The WHO Pharmaceuticals Newsletter provides you with the latest information on the safety of medicines and legal actions taken by regulatory authorities across the world. It also provides signals based on information derived from Individual Case Safety Reports (ICSRs) available in the WHO Global ICSR database, VigiBase®.

This newsletter includes two feature articles describing: the 40th meeting of the WHO International Working Group for Drug Statistics Methodology and the 39th Annual Meeting of Representatives of the National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring.

The Safety and Vigilance team in WHO wishes all its readers across the world a very healthy and prosperous year in 2017.
# Table of Contents

## Regulatory Matters

<table>
<thead>
<tr>
<th>Pharmaceuticals</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allopurinol</td>
<td>5</td>
</tr>
<tr>
<td>Alogliptin</td>
<td>5</td>
</tr>
<tr>
<td>Dapomycin</td>
<td>5</td>
</tr>
<tr>
<td>Direct-acting antivirals for hepatitis C</td>
<td>5</td>
</tr>
<tr>
<td>Famiclovir</td>
<td>6</td>
</tr>
<tr>
<td>Formalin containing products</td>
<td>6</td>
</tr>
<tr>
<td>Golimumab and certolizumab pegol</td>
<td>6</td>
</tr>
<tr>
<td>HMG-CoA reductase inhibitors</td>
<td>6</td>
</tr>
<tr>
<td>Interferon beta products</td>
<td>7</td>
</tr>
<tr>
<td>Levetiracetam and methotrexate</td>
<td>7</td>
</tr>
<tr>
<td>Lorazepam injection</td>
<td>7</td>
</tr>
<tr>
<td>Nivolumab</td>
<td>8</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>8</td>
</tr>
<tr>
<td>Peramivir</td>
<td>8</td>
</tr>
<tr>
<td>Polaprezinc</td>
<td>8</td>
</tr>
<tr>
<td>SGLT2 inhibitors</td>
<td>9</td>
</tr>
<tr>
<td>Testosterone and other Anabolic Androgenic Steroids (AAS)</td>
<td>9</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>9</td>
</tr>
<tr>
<td>Warfarin and azole antifungal drugs</td>
<td>10</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>10</td>
</tr>
</tbody>
</table>

## Safety of Medicines

<table>
<thead>
<tr>
<th>Pharmaceuticals</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brimonidine gel</td>
<td>11</td>
</tr>
<tr>
<td>Cervarix®</td>
<td>11</td>
</tr>
<tr>
<td>Cobicistat containing products and corticosteroids primarily metabolised by CYP3A</td>
<td>11</td>
</tr>
<tr>
<td>Direct-acting antivirals for hepatitis C</td>
<td>12</td>
</tr>
<tr>
<td>Etoricoxib</td>
<td>12</td>
</tr>
<tr>
<td>Havrix®</td>
<td>12</td>
</tr>
<tr>
<td>Incretin-based therapies</td>
<td>13</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>13</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>13</td>
</tr>
</tbody>
</table>
# Table of Contents

## Signal
- Denosumab and lichen planus ................................................................. 15
- Denosumab and vasculitis .................................................................. 19
- Etanercept and injection site ulceration / injection site necrosis – characterization of an ADR ................................................................. 23

## Feature
- The 39th Annual Meeting of Representatives of the National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring ......................................................... 28
Allopurinol

Risk of drug-induced hypersensitivity syndrome

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package inserts for allopurinol (Zyloric® and others) have been updated to include the risk of drug-induced hypersensitivity syndrome (DIHS) as a clinically significant adverse reaction. Information on cases of DIHS related type 1 diabetes mellitus (including fulminant type 1 diabetes mellitus) and ketoacidosis have also been included.

Allopurinol is used for the management of hyperuricaemia in patients with gout or in hypertensive patients with hyperuricaemia.

A total of two cases associated with type 1 diabetes mellitus related to DIHS have been reported in Japan. Of these, a causal relationship could not be excluded in one case.

Reference:
Revision of Precautions, MHLW/PMDA, 22 November 2016 (www.pmda.go.jp/english)
(See WHO Pharmaceuticals Newsletter No.5, 2016: Serious cutaneous adverse reactions and the role of genotyping in Singapore)

Alogliptin containing products, teneligliptin and linagliptin

Risk of pemphigoid

Japan. The MHLW and the PMDA have announced that the package inserts for alogliptin containing products (Nesina®, Liovel® and Inisync®), teneligliptin (Tenelia®) and linagliptin (Tradjenta®) have been updated to include the risk of pemphigoid as a clinically significant adverse reaction.

These products are indicated for type 2 diabetes mellitus.

A total of seven pemphigoid cases associated with alogliptin containing products, 14 cases with teneligliptin and 15 cases with linagliptin have been reported in Japan. Of these, a causal relationship could not be excluded in two, seven and ten cases, respectively.

Reference:
Revision of Precautions, MHLW/PMDA, 18 October 2016 (www.pmda.go.jp/english)

Daptomycin

Risk of acute generalized exanthematous pustulosis

Japan. The MHLW and the PMDA have announced that the package insert for daptomycin (Cubicin®) has been updated to include the risk of acute generalized exanthematous pustulosis as a clinically significant adverse reaction. In addition, the company core datasheet has been updated.

Daptomycin is an antibiotic used to treat systemic and life-threatening infections caused by gram-positive organisms.

A total of two cases associated with acute generalized exanthematous pustulosis have been reported in Japan. Of these, a causal relationship could not be excluded in one case.

Reference:
Revision of Precautions, MHLW/PMDA, 22 November 2016 (www.pmda.go.jp/english)

Direct-acting antivirals for hepatitis C

Risk of hepatitis B reactivation

USA. The US Food and Drug Administration (FDA) has requested that a boxed warning about the risk of hepatitis B virus (HBV) reactivation is added to the drug labels of direct-acting antivirals for hepatitis C (DDAs). This warning should also be included in the patient information leaflets or medication guides for these medicines.

DDAs are used to treat chronic hepatitis C virus (HCV) infection.

The FDA identified 24 cases of HBV reactivation from reports submitted to the FDA and from the published literature in HCV/HBV co-infected patients treated with DDAs from 22 November, 2013 to 18 July, 2016. Of the cases reported, two patients died and one required a liver transplant. HBV reactivation was not reported as an adverse event in the clinical trials submitted for the DAA approvals because patients with HBV co-infection were excluded from the trials.

Health-care professionals are recommended to screen all patients for evidence of current or prior HBV infection before starting treatment with DDAs, and to monitor patients using blood tests for HBV flare-ups or reactivation during treatment and post-treatment follow-up.

Reference:
Drug Safety Communication, US FDA, 4 October 2016 (www.fda.gov)
(See WHO Pharmaceuticals Newsletter No.3, 2016: Risk of reactivation of hepatitis B virus in Japan)
Famciclovir

Risk of shock and anaphylaxis

Japan. The MHLW and the PMDA have announced that the package insert for famciclovir (Famvir®) has been updated to include the risk of shock and anaphylaxis as clinically significant adverse reactions.

Famciclovir is indicated for herpes simplex and herpes zoster.

A total of three cases associated with shock or anaphylaxis have been reported in Japan. Of these, a causal relationship could not be excluded in one case.

Reference:
Revision of Precautions, MHLW/PMDA, 22 November 2016 (www.pmda.go.jp/english/)

Formalin containing products

Risk of shock and anaphylaxis

Japan. The MHLW and the PMDA have announced that the package inserts for formalin containing products used in dentistry have been updated to include the risk of shock and anaphylaxis as clinically significant adverse reactions. The contraindication for patients with a history of hypersensitivity to the ingredients of these products has also been included.

Formalin containing products are used for disinfection of infected root canals in dentistry or sealing, pain relief, sedation and pulp capping in paediatric dentistry among others.

A total of two cases associated with shock or anaphylaxis have been reported in Japan. Of these, a causal relationship could not be excluded in one case.

Reference:
Revision of Precautions, MHLW/PMDA, 22 November 2016 (www.pmda.go.jp/english/)

Golimmab and certolizumab pegol

Risk of inflammation of the liver

Canada. Health Canada has updated the Canadian product information for golimmab (Simponi®) and certolizumab pegol (Cimzia®) to include information on available evidence regarding the risk of inflammation of the liver.

Golimmab and certolizumab pegol are Tumour Necrosis Factor (TNF) alpha blockers used to treat inflammatory diseases such as rheumatoid arthritis, inflammatory bowel disease (e.g. Crohn’s disease or ulcerative colitis) and psoriasis.

Health Canada has reviewed the link between TNF alpha blockers and liver inflammation following publication of two serious cases in the scientific literature, in which patients were treated with the TNF alpha blockers, adalimumab (Humira®) and infliximab (Remicade®).

At the time of this review, five serious cases of liver inflammation were reported with certolizumab pegol, of which one case was reported in the Canada Vigilance database. There were no cases of liver inflammation reported with the use of golimmab.

Of these five cases reported with certolizumab pegol three cases were assessed to be potentially linked to certolizumab pegol. These three patients improved when they stopped using certolizumab pegol. For the remaining two cases, either there was insufficient information available to establish a link with certolizumab pegol use or there were other possible explanations for liver inflammation.

Health Canada’s review found a possible link between the risk of liver inflammation and the use of TNF alpha blockers. The Canadian product information for adalimumab, infliximab and etanercept (Enbrel®) already states liver inflammation as a very rare event that may lead to liver failure, but not for golimmab and certolizumab pegol.

Reference:

HMG-CoA reductase inhibitors

Risk of immune-mediated necrotizing myopathy

Japan. The MHLW and the PMDA have announced that the package inserts for HMG-CoA reductase inhibitors (fluvastatin, pravastatin, simvastatin, atorvastatin, pitavastatin, rosuvastatin) and their combination preparations have been updated to include the risk of immune-mediated necrotizing myopathy as a clinically significant adverse reaction.

HMG-CoA reductase inhibitors are indicated for hyperlipidaemia and familial hypercholesterolaemia.

A total of three cases associated with immune-mediated necrotizing myopathy have been reported in Japan. Of these, a causal relationship could not be
excluded in two cases. The MHLW/PMDA have stated that cases of immune-mediated necrotizing myopathy have also been reported overseas.

Reference: Revision of Precautions, MHLW/PMDA, 18 October 2016 (www.pmda.go.jp/english/)

Interferon beta products

Risk of pulmonary arterial hypertension

Canada. Health Canada has updated the Canadian product safety information for interferon beta products (type 1a (Avonex® and Rebif®) and type 1b (Betaseron® and Extavia®)) to include the risk of pulmonary arterial hypertension.

Interferon beta products are used to treat some forms of multiple sclerosis, a disease of the central nervous system.

Health Canada reviewed a possible link between the use of interferon beta products for treating multiple sclerosis and pulmonary arterial hypertension.

At the time of the review, there were two Canadian cases of pulmonary arterial hypertension that were possibly related to interferon beta use, and in both cases, the patients improved after treating the pulmonary arterial hypertension and stopping interferon beta use.

Worldwide, there were 136 case reports of pulmonary arterial hypertension in patients who were using interferon beta (which includes the two Canadian cases). In 14 cases, the pulmonary arterial hypertension may have been related to interferon beta use. In the remaining cases, the information available was too limited to make any conclusions.

Health Canada’s safety review concluded that there was a possible link between the use of interferon beta products for multiple sclerosis and the risk of developing pulmonary arterial hypertension.


Levetiracetam and methotrexate

Drug-drug interaction

Canada. Health Canada has recommended that the product information for levetiracetam and methotrexate products is updated to provide information about drug-drug interaction, which could lead to greater amounts of methotrexate in the blood. Product labelling now recommends that blood methotrexate and levetiracetam levels should be carefully monitored in patients treated with the two drugs at the same time.

Levetiracetam is used to help epilepsy treatment be more effective. Methotrexate is used to treat cancer or to treat arthritis.

Health Canada carried out a safety review after learning that the European Medicines Agency (EMA) was looking into a potential interaction between levetiracetam and methotrexate.

At the time of the review, there were no reported cases in the Canada Vigilance Database of patients who had received levetiracetam and methotrexate at the same time.

The manufacturer of levetiracetam provided 13 international reports of a potential interaction between levetiracetam and methotrexate. The review of these reports was limited by many factors such as pre-existing diseases, other medications taken, and lack of laboratory data (e.g. blood levels of methotrexate). Of these 13 reports, five noted that patients who were taking both levetiracetam and methotrexate at the same time had greater amounts of methotrexate in their blood.

Health Canada’s safety review concluded that there is a potentially greater risk of adverse effects when levetiracetam and methotrexate are taken together.


Lorazepam injection

Risks of amnesia and apnoea

Republic of Korea. The Ministry of Food and Drug Safety (MFDS) has announced that the package insert for lorazepam injection has been revised to include amnesia and apnoea as adverse reactions. Lorazepam injection is used as pre-anaesthetic medication, or treatment of anxiety before examinations such as endoscopy, or in other anxiety disorders which require immediate drug action.

Through a review of adverse events reported in Korea Adverse Event Reporting System (KAERS) from January 1989 to June 2015, the MFDS and the Korea Institute of Drug Safety and Risk Management (KIDS) have identified a total of 11 cases associated with amnesia and three cases associated with apnoea.

This recommendation announced by the MFDS was based on a signal analysis
evaluation process using adverse event reports. Reports for lorazepam injections and amnesia/apnoea were identified to be statistically significant compared to all the other reports from other drugs.

Reference:
Based on the communication from MFDS and KIDS, Republic of Korea, November 2016
(See WHO Pharmaceuticals Newsletter for a related case in No.2, 2016: Flunitrazepam - Precautionary measures for respiratory depression; and risk of apnoea, respiratory depression, and glossoptosis in Japan)

Nivolumab

Risk of excessive immunoreaction after discontinuation of treatment, immune thrombocytopenic purpura, myocarditis and rhabdomyolysis

Japan. The MHLW and the PMDA have announced that the package insert for nivolumab (Opdivo®) has been updated to include the risk of excessive immunoreaction after discontinuation of treatment as an important precaution; immune thrombocytopenic purpura, myocarditis and rhabdomyolysis as clinically significant adverse reactions.

Nivolumab is indicated for: radically unresectable malignant melanoma; unresectable, advanced, or relapsed non-small cell lung cancer; and radically unresectable or metastatic renal cell carcinoma.

A total of 50 cases of excessive immunoreaction after discontinuation of treatment with nivolumab have been reported in Japan. Of these, a causal relationship could not be excluded in 14 cases. The company core datasheet and foreign package inserts include descriptions about such adverse reactions.

For immune thrombocytopenic purpura, a total of five cases have been reported in Japan. Of these, a causal relationship could not be excluded in three cases.

A total of six and four cases have been reported for myocarditis and rhabdomyolysis, respectively. Of these, a causal relationship could not be excluded in three and all cases, respectively. In addition, the company core datasheet has been updated.

Reference:
Revision of Precautions, MHLW/PMDA, 18 October 2016 (www.pmda.go.jp/english/)

Olanzapine

Risk of urinary retention

Canada. Health Canada has updated safety information for olanzapine to strengthen warnings of the potential risk of urinary retention. The update is consistent with the safety information provided for the other atypical antipsychotic products.

Olanzapine is used to treat mental disorders including schizophrenia, bipolar disorder and in some cases, depression.

Health Canada has carried out a safety review investigating the potential risk of urinary retention with the use of atypical antipsychotics.

At the time of the review, Health Canada had received 38 Canadian reports related to urinary retention and the use of atypical antipsychotics. These reports, together with information from published literature indicate that most patients recovered or were recovering from the adverse effect after stopping the antipsychotic medication. In some cases, urinary retention re-occurred after the drug was re-administered, further supporting a potential link between the atypical antipsychotic and urinary retention.

At the time of the review, there were 1254 international reports of urinary retention with the use of any of the atypical antipsychotics.

The risk of urinary retention is mentioned in the product safety information for most of the atypical antipsychotics. However, the wording used to explain the risk of urinary retention for the approved drug olanzapine was not consistent with the evidence reviewed.

Reference:

Peramivir

Risk of acute renal failure

Japan. The MHLW and the PMDA have announced that the package insert for peramivir (Rapiacta®) has been updated to include the risk of acute renal failure as a clinically significant adverse reaction. Peramivir is indicated for influenza A or B virus infection.

A total of seven cases associated with acute renal failure have been reported in Japan. Of these, a causal relationship could not be excluded in two cases.

Reference:
Revision of Precautions, MHLW/PMDA, 18 October 2016 (www.pmda.go.jp/english/)

Polaprezinc

Risk of copper deficiency

Japan. The MHLW and the PMDA have announced that the package inserts for polaprezinc (Promac® and others) have
been updated to include the risk of copper deficiency as a clinically significant adverse reaction.

Polaprezinc is indicated for gastric ulcer.

A total of nine cases associated with copper deficiency have been reported in Japan. Of these, a causal relationship could not be excluded in eight cases, however four of these eight cases used the drug for a condition that was outside of the approved indication.

**Reference:**

### SGLT2 inhibitors

#### Risk of bone-related side effects

**Canada.** Health Canada has updated the safety information for canagliflozin to include the risk of bone-related adverse effects.

Sodium-glucose cotransporter-2 (SGLT2) inhibitors (canagliflozin (Invokana®), dapagliflozin (Forxiga®), empagliflozin (Jardiance®)) are drugs used to treat adults with type 2 diabetes.

Health Canada carried out a safety review to evaluate the risk of bone-related adverse effects with SGLT2 inhibitors. The review was triggered following a notice of international reports of bone-related adverse effects experienced in patients taking the SGLT2 inhibitor canagliflozin.

At the time of the review Health Canada had not received any Canadian reports of loss of bone mineral density or broken bones related to the use of SGLT2 inhibitors.

Recent medical studies have found an increased risk of losing bone mineral density and an increased risk of bone fracture occurring as early as 12 weeks of being on treatment with canagliflozin, but these adverse effects are still rare. An increased risk of bone fracture associated with the use of dapagliflozin was also noted in patients with kidney problems (moderate renal impairment). No evidence of bone-related adverse effects were found to date with the use of empagliflozin.

Health Canada’s safety review concluded that the evidence supported a link between the risks of bone fracture and loss of bone mineral density with the use of canagliflozin. For dapagliflozin, these risks were only identified in patients who had kidney problems and this is already explained in the safety information. No evidence of bone-related adverse effects were found to date with the use of empagliflozin.

**Reference:**

(See WHO Pharmaceuticals Newsletter No.5, 2015: Canagliflozin - increased risk of bone fractures and new information on risk of decreased bone mineral density in US)

### Testosterone and other Anabolic Androgenic Steroids (AAS)

#### Risks associated with abuse and dependence

**USA.** The US FDA has approved label changes for all prescription testosterone products. The labels will include a new warning which alerts prescribers to the abuse potential of testosterone and the serious adverse outcomes, especially those related to heart and mental health that have been reported in association with testosterone/anabolic androgenic (AAS) abuse.

Prescription testosterone products are approved as hormone replacement therapy for men who have low testosterone due to certain medical conditions.

The FDA received cases of abuse and dependence with serious outcomes such as: heart attack, heart failure, stroke, depression, hostility, aggression, liver toxicity and male infertility. Individuals abusing high doses of testosterone have also reported withdrawal symptoms such as depression, fatigue, irritability, loss of appetite, decreased libido and insomnia.

In addition to the new warning, information on the importance of measuring serum testosterone concentration, if abuse is suspected, has been added as a precaution.

**Reference:**

### Ustekinumab

#### Risk of interstitial pneumonia

**Japan.** The MHLW and the PMDA have announced that the package insert for ustekinumab (Stelara®) has been updated to include the risk of interstitial pneumonia as a clinically significant adverse reaction.

Ustekinumab is indicated for psoriasis vulgaris and psoriatic arthritis in patients with an inadequate response to conventional therapy.

A total of 16 cases associated with interstitial pneumonia have been reported in Japan. Of these, a causal relationship could not be excluded in six cases.
**Reference:**
Revision of Precautions, MHLW/PMDA, 18 October 2016 (www.pmda.go.jp/english/)

---

**Warfarin and azole antifungal drugs**

### Risk of bleeding due to drug-drug interaction

**Japan.** The MHLW and the PMDA have announced that the package inserts for warfarin and miconazole (Florid®) have been updated to include a contraindication of administering warfarin and miconazole concomitantly due to increased risk of bleeding.

The package inserts for other antifungal drugs (voriconazole (Vfend® and generics), itraconazole (Itrizole® and generics), fluconazole (Diflucan® and generics) and fosfluconazole (Prodif®)) have also been updated to include precautions about concomitant administration with warfarin.

Warfarin is used for treatment and prevention of thromboembolism. Miconazole, voriconazole, itraconazole, fluconazole and fosfluconazole are azole antifungal drugs.

A total of 41 cases associated with serious bleeding during concomitant administration or, after discontinuation of concomitant administration of miconazole and warfarin have been reported in Japan. Of these, a causal relationship could not be excluded in 31 cases (two of which occurred after treatment outside the approved dosage).

Due to the contraindication of concomitant administration of miconazole and warfarin, the use of other azole drugs, including those recommended as first-line treatments is expected. A total of five cases of marked increase in prothrombin time (PT) - international normalized ratio (INR) have been reported in patients treated with warfarin and other azole antifungal drugs in Japan. Of these, a causal relationship could not be excluded in two cases. Thus, MHLW/PMDA considered that caution is also required for concomitant administration of warfarin and other azole antifungal drugs.

**Reference:**
Revision of Precautions, MHLW/PMDA, 18 October 2016 (www.pmda.go.jp/english/)

(See WHO Pharmaceuticals Newsletter No.4, 2016: Miconazole - Potential for serious drug-drug interactions with warfarin in the United Kingdom)

---

**Zoledronic acid**

### Risk of Fanconi syndrome

**Japan.** The MHLW and the PMDA have announced that the package inserts for zoledronic acid (Zometa®, Reclast® and others) have been updated to include the risk of Fanconi syndrome as a clinically significant adverse reaction.

Zoledronic acid is indicated for hypercalcaemia of malignancy, bone lesion associated with multiple myeloma or bone metastases from solid tumours and osteoporosis.

A total of 11 cases associated with Fanconi syndrome have been reported in Japan. Of these, a causal relationship could not be excluded in seven cases. The company core datasheet has also been updated.

**Reference:**
Revision of Precautions, MHLW/PMDA, 22 November 2016 (www.pmda.go.jp/english/)

(See WHO Pharmaceuticals Newsletter No.4, 2015: Risk of acute phase response and renal effects in New Zealand)
Brimonidine gel

Risk of exacerbation of rosacea

The United Kingdom. The Medicines and Healthcare Products Regulatory Agency (MHRA) has provided advice to health-care professionals and patients on the application of brimonidine gel to decrease the risk of exacerbation of rosacea.

Brimonidine is a topical gel indicated for the symptomatic treatment of facial erythema of rosacea in adults.

Brimonidine gel treatment should be started with a small amount of gel (less than the maximum dose) for at least one week and the dose should be increased gradually, based on tolerability and response to treatment.

Symptom exacerbation is commonly reported in patients treated with brimonidine gel, and includes cases of rebound effect after the therapeutic effect wears off (approximately 8–12 hours after application). Cases in which exacerbation of symptoms (particularly erythema and flushing) has occurred during treatment soon after it was applied have been reported. Across all clinical studies, 16% of patients who were receiving brimonidine gel had symptom exacerbation. Most patients recovered after stopping treatment.

Reference:
Drug Safety Update, MHRA, Volume 10, issue 4:1, November 2016 (www.gov.uk/mhra)

Cervarix®

Potential risk of Guillain-Barré Syndrome: increased risk not identified

Canada. Health Canada has reviewed the potential link between Cervarix® and Guillain-Barré Syndrome (GBS).

Cervarix® is a vaccine used to protect against infection by the human papillomavirus (HPV) types 16 and 18 that cause cervical and anal cancer.

At the time of the review, there were no Canadian cases of GBS reported following vaccination with Cervarix®.

No cases of GBS were reported in clinical trials prior to marketing Cervarix®. After marketing, the manufacturer received 45 reports worldwide of GBS from May 2007 until November 2015. Only 10 of these reports had signs and symptoms of GBS. However, it was not possible to determine if there was a link between Cervarix® and GBS in these cases because not enough information was available for assessment, or there were other possible causes of GBS.

The review did find that the number of cases of GBS reported following vaccination with Cervarix® is much lower than the number expected in the general population.

Health Canada’s review of all available information did not find an increased risk of GBS following vaccination with Cervarix®. Health Canada will continue to monitor the adverse effect information involving Cervarix® to identify and assess potential harms.

Reference:

(See WHO Pharmaceuticals Newsletter No.6, 2012: Safety review shows balance of risks and benefits remains clearly positive in the United Kingdom)

Cobicistat containing products and corticosteroids primarily metabolised by CYP3A

Potential drug interaction: increased risk of systemic corticosteroid effects

Ireland. The Health Products Regulatory Authority (HPRA) has identified a potential interaction between cobicistat containing products and corticosteroids primarily metabolised by CYP3A, which could lead to an increase in systemic corticosteroid effects.

Cobicistat is a pharmacokinetic enhancer used as part of antiretroviral combination therapy in human immunodeficiency virus-1 (HIV-1) infected adults. Cobicistat is a selective mechanism-based inhibitor of the cytochrome P450 enzyme subfamily, CYP3A. Inhibition of CYP3A-mediated metabolism by cobicistat enhances the systemic exposure of CYP3A substrates.

The EMA’s Pharmacovigilance Risk Assessment Committee (PRAC) has recently reviewed cases of adrenal suppression and Cushing’s syndrome linked with an interaction between cobicistat containing products and corticosteroids that are metabolised by CYP3A.

The HPRA has stated that co-administration of CYP3A metabolised corticosteroids with cobicistat is not recommended unless the potential benefit to the patient outweighs the risk, in which case patients should be monitored for systemic corticosteroid effects. Alternative corticosteroids which are less dependent on CYP3A metabolism, e.g. beclomethasone for intranasal or inhalational use should be considered, particularly for long term use.
**Direct-acting antivirals for hepatitis C**

**Interaction potential with warfarin and other vitamin K antagonists: changes to INR**

**Ireland.** The HPRA has issued advice to health-care professionals on monitoring the international normalised ratio (INR) more closely in patients concurrently treated with vitamin K antagonists.

Direct-acting antivirals for hepatitis C are used to treat chronic hepatitis C virus (HCV) infection.

A signal of a potential drug interaction leading to a reduced INR has recently been identified with co-administration of direct-acting antivirals and vitamin K antagonists. The case reports on which the signal was based were reviewed by the EMA’s PRAC. The PRAC has recommended that the product information of direct-acting antivirals should be updated to include a recommendation for close monitoring of INR in patients treated with vitamin K antagonists, as liver function may change during treatment with direct-acting antivirals.

While no change in the pharmacokinetics of warfarin is expected, close monitoring of INR is recommended with all vitamin K antagonists.

**Reference:**
Drug Safety Newsletter, HPRA, October 2016

---

**Etoricoxib**

**Reduced initial dose recommendation for rheumatoid arthritis and ankylosing spondylitis**

**The United Kingdom.** The MHRA has recommended that the starting dose for treatment of rheumatoid arthritis or ankylosing spondylitis with etoricoxib is reduced to 60 mg once daily, with the option to increase to a maximum of 90 mg once daily if necessary.

Etoricoxib is indicated for the symptomatic relief of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, and the pain and signs of inflammation associated with acute gouty arthritis.

Etoricoxib is also indicated for the short-term treatment of moderate pain associated with dental surgery.

Following an EU-wide review in 2008 of the benefits and risks of etoricoxib, the marketing authorisation holder was required to conduct clinical trials to assess the efficacy and safety of etoricoxib 60 mg once daily for the treatment of rheumatoid arthritis and ankylosing spondylitis including comparison with etoricoxib 90 mg.

From these trials, there is evidence that the 60-mg dose is effective in rheumatoid arthritis and ankylosing spondylitis. However, for some patients, the 90-mg dose will be more efficacious, although it is not possible to predict which patients might benefit from the higher dose.

**Reference:**
Drug Safety Update, MHRA, Volume 10, issue 3:1, October 2016 (www.gov.uk/mhra)

---

**Havrix®**

**Potential risk of thrombocytopenia: No risk identified in review**

**Canada.** Health Canada has reviewed a potential link between vaccination with Havrix® and the development of thrombocytopenia after receiving a report of a patient developing a low platelet count following vaccination with Havrix®.

Havrix® is a vaccine used to protect against hepatitis A virus infection in people at risk of coming into contact with the virus.

At the time of the review, one case of thrombocytopenia following vaccination with Havrix® had been reported to the Canada Vigilance Program and three cases were also reported to the Canadian Adverse Events Following Immunization Surveillance System (CAEFISS).

No confirmed cases of thrombocytopenia were reported in clinical trials prior to marketing of Havrix®. From 1992 until 2015, the manufacturer received 99 international reports of thrombocytopenia. It was not possible to determine if there was a link between Havrix® and thrombocytopenia for either the Canadian or international cases because: the cases were either not confirmed as thrombocytopenia; there were other possible causes of thrombocytopenia; or there was not enough information provided for assessment.

The number of cases of thrombocytopenia following vaccination with Havrix® reported internationally and in Canada is much lower than the number expected in the general population.

No association between the hepatitis A vaccine and...
models have suggested that the use of incretin-based therapies may be linked to an increased risk of pancreatic cancer, results from clinical trials and many studies looking at the patterns, causes, and effects of health and disease conditions in people, do not support this link.


(See WHO Pharmaceuticals Newsletters No.3, 2013: Investigating findings on pancreatic risks with GLP-1-based therapies for type-2 diabetes in EU and No.2, 2013: Reports of possible increased risk of pancreatitis and pre-cancerous findings of the pancreas in US)

Levetiracetam

Only to be used with dosing syringe provided with package to avoid accidental overdose

EU. The EMA has recommended measures to ensure safe use of levetiracetam (Keppra® and generics) oral solution to avoid medication errors and the risk of overdose.

Parents and carers should only use the syringe provided with the package to measure the dose of levetiracetam. The packages and labels will be colour-coded to indicate the volume of the bottle, the volume of the dosing syringe, and the age range of the patient that the medicine should be used for.

Levetiracetam is a medicine for the treatment of epilepsy.

Cases of accidental overdose have been reported with levetiracetam oral solution; the majority of cases occurred in children aged between 6 months and 11 years. Most of the cases occurred when the medicine was used with an incorrect dosing syringe (e.g. a 10 ml syringe was used instead of a 1 ml one, leading to a 10-fold overdose), or because of a misunderstanding by the caregiver about how to properly measure the dose. Levetiracetam overdose often has no symptoms, but it may cause sleepiness, agitation, difficulty breathing and coma.


Ondansetron

Assessing potential harm to the foetus: insufficient information

Canada. Health Canada is working with the Drug Safety and Effectiveness Network to further investigate the extent of ondansetron (Zofran®) use during pregnancy and the risk to the foetus. Health Canada has requested that manufacturers submit information they may have regarding birth defects and use of ondansetron during pregnancy.

Ondansetron is indicated for nausea and vomiting associated with cancer treatment or surgery. It is not authorized in Canada to treat nausea and vomiting with ondansetron during pregnancy.

Health Canada carried out a safety review to assess the risk of birth defects with the use of ondansetron.

At the time of the review, Health Canada had received 14 reports of birth defects in the newborn babies of mothers treated with ondansetron. In four of these reports, there was insufficient information on the time of exposure of ondansetron during pregnancy. In two other reports, ondansetron was given after the organs of the fetus were already developed. In the remaining eight reports,
ondansetron was given to the mother at the stage the organs were developing. In these eight reports, a link between birth defects and ondansetron could not be ruled out. Information about the medical history of the mother, including additional medications she may have been taking, and exposure time were lacking. There were no patterns of birth defects.

Findings from published scientific studies were inconsistent and inconclusive. There were concerns with study design, and the majority had a number of limitations such as use of concomitant medications.

The findings from animal studies have not established that ondansetron can cause birth defects.

Available information were not sufficient to establish a link between the use of ondansetron during pregnancy and the risk of birth defects. Health Canada will continue to monitor safety information involving the use of ondansetron.

**Reference:**
A signal is defined by WHO as reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously. Usually more than a single report is required to generate a signal, depending upon the seriousness of the event and the quality of the information. A signal is a hypothesis together with data and arguments and it is important to note that a signal is not only uncertain but also preliminary in nature.

The signals in this Newsletter are based on information derived from individual case safety reports (ICSRs) available in VigiBase®, the WHO international database of suspected adverse drug reactions. The database contains over 14 million reports of suspected adverse drug reactions, submitted by National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring. VigiBase® is, on behalf of the WHO, maintained by the Uppsala Monitoring Centre (UMC) and periodic analysis of VigiBase® data is performed in accordance with UMC’s current routine signal detection process. More information regarding the ICSRs, their limitations and proper use, is provided in the UMC Caveat document available at the end of Signal (page 26). For information on the UMC Measures of Disproportionate Reporting please refer to WHO Pharmaceuticals Newsletter Issue No. 1, 2012.

UMC, a WHO Collaborating Centre, is an independent foundation and a centre for international service and scientific research within the field of pharmacovigilance. UMC’s vision is to improve worldwide patient safety and welfare by reducing the risk of medicines. For more information, visit www.who-umc.org. To leave a comment regarding the signals in this Newsletter, please contact: the Uppsala Monitoring Centre, Box 1051, SE-751 40 Uppsala, Sweden. E-mail: signals@who-umc.org.

Denosumab and lichen planus
Dr Ian Boyd, Australia

Summary
Denosumab is a human monoclonal antibody (IgG2) that targets and binds with high affinity and specificity to the receptor activator of nuclear factor kappa-B ligand (RANKL), preventing activation of its receptor, RANK, on the surface of osteoclast precursors and osteoclasts. Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function and survival, thereby decreasing bone resorption in cortical and trabecular bone. Denosumab is indicated for the treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures, and treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. After the elimination of suspected duplicates there are (as of 1 January 2016) 14 individual case safety reports in the WHO Global ICSR database, VigiBase®, of lichen planus (LP) in association with denosumab. The reports are from Canada, Denmark, Greece, the Netherlands, Serbia, Switzerland, and the United States. Denosumab was the only drug suspected in 12 of the 14 cases. The outcome of the LP was stated in six of the 14 reports. All six patients were reported as recovered or recovering. In these patients, the drug was reported as withdrawn in four cases while the outcome of the drug was unknown in the remaining two cases.

Case reports in VigiBase® suggest that there is a possible signal for the association of denosumab and LP. Time to onset is consistent with a drug induced effect. Dechallenge is generally supportive of a drug association but for a drug such as denosumab, which is administered every six months, the concept of drug withdrawal is not meaningful. There appears to be a positive rechallenge in one case. It is possible that denosumab may cause LP using a similar mechanism to that of TNF-α inhibitors.

Introduction
Denosumab is a human monoclonal antibody (IgG2) that targets and binds with high affinity and specificity to the receptor activator of nuclear factor kappa-B ligand (RANKL), preventing activation of its receptor, RANK, on the surface of osteoclast precursors and osteoclasts. Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function and survival, thereby decreasing bone resorption in cortical and trabecular bone. Denosumab is indicated for the treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures, and treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. The most common side effects with denosumab (seen in more than one patient in ten) are musculoskeletal pain and pain in the extremity. Uncommon cases of cellulitis; rare cases of hypocalcaemia, hypersensitivity, osteonecrosis of the jaw and atypical femoral fractures have been observed in patients taking denosumab.¹

Lichen planus (LP) is a chronic mucocutaneous disease that affects the skin, tongue, and oral mucosa. The disease presents itself in the form of papules, lesions or rashes. The commonly affected sites are near the wrist and the ankle. The cause
of LP is not known. While there are many theories to explain LP, it is believed it can be classified as an autoimmune disease. Some LP-type rashes (often referred to as lichenoid reactions) occur as adverse reactions to a variety of drugs including nonsteroidal anti-inflammatory drugs, anti-hypertensives such as angiotensin converting enzyme inhibitors and beta-blockers, tetracyclines, sulfonamides, penicillamine, allopurinol, gold, antibiotics, arsenic, iodides, chloroquine, quinidine, phenothiazines, and diuretics.

**Reports in VigiBase®**

As of 1 January 2016 there are 18 individual case safety reports of LP in association with denosumab in the WHO Global ICSR database, VigiBase® (Table 1).

### Table 1. Case overview of reports in VigiBase® of lichen planus in association with denosumab

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/Sex</th>
<th>Other suspected (S) or concomitant (C) drugs</th>
<th>Reactions (WHO-ART preferred terms)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>74/F</td>
<td>Calcium, colecalciferol, lornoxicam, pantoprazole, panadol extra* (all C)</td>
<td>Lichen planus, stomatitis aphthous, gastrointestinal disorder, oral pain</td>
<td>Unknown</td>
</tr>
<tr>
<td>2</td>
<td>68/F</td>
<td>Ascorbic acid/pyradoxine hydrochloride/biotin/vitaminc/Acetaminophen/folic acid/calcium/citrate/magnesium oxide/zinc oxide</td>
<td>Lichen planus, arthralgia, myalgia, rash</td>
<td>Unknown</td>
</tr>
<tr>
<td>3</td>
<td>-/-</td>
<td>None</td>
<td>Lichen planus</td>
<td>Unknown</td>
</tr>
<tr>
<td>4</td>
<td>64/F</td>
<td>Alprazolam, amitriptyline, calcium, calcium carbonate, calcium citrate/magnesium, fish oil, fluoxetine, guaifenesin, iron, levotyrosine, macrogl 3350, metemazine, sumatriptan, probiotic* (all C)</td>
<td>Lichen planus, anxiety, coughing, dysuria, headache, infection localised, insomnia, pain, pruritus, pruritus ani, rash, murcular rash, sinusitis, vaginal disorder, vaginal haemorrhage, vulvovaginal rash**</td>
<td>Unknown</td>
</tr>
<tr>
<td>5</td>
<td>66/F</td>
<td>None</td>
<td>Lichen planus</td>
<td>Unknown</td>
</tr>
<tr>
<td>6***</td>
<td>78/F</td>
<td>Adalimumab (S)</td>
<td>Lichen planus aggravated, acanthisis, dermatitis, eczema, hyperkeratosis, keratosis, osteoporosis, rash psoriasis</td>
<td>Recovering</td>
</tr>
<tr>
<td>7</td>
<td>66/F</td>
<td>Rituximab (S)</td>
<td>Lichen planus, anus discomfort, pruritus ani, vulva disorder</td>
<td>Unknown</td>
</tr>
<tr>
<td>8</td>
<td>72/F</td>
<td>Pantoprazole, pranoprolid, levothyroxine (all C)</td>
<td>Lichen planus</td>
<td>Recovered</td>
</tr>
<tr>
<td>9</td>
<td>71/F</td>
<td>Antidipine, atorvastatin, clopidogrel, dazepam, meclozine, amprozole, quinapril (all C)</td>
<td>Lichen planus, eczema, goitre, macule, rash pruritic, skin swelling, skin hyperpigmentation</td>
<td>Unknown</td>
</tr>
<tr>
<td>10</td>
<td>85/F</td>
<td>Lansoprazole (C)</td>
<td>Lichen planus, abdominal/pain,abcess/gential/female, abscess, alopecia, appetite/lost,backpain, blisters, burning sensation, cystitis, depressed mood, dematitis lichenoid, discomfort bodily, eye inflamed, erythema, heartburn, hiatus hernia, itching, nausea, oral pain, pain, popular rash, pruritus, rash, skin atophy, skin/esfoliation, skin/module, urinary tract infection, vaginitis, vaginal itching, vulvovaginal discomfort, weight decrease, body height decreased**, oral disorder**</td>
<td>Recovering</td>
</tr>
<tr>
<td>11***</td>
<td>-/-</td>
<td>Adalimumab (S)</td>
<td>Lichen planus, rash psoriasis, pruritus, urticaria</td>
<td>Recovering</td>
</tr>
<tr>
<td>12</td>
<td>69/F</td>
<td>Calcium carbonate, ergocalciferol (both C)</td>
<td>Lichen planus, drug eruption</td>
<td>Unknown</td>
</tr>
<tr>
<td>13***</td>
<td>77/F</td>
<td>Adalimumab (S)</td>
<td>Lichen planus aggravated, itching, psoriasis, urticaria</td>
<td>Recovering</td>
</tr>
<tr>
<td>14</td>
<td>65/F</td>
<td>Calcium, ergocalciferol, levothyroxine, lorazepam, omeprazole (all C)</td>
<td>Lichen planus, gum pain, skin reaction localised</td>
<td>Recovering</td>
</tr>
<tr>
<td>15***</td>
<td>78/F</td>
<td>Adalimumab (S)</td>
<td>Lichen planus aggravated, acanthisis, dermatitis, eczema, hyperkeratosis, keratosis, osteoporosis, rash psoriasis</td>
<td>Recovering</td>
</tr>
<tr>
<td>16***</td>
<td>78/F</td>
<td>Adalimumab (S)</td>
<td>Lichen planus aggravated, psoriasis</td>
<td>Recovering</td>
</tr>
<tr>
<td>17</td>
<td>59/F</td>
<td>None</td>
<td>Lichen planus</td>
<td>Recovering</td>
</tr>
<tr>
<td>18</td>
<td>86/F</td>
<td>None</td>
<td>Lichen planus</td>
<td>Recovered</td>
</tr>
</tbody>
</table>

* Reported drug
** MedDRA term
*** Cases 11, 13, 15 and 16 are suspected duplicates of case 6
After the elimination of four suspected duplicates, the remaining 14 reports were submitted from the United States (8 reports), Canada, Denmark, Greece, the Netherlands, Serbia and Switzerland (1 report each). The patients ranged in age from 59 to 86 years with a median of 69 years in the 13 reports which provided this information. There were 13 females and the gender was not stated in the remaining report.

Denosumab was the only drug suspected in 12 of the 14 cases. Adalimumab was an additional suspected drug in one case and rituximab was an additional suspected drug in another case. Concomitant drugs were reported in 10 of the 14 cases and indicated a patient population with a number of concomitant conditions indicated by the use of calcium (6 patients), drugs for the treatment of stomach acidity (5), vitamin D (4), other vitamins and/or minerals (3), and drugs for treatment of each of hypothyroidism and anxiety (3). Denosumab was reported to have been administered subcutaneously, as expected, in all seven cases which provided the information. The indication for use was stated in 11 reports and was osteoporosis or postmenopausal osteoporosis in all cases. Dosage was reported in seven cases and was 60 mg per six months in three reports, 60 mg without the frequency mentioned in four reports, and two other reports specified one dosage form per six months.

Time to onset was reported in seven of the reports and ranged from a few days to seven months after the drug was administered with a median of about 3-4 weeks.

The outcome of the LP was stated in six of the 14 reports. All six patients were reported as recovered or recovering. In these patients, the drug was reported as withdrawn in four cases while the outcome of the drug was unknown in the remaining two cases.

Other reactions were reported in nine of the 14 cases. These included rashes in five cases, dermatitis, eczema or another skin condition in four cases and pruritus in three cases.

Literature and Labelling

The product literature does not refer to LP but it notes that the skin reactions rash and eczema are common and that cases of cellulitis have been reported uncommonly. There are also no reports of LP in association with denosumab in the medical literature.

Discussion

Case reports in VigiBase® suggest that there is a possible signal for the association of denosumab and LP. Denosumab was the only drug suspected in 12 of the 14 cases. Adalimumab and rituximab were co-suspected in the two remaining cases. The product literature for these two drugs also do not refer to LP. There is, however, a report in the literature of two cases of LP-like eruptions after infliximab and adalimumab therapy for psoriasis. The authors noted that in addition, at that time (2009), 11 cases of LP or lichenoid drug eruptions have been previously reported in patients taking tumour necrosis factor (TNF)-α inhibitors, in addition to several cases of psoriasiform eruptions with a lichenoid histology. In a more recent report, a case of toxic epidermal necrolysis treated with infliximab, which subsequently triggered erosive LP involving the mouth and vulva was described. The authors noted that LP and lichenoid eruptions are an emerging side effect of TNF-α antagonists, with 14 cases reported to date. Seven cases were associated with infliximab, with the others attributed to etanercept, adalimumab and lenercept. There have been no reports in association with rituximab.

Time to onset was reported in seven of the reports and ranged from a few days to seven months after the drug was administered with a median of about 3-4 weeks. This would appear consistent with a drug induced effect.

The outcome of the LP was stated in six of the 14 reports. All six patients were reported as recovered or recovering. In these patients, the drug was reported as withdrawn in four cases while the outcome of the drug was unknown in the remaining two cases. For a drug that is injected periodically, mostly every six months for denosumab, the effect of drug withdrawal or dechallenge is not meaningful. In one report (case 6), the patient had pre-existing LP which was apparently aggravated by denosumab. In another report (case 8), it is unclear whether the patient had pre-existing LP but it was reported that LP worsened after the first administration of denosumab, then recovered and then worsened again after the second administration. This appears to be a positive rechallenge.

As indicated above, the cause of LP is not known and it is difficult to identify any patients in this case series who may be predisposed to LP. Lichenoid reactions, however, are known to occur as adverse reactions to drugs and this appears likely in these cases. As noted above, TNF-α inhibitors have been implicated in the induction of lichenoid reactions but because TNF-α has been implicated in the pathogenesis of LP, such induction is somewhat unexpected. It has been suggested that TNF-α inhibition may precipitate lichenoid reactions through disruption of a delicate balance between TNF-α and interferon-α in susceptible patients. Another suggested hypothesis is that the inhibition of TNF-α allows upregulation of other precursor pro-inflammatory cytokines, such as interferon-α, which causes
activation of both T cells and dendritic cells. Since RANKL is a member of the TNF superfamily, it is possible that denosumab may cause LP through a similar mechanism.

Conclusion

In summary, there are 14 reports associating LP with the use of denosumab. Denosumab was the only drug suspected in 12 of the 14 reports. Time to onset is consistent with a drug induced effect. Dechallenge is generally supportive of a drug association but for a drug such as denosumab, which is administered every six months, the concept of drug withdrawal is not meaningful. There appears to be a positive rechallenge in one case. It is possible that denosumab may cause LP using a similar mechanism to that of TNF-α inhibitors.

References


Response from Amgen

Amgen acknowledges that cases of lichen planus have been reported. As part of ongoing pharmacovigilance activities, Amgen has previously conducted a comprehensive safety assessment to evaluate the risk of lichen planus with the use of denosumab and reported the results in Periodic Benefit-Risk Evaluation Report/Periodic Safety Update Report Number 8. For evaluation of this safety signal, Amgen utilized a cumulative review of all study and non-study adverse event reports with denosumab as well as a review of the epidemiology data with lichen planus, nonclinical data and controlled clinical trial data. Biological plausibility was also assessed. Based upon the comprehensive review, no new safety risk was identified for lichen planus with the use of denosumab. The Amgen conclusion to close the signal lichen planus was endorsed by the Pharmacovigilance Risk Assessment Committee (dated 10 April 2015). The benefit:risk profile of denosumab remains favourable in the current approved indications and the product label adequately reflects the safety profile of Prolia. Amgen will continue to monitor events of lichen planus through ongoing routine pharmacovigilance activities.
**Denosumab and vasculitis**

*Dr Ian Boyd, Australia*

**Summary**
Denosumab is a human monoclonal antibody (IgG2) that targets and binds with high affinity and specificity to the receptor activator of nuclear factor kappa-B ligand (RANKL), preventing activation of its receptor, RANK, on the surface of osteoclast precursors and osteoclasts. Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function and survival, thereby decreasing bone resorption in cortical and trabecular bone. Denosumab is indicated for the treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures, and treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. The most common side effects with denosumab (seen in more than one patient in ten) are musculoskeletal pain and pain in the extremity. Uncommon cases of cellulitis; rare cases of hypocalcaemia, hypersensitivity, osteonecrosis of the jaw and atypical femoral fractures have been observed in patients taking denosumab.1

Vasculitis comprises a heterogeneous group of inflammatory vascular lesions that can involve any kind of blood vessel, irrespective of its lumen or location. Vasculitis gives rise to such conditions as ischaemia or thrombosis, which may cause serious organ damage and be life-threatening. Vasculitis is a necrotizing inflammatory lesion of blood vessels, leading to their occlusion or disruption, with clinical sequelae. The clinicopathological diagnosis of vasculitis is supported by the demonstration of elevated levels of acute-phase reactants (demonstrated by, for example, erythrocyte sedimentation rate, differential blood count showing thrombocytosis and leukocytosis, and C-reactive protein), high levels of rheumatoid factors and cryoglobulins, hypocomplementaemia, antinuclear antibodies (ANA), and anti-neutrophil cytoplasmic antibodies (ANCA) especially those ANCA against proteinase 3 or myeloperoxidase.2 Hypersensitivity vasculitis is an acute form of this condition that is marked by inflammation or redness of the skin that occurs when contact is made with an irritating substance. It is characterized by the appearance of red spots on the skin – most commonly, palpable purpura. Palpable purpura are raised spots that are usually red in color but may darken to a purple color. However, there are many other types of rashes that can occur. Substances that can cause skin inflammation include medications, infections or any other foreign object which may induce an allergic reaction.3 Hypersensitivity vasculitis is usually represented histopathologically as leukocytoclastic vasculitis (LCV) which is a term commonly used to denote a small vessel vasculitis. Hypersensitivity vasculitis is thought to be mediated by immune complex deposition. In this form of vasculitis, circulating antigens in the body (produced by factors such as medications, infections, and neoplasms) induce antibody formation. These antibodies bind to the circulating antigen and create immune complexes, which then deposit within vessels, activating complement and inducing inflammatory mediators. Inflammatory mediators, adhesion molecules, and local factors may affect the endothelial cells and may play a role in the development of vasculitis.

**Introduction**
Denosumab is a human monoclonal antibody (IgG2) that targets and binds with high affinity and specificity to the receptor activator of nuclear factor kappa-B ligand (RANKL), preventing activation of its receptor, RANK, on the surface of osteoclast precursors and osteoclasts. Prevention of the RANKL/RANK interaction inhibits osteoclast formation, function and survival, thereby decreasing bone resorption in cortical and trabecular bone. Denosumab is indicated for the treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures, and treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures. The most common side effects with denosumab (seen in more than one patient in ten) are musculoskeletal pain and pain in the extremity. Uncommon cases of cellulitis; rare cases of hypocalcaemia, hypersensitivity, osteonecrosis of the jaw and atypical femoral fractures have been observed in patients taking denosumab.1

Vasculitis comprises a heterogeneous group of inflammatory vascular lesions that can involve any kind of blood vessel, irrespective of its lumen or location. Vasculitis gives rise to such conditions as ischaemia or thrombosis, which may cause serious organ damage and be life-threatening. Vasculitis is a necrotizing inflammatory lesion of blood vessels, leading to their occlusion or disruption, with clinical sequelae. The clinicopathological diagnosis of vasculitis is supported by the demonstration of elevated levels of acute-phase reactants (demonstrated by, for example, erythrocyte sedimentation rate, differential blood count showing thrombocytosis and leukocytosis, and C-reactive protein), high levels of rheumatoid factors and cryoglobulins, hypocomplementaemia, antinuclear antibodies (ANA), and anti-neutrophil cytoplasmic antibodies (ANCA) especially those ANCA directed against proteinase 3 or myeloperoxidase.2 Hypersensitivity vasculitis is an acute form of this condition that is marked by inflammation or redness of the skin that occurs when contact is made with an irritating substance. It is characterized by the appearance of red spots on the skin – most commonly, palpable purpura. Palpable purpura are raised spots that are usually red in color but may darken to a purple color. However, there are many other types of rashes that can occur. Substances that can cause skin inflammation include medications, infections or any other foreign object which may induce an allergic reaction.3 Hypersensitivity vasculitis is usually represented histopathologically as leukocytoclastic vasculitis (LCV) which is a term commonly used to denote a small vessel vasculitis. Hypersensitivity vasculitis is thought to be mediated by immune complex deposition. In this form of vasculitis, circulating antigens in the body (produced by factors such as medications, infections, and neoplasms) induce antibody formation. These antibodies bind to the circulating antigen and create immune complexes, which then deposit within vessels, activating complement and inducing inflammatory mediators. Inflammatory mediators, adhesion molecules, and local factors may affect the endothelial cells and may play a role in the development of vasculitis.


role in the manifestations of this disease.4 Vasculitis and its consequences may be the primary or sole manifestation of a disease or alternatively, it may be a secondary component of another primary disease. Vasculitis may be confined to a single organ, such as the skin, or it may simultaneously involve several organ systems.5

It should be noted that in WHO-ART, vasculitis is a preferred term with many included terms. Vasculitis is also a high level term which apart from vasculitis includes the related preferred terms arteritis, Churg Strauss syndrome, polyarteritis nodosa, Takayasu’s arteritis, and Wegener’s granulomatosis. MedDRA is more specific with vasculitis as a preferred term and many of the terms which are included terms in WHO-ART are preferred terms in the same high level term.

Reports in VigiBase®

As of 1 January 2016 there are 32 individual case safety reports (ICSRs) of vasculitis in association with denosumab in VigiBase®, the WHO Global ICSR database (Table 1). After the elimination of two suspected duplicates, the reports were submitted from the United States (16 reports), Australia, Germany, Switzerland and the United Kingdom (2 reports each), and Argentina, France, Greece, Ireland, the Netherlands and Spain (1 report each). The patients ranged in age from 36 to 93 years with a median of 74 years in the 26 reports which provided this information. There were 28 females and two males.

Denosumab was the only drug suspected in all of the 30 cases except one. In this case, lercanidipine and sevelamer were also suspected. Concomitant drugs were reported in only 12 of the 30 cases and indicated a patient population with a number of concomitant conditions indicated by the use of vitamin D (7 patients), drugs for the treatment of hypertension (5), stomach acidity (5) and calcium (5), pain management (4), and drugs for treatment of hypothyroidism, lipid management and sleep disorders (2). Denosumab was reported to have been administered subcutaneously, as expected, in all 11 cases which provided the information. The indication for use was stated in 24 reports and included osteoporosis or postmenopausal osteoporosis in 22 reports, spondyloarthritis in one report and bone metastases in one report. Dosage was reported in 16 cases and was 60 mg per six months in eight reports, 60 mg without the frequency mentioned in four reports, 60 mg per one month in one report, one dosage form per six months in two reports and lastly 120 mg per four weeks in the case where bone metastases was the indication.

Time to onset was reported in only 11 of the reports and ranged from three days to nine months after the drug was administered with a median of about two months. Two cases reported onset after receiving the second dose – after one week and three months respectively.

The outcome of the vasculitis was stated in 16 of the 30 reports. Ten of the patients were reported as recovered or recovering, five were reported as not recovered and the remaining patient died, unrelated to the reaction. In the 10 reports with recovery, the drug was reported as withdrawn in five cases, dose not changed in one case while the action taken with the drug was unknown in the remaining four cases. In the five reports without recovery, the drug was reported as withdrawn in two cases while the action taken with the drug was unknown in the remaining three cases.

Other reactions were reported in 20 of the 30 cases. These included skin reactions in 15 cases including rashes in seven cases. These are probably related to vasculitis. A variety of other reactions were reported including arthralgia or similar reactions in four cases, malaise in four cases and gait abnormal in three cases.

Literature and Labelling

The product literature does not refer to vasculitis nor does it refer to any other vascular reactions. It notes that the skin reactions rash and eczema are common and that cases of cellulitis have been reported uncommonly.1 There are also no reports of vasculitis in association with denosumab in the medical literature.

Discussion

Case reports in VigiBase® suggest that there is a possible signal for the association of denosumab and vasculitis. Denosumab was the only drug suspected in 29 of the 30 cases. Lercanidipine and sevelamer were co-suspected in the remaining case. The product literature for these two drugs do not refer to vasculitis.6,7

Time to onset was reported in only 10 of the reports and ranged from three days to nine months after the drug was administered with a median of about two months. This would appear consistent with a drug induced effect since drug-induced vasculitis is an immune mediated reaction which would be expected to take weeks or months to develop. Indeed, one report in the literature has noted that vasculitis in association with antithyroid drugs had a time to onset with a range of 1 to 372 months (median: 42 months).8
### Table 1. Case overview of reports in VigiBase® of vasculitis in association with denosumab

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/Sex</th>
<th>Other suspected (S) or concomitant (C) drugs</th>
<th>Reactions (WHO-ART preferred terms)</th>
<th>Time to onset</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>36M</td>
<td>Calcium carbonate, vitamin D NOS, warfarin (all C)</td>
<td>Vasculitis, medication error (off label use)</td>
<td>-</td>
<td>Unknown</td>
</tr>
<tr>
<td>2</td>
<td>79F</td>
<td>None</td>
<td>Vasculitis, purpura, serum sickness, vomiting</td>
<td>8 months</td>
<td>Recovered</td>
</tr>
<tr>
<td>3</td>
<td>77F</td>
<td>None</td>
<td>Vasculitis</td>
<td>3 days</td>
<td>Unknown</td>
</tr>
<tr>
<td>4</td>
<td>74/F</td>
<td>Bisprolol, celecoxib, hydrochlorothiazide, levothyrione, losartan, calcio* (all C)</td>
<td>Vasculitis</td>
<td>1.5-2.5 months</td>
<td>Not recovered</td>
</tr>
<tr>
<td>5</td>
<td>73/F</td>
<td>None</td>
<td>Vasculitis, eczema</td>
<td>3 months</td>
<td>Recovered</td>
</tr>
<tr>
<td>6</td>
<td>78/F</td>
<td>None</td>
<td>Vasculitis, rash</td>
<td>-</td>
<td>Unknown</td>
</tr>
<tr>
<td>7</td>
<td>81/M</td>
<td>None</td>
<td>Vasculitis, cellulitis, rash pustular</td>
<td>3-4 months</td>
<td>Recovered</td>
</tr>
<tr>
<td>8</td>
<td>/F</td>
<td>None</td>
<td>Vasculitis</td>
<td>-</td>
<td>Unknown</td>
</tr>
<tr>
<td>9</td>
<td>83/F</td>
<td>Enalapril maleate/lercanidipine hydrochloride, omeprazole, alfalcacidol* (all C)</td>
<td>Vasculitis, bullous eruption, rash pustular</td>
<td>-</td>
<td>Not recovered</td>
</tr>
<tr>
<td>10</td>
<td>93/F</td>
<td>None</td>
<td>Vasculitis, asthenia, cheilosis, choking, face oedema, malaise, pruritus, somnolence, transient ischaemic attack</td>
<td>-</td>
<td>Unknown</td>
</tr>
<tr>
<td>11</td>
<td>71/F</td>
<td>Bromazepam, clomipramine, fentanyl, levothyroxine, morphine, nicorandil, pantoprazole, paracetamol, phloroglucinol/trimethylphloroglucinol, pregabalin, propofol, propranolol (all C)</td>
<td>Vasculitis</td>
<td>9 months</td>
<td>Not recovered</td>
</tr>
<tr>
<td>12</td>
<td>69/F</td>
<td>None</td>
<td>Vasculitis, skeletal pain</td>
<td>-</td>
<td>Unknown</td>
</tr>
<tr>
<td>13</td>
<td>/F</td>
<td>None</td>
<td>Vasculitis</td>
<td>-</td>
<td>Unknown</td>
</tr>
<tr>
<td>14</td>
<td>/F</td>
<td>None</td>
<td>Vasculitis, auto-antibody response, pulmonary disorder, renal failure acute</td>
<td>-</td>
<td>Unknown</td>
</tr>
<tr>
<td>15</td>
<td>69/F</td>
<td>None</td>
<td>Vasculitis, malaise, oedema, paraesthesia, rash, adverse drug reaction</td>
<td>-</td>
<td>Unknown</td>
</tr>
<tr>
<td>15**</td>
<td>78/F</td>
<td>Lercanidipine, sevelamer (both 2) Ace inhibitors, allopurinol, atenolol, celecoxib, gefitinib, nicorandil, omeprazole, perhexilene (all C)</td>
<td>Vasculitis, akinesia, cardiac arrest, condition aggravated, hyperparathyroidism, hypocalemia, hypophosphataemia, pruritus, skin exfoliation</td>
<td>3 days</td>
<td>Died – unrelated to reaction</td>
</tr>
<tr>
<td>17</td>
<td>81/F</td>
<td>Celecoxib/celecoxib, calcium carbonate, hydrochlorothiazide/aminolide/hydrochloride, omeprazole, plantago ovata, ranolic acid, tramadol, zoledronic acid, calcio* (all C)</td>
<td>Vasculitis, allergy, diverticulitis, purpura, skin discoulteration</td>
<td>-</td>
<td>Unknown</td>
</tr>
<tr>
<td>18</td>
<td>55/F</td>
<td>Capeplotbine, megestrol, murphine, paracetamol (all C)</td>
<td>Vasculitis, gait abnormal, hypokinesia</td>
<td>-</td>
<td>Recovering</td>
</tr>
<tr>
<td>19</td>
<td>64/F</td>
<td>None</td>
<td>Vasculitis, arthralgia, pain</td>
<td>-</td>
<td>Unknown</td>
</tr>
<tr>
<td>20</td>
<td>71/F</td>
<td>None</td>
<td>Vasculitis, allergy, confusion, malaise, skin nodule</td>
<td>-</td>
<td>Recovered</td>
</tr>
<tr>
<td>21</td>
<td>81/F</td>
<td>None</td>
<td>Vasculitis, abdominal pain, faeces discoloured, faecal incontinence, gait abnormal, hyperpyrexia, inflammation localized, limb pain, lymphangitis, musculoskeletal disorder, oedema, rash erythenatous, urinary incontinence, vascular disorder, vision abnormal</td>
<td>Within 2 weeks</td>
<td>Recovered</td>
</tr>
<tr>
<td>22</td>
<td>/F</td>
<td>None</td>
<td>Vasculitis</td>
<td>10 days</td>
<td>Recovering</td>
</tr>
<tr>
<td>23</td>
<td>88/F</td>
<td>Gabapentin (C)</td>
<td>Vasculitis, micturition frequency, neuralgia, oedema peripheral, skin disorder, sleep disorder, cancer pain**</td>
<td>-</td>
<td>Unknown</td>
</tr>
<tr>
<td>24</td>
<td>74/F</td>
<td>Atorvastatin, calcium, ceritine, deslanosaprazole, ergocalciferol, hydrochlorothiazide/valasartan, ranitidine, vitamin NOS, zolpidem (all C)</td>
<td>Vasculitis, anaemia, hypocalemia, immune system disorder, infection bacterial, infection viral, neutropenia, pulmonary oedema and 33 other reactions</td>
<td>15 weeks</td>
<td>Not recovered</td>
</tr>
<tr>
<td>25</td>
<td>68/F</td>
<td>Salmidic (C)</td>
<td>Vasculitis</td>
<td>-</td>
<td>Unknown</td>
</tr>
<tr>
<td>26</td>
<td>68/F</td>
<td>Metoprolol, tramadol, zolpidem (all C)</td>
<td>Vasculitis</td>
<td>1 month</td>
<td>Recovered</td>
</tr>
<tr>
<td>27</td>
<td>73/F</td>
<td>Ergocalciferol, hydrochlorothiazide (both C)</td>
<td>Vasculitis, angina pectoris, arthralgia, avascular necrosis bone, cystitis, gait abnormal, oedema peripheral, pharyngitis, pneumonia, rash, skeletal pain, upper respiratory tract infection, weight increase, bed rest**, wheelchair user**</td>
<td>-</td>
<td>Recovered</td>
</tr>
<tr>
<td>28</td>
<td>87/F</td>
<td>None</td>
<td>Vasculitis, abdominal pain, chest pain, dysphoea, rash</td>
<td>-</td>
<td>Unknown</td>
</tr>
<tr>
<td>29</td>
<td>76/F</td>
<td>None</td>
<td>Vasculitis, malaise, muscle injury</td>
<td>-</td>
<td>Unknown</td>
</tr>
<tr>
<td>30</td>
<td>61/F</td>
<td>None</td>
<td>Vasculitis</td>
<td>-</td>
<td>Recovering</td>
</tr>
<tr>
<td>31**</td>
<td>79/F</td>
<td>Sevelamer (S) Allopurinol, atenolol, celecoxib, gefitinib, nicorandil, omeprazole (all C)</td>
<td>Vasculitis, alopecia, cellllitis, hyperparathyroidism, hypocalemia, hypophosphataemia, oedema peripheral, ulcer**</td>
<td>-</td>
<td>Died – unrelated to reaction</td>
</tr>
<tr>
<td>32**</td>
<td>79/F</td>
<td>None</td>
<td>Vasculitis, alopecia, haemorrhage NOS, oedema, rash erythenatous, skin exfoliation, ulcer**, secretion discharge**</td>
<td>-</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

**NOS = Not otherwise specified**

* Reported drug
** MedDRA term
*** Cases 16, 31 and 32 are suspected duplicates
In this case series, the underlying time to onset may be 3 to 6 months and those patients who experienced a quick reaction have possibly received the drug or a similar one before and those patients who reacted after the second dose are following a similar pattern.

The outcome of the vasculitis was stated in 16 reports. In the 10 cases with recovery, the drug was reported as withdrawn in five cases and in the six cases without recovery, the drug was reported as withdrawn in two cases. For a drug that is injected periodically though, mostly every six months for denosumab, the effect of drug withdrawal is not meaningful.

Major causes of vasculitis include infections such as hepatitis B and hepatitis C, blood cancers, immune system diseases such as rheumatoid arthritis, lupus and scleroderma and reactions to drugs. Although the patients in this case series had a number of concomitant conditions only one patient was reported with one of these conditions, rheumatoid arthritis in case 25. Vasculitis can be confirmed by biopsy. Only two of the cases reported biopsy-proven vasculitis while in two cases, biopsies appeared to be negative. In two other cases, there was evidence for a different diagnosis so it is possible that not all 30 cases describe vasculitis.

In one of these reports, the authors suggested a relationship between the introduction of therapy with TNF-α inhibitors and anti-drug antibody production. The resulting immune complexes and recruitment of inflammatory mediators may lead to cutaneous vasculitis. In another report, the authors documented 233 cases of autoimmune disease associated with TNF-α inhibitors including 113 cases of vasculitis. Since RANKL is a member of the TNF superfamily, it is possible that denosumab may cause vasculitis through a similar mechanism.

**Conclusion**

In summary, there are 30 reports associating vasculitis with the use of denosumab. Denosumab was the only drug suspected in 29 of the 30 reports. Time to onset is consistent with a drug induced effect. Dechallenge is not particularly supportive of a drug association but for a drug such as denosumab which is administered every six months, the concept of drug withdrawal is not meaningful. Although the patients in this case series had considerable morbidity, there is little in the reports to indicate any other possible cause for vasculitis. It is possible that denosumab may cause vasculitis using a similar mechanism to that of TNF-α inhibitors.

**References**


Response from Amgen

Amgen acknowledges that cases of vasculitis have been reported. Based on a request from the Pharmacovigilance Risk Assessment Committee (PRAC), Amgen has performed a comprehensive safety assessment to evaluate the risk of vasculitis events with the use of denosumab and reported in Periodic Benefit-Risk Evaluation Report/Periodic Safety Update Report 7. For evaluation of this safety signal, Amgen utilized a cumulative review of all study and non-study adverse event reports with denosumab as well as a review of the epidemiology data of vasculitis, nonclinical data and controlled clinical trial data with denosumab. Biological plausibility was also assessed. Based on this comprehensive review, no new safety risk was identified for vasculitis in association with the use of denosumab. The Amgen conclusions to close the signal vasculitis was endorsed by the PRAC with no additional analyses required (dated 10 April 2014). The benefit:risk profile of denosumab remains favourable in the current approved indications and the product label adequately reflects the safety profile of Prolia. Amgen will continue to monitor events of vasculitis with denosumab through ongoing routine pharmacovigilance activities.

Etanercept and injection site ulceration / injection site necrosis – characterization of an ADR

Ms Marilina Castellano, Uppsala Monitoring Centre

The combination of injection site ulceration and etanercept was highlighted in VigiBase®, the WHO international database of suspected adverse drug reactions. This analysis focused on the WHO-ART preferred term (PT) ‘injection site ulceration’ and was then extended to the adjacent PT ‘injection site necrosis’, as they are a related phenomenon. Etanercept is a recombinant receptor inhibitor for the Tumour Necrosis Factor and it is indicated as an immunomodulator for the treatment of both primary and secondary arthritis in adults.\(^1\) Etanercept injection site reactions are well documented and characterised\(^2\); they are usually mild, including bleeding, bruising, erythema, itching, pain or swelling, and injection site ulcerations are not mentioned; these reactions usually occur within one month but recall injection site reactions can also occur at the most recent site of injection. In addition, serious skin reactions such as cutaneous vasculitis are also mentioned in the product information.\(^3\) In general, injection site ulcerations can be due to either an improper injection technique that may result in infection and consequently to ulceration or to the drug itself via different mechanisms. As an example, immunomodulators injected intramuscularly have been reported as causing necrotizing vasculitis.\(^4\) Serious skin reactions at the injection site represent a complication that may lead to therapy discontinuation: this notice aims to report cases of injection site ulceration and to characterize more accurately etanercept-induced injection site reactions.

As of January 2016, there are 29 reports for the PT injection site ulceration in VigiBase® and two more reports for the PT injection site necrosis. A widened search in VigiBase® revealed 444 reports for the PT injection site vesicles. The 31 reports originate from the United States, the United Kingdom and Colombia. The majority of these patients were receiving treatment for rheumatoid arthritis; psoriatic arthropathy and psoriasis were other reported indications. Among the co-reported terms were rash and pain. Seven cases described systemic symptoms such as oedema generalized, influenza like symptoms or nausea. Two cases co-reported injection technique errors and two injection site infections. One third of the cases provided additional details where the reaction was described as manifesting with nodules, welts or vesicles. In particular, one patient developed extensive erythema covered in small open sores and another experienced multiple ulcers that developed between calves and ankles at both legs. Reactions manifested from one week to five years after therapy was started where this information was provided, occurring within one month in the majority of cases. In six of these cases, the event occurred shortly or within two days after the injection was given, with one patient experiencing the event after each injection. Etanercept was the only suspected drug in all cases save one where infliximab was also suspected. Two cases are unlikely to be related to etanercept, as in one the reaction occurred at a shingle vaccine injection site, and in the other the reaction occurred before the therapy was started.

In the light of the ability of this medication to cause vasculitis\(^1\), together with the predisposition of the underlying disease\(^6\), detailed information provided by the original reports for this combination are consistent with manifestations of cutaneous vasculitis.\(^5\) These findings would therefore strengthen the hypothesis that
etanercept induced injection site reactions are immune-mediated. On the other hand, for the cases where either a wrong injection technique or local infection were reported, the likely explanation is that poor technique could have led first to infection and then to ulceration. As these patients are all adults, they are likely to self-inject the drug; more efforts should be put into providing patients with training.

References

Response from Pfizer
The Uppsala Monitoring Centre (UMC) invited Pfizer, as the Marketing Authorization Holder (MAH) for etanercept (Enbrel®) in Europe, to comment on a proposed communication from the UMC regarding a signal of injection site ulceration/injection site necrosis in patients treated with etanercept.

Pfizer agrees with the UMC that injection site reactions (ISRs) are well characterised and reported as very common adverse reactions associated with etanercept therapy, occurring at a frequency of ≥ 1/10. The local symptoms of ISRs are usually mild, including bleeding at the puncture site, bruising, erythema, itching, pain or swelling, and are generally transient and do not recur with treatment. In fact, less than 1.5% of ISR events reported to Pfizer as postmarketing cases are classified as serious, and less than 0.02% of events of ISRs reported from clinical trials are considered to be serious adverse events.

A cumulative search of Pfizer’s safety database up to 18 April 2016 for the Medical Dictionary for Regulatory Activities (MedDRA) Preferred Terms (PTs) Injection site ulcer and Injection site necrosis identified 39 and 7 cases, respectively. These 46 cases represent less than 0.04% of all cases of ISRs reported to Pfizer. Of these, 13 cases were reported as serious, representing less than 0.15% of all reported serious cases of ISRs. Pfizer expects, but cannot confirm, that there is significant overlap with the 31 cases retrieved for the search of the same PTs performed by the UMC in VigiBase® (WHO Global ICSR database). The majority of cases in Pfizer’s safety database were reported from the United States, with 1 case from the United Kingdom, and no cases reported from Colombia. Additional countries reporting cases to Pfizer include Argentina, Brazil, France, Japan, the Netherlands, Spain, and Switzerland. A review of these cases showed minimal relevant information including lack of information on diagnosis, treatment, concomitant medications, and descriptive information regarding the manifestations of the ISRs. The review did not reveal any cases which described suspected or confirmed cutaneous vasculitis.

Pfizer is of the view that the causes of serious ISRs are likely multifactorial. Hypersensitivity, infection due to improper injection technique or device failure, and cutaneous vasculitis have been described as potential causes. A small study that assessed biopsy data from etanercept-associated ISRs suggested T-lymphocyte mediated delayed type hypersensitivity reactions, with eventual induction of tolerance, as a possible mechanism of action. While cutaneous vasculitis is listed as a rare (≥ 1/10,000 to < 1/1,000) adverse reaction for etanercept, the currently available evidence in Pfizer’s safety database does not suggest that events reported as injection site ulceration or injection site necrosis are due to cutaneous vasculitis.

Pfizer strongly agrees that patient training in the use of proper injection technique to prevent infections that could lead to serious ISRs is very important. To this end, Pfizer maintains extensive region-specific educational programs, which differ according to individual market requirements. These programs for patients and health-care providers support the use of proper injection technique and include visual teaching guides, demonstration devices, and instructional materials in both print and video format. They also include a toll free number and website for patient assistance and questions in many regions.

Pfizer continues regular pharmacovigilance surveillance monitoring of the important risk of ISRs through review of postmarketing data, clinical trial data, and published literature. Pfizer
acknowledges UMC’s additional characterisation of ISRs and seeks further clarification through ongoing surveillance with a particular focus on identifying any causes for which the risk can be mitigated through increased awareness and patient and physician education.

References


CAVEAT DOCUMENT

Accompanying statement to data released from VigiBase®, the WHO international database of suspected adverse drug reactions

Uppsala Monitoring Centre (UMC) in its role as the World Health Organization (WHO) Collaborating Centre for International Drug Monitoring receives reports of suspected adverse reactions to medicinal products from National Centres in countries participating in the WHO pharmacovigilance network, the WHO Programme for International Drug Monitoring (PIDM). The information is stored in VigiBase®, the WHO international database of suspected adverse drug reactions (ADRs). It is important to understand the limitations and qualifications that apply to this information and its use.

The reports submitted to UMC generally describe no more than suspicions which have arisen from observation of an unexpected or unwanted event. In most instances it cannot be proven that a specific medicinal product (rather than, for example, underlying illness or other concomitant medication) is the cause of an event.

Reports submitted to National Centres come from both regulated and voluntary sources. Some National Centres accept reports only from medical practitioners; other National Centres accept reports from a broader range of reporters, including patients. Some National Centres include reports from pharmaceutical companies in the information submitted to UMC; other National Centres do not.

The volume of reports for a particular medicinal product may be influenced by the extent of use of the product, publicity, the nature of the reactions and other factors. No information is provided on the number of patients exposed to the product. Some National Centres that contribute information to VigiBase® make an assessment of the likelihood that a medicinal product caused the suspected reaction, while others do not. Time from receipt of a report by a National Centre until submission to UMC varies from country to country. Information obtained from UMC may therefore differ from those obtained directly from National Centres.

If in doubt or in need of help for interpretation of country specific data, UMC recommends to contact the concerned NC before using the data.

For the above reasons interpretations of adverse reaction data, and particularly those based on comparisons between medicinal products, may be misleading. The supplied data come from a variety of sources. The likelihood of a causal relationship is not the same in all reports. Any use of this information must take these factors into account.

Confidential data

According to WHO policy and UMC Guidelines, ADR reports sent from the WHO PIDM member countries to VigiBase® are anonymized, but they are still to be considered sensitive due to the nature of the data.

When receiving and using adverse reaction data ("Data"), the user agrees and acknowledges that it will be the controller of any such Data. Accordingly, the user shall adhere to all applicable legislation such as, but not limited to, EU and national legislation regarding protection of personal data (e.g. the Data Protection Directive 95/46/EC and Regulation (EC) No 45/2001, as applicable). Transfer of sensitive data to a third party is generally prohibited subject to limited exceptions explicitly stated in applicable legislation.

As the controller of the Data, the user shall be liable for any and all processing of the Data and shall indemnify and hold the UMC harmless against any claim from a data subject or any other person or entity due to a breach of any legislation or other regulation regarding the processing of the Data.

Non-permitted use of VigiBase® Data includes, but is not limited to:
• patient identification or patient targeting
• identification, profiling or targeting of general practitioners or practice

Any publication, in whole or in part, of information obtained from UMC must include a statement:
(i) regarding the source of the information
(ii) that the information comes from a variety of sources, and the likelihood that the suspected adverse reaction is drug-related is not the same in all cases,
(iii) that the information does not represent the opinion of the World Health Organization.

Omission of this statement may exclude the responsible person or organization from receiving further information from VigiBase®.

UMC may, in its sole discretion, provide further instructions to the user, responsible person and/or organization in addition to those specified in this statement and the user, responsible person and/or organization undertakes to comply with all such instructions.
The Anatomical Therapeutic Chemical (ATC) classification system and the Defined Daily Dose (DDD) serve as tools for Drug Utilization Research (DUR). DUR is undertaken to improve quality of drug use in health-care settings. DUR can also be used to compare drug consumption at international levels.

The WHO International Working Group for Drug Statistics Methodology consists of 12 members representing a wide range of professional backgrounds including: clinical pharmacology, clinical medicine, international public health, drug utilization and drug regulation. The members of the International Working Group originate from six WHO global regions and represent different types of users of the ATC/DDD system.

The 40th meeting of the WHO International Working Group for Drug Statistics Methodology was held at Pavillon Albert Gallatin, Chateau de Pentes, Geneva, Switzerland.

In the Open Session, industry representatives presented additional information to the experts to support their application for ATC codes and/or DDDs.

The meeting was chaired by Prof Morten Anderson and Dr Shanthi Pal who welcomed the participants, in particular, two new experts from American region and Western Pacific region. The WHO Collaborating Centre (CC) for drug statistics methodology in Oslo reported on its recent activities: the workshop in New Delhi in November 2015 on the margins of annual meeting of National Pharmacovigilance Centres; ATC/DDD training courses in Oslo and Burkina Faso; and the workshop integrating ATC/DDD system in pharmacovigilance and drug utilization research in Rabat, Morocco, which aimed to promote the quality of use of medicines, participation at the ATC/DDD related meetings and publication of the Drug Utilization Research handbook. The WHOCC Oslo also presented future activities such as development of accessible ATC/DDD Open Data, ATC/DDD Webinar and ATC/DDD Toolkit.

The Working Group discussed the ATC classification and DDD items for several medicinal products, the objections and alterations of existing ATC classifications and future challenges. The Working Group also discussed new DDDs for 18 drugs based on the available information including indications and doses used in various countries. In addition objections to the assigned DDDs and alterations of the DDDs were also discussed.

On the second day, Dr Suzanne Hill, Director of the Department of Essential Medicines and Health Products in WHO Headquarters, joined the meeting to speak about WHO’s activities on antimicrobial resistance (AMR) and the importance of the ATC/DDD system for measuring antibiotic consumption.

Decisions made through discussions by the Working Group on ATC classification or DDD assignment will be published on the website of the WHOCC in Oslo and in the publication, WHO Drug Information. Decisions on a new or revised ATC classification or DDD assignment are published initially in a temporary list. Any interested party wishing to dispute this decision has the opportunity to comment within a specified period after its publication.

The WHOCC Oslo publishes the complete ATC Index with DDDs and guidelines for ATC classification and DDD assignment annually. For more information, please see WHOCC Oslo website: http://www.whocc.no/
The 39th Annual Meeting of Representatives of the National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring

The National Pharmacovigilance Centre in Oman hosts the annual meeting of National Pharmacovigilance Centres, in Muscat, Oman

The annual meeting of National Pharmacovigilance Centres (NPCs) is a platform for representatives from around the world to meet and discuss pharmacovigilance issues. Each year an NPC hosts the meeting, and this year the NPC in Oman welcomed delegates to the Grand Millennium Hotel in Muscat, Sultanate of Oman. Nearly 200 representatives from around 50 countries travelled to the Sultanate of Oman to attend the four-day meeting from 14 to 17 November 2016.

Minister of Health attends the opening ceremony for the WHO meeting.

The 39th meeting was inaugurated by the Minister of Health, Dr Ahmed Mohamed Obaid Al-Saidi and the Regional director of the WHO Eastern Mediterranean office, Dr Ala Alwan.
Meeting Structure and content

At the end of the 38th annual meeting of NPCs in India in 2015, participants were invited to suggest topics for the 39th annual meeting. This set the agenda for 2016, reflecting the needs of Member States. The meeting sessions consisted of plenaries, updates, working groups, problems of current interest and for the first time, tutorials.

Plenary included regional challenges on pharmacovigilance (PV); the SCOPE\(^1\) project and value added to the WHO PIDM; mobile app for adverse drug reaction (ADR) reporting; countries in conflict and impact on pharmacovigilance; adverse events identification through social media; safety monitoring in seasonal malaria chemoprevention, and pregnancy and PV.

Updates: Included presentations on: ADR reporting and global statistics; and harmonizing multiple vigilance systems were given by WHO Collaborating Centres (WHO CC) for International Drug Monitoring, and WHO CC for Strengthening Pharmacovigilance Practices respectively.

Working Groups: Eight working groups were run over a period of two days. Prior to the workshop, delegates were provided with a list of objectives and outcomes and had the opportunity to attend two workshops of preference. During each workshop, moderated discussions were held and attendees formulated and agreed on a list of recommendations that were specifically targeted at WHO, WHO CCs and/or the NPCs. A delegated rapporteur amongst the workshop participants presented to the whole delegation during the plenary session on the last day of the meeting.

\(^1\) Strengthening Collaborations for Operating Pharmacovigilance in Europe
Feature

Working group topics consisted of: 1) Defining the pharmacovigilance research question for countries: how do we go about it; 2) Pharmacovigilance communication campaigns: how to measure impact; 3) What people want from pharmacovigilance: What is your big question; 4) Solutions to improve approaches to, and enhance consumer reporting; 5) What to teach pharmacovigilance beginners; 6) Why and when do we undertake cohort event monitoring?; 7) Herbal-drug interactions; 8) Statistical methods in pharmacovigilance.

The finalized and confirmed version of the recommendations will be available in the next issue of the WHO Pharmaceuticals Newsletter.

Problems of Current Interest:
The session on problems of current interest consisted of short presentations based on abstracts that were submitted prior to the meeting. There were a range of topics, some focused on particular ADRs of concern, for example tenofovir and renal impairment. Others discussed initiatives to improve reporting, quality of reports and information sharing. Delegates were given the opportunity to share their experiences, interact and help find solutions.

Tutorials: This year was the first to introduce tutorial sessions within the meeting. There were six different tutorial sessions that ran parallel to each other for three of the four days of the meeting. The tutorials sessions were: case by case signal detection (French and English), Vigilyze, what happens to potential signals, Vigiflow, interacting with the media.

Future meeting
Uganda has offered to host the 40th annual meeting of representatives of the NPCs participating in the WHO PIDM, from 7 to 10 November 2017.