rhizomelic pseudopolyarthritis (LLT)
» Polymyositis (PT)
» Polymyositis (LLT)
» Polymyositis haemorrhagica (LLT)
» Polymyositis hemorrhagica (LLT)

## Differential diagnosis of IMNM and extramuscular manifestations

Probably the most important feature that distinguishes statin-associated IMNM from a conventional statin myopathy is the progression of the clinical symptoms, even after the statin has been discontinued. Unlike other forms of IIM – and dermatomyositis and antisynthetase syndrome in particular – extramuscular symptoms are rarely dominant in IMNM (6).

In the MedDRA (Medical Dictionary for Regulatory Activities) terminology, muscular autoimmune disorders are classified according to **Table 2**. Yet extramuscular symptoms are also described in IMNM patients in the literature. Arthralgia and Raynaud's phenomenon occurred in isolated cases (19). Interstitial lung disease can also develop in IMNM patients, although this applies more to patients with anti-SRP-antibody-positive IMNM. To date, interstitial lung disease has rarely been described in patients with an anti-HMGCR antibody-associated variant of the disease (13, 16).

## Therapy of IMNM

There are currently no international guidelines for the therapy of IMNM. Some patients with a statin-triggered autoimmune myopathy and anti-HMG-CoA reductase autoantibodies experienced spontaneous remission after statin therapy had ended, without further measures. This suggests that, in patients with mild symptoms, discontinuation of the statins with clinical monitoring of symptoms and administration of immunosuppressive therapy only as required by the course and features of the patient's condition may also be a therapeutic option. In most patients, however, immunosuppression in addition to discontinuing statin therapy is necessary by analogy with other forms of autoimmune muscle disease.

The therapeutic options that are basically available, and often prescribed in combination, are corticosteroids, e.g. oral prednisone 1 mg/kg body weight, with other immunosuppressive substances (e.g. methotrexate, azathioprine, mycophenolate, cyclosporine, tacrolimus) and immunoglobulins (IVIG), depending on the severity of the condition (20). Studies have also shown immunoglobulins to be effective as single-entity therapy, particularly for statin-associated IMNM (21).

There have been reports of patients who initially showed progress without any immunosuppressive therapy but who subsequently derived great benefit from administration of IVIG (22). Immunoglobulins can therefore also be considered as first-line agents even in specific patient groups, e.g. those with diabetes.

There is evidence that many anti-HMGCR patients initially show only slight improvement after administration of prednisone and therefore require combination therapy, usually with two immunosuppressive agents, before an improvement in muscle strength occurs and CK values normalise (8).

However, these patients do tend to relapse when immunosuppressive therapy is tapered off after the symptoms have improved (12). Additional administration of rituximab may also have a positive effect on the course of the disease. This applies in particular to anti-SRP-associated IMNM and also to the statin-associated form of the disease. Moreover, plasmapheresis is also recommended in the literature as add-on therapy (6, 18, 23).

Unfortunately, no controlled clinical trials of the therapy of IMNM have been performed to date. The available data have been generated only from clinical experience and case reports. Few case reports have been published about this special form of myopathy. One of them concerned a 59-year-old male patient from Switzerland (24).

It has not been possible to study case series or perform cohort studies or even large-scale clinical trials because of the small number of cases. In a recently published review, four major literature databases were searched and a total of 16 English-language articles describing 100 IMNM cases were identified. On average, the patients were 65 years old, had a symmetrical proximal muscle weakness in 83 % of the cases, and had a mean CK of 6800 U/l. The majority of the patients received two or more immunosuppressants (25).

Based on the WHO Pharmacovigilance database, Swissmedic is currently cooperating with the regional pharmacovigilance centre in Zurich to study the largest existing series of cases of IMNM. The aim of this analysis is to produce a detailed description of this disease which occurs rarely during statin therapy.

Swissmedic recently informed healthcare professionals about this newly identified risk associated with statins (26). It would be desirable for physicians to be more alert to the risk, particularly in patients over 50 years of age who are experiencing muscle problems on therapy with statins. They should bear in mind not only conventional, self-limiting statin-associated myopathies but also, if muscle pain persists despite discontinuation of HMG-CoA reductase inhibitors, an autoimmune cause. In all unclear cases, the patient should be tested for HMGCR autoantibodies. This test is offered as part of myositis screening by specialised laboratories.

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## Cough and cold preparations containing codeine or dihydrocodeine: Update of the product information

As agreed with Swissmedic, the marketing authorisation holders of cough and cold preparations containing codeine or dihydrocodeine have made updates to the contraindications, indication restrictions and other changes to the Information for healthcare professionals and Patient information.

**Cough and cold preparations containing codeine or dihydrocodeine may not be administered to**

- children below 12 years;
- patients of any age who are known to be "ultra-rapid metabolisers";
- breast-feeding women.

**Cough and cold preparations containing codeine or dihydrocodeine are not recommended for adolescents between 12 and 18 years who have problems with breathing.**

### Background

#### Codeine

After ingestion, codeine is converted into the active metabolite morphine by the hepatic isoenzymes CYP2D6, of which several genetic polymorphisms are known to exist.

In some people (known as "ultra-rapid metabolisers"), codeine is converted into morphine faster than normal.

Since these patients with an "ultra-rapid CYP2D6 metaboliser" phenotype have high levels of CYP2D6, toxic serum levels of morphine can arise even with small doses and result in serious complications. The most important complication is respiratory depression.

Other symptoms of overdose include dizziness, deep sedation, slow or shallow breathing, nausea and vomiting, even cardiac and respiratory arrest.

Although these serious side effects can occur in patients of all age groups, a special risk exists in children below 12 years, since the conversion of codeine into morphine is more variable and less predictable.

In breast-feeding mothers who are "ultra-rapid CYP2D6 metabolisers" and receiving codeine treatment, there is a risk of a possibly fatal overdose in the baby as a result of receiving very large quantities of morphine via the breast milk.

If signs of opioid toxicity appear, close monitoring of patients is extremely important.

**Consequently, cough and cold preparations containing codeine should no longer be administered to children below 12 years, patients of any age who are known to be "ultra-rapid metabolisers" or breast-feeding women.**

Furthermore, codeine is not recommended for adolescents between 12 and 18 years with impaired respiration since it can lead to symptoms of opioid overdose. However, if a cough or cold preparation containing codeine is used, the patient should be monitored particularly for symptoms of respiratory depression.

#### Dihydrocodeine-containing cough and cold preparations

The contraindications and precautions stated for codeine also apply for cough and cold preparations containing dihydrocodeine. Comparable safety concerns exist for these medicinal products, and insufficient experience has been acquired in the above-mentioned risk groups.

#### Recommendations for healthcare professionals / patients

Patients taking cough and cold preparations containing codeine or dihydrocodeine should be monitored for the following symptoms: slow or shallow breathing, confusion, drowsiness, constricted pupils, nausea or vomiting,

constipation, loss of appetite. If such symptoms occur, the administration of the medicinal product must be stopped and medical advice sought immediately.

The product information (Information for healthcare professionals and Patient information) for cough and cold preparations containing codeine and dihydrocodeine have been modified accordingly. The latest information about medicinal products can be found on the Swissmedic website: [www.swissmedicinfo.ch](http://www.swissmedicinfo.ch).

### **Reporting adverse drug reactions**

Swissmedic recommends to use its dedicated portal to report adverse drug reactions (ADR). This portal, which is known as the Electronic Vigilance System (EIViS), can be used to directly submit ADR.

All necessary information can be found at [www.swissmedic.ch/elvis](http://www.swissmedic.ch/elvis).

## List of cough and cold preparations containing codeine or dihydrocodeine authorised in Switzerland (as of May 2017)

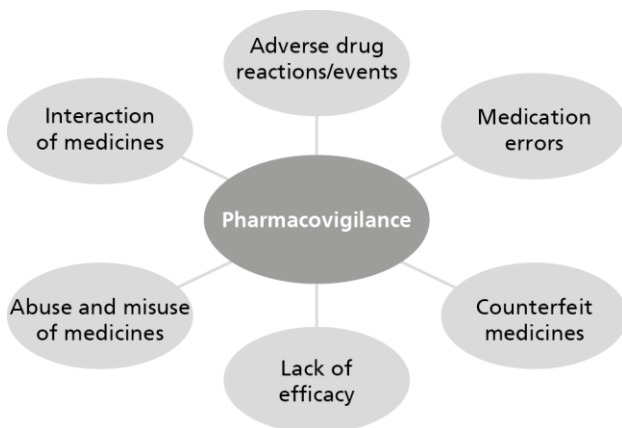
Company	Preparation	Dosage form
BGP Products GmbH	Codein Knoll®	Tablets
DR. BÄHLER DROPA AG	Dr. Bähler Bronchialpastillen mit Codein	Lozenges
Coop Vitality Health Care GmbH	Coop Vitality Bronchialpastillen mit Codein	Lozenges
FARMACEUTICA TEOFARMA SUISSE SA	Paracodin®	Drops
GEBRO PHARMA AG	Makatussin Comp., Hustensirup Makatussin, Hustentropfen	Syrup Drops
GSK Consumer Healthcare	Resyl® plus Tossamin® plus	Drops, Syrup Capsules for the day/for the night
Hänseler AG	Husten- und Bronchialsirup «S» mit Zucker	Syrup
Interdelta SA	Néo-Codion® N	Film-coated tablets
Iromedica AG	Bronchialpastillen VA mit Codein GEM Bronchialpastillen mit Codein Iropect® Bronchialpastillen MAKU Bronchialpastillen mit Codein Pharmacieplus Bronchialpastillen mit Codein Rotpunkt Apotheke Bronchialpastillen mit Codein Swidro Bronchialpastillen mit Codein Zürcher Bahnhof Apotheke Bronchialpastillen mit Codein	Lozenges Lozenges Lozenges Lozenges Lozenges Lozenges Lozenges Lozenges
Janssen-Cilag AG	Benylin® mit Codein N	Syrup
Streuli Pharma AG	Escotussin	Drops
Vifor Consumer Health SA	Pectocalmine® N, Sirup Pectocalmine® N ohne Zucker, Sirup	Syrup Syrup
Dr. Heinz Welti AG, Fabrikation chemisch-pharmazeutischer Produkte	Codicalm® Sano-Tuss N Sanotussin	Syrup Syrup Film-coated tablets

## Big Data in Pharmacovigilance – a Synopsis

### Introduction

The World Health Organization (WHO) defines Pharmacovigilance as “the science and activities relating to the detection, assessment, understanding and prevention of adverse effects and all other problems related to medicines” (1).

The scope of pharmacovigilance is complex and includes adverse drug reactions (ADR) or events, medication errors, counterfeit or substandard medicines, lack of efficacy, misuse and/or abuse, and interaction between medicines (see diagram) (2).



Pharmacovigilance relies heavily on spontaneous reporting in which suspected adverse drug reactions (ADR) are reported by health care professionals, manufacturers or directly by patients. Spontaneous reporting systems (SRS) provide the highest volume of information on patient safety related either to the products themselves or to their use. The most important function of SRS is early detection of safety signals (3).

A signal is defined by the WHO as “Reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously.”

While SRS are crucial and essential components of pharmacovigilance, they can never give a complete picture of patient safety information. Some of the limitations are (4):

- The number of reports received cannot be used as a basis for determining the incidence of a reaction as neither the total number of reactions occurring in the population nor the number of patients exposed to a health product is known.
- The data collected often have limited patient information regarding medical history, concomitant treatment(s), pre-existing conditions, time to onset, etc.
- There is underreporting of adverse reactions with both voluntary and mandatory surveillance systems, and reporting rates may vary widely for drugs as well as for jurisdictions.
- Numerical comparisons cannot be made between reactions associated with different health products based on the data in the line listings.
- The data reported do not represent all known safety information concerning the suspected health product(s) and cannot be used in isolation to make decisions regarding an individual's treatment regimen; other sources of information, including the prescribing information for the product, should be consulted.

These limitations force all regulatory agencies to find new ways to enhance the quality and quantity of ADR, including the use of “big data” in pharmacovigilance.



## What is “Big Data and Analytics”?

### “Big Data” in pharmacovigilance

Big data refers to a collection of structured and unstructured data that may be enormous, in the range of several billion gigabytes. In post-market surveillance, structured data may include SRS, electronic health records (EHR), electronic medical records (EMR), administrative health data (AHD), registries, etc. Unstructured data may include social media like Twitter, Facebook, patient forums, clinical narratives within EMR, etc. A definition of big data in post-market surveillance is lacking at this time although the EMA refers to big data as “an umbrella term describing large data sets from any source.”

Some regulatory agencies, like the United States Food and Drug Administration (US FDA) (5) and European Medicines Agency (EMA) (6) have already considered AHD and EMR as part of their post-market surveillance systems. Further research is required to demonstrate the benefit of using unstructured data in post-market surveillance.

While benefits of big data in post-market surveillance are increasingly being recognised, its integration and utilisation in the current post-market surveillance frameworks requires clearly defined objectives, plans, and financial resources.

### Relevant Data Sources

#### Spontaneous Reporting

SRS are designed to gather individual case safety reports (ICSR) of suspected ADR from a variety of sources, including clinicians, pharmacists, other healthcare professionals, pharmaceutical companies, medical literature, patients and the general public. They remain the cornerstone of pharmacovigilance; they cover all types of drugs used in any setting. Their function is to identify potential safety issues

as soon as possible, and to continuously monitor and evaluate potential safety issues in relation to reported ADR.

The increase of ICSR in SRS has allowed the application of data mining and statistical techniques for signal detection. However, the success of signal detection in SRS is hampered by the concept of voluntary reporting, including factors that may influence the reporting rate and quality of data, lack of an accurate quantification of the frequency of events or the identification of possible risk factors for their occurrence, and missing denominators. To overcome some of these limitations, the US FDA (7) and EMA adopted other sources of databases including EMR and AHD (8).

#### Healthcare System Databases

Health Care System databases may include the following:

- EHR: Refers to an electronic record of health-related information on an individual that conforms to nationally recognised interoperability standards and that can be created, managed, and consulted by authorised clinicians and staff across more than one health care organisation. These are complete health records under the custodianship of a health care provider(s) that holds all relevant health information about a person over their lifetime. This is often described as a person-centric health record, which can be used by many approved health care providers or health care organisations (9). EHR can include all personal health information belonging to an individual; entered and accessed electronically by healthcare providers over the person’s lifetime; and extends beyond acute inpatient situations including all ambulatory care settings at which the patient receives care (10).
- EMR: Refers to an electronic record of health-related information on an individual

ual that can be created, gathered, managed, and consulted by authorised clinicians and staff within one health care organisation. These are partial health records under the custodianship of a health care provider(s) that holds a portion of the relevant health information about a person over their lifetime. This is often described as a provider-centric or health organisation-centric health record of a person. EMR systems comprise patient information including socio-demographic characteristics, medical and drug history, diagnostic information including laboratory results, treatments and outcomes (11).

- **AHD:** This is generated through the routine administration of health care programs. These databases include characteristics of individual members, basic demographic data, therapeutic procedures, treatments and outcomes, diagnoses of hospital admissions, reimbursed prescriptions of drugs, etc.
- **Registries:** Contain standardised information about a group of patients who share the same condition or experience.

Although these databases are designed primarily for routine clinical care they have been frequently utilised for observational studies. Their representativeness of routine clinical care makes it feasible to study real world safety data, effectiveness and prescription patterns. In addition, these databases have been used in pharmacovigilance predominantly to confirm signals from SRS on an ad hoc basis (12).

Such databases are also an important source of data for detection of ADR. However, extracting signals from these databases requires specific methods to analyse the unique issues that arise from working with non-ICSR data.

## Non-conventional Data Sources

Non-conventional data sources are primarily non-structured data that may be used to complement existing SRS. Non-conventional data sources include the biomedical literature (including amateur press), social media (including Twitter, Facebook, patient forums, etc.) and web search terms. Further research is required to demonstrate the benefit of using these data in post-market signal detection.

## Opportunities of big data in pharmacovigilance

Increased interest exists in evaluating big data analytics for pharmacovigilance because it has the potential to supplement traditional spontaneous reporting systems in several ways:

- It could be a cost-effective (re)use of existing administrative data to enable active surveillance.
- It could provide more timely signal detection over traditional spontaneous reporting systems.
- It has the potential to complement traditional systems (such as clinical trials and SRS) with real world data, and to use epidemiological methods to estimate the incidence of adverse events in populations.
- It could provide a better way to identify and investigate medicine-adverse event associations that happen over a longer period of time (which could be missed by spontaneous reporting).
- It enhances the ability to investigate signals across different sub-populations and to control for confounders.

## Challenges

While potential benefits of big data in post-market surveillance have been acknowledged, a number of challenges were highlighted as well, particularly with the integration and utilisation of big data in the current

pharmacovigilance framework. The **common challenges** identified include:

#### Security and privacy

- Privacy & legal considerations for sharing of data between countries and even between different national databases or data holders.

#### Partnerships

- Building domestic and international partnerships to access data sources that are not held by the regulator.

#### Infrastructure and capacity

- Building internal capacity to leverage new data sources, including both IT infrastructure and the expertise to use it effectively.
- Building infrastructure and common data models to support datasets and develop innovative methods to link together different data sources.
- Resources required to develop, evaluate and use data may be substantial and will involve multi-disciplinary teams.

#### Standards

- Developing international standards, principles and best practices for sharing, combining and validating data from multiple sources and databases.
- Establishing internationally harmonised standards to accept results of big data analysis by other regulatory agencies.
- Developing common data models to share data.
- Different coding systems for spontaneous AE databases and health care data, needing extraction and mapping of ADR.

#### Data analysis

- Establishing methods and standards to efficiently evaluate data for secondary uses, which may be biased due to a number of factors, including practitioner behaviour,

administrative dataset is mainly for financial purposes, EMR is primary for clinical management.

- Incomplete data due to partial participation by healthcare providers (public vs. private).
- Challenges in converting free text data to structured data.
- The rules governing data collection may change over time and electronic access to historical records may be limited.

Despite significant recognised challenges, various international research projects and collaboration programs have already been initiated to explore and to exploit the huge potential and presumed benefits of big data in pharmacovigilance.

Currently, Swissmedic is actively participating in collaboration initiatives to build up and take advantage of big data analysis as soon as such pharmacovigilance systems have been established.

#### References

- (1) <http://apps.who.int/medicinedocs/pdf/s4893e/s4893e.pdf>
- (2) [http://www.who.int/medicines/areas/quality\\_safety/safety\\_efficacy/EMP\\_PV\\_Indicators\\_web\\_ready\\_v2.pdf](http://www.who.int/medicines/areas/quality_safety/safety_efficacy/EMP_PV_Indicators_web_ready_v2.pdf)
- (3) <http://www.dsru.org/consulting-on-risk-management/signal-detection/>
- (4) [http://www.hc-sc.gc.ca/dhp-mps/medeff/databasdon/conditions\\_search-recherche-eng.php](http://www.hc-sc.gc.ca/dhp-mps/medeff/databasdon/conditions_search-recherche-eng.php)
- (5) <http://www.fda.gov/downloads/ScienceResearch/DataMiningatFDA/UCM443675.pdf>
- (6) [http://www.ema.europa.eu/docs/en\\_GB/document\\_library/Regulatory\\_and\\_procedural\\_guide\\_line/2009/11/WC500011434.pdf](http://www.ema.europa.eu/docs/en_GB/document_library/Regulatory_and_procedural_guide_line/2009/11/WC500011434.pdf)
- (7) <http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM464043.pdf>
- (8) <http://onlinelibrary.wiley.com/doi/10.1038/clpt.2012.54/pdf>
- (9) <https://www.infoway-inforoute.ca/en/what-we-do/blog/digital-health-records/6852-emr-ehr-and-phr-why-all-the-confusion>
- (10) <http://www.wpro.who.int/publications/docs/EHRmanual.pdf>
- (11) [http://cdn.intechopen.com/pdfs/38579/InTech-Data\\_mining\\_techniques\\_in\\_pharmacovigilance\\_analysis\\_of\\_the\\_publicly\\_accessible\\_fda\\_adverse\\_event\\_reporting\\_system\\_aers.pdf](http://cdn.intechopen.com/pdfs/38579/InTech-Data_mining_techniques_in_pharmacovigilance_analysis_of_the_publicly_accessible_fda_adverse_event_reporting_system_aers.pdf)
- (12) <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3685297/>

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## Regulatory

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### Pharmaceutical industry: Back reporting of Swissmedic reports

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The regional pharmacovigilance centres receive reports of adverse drug reactions from healthcare professionals and patients, process them and then send them to the Swissmedic national pharmacovigilance centre, where the reports are evaluated once again and forwarded to the marketing authorisation holder(s) of the suspect medicinal product(s).

Swissmedic would like to take this opportunity to point out the following:

- These individual case reports should **not** be sent by the pharmaceutical companies concerned to Swissmedic (“back reporting”), since this leads to duplicates by double-reporting and causes a considerable amount of extra administrative work for all involved.
- Reports forwarded to pharmaceutical companies by Swissmedic have already been medically evaluated. If a pharmaceutical company disagrees with this evaluation, this is **not** a reason for sending the report to Swissmedic. If Swissmedic wants a pharmaceutical company's evaluation of a report or situation, a corresponding statement is requested.
- If a pharmaceutical company possesses relevant **follow-up information**, this must be sent to Swissmedic as a follow-up report with reference to the initial report.

### ELViS training courses

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From early 2017 on, the ELViS training courses for marketing authorisation holders are not being held anymore. The training document can be found below:

[www.swissmedic.ch/elvis-training-manual](http://www.swissmedic.ch/elvis-training-manual).

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## Information on the Swissmedic website

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

### Health Professional Communication

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10.05.2017

[DHPC – Keytruda® \(Pembrolizumab\): Schwere Hautreaktionen](#)

Tödlicher Fall von Stevens-Johnson Syndrom und tödlicher Fall von toxischer epidermaler Nekrolyse

03.05.2017

[DHPC – Cipralox® \(Escitalopram\), Seropram® \(Citalopram\)](#)

Aufnahme von Rhabdomyolyse als unerwünschte Wirkung in die Arzneimittelinformation von Escitalopram- und Citalopram-haltigen Arzneimitteln

03.04.2017

[Wichtige Information – Carnitene sigma-tau, Injektionslösung](#)

Produktmangel einer Charge

31.03.2017

[DHPC – Rapifen® Injektionslösung \(Alfentanil\)](#)

Rapifen Packungsbeilage – fehlerhafte Tabelle

15.03.2017

[DHPC – Gilenya® \(Fingolimod\)](#)

Risiko von Melanom und Lymphom

01.03.2017

[DHPC – Imnovid® \(Pomalidomid\)](#)

Neuer wichtiger Hinweis – Hepatitis-B-Virus-Status vor Beginn der Behandlung mit Pomalidomid abzuklären

11.02.2017

[DHPC – Noxafil® \(Posaconazol\)](#)

Noxafil® Tabletten und orale Suspension sind nicht austauschbar

27.01.2017

[HPC – Correct use of retinoids in dermatology](#)

Due to the highly teratogenic potential of retinoids, the precautions related to women of child-bearing age must be followed scrupulously.

18.01.2017

[DHPC – Xarelto® \(Rivaroxaban\)](#)

Risiko von Stevens-Johnson-Syndrom und von Agranulozytose

21.12.2016

[DHPC – Prolia® \(Denosumab\)](#)

Risiko von multiplen Wirbelfrakturen im Zusammenhang mit Knochenmineralverlust nach Absetzen von Prolia®

01.11.2016

[HPC – Hepatitis E bei Transplantatempfängern](#)

In Europa werden Hepatitis E Virus (HEV) Infektionen durch Nahrungsmittel beobachtet, und in seltenen Fällen auch Übertragungen durch Bluttransfusionen.

### Announcements

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09.05.2017

[Informationsveranstaltung zur Neuausrichtung der Zusammenarbeit mit Verbänden und Organisationen der Fach- und Medizinalpersonen](#)

01.05.2017

[Dringliche Änderung der Monographie Erythromycinethylsuccinat in der Europäischen Pharmakopöe](#)

Um einem möglichen Versorgungsengpass auf dem europäischen Markt vorzubeugen, wurde am 1. Mai eine dringliche Änderung der Europäischen Pharmakopöe in Kraft gesetzt.

10.04.2017

[Simplified self-medication – changes in the way medicinal products are dispensed](#)

05.04.2017

[Neuausrichtung der Zusammenarbeit mit Verbänden und Organisationen der Fach- und Medizinalpersonen](#)

01.04.2017

[Nachtrag 9.1 der Europäischen Pharmakopöe in Kraft](#)

Der Institutsrat hat den Nachtrag 9.1 der Europäischen Pharmakopöe auf den 1. April 2017 in Kraft gesetzt.

29.03.2017

[Regierungsrat Lukas Engelberger in den Institutsrat von Swissmedic gewählt](#)

Der Vorsteher des Gesundheitsdepartements des Kantons Basel Stadt ersetzt ab dem 1. April Alt-Regierungsrat Carlo Conti.

24.03.2017

[Adaptation of Information sheet RMP / ICH E2E – Information for submissions \(available in German only\)](#)

Adaptation of Information sheet

14.03.2017

[Swissmedic agrees closer collaboration in therapeutic products field with Austrian partner authority](#)

Press release

07.03.2017

[Illegally imported medicinal products in 2016: major risk among prescription-only medicines](#)

Press release

06.02.2017

[Pyrrolizidine alkaloids in medicinal products](#)

Risk evaluation and assays required to ensure quality and safety

31.01.2017

[Blood donation criteria for men who have sex with men: blanket exclusion to be lifted](#)

Swissmedic has approved an application submitted by Swiss Transfusion SRC

30.01.2017

[News about electronic pharmacovigilance reports](#)

From 2017, the ELViS training courses are no longer being organised.

01.01.2017

[Neue Ausgabe der Europäischen Pharmakopöe in Kraft](#)

Der Institutsrat hat die Ausgabe 9.0 der Europäischen Pharmakopöe auf den 1. Januar 2017 in Kraft gesetzt.

22.12.2016

[Swissmedic's approach to handling EC certificates for medical devices](#)

Swissmedic has decided to follow the harmonised European procedure.

19.12.2016

[Swissmedic patient / consumer organisations working group](#)

Pilot to be extended by another two years

14.12.2016

[Adaptation of formal requirements for marking/highlighting changes in manuscripts of medicinal product information \(information for healthcare professionals and patient information\)](#)

The new requirements for manuscript presentation apply to all new submissions made to Swissmedic as of 1 January 2017.

01.12.2016

[35 new psychoactive substances added to Narcotics List](#)

The Federal Department of Home Affairs (FDHA) has prompted to add 35 substances to the Narcotics List.

Please find the complete list at the following web address: [www.swissmedic.ch/updates](http://www.swissmedic.ch/updates)