The aim of the Newsletter is to disseminate information on the safety and efficacy of pharmaceutical products, based on communications received from our network of "drug information officers" and other sources such as specialized bulletins and journals, as well as partners in WHO. The information is produced in the form of résumés in English, full texts of which may be obtained on request from:

Quality Assurance and Safety: Medicines, EMP-HSS, World Health Organization, 1211 Geneva 27, Switzerland, E-mail address: pals@who.int

This Newsletter is also available on our Internet website: http://www.who.int/medicines

Further information on adverse reactions may be obtained from the WHO Collaborating Centre for International Drug Monitoring, Box 1051, 751 40 Uppsala, Tel: +46-18-65.60.60, Fax: +46-18-65.60.80, E-mail: info@who-umc.org, Internet: http://www.who-umc.org

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No. 6, 2013

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 from the Uppsala Monitoring Centre's SIGNAL document.

This is the last issue of the newsletter in 2013. We thank you for your interest in this publication and wish you a very good year in 2014.
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Apixaban, dabigatran and rivaroxaban

**Risk of serious haemorrhage—clarified contraindications apply to all three medicines**

UK. The Medicines and Healthcare products Regulatory Agency (MHRA) announced that the contraindications for dabigatran (Pradaxa®) which include a range of conditions where the patient is at significant risk of major bleeding, also applied to the other two new oral anticoagulants apixaban (Eliquis®) and rivaroxaban (Xarelto®).

Dabigatran is a potent, orally active, direct inhibitor of free thrombin, fibrin-bound thrombin and thrombin-induced platelet aggregation. Apixaban and rivaroxaban are direct, highly selective, orally active inhibitors of activated factor X (factor Xa).

All three new oral anticoagulants are licensed for:
- prevention of venous thromboembolic events in adults who have had elective total hip-replacement or knee-replacement surgery
- prevention of stroke and systemic embolism in adults with non-valvular atrial fibrillation and one or more cardiovascular risk factors

Rivaroxaban is additionally licensed for:
- treatment of deep-vein thrombosis and pulmonary embolism, and prevention of their recurrence, in adults

The following contraindications now apply to all three new oral anticoagulants, dabigatran, apixaban and rivaroxaban, for all doses and indications:
- A lesion or condition, if considered a significant risk factor for major bleeding. This may include:
  - current or recent gastrointestinal ulceration
  - presence of malignant neoplasm at high risk of bleeding
  - recent brain or spinal injury
  - recent brain, spinal, or ophthalmic surgery
  - recent intracranial haemorrhage
  - known or suspected oesophageal varices
  - arteriovenous malformation
  - vascular aneurysms, or major intraspinal or intracerebral vascular abnormalities
- Concomitant treatment with any other anticoagulant agent—eg, unfractionated heparin, low molecular weight heparin (such as enoxaparin or dalteparin), heparin derivatives (such as fondaparinux), or oral anticoagulants (such as warfarin). Exceptions are switching of therapy to or from the medicine, or when unfractionated heparin is given at doses necessary to maintain an open central venous or arterial catheter

Additional advice and information for health-care professionals:
- Special care should be taken when deciding to prescribe these anticoagulant medicines to patients with other conditions, procedures, and concomitant treatments (eg, non-steroidal anti-inflammatory drugs, antiplatelets), which may increase the risk of major bleeding
- Attention should be paid to renal function. Impaired renal function may constitute a contraindication or recommendation not to use the anticoagulant medicine, or may require a dose reduction; recommendations differ for the three medicines
- The contraindications, posology, and warnings and precautions for use specific to each medicine, together with the individual’s risk factors for bleeding (eg, renal function), should be considered before prescribing these medicines

It is also notified that there is no specific antidote available for any of these three new oral anticoagulants.

(See WHO Pharmaceuticals Newsletters Nos. 1 and 6, 2012 for safety review of post-market reports of serious bleeding events in the USA, Australia and New Zealand; Risk of serious haemorrhage, need for renal function testing in UK, and No.4, 2012 for modifications to product information for clearer guidance in EU).

Reference:
Drug Safety Update, October 2013, Volume 7, issue 3, A1 MHRA, ([www.mhra.gov.uk](http://www.mhra.gov.uk)).

**Bevacizumab**

**Necrotising fasciitis**

Australia. The Therapeutic Goods Administration (TGA) advised health professionals that the Product Information (PI) for bevacizumab (Avastin®) was updated to include a precaution about necrotising fasciitis. It is recommended that bevacizumab be discontinued and appropriate therapy
Combined hormonal contraceptives

Benefits continue to outweigh risks

Europe. The European Medicines Agency completed its review of combined hormonal contraceptives (CHCs), particularly of the risk of venous thromboembolism (VTE) associated with their use. The European Medicines Agency’s Committee for Medicinal Products for Human Use (CHMP) concluded that the benefits of CHCs in preventing unwanted pregnancies continue to outweigh their risks, and that the known risk of VTE with all low-dose CHCs (ethinylestradiol < 50 mcg) is small. Differences exist between CHCs in their risk of VTE depending on the type of progestogen they contain. Currently available data indicate that CHCs containing the progestogens levonorgestrel, norethisterone or norgestimate have the lowest risk of VTE.

The review also looked at the risk of arterial thromboembolism (ATE). This risk is very low and there is no evidence for a difference in the level of risk between products depending on the type of progestogen.

The review reinforced the importance of ensuring that clear and up-to-date information is provided to women who use these medicines and to the healthcare professionals giving advice and clinical care.

The product information of CHCs will be updated to help women make informed decisions about their choice of contraception together with their healthcare professional. It is important that women are made aware of the risk of VTE and its signs and symptoms, and that doctors take into consideration a woman’s individual risk factors when prescribing a contraceptive. Doctors should also consider how the risk of VTE with a particular CHC compares with other CHCs.

The CHMP opinion, in agreement with the previous recommendation by the Pharmacovigilance Risk Assessment Committee (PRAC), will now be sent to the European Commission for the adoption of a legally binding decision to update the product information of all CHCs throughout the EU.

Health-care professionals are also advised that:

- When prescribing a CHC, careful consideration should be given to the individual woman’s current risk factors, particularly those for VTE, and the difference in risk of VTE between products. CHCs are contraindicated if a woman has one serious or multiple risk factors that put her at high risk of blood clots.

- Because a woman’s individual risk factors will change over time, there is a need to regularly re-assess the suitability of her contraceptive. It is also important to raise awareness of the signs and symptoms of VTE and ATE when prescribing a CHC.

- Health-care professionals should always consider the possibility of a CHC-associated thromboembolism when presented with a woman who has symptoms.

(See WHO Pharmaceuticals Newsletter No.2, 2013 for review of Diane 35 and other medicines started following the decision by the French medicines regulatory agency to suspend the drug in EU and Canada and No.4, 2013 for benefits of Diane 35 and its

Reference:
Dexmedetomidine hydrochloride

Risk of cardiovascular events

Australia. The TGA reminded health professionals that careful patient selection and consideration of the setting in which dexmedetomidine hydrochloride (Precedex®) is used are crucial to ensuring its safe use and that it should only be used for the approved indications and should be administered in accordance with the instructions in the PI. It is also reminded that a controlled infusion device should be used for the administration of dexmedetomidine, and the dose and rate of infusion should not exceed that recommended in the PI.

Particular caution is required in the following situations:
- patients with hypovolaemia, as dexmedetomidine decreases sympathetic nervous system activity
- patients with some level of autonomic system dysfunction, such as those with diabetes and the elderly
- patients of all ages with high vagal tone
- with concomitant use of vasodilators, negatively chronotropic agents, and/or other agents with alpha2-adrenoceptor agonist activity, such as clonidine and droperidol.

Dexmedetomidine is a relatively selective alpha2-adrenoceptor agonist used for sedation. In an intensive care setting, dexmedetomidine is indicated for sedation of initially intubated patients. However, use of the drug by continuous infusion should not exceed 24 hours. Dexmedetomidine is also indicated for procedural sedation. It can be used for non-intubated patients before and/or during surgeries and other procedures.

Atrial fibrillation, bradycardia and hypotension are all listed as adverse effects or precautions in the current PI for dexmedetomidine. There is a warning in the Precautions section regarding use in the elderly, in patients with high vagal tone, or chronic diseases, such as diabetes and heart failure, and with concomitant drugs with a similar pharmacological action. In the past 10 years, the TGA has received a small number of spontaneous reports of cardiovascular events involving dexmedetomidine (of a kind listed as known adverse events in the PI).

Reference:

Ezogabine

Linked to retinal abnormalities and blue skin discoloration

USA. The U.S. Food and Drug Administration (FDA) warned the public that ezogabine (Potiga®) can cause blue skin discoloration and eye abnormalities characterized by pigment changes in the retina. The US FDA does not currently know if these changes are reversible. The US FDA approved changes to the drug label, underscoring risks of abnormalities to the retina in the eye, potential vision loss, and skin discoloration, all of which may become permanent. The revised label includes a new boxed warning, because of the risk of abnormalities to the retina. It is advised that ezogabine use be limited to patients who have not responded adequately to several alternative therapies to decrease the frequency of seizures, or epilepsy, and for whom the benefits of treatment outweigh the risks.

Ezogabine is approved as adjunctive treatment of partial-onset seizures in adult patients 18 years and older. Pigment changes in the retina have the potential to cause serious eye disease with loss of vision. It is not yet known whether the retinal pigment changes caused by ezogabine lead to visual impairment, although several patients have been reported to have impaired visual acuity. In some cases, retinal abnormalities have been observed in the absence of skin discoloration. The skin discoloration in the reported cases appeared as blue pigmentation, predominantly on or around the lips or in the nail beds of the fingers or toes, but more widespread involvement of the face and legs has also been reported. Scleral and conjunctival discoloration, on the white of the eye and inside eyelids, has been observed as well. The skin discoloration generally occurred after four years of treatment with ezogabine, but has appeared sooner in some patients.

In light of this new safety information all patients taking ezogabine should have a baseline eye exam and periodic eye exams that should include visual acuity testing and dilated fundus photography, and may include fluorescein angiograms (FA), ocular coherence tomography (OCT), perimetry, and electroretinograms (ERG). Ezogabine should be discontinued if ophthalmic changes are observed unless no other treatment options are available. If a patient develops skin discoloration, serious
consideration should be given to changing to an alternate medication. Patients who are taking ezogabine and develop any changes in their vision or any discoloration of their skin, including of their lips and nail beds, should contact their health care professional right away.

Patients should not stop taking ezogabine without talking to their health-care professional. Stopping such treatment suddenly can cause serious and life-threatening medical problems such as recurrence of seizures.

(See WHO Pharmaceuticals Newsletter NO.3, 2013 for link to retinal abnormalities and blue skin discoloration in the USA).

References:

Fentanyl patches

Packaging changes to minimize risk of accidental exposure

USA. The US FDA required colour changes to the writing on fentanyl (Duragesic® and generics) pain patches so they can be seen more easily. The US FDA continues to learn of deaths from accidental exposure to fentanyl patches. Fentanyl patch is a strong prescription pain medicine that contains a narcotic opioid.

Patients and health-care professionals are reminded that fentanyl patches are dangerous even after they’ve been used because they still contain high amounts of strong narcotic pain medicine. Accidental exposure to these patches can cause serious harm and death in children, pets, and others.

In an effort to minimize the risk of accidental exposure to fentanyl patches, the US FDA is requiring the manufacturer of fentanyl to print the name and strength of the drug on the patch in long-lasting ink, in a colour that is clearly visible to patients and caregivers. The current ink colour varies by strength and is not always easy to see. This change is intended to enable patients and caregivers to more easily find patches on patients’ bodies and see patches that have fallen off, which children or pets could accidentally touch or ingest. The manufacturers of generic fentanyl patches are being requested to make similar changes.

Patients are recommended to be aware that patches that are not stuck to the skin tightly enough may accidentally fall off a patient and stick to someone in close contact, such as a child. Used fentanyl patches require proper disposal after use — fold the patch, sticky sides together, and flush it down the toilet right away.

(See WHO Pharmaceuticals Newsletter No.2, 2009 for Warning about accidental child exposure and No.4, 2005 for labelling update in Canada)

References:

Low Molecular Weight Heparins

Recommendations to decrease risk of spinal column bleeding and paralysis

USA. The US FDA recommended that health-care professionals carefully consider the timing of spinal catheter placement and removal in patients taking anticoagulant drugs, such as enoxaparin, and delay dosing of anticoagulant medications for some time interval after catheter removal to decrease the risk of spinal column bleeding and subsequent paralysis after spinal injections, including epidural procedures and lumbar punctures. These new timing recommendations, which can decrease the risk of epidural or spinal hematoma, will be added to the labels of anticoagulant drugs known as low molecular weight heparins, including Lovenox® and generic enoxaparin products and similar products.

Epidural or spinal hematomas are a known risk of enoxaparin in the setting of spinal procedures and are already described in the Boxed Warning and the Warnings and Precautions sections of the labels for Lovenox® and generic enoxaparin products. However, these serious adverse events continue to occur. To address this safety concern, the US FDA worked with the manufacturer of Lovenox®, Sanofi-Aventis, to further evaluate this risk and to update the Warnings and Precautions section of the Lovenox label with these additional timing recommendations. The labels for generic enoxaparin products will also be revised accordingly, as will those of other low molecular weight heparin-type products.

It is important to note that all anticoagulants carry the risk of causing spinal bleeding when used in conjunction with epidural/spinal anaesthesia or spinal puncture. The US FDA is continuing to evaluate the safety of other anticoagulants to determine if additional label changes are needed.

References:
**Mefloquine**

**Strengthened warnings on neuropsychiatric side effects**

**UK.** The MHRA announced that, although the risk of neuropsychiatric side effects with mefloquine is well-established, a recent review of the prescribing information has led to strengthened warnings and new measures to help minimise risks. The overall safety profile of the drug has also been clarified in the product information.

Mefloquine (Lariam®) is used for prophylaxis and treatment of *Plasmodium falciparum* malaria. Official guidance on the appropriate use of antimalarial medicines and the prevalence of resistance should be considered when prescribing mefloquine.

Updated information and advice for health-care professionals:
- Psychiatric symptoms associated with use of mefloquine such as nightmares, acute anxiety, depression, restlessness, or confusion should be regarded as potentially prodromal for a more serious event.
- Cases of suicide, suicidal thoughts, and self-endangering behaviour such as attempted suicide have been reported in association with use of mefloquine.
- Adverse reactions may occur and persist up to several months after discontinuation of mefloquine because of its long half-life. In a small number of patients, dizziness or vertigo and loss of balance have been reported to continue for months after discontinuation of the drug.
- To minimise the risk of these adverse reactions, mefloquine must not be used for chemoprophylaxis in patients with active or a history of psychiatric disturbances such as depression, anxiety disorders, schizophrenia, or other psychiatric disorders.
- If neuropsychiatric reactions or changes to mental state occur during mefloquine chemoprophylaxis, the patient should be advised to stop taking mefloquine and seek medical advice as soon as possible so that it can be replaced by another medicine for malaria prevention.

It is also notified that the Marketing Authorisation Holder is issuing a letter to health-care professionals, a prescriber checklist, and patient alert card to aid compliance with these warnings, and to ensure patients are more aware of the neuropsychiatric side effects and to react promptly when these occur in malaria chemoprophylaxis.

(See WHO Pharmaceuticals Newsletter No.5, 2013 for risk of serious psychiatric and nerve side effects in the USA)

**Reference:**

**Ofatumumab and rituximab**

**New boxed warning, recommendations to decrease risk of hepatitis B reactivation**

**USA.** The US FDA approved changes to the prescribing information of ofatumumab (Arzerra®) and rituximab (Rituxan®) to add new Boxed Warning information about the risk of reactivation of hepatitis B virus (HBV) infection. The revised labels also include additional recommendations for screening, monitoring, and managing patients on these drugs to decrease this risk.

In patients with prior HBV infection, HBV reactivation may occur when the body's immune system is impaired. HBV reactivation has occurred in patients with prior HBV exposure who are later treated with drugs classified as CD20-directed cytolytic antibodies, including ofatumumab and rituximab. Some cases have resulted in fulminant hepatitis, hepatic failure, and death.

Ofatumumab is used to treat chronic lymphocytic leukemia (CLL) in patients who have further disease after treatment with the anti-cancer drugs fludarabine and alemtuzumab. Rituxan is used to treat non-Hodgkin's lymphoma and CLL. It is also used to treat other medical conditions, including rheumatoid arthritis, granulomatosis with polyangiitis, and microscopic polyangiitis.

To decrease the risk of HBV reactivation, the US FDA recommended that health-care professionals:
- Screen all patients for HBV infection before starting treatment with ofatumumab or rituximab by measuring hepatitis B surface antigen (HBsAg) and hepatitis B core antibody (anti-HBc).
- Consult with hepatitis experts regarding monitoring and use of HBV antiviral therapy when screening identifies patients at risk of HBV reactivation due to evidence of prior HBV infection.
- Monitor patients with evidence of prior HBV infection for clinical and laboratory signs of hepatitis B or HBV reactivation.
during ofatumumab or rituximab therapy and for several months thereafter, since reactivations have occurred several months following completion of therapy with these drugs.

- In patients who develop reactivation of HBV while on ofatumumab or rituximab, immediately discontinue the drug and start appropriate treatment for HBV. Also discontinue any chemotherapy the patient is receiving until the HBV infection is controlled or resolved. Because of insufficient data, no recommendation can be made regarding the resumption of ofatumumab or rituximab in patients who develop HBV reactivation hepatitis.

For Patients:
- Before receiving ofatumumab or rituximab, tell your health-care professional if you have or have had any severe infections, including HBV.
- If you have had HBV infection, your health-care professional should monitor you for HBV infection during treatment and for several months after you stop treatment with ofatumumab or rituximab.

References:

Ponatinib

Risk of serious blood clots in arteries and veins

USA(1). The US FDA investigated an increasing frequency of reports of serious and life-threatening blood clots and severe narrowing of blood vessels (arteries and veins) of patients taking ponatinib (Iclusig®). Data from clinical trials and post market adverse event reports show that serious adverse events have occurred in patients treated with the drug, including heart attacks resulting in death, worsening coronary artery disease, stroke, narrowing of large arteries of the brain, severe narrowing of blood vessels in the extremities, and the need for urgent surgical procedures to restore blood flow.

The US FDA asked, and Ariad Pharmaceuticals agreed, to suspend marketing and sales of ponatinib, because of the risk of life-threatening blood clots and severe narrowing of blood vessels. The US FDA will continue to evaluate the drug to further understand its risks and potential patient populations in which the benefits of the drug may outweigh the risks. Patients currently receiving the drug should discuss with their health-care professionals the risks and benefits of continuing treatment with the drug. The US FDA provided instructions to health-care professionals whose patients have been taking ponatinib and are benefiting from the drug, on how to continue those patients on the drug.

Ponatinib is a prescription medicine used to treat adults diagnosed with chronic phase, accelerated phase, or blast phase chronic myeloid leukemia (CML) or Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL), who are no longer benefiting from previous treatment or who did not tolerate other treatment. At the time of ponatinib’s approval in December 2012, the drug label contained information about the risks of blood clots in the Boxed Warning and Warnings and Precautions sections.

Patients taking the drug should seek immediate medical attention if they experience symptoms suggesting a heart attack such as chest pain or pressure, pain in their arms, back, neck or jaw, or shortness of breath; or symptoms of a stroke such as numbness or weakness on one side of the body, trouble talking, severe headache, or dizziness.

Europe(2). The CHMP made a number of recommendations to help minimise the risk of
blood clots obstructing arteries or veins in patients taking ponatinib (Iclusig®).

The CHMP recommended that ponatinib should not be used in patients who have had a heart attack or stroke in the past, unless the potential benefits to them outweigh the risks. In addition, the cardiovascular risks of all patients should be assessed and measures should be taken to reduce risks before starting and during treatment with ponatinib. Patients who have high blood pressure should have their blood pressure controlled and healthcare professionals should consider interrupting treatment if hypertension is not controlled. Treatment with the drug should be stopped immediately in any patient with signs of blood clots obstructing arteries or veins.

The CHMP’s recommendations follow a review of updated clinical trial data indicating that blood clots were occurring at a higher rate than was observed at the time of the medicine’s initial authorisation. Conditions related to blood clots, such as heart attacks and strokes, were already considered to be possible side effects of ponatinib and were listed in the EU product information.

The EMA plans to conduct a further in-depth review of relevant data on the benefits and risks of ponatinib and will make recommendations on whether there should be further changes to how the medicine is used.

**References:**

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**Risperidone- or paliperidone-containing products**

**Risk of Intraoperative Floppy Iris Syndrome (IFIS)**

**Canada (1).** Janssen Inc., in consultation with Health Canada, provided health-care professionals with important new safety information regarding the risk of Intraoperative Floppy Iris Syndrome (IFIS) associated with the use of risperidone (Risperdal®, Risperdal® M-Tab®, Risperdal® Consta®), paliperidone (Invega®) and paliperidone palmitate (Invega Sustenna®). These products are primarily prescribed for the treatment of schizophrenia; however, the risk applies to all patients undergoing cataract surgery, who have been exposed to these products, irrespective of indication. The WARNINGS AND PRECAUTIONS section of the Product Monographs for these drugs were updated to include this new safety information.

According to Health Canada, cases of IFIS were reported with the use of risperidone. No reports were received with the use of paliperidone. Paliperidone is the major active metabolite of risperidone and they are pharmacologically very similar. Therefore, a risk of IFIS in patients undergoing cataract surgery and receiving paliperidone cannot be excluded.

IFIS is a recently described intraoperative complication that has been observed during cataract surgery in patients receiving risperidone. IFIS is characterized by a triad of intraoperative signs (billowling of a flaccid iris stroma, progressive intraoperative pupil constriction and a propensity for iris prolapse) that may present with varying degrees of severity and is associated with an increased rate of cataract surgical complications.

It is recommended that cataract surgeons should inquire about current or prior use of risperidone- or paliperidone-containing products and approach the surgery with caution. If IFIS is suspected, modifications to surgical technique may be required.

**UK (2).** The MHRA announced that cases of IFIS during cataract surgery have been reported in patients taking the atypical antipsychotics risperidone or paliperidone.

The MHRA advised that primary-care physicians should document the use of α1-adrenergic antagonists—including risperidone and paliperidone—when making a referral for cataract surgery. When taking a medication history before cataract surgery, patients should be questioned about current or past use of risperidone or paliperidone. Cataract surgeons should approach surgery with caution. If IFIS is suspected, measures to prevent the iris from prolapsing during cataract surgery may be required. The potential benefit of stopping risperidone or paliperidone before cataract surgery on the risk of IFIS has not been established and must be weighed against the risk of stopping antipsychotic therapy.

The MHRA also notified that, to date, no cases of IFIS have been reported for paliperidone; however, this drug is an active metabolite of risperidone and has α1-adrenergic antagonist actions. Therefore, this information and advice applies also to paliperidone.

**Reference:**
Rotavirus vaccination

Risk of intussusception

Australia. The TGA advised health professionals that a recently completed study confirmed that there is an elevated risk of intussusception following the first and second doses of rotavirus vaccines, Rotarix® and RotaTeq®. Health professionals are advised that information about the risk of intussusception following rotavirus vaccination has been added to the postmarketing adverse events sections of the Product Information of these vaccines. Health professionals should advise parents and caregivers of the risks and signs of intussusception, and the importance of seeking early medical attention if they suspect their child has intussusception.

The TGA, working in collaboration with state health authorities, completed an investigation into this association. According to the TGA, there was clear evidence of an elevated risk of intussusception following the first dose of both rotavirus vaccines. There was also some elevated risk of intussusception 1–7 days following the second dose of both vaccines. There was no evidence of increased risk of intussusception following a third dose of RotaTeq®. Prior to the introduction of rotavirus vaccination, there were an estimated 10 000 hospitalisations annually in children under five years due to rotavirus gastroenteritis. Since the introduction of Rotarix® and RotaTeq® onto the National Immunisation Program, emergency department visits for acute gastroenteritis in young children have declined and hospitalisations for rotavirus gastroenteritis in the under-five year age group have been reduced by over 70%. Based on the established benefits of rotavirus vaccination and the rare occurrence of intussusception, both the World Health Organization and the Australian Technical Advisory Group on Immunisation have recommended the continued use of rotavirus vaccine for infants.

(See WHO Pharmaceuticals Newsletter No.2, 2011 for risk of intussusception in Australia)

Reference:

Salbutamol and terbutaline

Restricted use for tocolysis in premature labour

UK. The MHRA announced that the use of short-acting β2 agonists (SABAs), salbutamol and terbutaline, for tocolysis in premature labour was restricted to 48 hours’ maximum parenteral use under specialist supervision, after a European safety review. Oral SABAs should not be used in any obstetric indication. The review was triggered by reports of serious cardiovascular events, including myocardial infarction and pulmonary oedema, after tocolytic use in premature labour.

Salbutamol and terbutaline are SABAs with the obstetric indication of inhibition of premature labour.

The oral SABA preparations were found to be ineffective in the provision of acute tocolysis in premature labour, and are not consistently effective at maintaining uterine quiescence. Use of oral SABAs has been associated with a risk of serious and potentially fatal cardiovascular events such as myocardial infarction and pulmonary oedema in the mother and cardiomegaly in the fetus, which increased with duration of use. Therefore, the risks associated with use of the oral formulations were considered to outweigh the benefits.

The product information for salbutamol and terbutaline will be amended to remove the obstetric indications from the oral products; there will also be no reference to use of oral products in the product information for parenteral formulations.

The parenteral SABA formulations were considered to be efficacious in short-term use up to 48 hours. A short delay to the onset of premature labour enables transfer of the patient to facilities that enable administration of corticosteroids and that can support neonatal care.

Additional advice will be added to the product information for parenteral SABA formulations to promote pretreatment screening for pre-existing heart disease, and to advise continuous monitoring of mother and fetus during treatment.

Health-care professionals are also advised that tocolysis should not be initiated when:

• Gestational age is less than 22 weeks, or when there is any condition to mother or fetus for which prolongation of pregnancy would be hazardous
• (Pre-existing) risk factors for ischaemic heart disease or a pre-existing medical condition mean that use of a SABA would be harmful (eg, pulmonary hypertension, cardiac
disorders such as hypertrophic obstructive cardiomyopathy or aortic stenosis)

In patients with pre-existing heart disease there are further warnings, including the need for assessment by a physician experienced in cardiology.

(See WHO Pharmaceuticals Newsletter NO.4, 2007 for Myocardial ischemia in pregnancy in Canada)

Reference:

Thiocolchicoside

Restricting use by mouth or injection

Europe. The CHMP recommended that the authorised uses for thiocolchicoside-containing medicines for use by mouth or injection should be restricted across EU. These medicines are now recommended only as adjuvant treatment for acute muscle contractures in spinal pathology, for adults and adolescents from 16 years of age. It is not recommended for longer-term treatment of chronic conditions. In addition, the dose of thiocolchicoside by mouth or injection should be restricted.

Health-care professionals are also informed that;
• The maximum recommended oral dose is 8 mg every 12 hours; treatment duration should be no more than 7 consecutive days. When given intramuscularly, the maximum dose should be 4 mg every 12 hours, for up to 5 days.
• Medicines containing thiocolchicoside should not be used during pregnancy and lactation, nor in women of childbearing potential who are not taking appropriate contraceptive measures.
• Patients being treated with systemic thiocolchicoside should have their treatment reviewed at the next scheduled appointment, and appropriate alternative treatments should be considered.
• Pharmacists should refer any patients who present a repeat prescription to their treating physician.
• Prescribers will be sent a letter giving them further information on the restriction of indication of systemic thiocolchicoside.

Thiocolchicoside is used as a muscle relaxant in the treatment of painful muscular conditions. It is thought to act on receptors in the nervous system that are involved in the regulation of muscle function.

The Committee’s recommendations were based on a review of available data from pre-clinical and clinical studies, published literature and post-marketing experience, and consultations with an expert working party on medicines safety. The Committee concluded that benefit-risk for the medicine remained positive provided appropriate risk-mitigating measures were taken, including restricting the maximum dose and duration of use and contra-indicating use during pregnancy and lactation and in children.

Reference:

Tigecycline

Increased risk of death

USA. The US FDA notified health-care professionals and their medical care organizations of a new Boxed Warning describing an increased risk of death when intravenous tigecycline (Tygacil®) is used for FDA-approved uses as well as for non-approved uses. It is recommended that health-care professionals should reserve tigecycline for use in situations when alternative treatments are not suitable. These changes to the Prescribing Information are based on an additional analysis that was conducted for FDA-approved uses after FDA issuing a Drug Safety Communication about this safety concern in September 2010.

This analysis showed a higher risk of death among patients receiving tigecycline compared to other antibacterial drugs: 2.5% (66/2640) vs. 1.8% (48/2628), respectively. The adjusted risk difference for death was 0.6% with corresponding 95% confidence interval (0.0%, 1.2%). In general, the deaths resulted from worsening infections, complications of infection, or other underlying medical conditions.

Tygecycline is FDA-approved to treat complicated skin and skin structure infections (cSSSI), complicated intra-abdominal infections (cIAI), and community-acquired bacterial pneumonia (CABP).

References:
Regulatory Matters

Trastuzumab emtansine and trastuzumab

Potential risk for medication error due to name confusion

Canada. Hoffmann-La Roche Limited (Roche), in consultation with Health Canada, informed health-care professionals of the potential risk for medication error due to the similarity in the non-proprietary names of Kadcyla™ (trastuzumab emtansine) and another breast cancer medication, Herceptin® (trastuzumab), and the importance of ensuring that the correct product is administered to patients.

On September 11, 2013, Health Canada authorized trastuzumab emtansine for the following indication:

Trastuzumab emtansine, as a single agent, is indicated for the treatment of patients with HER2-positive, metastatic breast cancer who received both prior treatment with trastuzumab and a taxane, separately or in combination. Patients should have either received prior therapy for metastatic disease, or developed disease recurrence during or within 6 months of completing adjuvant therapy.

Health-care professionals are advised the following:
- Trastuzumab emtansine and trastuzumab are NOT the same product.
- There is a potential risk for medication error between trastuzumab emtansine and trastuzumab.
- Health-care professionals should use both the brand name (Kadcyla™) and its full non-proprietary name (trastuzumab emtansine) when prescribing the medication to patients.

- When preparing and administering trastuzumab emtansine, health-care professionals should check:
  o The prescription, to ensure that trastuzumab emtansine is the intended medication to be administered;
  o The dosage, to ensure that the recommended dose of trastuzumab emtansine is;
  o The vial labels, to ensure that the drug is trastuzumab emtansine and not trastuzumab.

The doses, treatment schedules and authorized indications for trastuzumab emtansine and trastuzumab are different. The dosage for these drugs are as follows:
- Trastuzumab emtansine is administered every 3 weeks (3.6 mg/kg)
- Trastuzumab is administered every 3 weeks (8 mg/kg loading dose; 6 mg/kg maintenance dose), or weekly (4 mg/kg loading dose; 2 mg/kg maintenance dose)

It is also advised that health-care professionals must be aware that confusion between these drugs may lead to dosing errors and potential harm to patients. In addition to the measures above, Roche differentiated the packaging for these drugs by the use of different colours. Such precautions should help to reduce the potential for medication errors.

(See WHO Pharmaceuticals Newsletter No.3, 2013 for Potential medication errors resulting from name confusion in the USA).

Reference:

Vancomycin

Risk of nephrotoxicity associated with intravenous infusion of vancomycin

Australia. The TGA reminded health professionals of the risk of nephrotoxicity associated with intravenous infusion of vancomycin and the need for appropriate serum monitoring. Monitoring is especially important in patients with renal impairment and/or other risk factors, as well as in patients who are being treated with the drug for a prolonged period. Unmonitored and prolonged use of vancomycin administered in an intravenous infusion to a renally compromised patient can result in severe and potentially irreversible nephrotoxicity.

Obesity and being elderly are additional risk factors for vancomycin-induced nephrotoxicity.

The PI and the Australian Therapeutic Guidelines include advice for effective monitoring and dose adjustment of vancomycin. Monitoring is recommended for all patients treated with this drug for a prolonged period (more than 48–72 hours).

Vancomycin is an amphoteric glycopeptide antimicrobial drug used to treat potentially life-threatening infections that cannot be effectively treated with another less toxic drug.

Reference:
Antiepileptic drugs

New advice on switching between different manufacturers’ products for a particular drug

UK. The MHRA informed that different antiepileptic drugs (AEDs) vary considerably in their characteristics, which influences the risk of whether switching between different manufacturers’ products of a particular drug may cause adverse effects or loss of seizure control. AEDs have been divided into three risk-based categories to help health-care professionals decide whether it is necessary to maintain continuity of supply of a specific manufacturer’s product.

According to MHRA, concerns about switching between different manufacturers’ products of an oral AED have been raised by patients and prescribers. These include switching between branded originator and generic products, and between different generic products of a particular drug. The main reasons for these concerns are the narrow therapeutic index of some AEDs and the potentially serious consequences of therapeutic failure. Drug–drug interactions and the relatively low solubility or bioavailability (or both) of some AEDs are other important factors.

The Commission on Human Medicines (CHM) reviewed spontaneous adverse reactions received by MHRA and publications that reported potential harm arising from switching of AEDs in patients previously stabilised on a branded product to a generic. Following this review, CHM concluded that reports of loss of seizure control and/or worsening of side effects around the time of switching between products could be explained as chance associations, but that a causal role of switching could not be ruled out in all cases.

The CHM considered the characteristics of AEDs and advised that they could be classified into three categories based on therapeutic index, solubility, and absorption to help prescribers and patients decide whether it was necessary to maintain continuity of supply of a specific manufacturer’s product. These categories are listed below:

- Category 1 – phenytoin, carbamazepine, phenobarbital, primidone. For these drugs, doctors are advised to ensure that their patient is maintained on a specific manufacturer’s product.
- Category 2 – valproate, lamotrigine, perampanel, retigabine, rufinamide, clobazam, clonazepam, oxcarbazepine, eslicarbazepine, zonisamide, topiramate. For these drugs, the need for continued supply of a particular manufacturer’s product should be based on clinical judgement and consultation with patient and/or carer, taking into account factors such as seizure frequency and treatment history.
- Category 3 - levetiracetam, lacosamide, tiagabine, gabapentin, pregabalin, ethosuximide, vigabatrin. For these drugs, it is usually unnecessary to ensure that patients are maintained on a specific manufacturer’s product unless there are specific reasons such as patient anxiety and risk of confusion or dosing errors.

MHRA advised that:
- Different AEDs vary considerably in their characteristics, which influences the risk of whether switching between different manufacturers’ products of a particular drug may cause adverse effects or loss of seizure control.
- AEDs have been divided into three categories to help healthcare professionals decide whether it is necessary to maintain continuity of supply of a specific manufacturer’s product.
- If it is felt desirable for a patient to be maintained on a specific manufacturer’s product, this should be prescribed either by specifying a brand name, or by using the generic drug name and name of the manufacturer (otherwise known as the Marketing Authorisation Holder).
- This advice relates only to AED use for treatment of epilepsy; it does not apply to their use in other indications (eg, mood stabilisation, neuropathic pain).

Pharmacists are also advised that:
- Dispensing pharmacists should ensure the continuity of supply of a particular product when the prescription specifies it. If the prescribed product is unavailable, it may be necessary to dispense a product from a different manufacturer to maintain continuity of treatment of that AED. Such cases should be discussed and agreed with both the prescriber and patient (or carer).
- Usual dispensing practice can be followed when a specific product is not stated.

Reference:
Drug Safety Update, November
Atomoxetine

Risk of suicidal ideation and behaviour in children and adolescents

Australia. The Therapeutic Goods Administration (TGA) informed that serious adverse events were reported to the TGA, including one case involving the death of a child receiving atomoxetine; TGA emphasized the importance of health professionals adequately informing parents and caregivers of the risks of suicidal ideation and behaviour in children and adolescents being prescribed atomoxetine (Strattera®).

Atomoxetine is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD), as defined by DSM-IV criteria, in children aged 6 years and over, adolescents and adults. The risks of suicidal ideation and behaviour with atomoxetine are well known and are reinforced in the Product Information in the precautions section, as well as in a boxed warning.

It is recommended that, when considering prescribing atomoxetine in children and adolescents, health professionals should carefully weigh the risks of suicidality against the benefits of atomoxetine therapy. Patients who are prescribed atomoxetine should be carefully monitored for suicidality, especially in the first few months of treatment and whenever there is a change in dose. Parents and caregivers should warn of the risks and alert the need to monitor for signs of unusual changes in behaviour or precursors of suicidality, such as anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania or mania. Parents and caregivers should also be advised of the importance of seeking immediate medical attention if such signs are identified.

Reference:

Cabazitaxel

Risk of medication error resulting in overdose

UK. The MHRA advised that all health-care professionals involved in the preparation of cabazitaxel (Javtana®) for infusion should be aware that the entire contents of the solvent vial must be added to the concentrate vial to produce a concentrate-solvent mixture with the intended concentration of 10 mg/mL cabazitaxel. Pharmacists should review worksheets that are used in the preparation of cabazitaxel to ensure that they correctly inform pharmacy staff to add the entire content of the solvent vial to the concentrate vial.

Cabazitaxel in combination with prednisone or prednisolone is indicated for the treatment of patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing regimen. It is supplied as a vial of concentrate and a vial of solvent. The concentrate must first be diluted with the solvent supplied before adding to the infusion solution.

There have been reports of medication error that have occurred because the entire fill volume of the solvent vial was not added to the concentrate vial. This has resulted in some patients receiving a higher dose (15–20% higher) of cabazitaxel than was intended.

The solvent vial and the concentrate vial each contain an overfill to compensate for liquid lost during the initial dilution process. Therefore, the entire contents of the solvent vial must be added to the concentrate vial to ensure that the resulting concentrate-solvent mixture contains the intended concentration of 10 mg/mL cabazitaxel and has a minimal extractable volume of 6 mL.

The required volume of the concentrate-solvent mixture should be diluted immediately (within 1 hour) to prepare the solution for infusion, as described in the Summary of Product Characteristics, which should be consulted before preparing the cabazitaxel solution for infusion.

Reference:

Cinacalcet

New warnings for the risk of QT prolongation and arrhythmia

Canada. Health Canada completed a safety review of cinacalcet (Sensipar®) that identified a possible link between the drug and abnormal heart rhythm associated with low blood calcium. Stronger warnings were added to the drug label to inform patients about the risk of QT prolongation and arrhythmia associated with the use of cinacalcet and to advise health professionals to monitor and report heart-related side effects.

Cinacalcet is used for treating disorders of the parathyroid gland that result in abnormal blood calcium levels. Cinacalcet is well known to cause hypocalcemia. The risk of low blood calcium associated with the use of the drug is clearly outlined on the Canadian drug label. Low blood
calcium can cause electrical changes in the heart known as "QT prolongation" and arrhythmia. Arrhythmia can be serious and, in some cases, may lead to sudden death. QT prolongation and arrhythmia were reported in a small number of patients with low blood calcium treated with cinacalcet. Health Canada reviewed all available information.

According to Health Canada, it is difficult to determine with certainty what role cinacalcet may have played in the development of QT prolongation or arrhythmia, as other risk factors were present at the same time. However, given the effect of low blood calcium on the heart, the possibility of developing QT prolongation or arrhythmia with the use of cinacalcet could not be ruled out.

Patients are recommended that:
- Before starting cinacalcet, talk to their doctor if they have heart rhythm problems or take medicines known to cause heart rhythm problems or if they have low levels of blood calcium, or have had heart problems (low blood pressure or worsening heart failure).
- Tell their doctor if they experience an unusually fast or pounding heartbeat.
- Tell their doctor immediately if they start to get numbness or tingling around the mouth, muscle aches or cramps and seizures. These may be signs that calcium level is too low.
- Talk to their doctor or pharmacist about any questions or concerns regarding cinacalcet treatment.

Health-care professionals are recommended to:
- Carefully monitor patients for signs of low blood calcium.
- Prescribe cinacalcet with caution in patients with other risk factors for QT prolongation, such as known congenital long QT syndrome (an inherited heart condition), or in patients who are taking other drugs known to cause QT prolongation.
- For patients treated with cinacalcet for chronic kidney disease and receiving dialysis, reduce dose or stop use if low blood calcium, signs of QT prolongation, or arrhythmia continue. For these patients, cinacalcet should not be started if they have severe hypocalcemia.

(See WHO Pharmaceuticals Newsletter No. 2, 2013 for cautions against use in children in Canada)

Reference:

Gadolinium-containing contrast agents

Update on Nephrogenic Systemic Fibrosis/Nephrogenic Fibrosing Dermopathy (NSF/NFD)

Canada. Health Canada announced that current evidence suggested that the extent of risk for a rare and potentially fatal disease, Nephrogenic Systemic Fibrosis (NSF) in patients with kidney disease following exposure to any specific Gadolinium (Gd)-containing contrast agents (GBCA) vary among the agents, while NSF development is considered a potential class-related effect of all GBCAs.

Gadolinium (Gd)-containing contrast agents (GBCA) are indicated for providing contrast enhancement in the magnetic resonance imaging (MRI) investigations. Eight GBCA products are currently authorized for sale in Canada: gadofoveset trisodium (Ablavar®) gadobutrol (Gadovist®), gadopentetate dimeglumine (Magnevist®), gadobenate dimeglumine (MultiHance®), gadodiamide (Omniscan™), gadoversetamide (OptMARK™), gadoxetide (ProHance®) and gadoxetate disodium (Primovist®).

Health Canada has worked with the Canadian Marketing Authorization Holders of the GBCAs to update the prescribing information for these agents. NSF can result in fatal or debilitating systemic fibrosis. In such cases, the skin fibrosis extends beyond the dermis and involves subcutaneous tissues, muscles and internal organs.

NSF cases have been reported following single and multiple administrations of GBCAs. It is not always possible to identify a single causal agent. NSF has also been reported to occur following the sequential administration of some lower risk GBCAs.

Repeated or higher than recommended doses of a GBCA and the degree of renal function impairment at the time of exposure are risk factors for NSF. The risk of NSF in patients with mild to moderate renal insufficiency is not well characterized, and the cautious utilization of the lowest possible dose of GBCA in these patients is recommended. When administering a GBCA, the
SAFETY OF MEDICINES

recommended dose should not be exceeded and a sufficient period of time should be allowed for elimination of the agent from the body prior to any re-administration.

For patients receiving hemodialysis, health-care professionals may consider prompt hemodialysis following GBCA administration in order to enhance the contrast agent’s elimination. However, it is not known currently if hemodialysis can help to prevent NSF.

(See WHO Pharmaceuticals Newsletters No.6, 2009 for risk of nephrogenic systemic fibrosis in patients with renal impairment in Canada and No.1, 2008 for risk of nephrogenic systemic fibrosis in Australia.)

Reference:

Sodium valproate

Risk of neurodevelopmental delay in children following maternal use

UK. The Medicines and Healthcare products Regulatory Agency (MHRA) announced that there is new evidence on neurodevelopmental delay in children following maternal use of sodium valproate. Sodium valproate (Epilim®) has been authorised since 1973 for the treatment of epilepsy. Depakote® is the brand of sodium valproate authorised for the treatment of the manic phase of bipolar disorder. The use of sodium valproate is associated with a greater risk of some types of these malformations (in particular neural tube defects) than with some other antiepileptic drugs. This risk is clearly reflected in the product information provided for patients and prescribers.

The most recent publications on an association between fetal valproate exposure and neurodevelopmental delay or autism spectrum disorder have prompted a re-evaluation of the balance of benefits and risks of this medicine. A European review is underway to evaluate all currently available evidence on the association between fetal valproate exposure and neurodevelopmental delay or autism spectrum disorder.

Health-care professionals are reminded that sodium valproate should not be used during pregnancy and in women of childbearing potential unless clearly necessary. Women of childbearing potential should not start treatment with sodium valproate without specialist neurological or psychiatric advice as appropriate depending on the indication. Adequate counselling should be made available to all women with epilepsy of childbearing potential to weigh the risk of teratogenic and neurodevelopmental effects against the benefits of treatment.

(See WHO Pharmaceuticals Newsletter No.3, 2013 for Contraindicated for pregnant women for prevention of migraine headaches and No. 4, 2012 for risk of impaired cognitive development in children exposed in utero in the USA).

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 the WHO Global ICSR database, VigiBase™. The database contains over 7 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 section (page 33). For information on the UMC Measures of Disproportionate Reporting please refer to WHO Pharmaceuticals Newsletter Issue No. 1, 2012.

Abiraterone and Thrombocytopenia

Dr. Raquel Herrera Comoglio, Argentina

Summary

Drug-induced thrombocytopenia (DIT) is a relatively common clinical disorder that can be a consequence of decreased platelet production (mainly because of bone marrow cytotoxicity) or accelerated platelet destruction (especially through immune mediated mechanisms).

Abiraterone has been approved since 2011 in combination with prednisone for the treatment of patients with metastatic castration-resistant prostate cancer (mCRPC). Abiraterone is an inhibitor of the enzyme 17a-hydroxylase/C17,20-lyase (CYP17), which catalyses the conversion of pregnenolone and progesterone into testosterone precursors (dihydroepiandrosterone, DHEA, and androstenedione) in testicular, adrenal and prostatic tumour tissues.

Thrombocytopenia (or decreased platelet count) is not listed in the product information for abiraterone. No case reports for thrombocytopenia during or after abiraterone treatment were found published. Thrombocytopenia with the use of abiraterone is mentioned as occurring in two patients out of 39 in an observational study of the compassionate use of this drug.

From September 2011 up to April 16th 2013, 26 Individual Case Safety Reports (ICSRs) with the combination abiraterone and thrombocytopenia were retrieved from the WHO Global ICSR Database, VigiBase™. In spite of the very complex clinical condition (metastatic prostate cancer) and the scarcity of data in many reports, the analysis of these 25 cases (after removal of one duplicate) from VigiBase would suggest that abiraterone may decrease platelet count, possibly through the platelet production process.

Introduction

In castration-resistant prostate cancer (CRPC) it has been suggested that androgens from non gonadal sources (both adrenal and intratumoral) continue to drive androgen receptors’ (AR) signaling and contribute to prostate cancer progression after androgen deprivation therapy. Systemic inhibition of androgen biosynthesis may be achieved through the inhibition of CYP17, which blocks two sequential reactions involved in the final stages of androgen production.1

Abiraterone acetate is a potent and selective CYP17 inhibitor, including both 17,20-lyase and 17-alpha-hydroxylase activities.2,3,4 It blocks the synthesis of androgens in the testis, adrenal glands, and prostate, without causing adrenal insufficiency, which is a known side effect of the non-selective CYP17 inhibitor keto-conazole. The effect of abiraterone on CYP17 differs from the effect of ketoconazole in being irreversible, selective and 10-times more potent.1-5 In order to avoid or prevent clinical consequences of abiraterone's effect on corticosteroid endogenous
Drug-induced thrombocytopenia (DIT) is a relatively common adverse drug reaction; when severe, its consequences may be serious. Two main pathways for DIT have been described: a decrease in platelet production — mainly because of bone marrow toxicity, i.e. a non-immune mechanism; and an increase in platelet destruction, predominantly caused by immune mechanisms but also by non-immune mechanisms.

Drug-induced non-immune thrombocytopenia can result from a loss of bone marrow cellularity and an impairment of megakaryocyte proliferation and maturation. The time course of DIT related to marrow suppression is generally slow, reflecting the time required to deplete the megakaryocyte population. Cytotoxic chemotherapy causes thrombocytopenia by bone-marrow suppression; selective inhibition of megakaryocyte production, mediated by thiazide diuretics, ethanol, tolbutamide and antivirals, could lead to isolated thrombocytopenia.

Non-immune platelet destruction, associated with a small number of antineoplastic agents such as bleomycin, can occur in thrombotic microangiopathy. Drug-induced immune thrombocytopenia is characterized by drug-dependent antibodies that bind to platelets and cause their destruction, and can be triggered by a wide range of medications, including cytotoxic agents. In immunemediated thrombocytopenia, time to onset is reported.

To be on the order of 1 to 2 weeks following the patient’s first exposure to an immunogenic drug, and of 2-3 days if the drug has been taken previously. Heparin-induced thrombocytopenia, which affects up to 10% of patients treated (especially with unfractionated heparin), produce immune complexes that induce platelet activation and typically occurs five or more days after the start of heparin therapy. It can be complicated by arterial or venous thrombotic events.

Reports in VigiBase
A total of 26 Individual Case Safety Reports (ICSRs) were retrieved from the WHO Global ICSR Database, VigiBase™ on April 16th 2013 and reviewed case by case. The ICSRs came from the United Kingdom (seven), Germany (seven), the United States (six), Spain, Austria and Canada (two cases each). A likely duplicate report from Germany was identified, therefore only 25 cases were considered. The two ICSRs from Spain (case 4 and case 13) show many similarities but have been considered as two different reports. Most of the ICSRs (88%) are spontaneous reports and data are scarce in many of them. Age (reported in 12 ICSRs) ranged from 58 to 85 years, and masculine sex is stated in all cases but two. The dose for abiraterone (1 g daily) was reported in 23 cases (92%). The reports were classed as serious in all but one ICSR (96%), and there were three fatal cases. The main characteristics of the ICSRs are shown in Table 1.

Abiraterone is reported as the only suspected drug in 20 ICSRs (80%), and in 10 ICSRs (40%), abiraterone is the only drug mentioned. Co-suspected drugs are prednisolone (two cases), prednisone (two cases, in one case together with an unspecified antiplatelet therapy), and teicoplanin (one case). Prednisone is reported as a concomitant drug in seven other cases and prednisolone in three cases. Suspected and concomitant medications are shown in Table 1.

Time to onset is stated in 12 out of 25 ICSRs (48%). Apart from one case which reports — perhaps by mistake — a minus 15 days time to onset, the remaining 11 ICSRs (44%) report times to onset ranging from 18 days to four months. In seven cases, where time to onset cannot be determined, the duration of treatment for abiraterone has been reported as one month (four cases), three days, and 76 days; one report mentions 18 cycles.

Platelet count was reported in eight ICSRs. Thrombocytopenia was severe in four cases (one case with 5,000 platelets and three cases with 19,000 platelets). Moderate thrombocytopenia was reported in three ICSRs with a platelet count of 39,000 (case 2), 26-24,000 (case 24), and 54,000/46,000 (case 25) and two cases reported mild thrombocytopenia (100,000 platelets in case 9 and 68,000 platelets in case 19).

Abiraterone was withdrawn in seven cases: two patients recovered (one with sequelae), two patients were reported as not recovered at the date of report, there was one case with unknown outcome, one death, and one with no reported outcome. Dose was reported as not changed in seven cases: in four cases the reported outcome was "recovered" (two cases) or "recovering" (two cases), in one case the outcome was "not recovered" and the outcome was unknown in the two remaining cases. Recurrence after rechallenge is mentioned in one report, with no more data available.

In 11 ICSRs (44%), causality was assessed as possible, and in nine (37.5%) causality is not.
reported. Among the remaining five ICSRs, two were reported as conditional, two as very likely/certain and one as not related.

Anaemia is co-reported as an adverse effect in four reports (one of which also reported spleen enlarged), and leucocytopenia is co-reported in two reports. There was one patient with myelodysplasia. Progression of pre-existing disease is reported as an adverse drug reaction in case 20 (with fatal outcome) and case 22.

Three deaths were reported. Case 7 reports the death of a man after 76 days of abiraterone treatment; no time to onset is reported. Other adverse effects are also reported for this patient, including oedema peripheral and hypokalemia. Case 20 reports the death of a man after three days of abiraterone/prednisone treatment (disease progression is also mentioned as an adverse effect). In case 24, a 63-year-old patient with advanced metastatic prostate cancer (bone and liver metastases and urinary tract obstruction) presented with acute renal failure, thrombocytopenia and hyperbilirubinemia 58 days after starting abiraterone/prednisone treatment; thrombocytopenia was assessed as not related, hepatic insufficiency as possible and hyperbilirubinaemia as probable (patient from clinical trial).

Of the three ICSRs from clinical trials, in two, the association between abiraterone and thrombocytopenia was assessed as certain or very likely and in the other case (described above) as not related. In case 5 (from clinical trial COU-AA-302, causality assessed as certain) a 69-year-old patient was hospitalized because of grade 3 thrombocytopenia, which worsened in spite of administration of one pack of platelet concentrate together with two packs of blood cells concentrate; he also presented with grade 2 anaemia; further biopsia revealed carcinosis. In case 25, with causality assessed as very likely/certain, a 70-year-old patient hospitalized because of symptoms of pulmonary embolism 66 days after having started the therapy with abiraterone also presented with non-serious thrombocytopenia (54,000 platelets/mL). This patient, with a medical history of pulmonary embolism and with a long-term dalteparin treatment as preventive therapy, was diagnosed with acute myeloid leukemia two months later.

**Literature and Labelling**

There is no reference to thrombocytopenia as a possible side effect of abiraterone in the US FDA label or the European Medicines Agency Summary of Product Information. The Australian Public Assessment Report does not mention thrombocytopenia as an adverse effect of abiraterone, although on page 88 it is stated that “in study COU-AA-301. No other haematologic Grade 2, 3 or 4 abnormality (i.e. neutrophils, platelets, WBC) during treatment occurred in greater than 5% of subjects in the abiraterone acetate group or in greater than 3% of subjects in the placebo group”.

A PubMed search using the search query “abiraterone AND thrombocytopenia” retrieved only one result, an article in German reporting the first clinical experiences of abiraterone in compassionate use. In this article, two patients, of 39 treated with abiraterone acetate, presented with thrombocytopenia. No results were found for PubMed searches using the search query “abiraterone AND platelet” or “abiraterone AND megakaryocyte”.

In the published reports of two Phase III abiraterone trials, (COU-AA-301 final report and COU-AA-302 interim analysis) there is no mention of thrombo-cytopenia or a decrease in platelet counts as an adverse effect. Of note, case 5 reports thrombocytopenia in a participant of the CAU-AA-302 trial.

In the only clinical trial with abiraterone has results posted (March 2013). Neither thrombocytopenia nor platelet count decreased are listed as adverse events.

**Discussion**

Many ICSRs are incomplete. Metastatic cancer with bone marrow involvement can also cause thrombo-cytopenia and can act as a confounder: out of five cases reporting concomitant anaemia or pancytopenia, in three cases (case 5, 11 and 19) bone marrow puncture found evidence of carcinosis, and in case 9, spleen enlargement is also reported with thrombocytopenia and normocytic anaemia. In spite of these two main limitations, the analysis of the 25 ICSRs seems to show a predominant pattern of onset of two or more weeks, which would be consistent with a drug-induced thrombocytopenia through a non-immune mechanism.

In case 15, thrombocytopenia may be related to the co-suspected drug teicoplanin (time to thrombo-cytopenia onset is reported 11 days after teicoplanin treatment and 56 days after abiraterone treatment). In all other cases with co-suspected or concomitant drugs, temporal relationships suggest that abiraterone is the most likely causative agent. Diclofenac can cause thrombocytopenia - chronic and silent or acute, through an immune mechanism: in case 5 (causality assessed as "certain"), thrombocytopenia's onset occurred after 46 days of abiraterone therapy and 5 months of diclofenac treatment. Leuprolerin, that can rarely cause thrombocytopenia, was given from an unknown date in case 3, 19 and 23, and for 22 months in case 5. Clopidogrel, that impairs platelet function, was given from an unknown date to a patient who recovered from thrombocytopenia with no dose changes (case 23). Serotonin reuptake-inhibitors...
(SSRIs) have been linked to platelet dysfunction as a consequence of serotonin-uptake blockade into platelets: however, in case 6, no dates are given for citalopram, and in case 23 duloxetine was given from an unknown date. In case 25, the patient had long-term treatment with dalteparin because of a history of pulmonary embolism and presented with pulmonary embolism and thrombocytopenia 68 days after starting treatment with abiraterone.

Gender differences in platelet function are well known, although the role of endogenous and synthetic hormones has not been fully elucidated. Androgens affect red blood cell production and anaemia is a known effect of testosterone suppression. It has been hypothesized that sex hormones may have a role in the production of platelets from megakaryocytes. For instance, it has been shown that in vitro human platelet aggregation induced by arachidonic acid is enhanced by androgens, and androgen therapy has improved platelet counts in patients with myelodysplasia and thrombocytopenia. The drop in endogenous androgens through CYP17 inhibition by abiraterone may be a factor in the development of thrombocytopenia in patients with other predisposing factors.

**Conclusion**

In most of the ICSRs entered into VigiBase, the temporal relationship between abiraterone and thrombocytopenia suggests a possible causal relationship. Platelets have a circulating lifespan of around 10 days, and about one third of the platelets are sequestered in the spleen at any time. Approximately 100 x 10⁹ platelets must be released from mature megakaryocytes into the circulation each day in order to maintain a normal platelet count. In the ICSRs, abiraterone treatment durations range from 18 days to four months. The temporal relationship between the start of abiraterone therapy and reported thrombocytopenia would suggest a process affecting platelet production, more prolonged than the mechanism of immune DIT. In the literature, an observational study reports two cases of thrombocytopenia (5%) in 39 patients treated with abiraterone and this combined with the analysis of reports in VigiBase, would suggest that abiraterone might be associated with thrombocytopenia, and requires further investigation.

**References**

2. European Medicines Agency. Zytiga, abiraterone acetate INN.


Table 1. Abiraterone and thrombocytopenia - Characteristics of 25 cases retrieved in VigiBase™

<table>
<thead>
<tr>
<th>Case</th>
<th>Age</th>
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<th>Duration of treatment</th>
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<th>Other suspected (S) or concomitant (C) drugs</th>
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<tr>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>39.000</td>
<td>Prednisone, leuprolin, simvastatin, metoprolol, denosumab (all C)</td>
<td>-/-</td>
<td>Unknown</td>
</tr>
<tr>
<td>3</td>
<td>69</td>
<td>3 m</td>
<td>-</td>
<td>19.000</td>
<td>Leuprolin, diclofenac, colecalciferol, calcium, zoledronic acid (all C) Prednisolone (S)</td>
<td>Drug withdrawn/-</td>
<td>Recovered</td>
</tr>
<tr>
<td>4</td>
<td>83</td>
<td>1 m</td>
<td>5.000</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Not recovered</td>
</tr>
<tr>
<td>5</td>
<td>68</td>
<td>46 d</td>
<td>46 d</td>
<td>19.000</td>
<td>Methadone, citalopram, hydrochlorothiazide, furosemide (all C) Prednisone (C)</td>
<td>-</td>
<td>Not recovered</td>
</tr>
<tr>
<td>6*</td>
<td>58</td>
<td>-15 d</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>No dose change/-</td>
<td>Not recovered</td>
</tr>
<tr>
<td>7</td>
<td>-</td>
<td>76 days</td>
<td>-</td>
<td>-</td>
<td>Prednisone (C)</td>
<td>-</td>
<td>Death</td>
</tr>
<tr>
<td>8</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Prednisone (C)</td>
<td>No dose change/-</td>
<td>Unknown</td>
</tr>
<tr>
<td>9</td>
<td>-</td>
<td>4 weeks</td>
<td>100.000</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Unknown</td>
</tr>
<tr>
<td>10</td>
<td>73</td>
<td>4 m</td>
<td>19.000</td>
<td>-</td>
<td>Prednisone, fentanyl (all C)</td>
<td>Drug withdrawn/ No recurrence</td>
<td>Recovered with sequelae</td>
</tr>
<tr>
<td>11</td>
<td>85</td>
<td>32 days</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Drug withdrawn/-</td>
<td>Not recovered</td>
</tr>
<tr>
<td>12</td>
<td>-</td>
<td>34 or 42 days</td>
<td>-</td>
<td>-</td>
<td>Docetaxel (C) Prednisone (S)</td>
<td>Drug withdrawn/-</td>
<td>-</td>
</tr>
<tr>
<td>13**</td>
<td>80</td>
<td>1 m</td>
<td>1m</td>
<td>-</td>
<td>Prednisone (C)</td>
<td>Drug withdrawn/-</td>
<td>Not recovered</td>
</tr>
<tr>
<td>14</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Prednisolone (C)</td>
<td>-/-</td>
<td>Recovered</td>
</tr>
<tr>
<td>15</td>
<td>67</td>
<td>56 d</td>
<td>-</td>
<td>-</td>
<td>Teicoplanin (S)</td>
<td>-/-</td>
<td>Not recovered</td>
</tr>
<tr>
<td>16</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>17</td>
<td>-</td>
<td>18 cycles previously</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-/-</td>
<td>Unknown</td>
</tr>
<tr>
<td>18</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-/-Reaction recurring</td>
<td>-</td>
</tr>
<tr>
<td>19</td>
<td>66</td>
<td>20 d</td>
<td>6-8 weeks</td>
<td>68.000 40.000 53.000</td>
<td>Prednisolone, leuprolin Denosumab, erythropoietin human fentanyl (all C)</td>
<td>No dose change</td>
<td>Recovering</td>
</tr>
<tr>
<td>20***</td>
<td>-</td>
<td>-</td>
<td>Up to 3 days</td>
<td>-</td>
<td>Prednisone (S)</td>
<td>-/-</td>
<td>Unknown/ Death</td>
</tr>
<tr>
<td>21</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-/-</td>
<td>Unknown</td>
</tr>
<tr>
<td>22****</td>
<td>75</td>
<td>42 d</td>
<td>-</td>
<td>-</td>
<td>Prednisolone, amitryptiline, Lansoprazole (all C)</td>
<td>No dose change/-</td>
<td>Recovering</td>
</tr>
<tr>
<td>23</td>
<td>18</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Prednisone, leuprolin, megestrol duloxetine, denosumab, morphine paracetamol/hydrocodone macrogel, ergocalciferol, clopidogrel, metoprolol (all C)</td>
<td>No dose change/-</td>
<td>Recovered</td>
</tr>
<tr>
<td>24</td>
<td>63</td>
<td>28 d</td>
<td>26.000 24.000</td>
<td>-</td>
<td>Prednisone, degarelix, ibandronic acid, pantoprazole (all C)</td>
<td>Drug withdrawn/ No recurrence</td>
<td>Death</td>
</tr>
<tr>
<td>25</td>
<td>70</td>
<td>68 d</td>
<td>53.000 26.000</td>
<td>-</td>
<td>Degarelix, zoledronic acid, dalteparin, pantoprazol (all C) Prednisolone (S)</td>
<td>Drug withdrawn/-</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

*Abiraterone dose reported 500 mg
**Possible duplicate of case 4
***Abiraterone started on March 19th 2012 – Death occurred on March 22nd
****Abiraterone reported dose 1000 mg 2per day
Response from Janssen
This is in response to the WHO Signal report of 25 Individual Case Safety Reports (ICSRs) that were retrieved from VigiBase™ (September 2011 - April 16th 2013) of thrombocytopenia in patients receiving abiraterone acetate. Data are provided below from a thorough Company investigation in March 2013 to assess the potential causal relationship between thrombocytopenia and abiraterone acetate. The Company concludes that thrombocytopenia is not associated with the use of abiraterone acetate, but continues to monitor and review the signal in Periodic Benefit Risk Evaluation Reports.

Epidemiology
Thrombocytopenia is an expected condition in patients with metastatic prostate cancer, particularly in patients with bone marrow metastasis. The cause of the thrombocytopenia can be multifactorial, including the underlying disease, concurrent medical conditions, or concomitant therapies. A low platelet count may be caused by replacement of bone marrow with metastatic prostatic carcinoma or the result of chronic disseminated intravascular coagulation (DIC) syndrome (Ruffion 2000), which is common in patients with prostate cancer and is associated with progressive disease. Its incidence is approximately 13% to 30%; however, only 0.4% to 1.65% of patients present with clinical signs and symptoms. Thus this disease-related cause for thrombocytopenia typically goes undetected (Smith 1999). Bone marrow metastasis can also result in anemia and thrombocytopenia (Neider 2010).

Preclinical and Clinical Data from Company-sponsored Studies
Data from pivotal toxicology studies in rats (26 weeks) and monkeys (39 weeks), administered abiraterone at doses that were 5-fold and 2-fold higher, respectively, than clinical exposure, showed only a minimal decrease in platelet count in rats and no decrease in platelet count in monkeys.

In 2 randomized, placebo-controlled Phase 3 studies (COU-AA-301 and COU-AA-302) with prostate cancer treated with abiraterone acetate, the incidence of thrombocytopenia and platelet count decrease was similar among subjects who received abiraterone acetate (3.0% and 1.2%, respectively) and those who did not (2.5% and 0.9%, respectively) (table 1).

Table 1: Treatment-emergent Adverse Events of Thrombocytopenia and Platelet Count Decreased (Integrated Safety Population)

<table>
<thead>
<tr>
<th>MedDRA Preferred Term</th>
<th>COU-AA-301</th>
<th>COU-AA-302</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total Subjects (%)</td>
<td>Total Subjects (%)</td>
<td>Total Subjects (%)</td>
</tr>
<tr>
<td></td>
<td>AA (N=791)</td>
<td>Placebo (N=394)</td>
<td>AA (N=542)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo (N=540)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>30 (3.8%)</td>
<td>15 (3.8%)</td>
<td>10 (1.8%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8 (1.5%)</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>14 (1.8%)</td>
<td>7 (1.8%)</td>
<td>2 (0.4%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>16 (1.2%)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>8 (0.9%)</td>
</tr>
</tbody>
</table>

Key: AA=Abiraterone acetate; MedDRA=Medical Dictionary for Regulatory Activities; N=number

Table 2: Treatment-Emergent Adverse Events of Thrombocytopenia, Event Rate per 100 Patient-Years of Exposure (Integrated Safety Population)

<table>
<thead>
<tr>
<th>MedDRA Preferred Term</th>
<th>COU-AA-301</th>
<th>COU-AA-302</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total Events per 100</td>
<td>Total Events per 100</td>
<td>Total Events per 100</td>
</tr>
<tr>
<td></td>
<td>Subject-Years</td>
<td>Subject-Years</td>
<td>Subject-Years (%)</td>
</tr>
<tr>
<td></td>
<td>AA (N=603.8)</td>
<td>Placebo (N=199.6)</td>
<td>AA (N=646.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Placebo (N=466.3)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>45 (7.5)</td>
<td>21 (10.5)</td>
<td>17 (2.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>14 (3.0)</td>
</tr>
<tr>
<td>Platelet count decreased</td>
<td>25 (4.1)</td>
<td>20 (10.0)</td>
<td>4 (0.6)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1 (0.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>29 (2.3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>21 (3.2)</td>
</tr>
</tbody>
</table>

Key: AA=Abiraterone acetate; MedDRA=Medical Dictionary for Regulatory Activities; N=Number of subjects
The median exposure (i.e., time on treatment) to abiraterone acetate was approximately twice as long as that of placebo. An analysis adjusted for the duration of exposure (with rates reported as the number of events per 100 subject-years of exposure) showed lower rates of thrombocytopenia and platelet count decreases in the abiraterone acetate group (5.0 and 2.3, respectively) than in the placebo group (5.3 and 3.2, respectively) (Table 2). The data support the conclusion that thrombocytopenia is not associated with the use of abiraterone acetate.

Analysis of Individual Case Safety Reports

Recently, the Company searched its own safety database for all medically confirmed and valid cases of thrombocytopenia, regardless of causality, that were reported in patients receiving abiraterone acetate from launch (28 April 2011) through March 15th 2013. Seventy-one spontaneous, clinical study and registry cases (median age of 69 years) from 19 countries were retrieved. The latency from the initiation of abiraterone acetate therapy to the first onset of thrombocytopenia was <1 month in 11 cases, 1 to 3 months in 19 cases, 3 to 6 months in 8 cases, >6 months in 7 cases, and not reported in 26 cases. All cases were reviewed for a potential drug effect relationship in accordance with the CIOMS Threshold Criteria (CIOMS Working Groups 1999). No sentinel cases were found. The only positive rechallenge case did not report critical information to allow medical assessment. Of 11 cases reporting dechallenge information, 6 reported negative dechallenge (e.g., thrombocytopenia did not resolve after abiraterone acetate therapy was withdrawn) and the rest recovered with platelet transfusion or reported insufficient information.

In summary, risk factors (such as concomitant medication, concurrent condition, or medical history) or insufficient information confounded case assessment of a clear relationship between thrombocytopenia and abiraterone acetate therapy in all 71 cases. The most frequently reported relevant concurrent medical conditions were disease progression and bone marrow metastases/cancer/infiltration thrombocytopenia.

Conclusion

Abiraterone acetate is indicated for the treatment of patients with castrate-resistant metastatic prostate cancer. Thrombocytopenia due to metastatic bone marrow involvement and DIC is not uncommon in this disease stage. In addition, many other concomitant medical conditions and concurrent medications used in this patient population may also cause thrombocytopenia. These factors limit the ability to identify thrombocytopenia as an adverse effect of abiraterone acetate. Based on the review of the Company safety database, thrombocytopenia is not considered associated with the use of abiraterone acetate. Key factors supporting this conclusion include the available data on rechallenge, dechallenge, and plausible latency cases, all of which reported concomitant medication or concurrent medical conditions, including but not limited to disease progression and bone metastases that confounded the case assessment. In addition, analysis of data from 2 double-blind controlled studies demonstrated a similar incidence of thrombocytopenia between subjects treated with abiraterone acetate and placebo that was lower with abiraterone acetate treatment once adjusted for exposure duration. Based on all of the available safety data, thrombocytopenia is not associated with the use of abiraterone acetate.

References

Baclofen and Renal failure

Prof. Michael Langman, United Kingdom

Summary
After the combination baclofen-renal failure was identified as a possible signal, 67 Individual Case Safety Reports (ICSRs) of renal failure [31 acute, 32 chronic or acute (not stated which), and four with chronic renal failure] in patients taking baclofen were considered. Baclofen is excreted by the kidneys and orally administered drug accumulation in patients with pre-existing borderline renal function/compromised vascular systems could affect vascular control and worsen renal function.

With baclofen given intrathecally, the consequences of possible central spread through inadvertent subdural drug delivery, or wash back centrally in subarachnoid injection should be considered, with a direct drug effect on central mechanisms modulating vascular control and leading to renal failure.

Introduction
The drug-ADR combination of baclofen and renal failure was highlighted during testing of a new quantitative method for detecting potential signals at the UMC in 2012. As of 15 November 2012, 67 Individual Case Safety Reports (ICSRs) had been entered into the WHO Global ICSR Database, VigiBase™, raising a possible relationship between baclofen use and the occurrence of renal failure. The drug is mostly used in treating chronic spasticity, as typically associated with spinal cord damage and multiple sclerosis. Labelled adverse effects include hypotension and cardiovascular depression. Kidney failure is labelled in the US FDA Label for the injection but not for the oral formulation and renal failure is not labelled in the UK Summary of Product Characteristics (SPC). The 31 ICSRs of acute renal failure (21 male, nine female, one sex not stated) and four of chronic failure (two male and two female) were considered case-by-case. Detail is, as usual, limited. Four ICSRs of acute renal failure are likely duplicates. Patients were generally in the sixth decade of life or older and often, where reported, receiving a wide variety of other medications, including, but not only, cardiovascular, non-steroidal anti-inflammatory and antibiotic medications. Several reports list significant comorbidities such as septicaemia, rhabdomyolysis and multi-organ failure that have to be taken into consideration as possible confounding factors.

Six of the acute cases were receiving intrathecal baclofen, 19 oral, five unclear and one “other”. The cases with raised creatinine are assumed to not add information. The 32 cases of renal failure of unstated duration did not appear to present any features differing materially from the other 35, but confidence in the reliability of separation between acute and chronic renal disease is likely to be limited.

The ICSRs were entered into VigiBase from 1993 to present and from eight countries, Germany, United States, France, Australia, United Kingdom, Ireland, Austria and Canada. The IC values for renal failure acute were: IC -0.89, IC_{0.05} -1.44, for renal failure: IC -0.43, IC_{0.05} -0.98 and for renal failure chronic: IC -0.64, IC_{0.05} -2.38.

Literature and Labelling
The British National Formulary lists many cautions when using baclofen in pre-existing disease such as psychiatric disease, respiratory disorders and bladder outlet obstruction. Recorded adverse effects include hypotension, respiratory or cardiovascular depression, and urinary disturbances. The US FDA Label lists renal failure, oliguria, renal calculus as well as hypotension and bradycardia as adverse drug events.

Discussion
Baclofen is a GABA[B] receptor agonist. Microinjection in rats into the paraventricular nucleus has been found to induce a dose-dependent fall of arterial pressure, accompanied by reduced heart rate and reduced renal sympathetic nerve activity in a rat model which is claimed to simulate chronic heart failure. However, a second paper presents data, again in rats, showing that intravenous baclofen, whilst suppressing renal sympathetic activity, appear to prevent ischaemia-reperfusion injury. No relevant data from studies in humans could be found in a search of PubMed.

Baclofen is normally excreted unchanged in the urine and therefore renal failure which might be present in some patients with chronic neurological disease e.g. cord transection with bladder outlet obstruction, might be expected to lead to raised blood drug levels. Central spread in intrathecal treatment, notably through posture and use of dense preparations, could cause significant amounts of drug to reach the brain. Systemic absorption at other sites could also occur.

Experimental studies in pigs have shown that position and specific gravity (baricity) can affect drug distribution. Central effects might also be associated with inadvertent subdural drug administration as opposed to subarachnoid.
Adverse cardiovascular effects centrally caused might result in renal failure particularly in individuals with compromised homoeostatic processes.

For ICSRs where baclofen is given orally, the case reports do not present compelling data to suggest that renal failure can be precipitated by baclofen. This is not a new drug and its adverse effects might be expected to be well-understood. Animal studies can be taken to suggest that central cardiovascular actions could be compromised by the drug and could predispose to kidney failure, however other studies suggest the converse. On balance it is plausible that oral baclofen could accumulate in patients with borderline renal function and further depress renal function.

For patients given intrathecal treatment, it could be speculated that extended use of intrathecally administered drugs in patients who are older and/or have multiple coincident illnesses could result in adverse effects not previously recognised. Note that the route of baclofen administration is not explicitly stated in a quarter of the acute renal failure ICSRs but in about a fifth intrathecal treatment was given. Intrathecal use could result in inadvertently high concentrations in central areas, activating mechanisms described in the study by Wang et al. Inadvertent injection into the subdural space could have the same effect.

Conclusion
The reported cases may suggest a hitherto unrecognised significant adverse effect. Although the data collected are not compelling, a drug effect through intrathecal use seems plausible if inadvertent central spread took place. Oral drug use in patients with compromised renal excretory mechanisms could also result in reduced drug excretion leading to high circulating drug levels and possible adverse effects on cardiovascular control and worsened kidney function.

Golimumab and Meningitis
Dr. Ariel E. Arias, Canada

Summary
Golimumab is a monoclonal antibody that prevents the binding of tumor necrosis factors (TNF) to its receptors and has been licensed for the treatment of chronic inflammatory diseases such as rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. The drug was approved as late as in 2009. We discuss a series of eight Individual Case Safety Reports (ICSRs) on the association of golimumab and meningitis that have been received from five different countries to the WHO Global ICSR Database, VigiBaseTM. The association has been statistically disproportionately reported into the database. Although rare, the occurrence of meningitis has already been reported in association with the other anti-TNF products in the class. Current information supports a signal of meningitis in association with golimumab, and we recommend its inclusion in the product label.

Introduction
Golimumab is described as a human IgG1 monoclonal antibody that forms high affinity, stable complexes with both the soluble and the transmembrane bioactive forms of human tumor necrosis factors (TNF), which prevents the binding of TNF to its receptors. There is no evidence of the golimumab antibody binding to other TNF

References


superfamily ligands; in particular, it did not bind or neutralize human lymphotoxin.\textsuperscript{1,3} Golimumab modulated the in vitro biological effects mediated by TNF in several bioassays, including the expression of adhesion proteins responsible for leukocyte infiltration, E-selectin, Intercellular Adhesion Molecule-1 (ICAM-1), Vascular Cell Adhesion Molecule-1 (VCAM-1), and the secretion of pro-inflammatory cytokines: IL-6 and 8, granulocyte colony-stimulating factor (G-CSF) and granulocyte macrophage colony-stimulating factor (GM-CSF). TNF-a is an important mediator of articular inflammation, and elevated TNF-a levels in the blood, synovium, and joints have been implicated in the pathophysiology of several chronic inflammatory diseases such as rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. Golimumab has been primarily licensed in many countries for the treatment of rheumatoid arthritis, as well as spondyloarthropathies such as psoriatic arthritis and ankylosing spondylitis.\textsuperscript{1,2,3} It has been licensed in some countries for the treatment of moderate to severe ulcerative colitis with an inadequate response or intolerance to prior treatment, or when requiring continuous steroid therapy.\textsuperscript{3}

Although clinical experience with golimumab is somewhat limited, after direct and indirect comparisons on efficacy and safety, some authors have concluded that infliximab, adalimumab, etanercept and golimumab offer similar benefit/risk ratios and could be regarded as equivalent treatment alternatives in psoriatic arthritis.\textsuperscript{4} However, because of the paucity of data available, similar types of adverse events as those seen with other TNF-a inhibitors, need to be considered as of special concern for patients treated with golimumab therapy.\textsuperscript{5} We discuss here a series of eight Individual Case Safety Reports (ICSRs) on the association of golimumab and meningitis that have been reported from five different countries to the WHO Global ICSR Database, VigiBase™.

Reports in VigiBase

Eight ICSRs of meningitis in association with golimumab have been reported to VigiBase from the United States, United Kingdom, Canada, Spain and Switzerland as of May 2013. The subjects, six females and two males, were between 36 and 64 years of age. The reaction was further described as viral meningitis in four cases and aseptic meningitis in one case, with no additional description in the three other cases. There were no fatalities but in four cases the outcome of the reaction was unknown or not reported.

Golimumab was the only suspected medicine in all the ICSRs and was used subcutaneously, mainly 50 mg once a month, to treat arthritis (three reports), ankylosing spondylitis, psoriatic arthritis, and immune system disorder (in one case each).

The indication for use was not reported in two cases, and there was almost no information on the length of the therapy or the reaction onset. There was only one rechallenge reported in the ICSRs, and the effect of this was unknown. Four of the case reports were reported by a physician or other health care professionals. The IC and the ICD values for the association were 1.53 and 0.36 respectively.

Literature and Labelling

We could not find any published reports of meningitis in association with golimumab use in the literature to date, although various types of opportunistic and viral infections including sepsis, and cases of new onset or exacerbation of central nervous system demyelinating disorders are well labelled adverse drug reactions for this product. There is no information on the risk of meningitis in any verified product informations.\textsuperscript{1,2,3} The FDA label includes a warning for infections due to opportunistic infections including legionella and listeria.\textsuperscript{3} Listeriosis in patients treated with TNF inhibitors can present as meningitis,\textsuperscript{6} however, none of the reports in VigiBase have other infections co-reported.

Discussion and Conclusion

This relatively small series of cases reporting a suspected association between golimumab and the occurrence of meningitis have been observed in several countries and in all ICSRs the anti-TNF antibody was reported as the only suspected drug. Golimumab was generally reported to be used for a licensed indication and at the recommended dosage. An alternative product or combination of products that might explain the occurrence of the suspected reaction was not readily identified from the ICSRs. The positive IC and IC\textsubscript{025} values showed that the meningitis-golimumab association has been statistically disproportionally reported into the database.

Although clinical experience with this product is limited, golimumab is considered to have a relatively similar safety profile and to offer a similar benefit/risk ratio compared to other anti-TNF products.\textsuperscript{4,5} Meningitis is not commonly associated with rheumatoid arthritis or spondyloarthropathies; however, it has been reported in association with various anti-TNF drugs used to treat such disorders including infliximab, adalimumab, and etanercept. ICSRs of meningitis from various types of infectious origin have been observed in association with both infliximab and etanercept therapy.\textsuperscript{7-12} Interestingly, cases of meningitis of non-infectious origin have also been reported.\textsuperscript{13} Since golimumab is similar in structure to infliximab, it has been suggested that a comparable pattern of opportunistic infections could be expected with it after further clinical use.\textsuperscript{14} Since half of the cases in the series of ICSRs with golimumab were reported as viral
meningitis, it would be interesting to know if golimumab could represent a particular risk for this type of adverse reaction.

As far as we know, the association has not been previously reported in the literature and the risk of meningitis is not mentioned in the product labelling for golimumab. Opportunistic infections are well recognised adverse reactions of the anti-TNF class of drugs. Meningitis is a particularly serious and life threatening complication of several types of infectious diseases and is specifically mentioned in the product labelling of the other anti-TNF products. Current information supports a signal of meningitis in association with golimumab, and we recommend its inclusion in the product label.

References


Response from Janssen Biologics B.V.

Simponi is one of several TNF-blocking agents that are available for the treatment of diseases such as rheumatoid arthritis and ulcerative colitis. Janssen works closely with health authorities to accurately inform patients and prescribers about the safety profile of Simponi. To date, meningitis has not been considered an adverse drug reaction for Simponi. However, TNF-blocking agents, including Simponi, have been associated with a variety of infections, including serious infections, from all types of organisms, including bacterial, viral, and fungal organisms, and the prescribing information for Simponi reflects this information.

Janssen will continue to monitor serious infections, including meningitis, and all potential adverse reactions, reported with Simponi.
Pazopanib and Pericardial Effusion

Dr. Ian Boyd, Australia

Summary
Pazopanib is an orally administered, potent multi-target tyrosine kinase inhibitor (TKI) of Vascular Endothelial Growth Factor Receptors. It is indicated for the first line treatment of advanced renal cell carcinoma (RCC) and the treatment of selective subtypes of advanced soft tissue sarcoma (STS). In the WHO Global Individual Case Safety Report (ICSR) Database, VigiBaseTM, there are currently (25 January 2013) 11 ICSRs of pericardial effusion in association with pazopanib. The ICSRs are from the United States, Germany, Greece, Ireland and Singapore. The association has an IC value of 2.65 with an IC025 value of 1.68. There are two probable duplicates, which leaves a total of nine ICSRs. Pazopanib was the only drug suspected in all but one. The outcome was stated in seven ICSRs. The patients were reported as recovered or recovering in four cases, not recovered in two cases and the outcome was fatal in one case. In all of these cases, the drug was reported to have been withdrawn. In two of the cases, the reaction recurred on rechallenge.

The association of pericardial effusion with pazopanib appears to be a signal. Pazopanib was the only drug suspected in eight of the nine cases and causality is plausible in six cases. While the time to onset is not particularly suggestive of a drug-induced effect, the observation of recovery after dechallenge in the three cases in which recovery was documented, is also supportive of the signal. In addition, the fact that the reaction recurred on rechallenge in two cases is strongly suggestive. A report in the literature indicated that pericardial effusion occurred in 3% of patients in a clinical trial and the observation that pericardial effusion is associated with other TKIs points to the fact that pericardial effusion may be a class effect of TKIs. Reports of pericardial effusion in VigiBase support this proposition.

Introduction
Pazopanib is an orally administered, potent multi-target tyrosine kinase inhibitor (TKI) of Vascular Endothelial Growth Factor Receptors (VEGFR)-1, -2, and -3, platelet-derived growth factor (PDGFR)-α and -β, and stem cell factor receptor (c-KIT). It is indicated for the first line treatment of advanced renal cell carcinoma (RCC) and the treatment of selective subtypes of advanced soft tissue sarcoma (STS). The most common adverse reactions identified in the RCC or STS trials included: nausea, headache, fatigue, anorexia, vomiting, dysgeusia, stomatitis, weight decreased, pain, elevated alanine aminotransferase and elevated aspartate aminotransferase. The most important serious adverse reactions identified in the RCC or STS trials were transient ischaemic attack, ischaemic stroke, myocardial ischaemia, myocardial and cerebral infarction, cardiac dysfunction, gastrointestinal perforation and fistula, QT prolongation and pulmonary, gastrointestinal and cerebral haemorrhage, all adverse reactions being reported in <1% of treated patients. Other important serious adverse reactions identified in STS trials included venous thromboembolic events, left ventricular dysfunction and pneumothorax. Fatal events that were considered possibly related to pazopanib included gastrointestinal haemorrhage, pulmonary haemorrhage/haemoptysis, abnormal hepatic function, intestinal perforation and ischemic stroke.1

Pericardial effusion is the accumulation of fluid in excess of normal in the pericardial cavity. It can be confirmed by the demonstration of fluid in the pericardial cavity by echocardiography. Pericardial effusion may present in either acute or chronic form. It may be the first sign of acute pericarditis. It may also occur in heart failure and cardiomyopathy of various types, and in myxoedema.2 The cause of abnormal fluid production depends on the underlying aetiology, but it is usually secondary to injury or insult to the pericardium (that is, pericarditis). Transudative fluids result from obstruction of fluid drainage, which occurs through lymphatic channels. Exudative fluids occur secondary to inflammatory, infectious, malignant, or autoimmune processes within the pericardium.3 The fluid may be serious, serofibrinous, serosanguineous or chylous.2

Signs and symptoms of pericardial effusion include chest pain, pressure or discomfort, light-headedness or syncope, palpitations, cough, dyspnoea, hoarseness, anxiety and confusion, and hiccoughs.2 Examination findings in patients with pericardial effusion include the classic Beck triad of pericardial tamponade: hypotension, muffled heart sounds and jugular venous distention. Other examination findings include pulsus paradoxus, pericardial friction rub, tachycardia, hepatoujugular reflex, tachypnoea, decreased breath sounds, Ewart sign (dullness to percussion beneath the angle of left scapula), hepatosplenomegaly, weakened peripheral pulses, edema, and cyanosis.3

As an adverse drug reaction it occurs relatively commonly in drug-induced systemic lupus erythematosus; it may also occur as an immunological reaction to a drug.2
Reports in VigiBase

As of 25 January 2013 there are 11 Individual Case Safety Reports (ICSRs) of pericardial effusion in association with pazopanib in the WHO Global ICSR Database, VigiBase™ (Table 1). The association has an IC value of 2.65 with an IC025 value of 1.68. The ICSRs were submitted from Germany, the United States (four cases each), Greece, Ireland and Singapore (one case each). After the removal of two suspected duplicates from the US, the patients ranged in age from 21 to 80 years with a median of 44 years. The gender distribution was five females and four males.

Pazopanib was the only drug suspected in all but one of the nine cases. The other suspected drug was moxifloxacin. Concomitant drugs were reported in four cases but there was little pattern in these reports apart from the use of antihypertensives (in three cases), proton pump inhibitors (two cases) and NSAIDs (two cases). Pazopanib was reported to have been administered orally, as expected, in all eight cases which provided this information. The indication for use was clearly stated in seven reports and included treatment of sarcoma (three cases), metastatic renal cell carcinoma (three cases) and malignant lung neoplasm (one case).

Time to onset was reported in six of the reports. It ranged from eight weeks to six months with a median of four months in five cases but in the other case (Case 4) pericardial effusion was present before pazopanib was commenced so pazopanib is unlikely to be a cause in this case. Two of the other reports have a doubtful association. In Case 1, the reporter considered that pericardial effusion may have been caused by pleural lesions as a consequence of disease progression and the patient died from disease progression soon after. In Case 10, pericardial fluid was present before treatment commenced but there was increased fluid in association with pazopanib. Removal of Case 1, 4 and 10 from the assessment results in six cases with a plausible association.

The outcome was stated in seven ICSRs. The patients were reported as recovered or recovering in four cases, not recovered in two cases and the outcome was fatal in the remaining case although the outcome of the pericardial effusion was unknown. In all of these cases, the drug was reported to have been withdrawn. In two of these cases (Case 5 and 7), the reaction recurred on rechallenge. The drug was also withdrawn in the two cases where the outcome remains unknown.

Other reactions were described in six reports. In general, these reactions appeared indicative of a patient population with severe disease and included abnormal hepatic function (three cases), pleural effusion, cardiac tamponade and fatigue (each in two cases).

Literature and Labelling

The product literature does not refer to pericardial effusion. There is a warning on the possibility of cardiac dysfunction such as congestive heart failure and decreased left ventricular function. Such cardiac dysfunction could result in the development of pericardial effusion but as none of the reports document these other cardiac reactions, this does not appear to be a cause. In the literature, pericardial effusion was reported to occur in 3% of Asian patients in a Phase II trial of pazopanib with recurrent/metastatic undifferentiated nasopharyngeal carcinoma. Moreover, it has been noted that other tyrosine kinase inhibitors such as nilotinib and dasatinib are known to be associated with pericardial effusion. Moreover, pericardial effusion is reported as an adverse effect in the product information of other TKIs including imatinib, nilotinib and dasatinib.

Discussion and Conclusion

Case reports in VigiBase suggest that there is a signal for the association of pazopanib and pericardial effusion. Pazopanib was the only drug suspected in all but one of the nine ICSRs. In the report in which there was another suspected drug (Case 4) pericardial effusion was present before pazopanib was commenced so pazopanib is unlikely to be a cause in this case. Two of the other reports have a doubtful association. In Case 1, the reporter considered that pericardial effusion may have been caused by pleural lesions as a consequence of disease progression and the patient died from disease progression soon after. In Case 10, pericardial fluid was present before treatment commenced but there was increased fluid in association with pazopanib.

Time to onset is not particularly suggestive of a signal. In the six reports in which causality is plausible, the time to onset ranged from eight weeks to six months which appears rather long for a drug-induced effect. However, pericardial effusion may be present without symptoms so it is possible that the time to onset was shorter than reported.

Dechallenge is also possibly suggestive of a signal. In the six reports in which causality is plausible, the outcome was stated in four reports. The patients were reported as recovered in three cases of these four and not recovered in the other case. In all of the six cases, the drug was reported to have been withdrawn. Importantly, in two cases the reaction recurred on rechallenge.

In the literature, pericardial effusion was reported to occur in 3% of Asian patients in a Phase II trial of pazopanib with recurrent/metastatic undifferentiated nasopharyngeal carcinoma. In addition, it has been noted that other TKIs such as nilotinib and dasatinib are known to be associated with pericardial effusion. Moreover, pericardial effusion is reported as an adverse effect in the
product information of other TKIs including imatinib, nilotinib and dasatinib.

In VigiBase, there have been 5651 occurrences of pericardial effusion. Only 13 drugs have a hundred or more reports of the association and two of these are the TKIs dasatinib (120) and imatinib (107). In addition, there are many reports with erlotinib (66), sunitinib (49), nilotinib (21), sorafenib (17) and gefitinib (14) and it seems likely that pericardial effusion is a class effect of TKIs.

References

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/ Gender</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>75/F</td>
<td>None</td>
<td>Pericardial effusion</td>
<td>Recovering</td>
</tr>
<tr>
<td>2</td>
<td>50/M</td>
<td>None</td>
<td>Pericardial effusion</td>
<td>Recovered</td>
</tr>
<tr>
<td>3</td>
<td>77/M</td>
<td>None</td>
<td>Pericardial effusion, hepatic enzymes increased, medicine ineffective, cardiac tamponade</td>
<td>Not recovered</td>
</tr>
<tr>
<td>4</td>
<td>21/F</td>
<td>Moxifloxacin(S), moxifloxacin(C)</td>
<td>Pericardial effusion, multiple organ failure, cardiac tamponade, pleural effusion, cardiomegaly, hepatorenal syndrome, pneumonia, renal failure chronic, hepatic failure, fatigue, hepatic function abnormal</td>
<td>Died but outcome of pericardial effusion unknown</td>
</tr>
<tr>
<td>5</td>
<td>39/F</td>
<td>Lansoprazole, amiodipine, dexamethasone (all C)</td>
<td>Pericardial effusion, hepatic function abnormal, oedema generalised, effusion (MedDRA term), pleural effusion, serositis (MedDRA term)</td>
<td>Recovered from initial episode but recurred on rechallenge with unknown recovery</td>
</tr>
<tr>
<td>6</td>
<td>80/F</td>
<td>Ramipril, Carvedilol, pantoprazole, torasemide (all C)</td>
<td>Pericardial effusion, fatigue, hypotension</td>
<td>Unknown</td>
</tr>
<tr>
<td>7</td>
<td>42/M</td>
<td>Metoprolol, magnesium, lisonopril, docusate, vitamins nos, prochlorperazine, hydromorphone, mirtazapine, ondansetron, amiodipine, ibuprofen (all C)</td>
<td>Pericardial effusion, disease recurrence (MedDRA term)</td>
<td>Unknown</td>
</tr>
<tr>
<td>8*</td>
<td>42/M</td>
<td>None</td>
<td>Pericardial effusion</td>
<td>Unknown</td>
</tr>
<tr>
<td>9*</td>
<td>42/M</td>
<td>Vitamins nos, prochlorperazine, mirtazapine, ondansetron, amiodipine, magnesium oxide (all C)</td>
<td>Pericardial effusion</td>
<td>Unknown</td>
</tr>
<tr>
<td>10</td>
<td>30/F</td>
<td>None</td>
<td>Pericardial effusion, diarrhoea</td>
<td>Not recovered</td>
</tr>
<tr>
<td>11</td>
<td>44/M</td>
<td>Pregabalin, ibuprofen, glimepiride (all C)</td>
<td>Pericardial effusion, myalgia</td>
<td>Recovered</td>
</tr>
</tbody>
</table>

*Case 8 and 9 are probably duplicates of Case 7
CAVEAT DOCUMENT

Accompanying statement to data released from the Uppsala Monitoring Centre, WHO Collaborating Centre for International Drug Monitoring

Uppsala Monitoring Centre (UMC) in its role as the 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. Limited details about each suspected adverse reaction are received by the UMC. The information is stored in the WHO Global Individual Case Safety Report database, VigiBase. 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.

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.

Some National Centres strongly recommend that anyone who intends to use their information should contact them for interpretation.

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.