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:

Safety and Vigilance,
EMP-HIS,
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/medicine

Further information on adverse reactions may be obtained from the WHO Collaborating Centre for International Drug Monitoring
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E-mail: info@who-umc.org
Internet: http://www.who-umc.org

No. 6, 2014

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

The current issue also includes the recommendations from the 16th International Conference of Drug Regulatory Authorities (ICDRA) held in Brazil, 26 – 29 August 2014.

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Agomelatine

Risk of liver toxicity

Europe. The European Medicines Agency (EMA) recommended that further measures for agomelatine (Valdoxan® and Thymanax®) should be put in place to minimise the risk of liver toxicity. Agomelatine is used to treat major depression in adults.

A patient booklet will be distributed to all patients taking agomelatine so that they are aware of the risk to the liver and the signs of liver problems to look out for. This booklet also includes information on the importance of monitoring liver function.

Warnings in the product information will also be strengthened to emphasise that liver function tests should be performed in patients both before starting the medicine and regularly during treatment.

Health-care professionals should follow these recommendations:

- Baseline liver function tests should be performed in every patient and treatment should not be started in patients with transaminases exceeding 3 times the upper limit of normal.
- Liver function must be monitored regularly during treatment, at 3, 6, 12 and 24 weeks and regularly thereafter when clinically indicated.
- Treatment must be discontinued immediately if the increase in serum transaminases exceeds 3 times the upper limit of normal, or if patients present with symptoms or signs of potential liver injury.
- Patients should be informed of the symptoms of potential liver injury and the importance of liver function monitoring, and should be advised to stop taking agomelatine immediately and to seek urgent medical advice if these symptoms appear.

Reference:
Press release, EMA, 26 September 2014 (www.ema.europa.eu)

Azithromycin

Drug Reaction/Rash with Eosinophilia and Systemic Symptoms (DRESS)

Canada. Health Canada published that a safety review was initiated to evaluate the possible link between a medical condition called DRESS which stands for Drug Reaction/Rash with Eosinophilia and Systemic Symptoms, and the antibiotic azithromycin (Zithromax®, Zmax® and its generics). This review was prompted from an adverse reaction report submitted to Health Canada.

Azithromycin belongs to a group of antibiotics called macrolides and is available as an oral liquid, a tablet and an injectable product.

DRESS describes a group of rare but serious and potentially life-threatening adverse reactions to medications. These reactions usually occur two weeks to two months after starting a medication. Patients may experience symptoms such as a fever, a severe skin rash with swollen face or peeling of the skin over large areas of the body. Abnormal changes in blood cells or organ function such as the liver and kidney may also occur. The reasons why DRESS can occur with some medications are unknown.

The current available evidence suggests the possibility that DRESS may occur with azithromycin use. Furthermore, DRESS is a known risk for a similar antibiotic, clarithromycin. Other serious, rare, allergic skin reactions such as Toxic Epidermal Necrolysis (TEN) and Stevens-Johnson Syndrome (SJS) are described in the prescribing information for azithromycin. Common features between all three conditions may make it more difficult for early diagnosis.

The prescribing information for azithromycin has been updated to include the possible risk of DRESS.

It is important for health-care professionals and patients to be aware of the possibility of these rare serious reactions, and for steps to be taken for early detection of DRESS due to the fact that the treatment of TEN and SJS is different from DRESS.

Reference:
Advisories, Warnings and Recalls, Health Canada, 21 October 2014 (www.hc-sc.gc.ca)

Basiliximab

Indicated for renal transplantation only

UK. The Medicines and Healthcare Products Regulatory Agency (MHRA) informed that basiliximab (Simulect®) is indicated for preventing acute organ rejection only for allogeneic renal transplantation in patients receiving organ transplantation for the first time.

A European regulatory review investigated the safety and efficacy of basiliximab for off-label use in heart transplantation. This review was triggered by three unexplained deaths in Sweden in patients who received basiliximab for heart transplantation. All three patients had signs and
symptoms of thromboembolic events and potential cardiac disorders.

The review found no adequately powered randomised studies of basiliximab in heart transplantation. The clinical trials that have been done in heart transplantation did not prove basiliximab to be effective. Furthermore, serious cardiac side effects such as cardiac arrest, atrial flutter, and palpitations were observed more frequently with basiliximab than with other induction agents. Therefore a new warning has been included in the basiliximab product information regarding the lack of proven safety and efficacy in heart transplantation.

Reference:
Drug Safety Update, October 2014, Volume 8, issue 3, S1 MHRA, (www.mhra.gov.uk)

Clopidogrel

Association of with acquired haemophilia

Egypt. Egyptian Pharmaceutical Vigilance Center (EPVC) has warned about the association of clopidogrel with acquired haemophilia.

Clopidogrel is an oral, thienopyridine class antiplatelet agent; it is indicated for the prevention of atherothrombotic events in myocardial infarction, ischaemic stroke, established peripheral arterial disease, acute coronary syndrome including non-ST segment elevation myocardial infarction and unstable angina, and ST segment elevation acute myocardial infarction with aspirin in medically treated patients eligible for thrombolytic therapy. Clopidogrel is also indicated in combination with aspirin for the prevention of atherothrombotic and thromboembolic events in atrial fibrillation in patients unsuitable for vitamin K antagonist treatment.

EPVC has recommended:
- Acquired haemophilia must be promptly recognised to minimise the time the patient is at risk of bleeding and avoid major bleeding.
- In case of confirmed isolated activated Partial Thromboplastin Time (aPTT) prolongation with or without bleeding, acquired haemophilia should be considered.
- Patients with a confirmed diagnosis of acquired haemophilia should be managed and treated by specialists, clopidogrel should be discontinued and invasive procedures should be avoided.

(See WHO Pharmaceuticals Newsletter No.1, 2014 for information on Risk of acquired haemophilia in the UK)

Colistin, colistimethate sodium (known as polymyxins)

Recommendations issued for safe use in patients with serious infections resistant to standard antibiotics

Europe. The EMA has reviewed the safety and effectiveness of products containing the antibiotics colistin or colistimethate sodium (known as polymyxins) and recommended changes to their product information to ensure safe use in the treatment of serious infections that are resistant to standard antibiotics.

Polymyxin-based products have been available since the 1960s, but their use quickly decreased due to the availability of antibiotics with fewer potential side effects. Due in part to this limited use, colistimethate sodium has retained activity against a number of bacteria which have become resistant to commonly used antibiotics. This has led to a resurgence in recent years in the use of polymyxins in patients with few other options. However, current experience has raised concerns that the existing product information, in particular relating to dosing and the way the medicine is handled in the body (pharmacokinetics), might need updating. The European Commission therefore requested the EMA to review the available data and make recommendations on whether the marketing authorisations for these medicines should be changed and the product information amended appropriately.

The Agency reviewed the available clinical, pharmacological and pharmacokinetic data and considered that in the interim the product information should be updated throughout the EU to reflect what was currently known.
- Doses should always be expressed in IU of colistimethate sodium. To address the differences in the way in which the strength of colistimethate sodium and colistin are expressed in the EU and in other regions such as the USA and Australia, which has led to errors in reporting in the medical literature and could potentially lead to serious medication errors, the following table has been recommended for inclusion in product information:
Intravenous colistimethate sodium is indicated in adults and children including neonates for the treatment of serious infections due to aerobic Gram-negative pathogens in patients with limited treatment options. Consideration should be given to co-administration with another antibacterial agent whenever this is possible.

Dosage should be in line with relevant treatment guidelines. Based on the limited available evidence the recommended dose in adults is 9 million IU daily in 2 or 3 divided doses as a slow intravenous infusion; in critically ill patients a loading dose of 9 million IU should be given. Doses should be reduced according to creatinine clearance in patients with renal impairment.

In children, the suggested dose is 75,000 to 150,000 IU/kg daily, in 3 divided doses.

Intravenous colistimethate sodium does not cross the blood-brain barrier to a significant extent. Where appropriate, adult doses of 125,000 IU for intraventricular administration and no more than this for intrathecal administration are recommended.

Use of intravenous colistimethate sodium together with other medications that are potentially nephrotoxic or neurotoxic should be undertaken with great caution.

When given by inhalation, colistimethate sodium solutions may be used for the management of chronic pulmonary infections due to Pseudomonas aeruginosa in adults and children with cystic fibrosis. The recommended dose in adults is 1 to 2 million IU given 2 to 3 times a day, and in children 0.5 to 1 million IU twice daily, adjusted according to the severity of the condition and the response.

A parallel review is currently underway, looking at the quality of the products and the way the potency of colistimethate sodium is measured and tested, and may result in further changes to the product information once complete.

Reference:

Colobreathe® (colistimethate sodium dry powder for inhalation)

Risk of capsule breakage

UK. The MHRA reported that it has received reports of colistimethate sodium (Colobreathe®) capsules shattering when pierced by their inhaler device. The instructions for inhaler use have been revised to reduce this risk.

Colistimethate sodium dry powder for inhalation is indicated for the management of chronic Pseudomonas aeruginosa lung infections in patients with cystic fibrosis aged 6 years and older.

Colistimethate sodium is inhaled as a powder from a gelatine capsule using the supplied inhaler device. A piston within the inhaler pierces the capsule allowing the capsule contents to be inhaled.

To date, MHRA have received 26 reports of capsules shattering when pierced. The filter in the inhaler catches pieces of broken capsule shell more than 2 mm wide. However, smaller pieces could be swallowed or inhaled. Some reports of broken capsules have been associated with throat irritation and coughing, although there are no serious safety concerns and patients need not be alarmed if this happens.

The manufacturer has revised the instructions for inhaler use to reduce the risk of capsules breaking. These revised instructions have been included in the patient information leaflet and summary of product characteristics.

Advice for health-care professionals:

- Demonstrate the new inhaler instructions to patients. The key points are:
  - insert the capsule widest end first into the inhaler chamber.
  - pierce the capsule gradually using a two-step process
  - only pierce each capsule once
- Supervise patients taking their first dose.
- Tell patients and carers to refer to the instructions in the patient information leaflet that comes in the pack.

Reference:
Drug Safety Update, November 2014, Volume 8, issue 4, A2
MHRA, (www.mhra.gov.uk)

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</tr>
<tr>
<td>9 000 000</td>
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</table>
Denosumab

Risk of Osteonecrosis of the Jaw and Hypocalcaemia

Egypt. EPVC has informed a risk of osteonecrosis of the Jaw (ONJ) and hypocalcaemia with denosumab.

Denosumab is a human monoclonal IgG2 antibody produced in a mammalian cell line (CHO) and is used for prevention of skeletal related events (pathological fracture, radiation to bone, spinal cord compression or surgery to bone) in adults with bone metastases from solid tumors. ONJ is a condition in which the jawbone becomes necrotic, exposed, and does not heal within 8 weeks. The etiology of ONJ is not clear, but may be associated with inhibition of bone remodeling. Known risk factors for ONJ include invasive dental procedures (e.g., tooth extraction, dental implants, oral surgery), poor oral hygiene, or other pre-existing dental disease. Other risk factors for ONJ are advanced malignancies, infections, older age, concomitant therapies (e.g., chemotherapy, corticosteroids, angiogenesis inhibitors, radiotherapy to the head and neck), smoking, and previous treatment with bisphosphonates. While on treatment, patients should avoid invasive dental procedures if possible.

EPVC has recommended:

- Before starting denosumab, a dental examination with appropriate preventive dentistry is recommended.
- Do not start denosumab in patients with an active dental or jaw condition requiring surgery, or in patients who have not recovered following oral surgery.
- Tell patients receiving denosumab to maintain good oral hygiene practices, receive routine dental check-ups, and immediately report any oral symptoms such as dental mobility, pain, or swelling during treatment with denosumab.
- Pre-existing hypocalcaemia must be corrected prior to initiating therapy with denosumab.
- Supplementation with calcium and vitamin D is required in all patients unless hypercalcaemia is present.
- Monitoring of calcium levels should be conducted:
  - prior to the initial dose of denosumab
  - within two weeks after the initial dose
  - if suspected symptoms of hypocalcaemia occur
- Consider monitoring calcium levels more frequently during therapy in patients with risk factors for hypocalcaemia (e.g. patients with severe renal impairment, creatinine clearance <30 ml/min), or if otherwise indicated based on the clinical condition of the patient.

References: Egyptian Pharmaceutical Vigilance Center (EPVC), Newsletter, November 2014, Volume 5, Issue 11.

(See WHO Pharmaceuticals Newsletter No.5, 2014 for Updated recommendations on minimising the risk of osteonecrosis of the jaw and hypocalcaemia in the UK, No.3, 2013 for Severe hypocalcaemia in Australia, No.6, 2012 for Fatal cases of severe symptomatic hypocalcaemia in the UK and for Association with the risk of atypical femoral fractures in Canada and No.4, 2012 for Risk of severe symptomatic hypocalcaemia, including fatal cases in Canada and for Osteonecrosis of the Jaw (ONJ) in New Zealand)

Immunoglobulins

Risk of blood clots (thrombosis)

Canada. Health Canada informed that a safety review was initiated to examine the information in the Canadian product monograph on the risk of blood clots (thrombotic events) for all non-hyperimmune immunoglobulin products (referred to as immunoglobulins for the purpose of this summary). The review was prompted by the ongoing assessment of information regarding these products and this adverse event, including data provided by manufacturers, two scientific and medical publications as well as regulatory actions by the US FDA.

The immunoglobulins are a large and diverse group of products derived from human blood and their use in clinical settings varies widely from region to region.

Based on information reviewed, it was determined that there is enough evidence for updating the information for all immunoglobulin products.

The following actions have been undertaken by Health Canada:

- The Canadian product information for all immunoglobulin products has been updated to include a Boxed Warning and an updated Warnings and Precautions section with information regarding the risk of thrombosis, by describing the type of events that may occur as well as risk factors.
- A risk communication will be issued to inform about the risk of thrombosis with immunoglobulin products.
- Monitoring of thrombosis cases for all immunoglobulin products will continue, with a
particular focus on the intramuscular and subcutaneous immunoglobulin products.


Ponatinib

Risk of blood clots and blockages in the arteries Europe. The EMA reviewed the benefits and risks of ponatinib (Iclusig®), a medicine used for the treatment of leukaemia (cancer of the white blood cells), and recommended strengthened warnings in the product information aimed at minimising the risk of blood clots and blockages in the arteries.

Ponatinib is authorised for use in patients with chronic myeloid leukaemia (CML) and acute lymphoblastic leukaemia (ALL) who cannot take or tolerate several other medicines of the same class (known as ‘tyrosine-kinase inhibitors’).

The benefit-risk balance of ponatinib remains positive in all authorised indications, and the starting dose remains 45mg per day.

The product information will be updated with strengthened warnings about the risks with ponatinib, and to also provide health-care professionals with the latest evidence in case they wish to consider reducing the dose of ponatinib in patients with ‘chronic phase’ CML who are responding well to treatment, and who might be at particular risk of blood vessel blockage. Additionally, health-care professionals should stop ponatinib if a complete response has not occurred within three months of treatment, and should monitor patients for high blood pressure or signs of heart problems.

Health-care professionals should follow these recommendations:
- The cardiovascular status of the patient should be assessed before starting therapy with ponatinib, and regularly monitored during treatment.
- Treatment with ponatinib should be stopped if a complete haematologic response has not occurred by three months. Dose modifications or treatment interruption (temporary or permanent) should be considered to manage treatment toxicity.
- If a reduced dose of ponatinib is used, doctors should monitor patients for maintenance of therapeutic response.
- Any assessment relating to dose reduction should take into account a number of factors, including the patient’s cardiovascular risk, side effects of therapy, and time to cytogenetic response.

(See WHO Pharmaceuticals Newsletter No. 1, 2014 for Risk of serious blood clots in arteries and veins in the USA, No.1, 2014 for Risk of vascular occlusive events in the UK, No.6, 2013 for Risk of serious blood clots in arteries and veins in the USA and Europe)

Rituximab

Risk of Hepatitis B reactivation and usage in population with high risk of Hepatitis C Virus (HCV) infestation Egypt. EPVC has issued information on the risk of hepatitis B reactivation with rituximab and its usage in population known to bear a high potential risk of hepatitis C virus infestation.

Rituximab is a genetically engineered chimeric mouse/human monoclonal antibody representing a glycosylated immunoglobulin with human IgG1 constant regions and murine light-chain and heavy-chain variable region sequences and is used to treat diseases which are characterized by excessive numbers of B cells, overactive B cells, or dysfunctional B cells.

EPVC has recommended the following:
- Due to the High prevalence rate of HCV positive patients amongst the Egyptian population, patient should be screened for serum hepatitis C viral antibody (HCV Ab) in addition to the previously known hepatitis B virus surface antigen (HBV sAg) testing, before the initiation of treatment.
- Caution is required when rituximab is prescribed for patients with a history of recurrent or chronic infection or an underlying disease that favors the occurrence of severe infections. Patients who develop an infection after treatment with rituximab should be promptly investigated and appropriately treated.
- Based on the current data and following the updated new clinical guidelines, it is recommended that HBV screening be performed in all patients before the initiation of treatment with rituximab in all indications, and that patients with positive HBV serology should consult with a liver disease specialist before start of treatment. Those patients should be monitored and managed following local standards.
Sulfamethoxazole-trimethoprim

Risk of Drug-induced Immune Thrombocytopenia

Canada. Health Canada conducted a safety review to evaluate the available information regarding the potential risk of drug-induced immune thrombocytopenia, also known as a low number of platelets in the blood, with products containing sulfamethoxazole and/or trimethoprim (SMX-TMP). US FDA has announced changes to the prescribing information for SMX-TMP containing products.

Sulfamethoxazole (SMX) and trimethoprim (TMP) are different antibiotics that can be used alone or in combination. When used separately, these antibiotics only stop the growth of bacteria. However, when combined together, these antibiotics kill the bacteria. It can lead to a better outcome for the patient. SMX-TMP containing products are used for the treatment of various infections such as bladder, lung, and ear infections. These products have been on the Canadian market since 1973.

A number of case reports of thrombocytopenia associated with SMX-TMP have been published over the years. A search of the medical literature identified three population studies. The analysis of these studies showed an increased risk of thrombocytopenia with the use of SMX-TMP. The risk appears to be increased in some patients such as those with the Acquired Immune Deficiency Syndrome (AIDS).

At the time of the review, Health Canada had received 130 adverse reaction reports of thrombocytopenia with the use of SMX-TMP containing products. More than half of these reported thrombocytopenia without any other blood disorder. A fatal outcome was reported for 12 of these cases.

Taking into account the studies and case reports, it is possible that SMX/TMP can contribute to the development of drug-induced immune thrombocytopenia in some patients. Overall, the incidence of this reaction appears to be very low.

The US prescribing information includes a warning on the risk of immune thrombocytopenia and a contraindication in patients allergic to SMX-TMP or with a history of drug-induced thrombocytopenia.

Health Canada is currently working with the manufacturers to update the prescribing information for SMX-TMP containing products. This will inform health professionals and patients of the potential risk of drug-induced immune thrombocytopenia with SMX-TMP containing products. The prescribing information will include a new contraindication indicating that SMX-TMP containing products should not be used in patients with a known hypersensitivity including a history of drug-induced immune thrombocytopenia.

Zopiclone

Risk of next-day impairment

Canada. Health Canada informs about important new dosing information which has been added to the Product Monograph for zopiclone (Imovane®) related to the risk of next-day impairment.

Like other sedative/hypnotic drugs, zopiclone has Central Nervous System (CNS)-depressant effects and can cause next-day impairment of activities requiring alertness, including driving a car. The impairment can be present despite the patient feeling fully awake. Even if zopiclone is taken as instructed, some patients may still have zopiclone blood levels high enough to produce impairment.

Health Canada has informed that

- The recommended starting dose has been reduced to 3.75 mg (one-half of the 7.5 mg tablet). Zopiclone should be taken once per night at bedtime. The lowest effective dose for each patient should be used.
- The prescribed dose should not exceed 5 mg in elderly patients, in patients with hepatic or renal impairment or those currently treated with potent CYP3A4 inhibitors. Dose adjustment may be required with concomitant use with other CNS-depressant drugs.
- Patients should be instructed to wait for at least 12 hours after dosing before driving or engaging in other activities requiring alertness.
full mental alertness, especially for elderly patients and for patients who take the 7.5 mg dose.

The changes in dosage recommendations are supported by data available for zopiclone 7.5 mg showing increased risk of driving impairment when evaluated up to 11 hours after an evening dose. The risks are higher in the elderly and other special populations with increased residual blood levels (hepatic and renal impairment). For some patients taking lower doses, zopiclone blood levels in the morning may be high enough to produce impairment. Therefore, all patients who use zopiclone should be cautioned about the risks of next-day impairment.

Treatment with zopiclone should usually not exceed 7-10 consecutive days. Use for more than 2-3 consecutive weeks requires complete re-evaluation of the patient.

The updated Product Monograph for zopiclone is posted on Health Canada’s websites.

Reference:
Advisories, Warnings and Recalls, Health Canada, 19 November 2014 (www.hc-sc.gc.ca)

(See WHO Pharmaceuticals Newsletter No.3, 2014 for related information on eszopiclone in the USA)
Amitriptyline

Possible risk of peripheral coldness (cold hands and/or feet) or Raynaud’s phenomenon

New Zealand. Medsafe notes that Lareb, the Dutch Pharmacovigilance Centre, has identified a signal of peripheral coldness associated with the use of tricyclic antidepressants.

Amitriptyline is a tricyclic antidepressant indicated for the treatment of depression. Tricyclic antidepressants are also used for other unapproved indications.

In view of the signal from Lareb, Medsafe is placing this safety concern on the medicines monitoring scheme to obtain further information.


Boceprevir and telaprevir

Baseline predictive factors for sepsis, worsening liver function, and mortality

UK. Boceprevir (Victrelis®) and telaprevir (Incivo®) are protease inhibitors indicated for the treatment of chronic hepatitis C genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adults with compensated liver disease.

A European review identified the following baseline markers as predictive factors for morbidity requiring hospitalisation (eg, sepsis, worsening liver function) and mortality in cirrhotic patients treated with either boceprevir or telaprevir in combination with peginterferon alfa and ribavirin:

- low platelet count
- hypoalbuminaemia
- coagulopathy (for boceprevir only)

Boceprevir and telaprevir are not recommended for patients who have a low platelet count or hypoalbuminaemia before starting either of these medicines. Boceprevir is also not recommended for patients who have coagulopathy before starting it. If treatment is started, closely monitor for infection, worsening liver function, and anaemia, as described in the summary of product characteristics.

Reference: Drug Safety Update, November 2014, Volume 8, issue 4, S1 MHRA, (www.mhra.gov.uk)

Interferon beta

Risks of thrombotic microangiopathy and nephrotic syndrome

UK. The MHRA advised to health-care professionals to be vigilant for early signs or symptoms of thrombotic microangiopathy and nephrotic syndrome linked to interferon beta treatment and treat these conditions promptly if they occur.

Interferon beta-1a and interferon beta-1b are immunomodulatory drugs indicated for the treatment of remitting relapsing multiple sclerosis.

A European review suggested that there may be an association between interferon beta treatment and thrombotic microangiopathy and between interferon beta treatment and nephrotic syndrome.

MHRA provided advice for health-care professionals:

Thrombotic microangiopathy:

- Be vigilant for signs and symptoms of thrombotic microangiopathy. Clinical features of thrombotic microangiopathy include:
  - thrombocytopenia
  - new onset hypertension
  - fever
  - central nervous system symptoms (eg, confusion and paresis)
  - impaired renal function

- If you observe clinical features of thrombotic microangiopathy, test blood platelet levels, serum lactate dehydrogenase levels, and renal function. Also test for red blood cell fragments on a blood film.

- If thrombotic microangiopathy is diagnosed, treat promptly (consider plasma exchange) and stop interferon beta treatment immediately.

Nephrotic syndrome:

- Monitor renal function periodically.

- Be vigilant for early signs or symptoms of nephrotic syndrome such as oedema, proteinuria, and impaired renal function especially in patients at high risk of renal disease.

- If nephrotic syndrome occurs, treat promptly and consider stopping interferon beta treatment.


(See WHO Pharmaceuticals Newsletter No.1, 2014 for Thrombotic microangiopathy in the UK (recombinant interferon beta))

Zoledronic acid

Possible risk of tendon injury/tendinitis

New Zealand. Medsafe issued the communication that the Centre for Adverse Reactions...
Monitoring (CARM) has received four reports of zoledronic acid associated with tendon injuries which included tendon rupture, tendinitis and tenosynovitis.

Zoledronic acid belongs to a class of drug called bisphosphonates which reduce the rate of bone turnover and is indicated for

- treatment of osteoporosis in postmenopausal women to reduce the incidence of hip, vertebral and non-vertebral fractures and to increase bone mineral density
- treatment of osteoporosis in men
- treatment of Paget’s disease of bone
- treatment and prevention of glucocorticoid-induced osteoporosis
- prevention of clinical fractures in patients after hip fracture
- prevention of skeletal-related events (pathological fracture, spinal cord compression, radiation to bone or surgery to bone) in patients with advanced malignancies involving bone
- treatment of tumour-induced hypercalcaemia

Medsafe is placing this safety concern on the medicines monitoring scheme to obtain further information on this possible adverse reaction.

Reference:
Safety Information, Medsafe, 20 October 2014. (www.medsafe.govt.nz/)
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 10 million reports of suspected adverse drug reactions, submitted by National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring. VigiBase® is, on behalf of the WHO, maintained by the Uppsala Monitoring Centre (UMC) and periodic analysis of VigiBase® data is performed in accordance with UMC’s current routine signal detection process.

More information regarding the ICSRs, their limitations and proper use, is provided in the UMC Caveat document available at the end of SIGNAL (page 35). For information on the UMC Measures of Disproportionate Reporting please refer to WHO Pharmaceuticals Newsletter Issue No. 1, 2012.

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

Agomelatine and thrombocytopenia
Dr. Anita Conforti and Ermelinda Viola, Italy

Summary
Agomelatine is a melatonergic drug used in patients with major depression. The mechanism of agomelatine’s antidepressant effect is attributed to its action on melatonergic receptors (MT1/MT2) present in the CNS, as well as to its 5-HT2C antagonism. By improving sleep and resynchronizing disrupted circadian rhythms, agomelatine exerts its novel mode of antidepressant action. After excluding two duplicates, 12 reports of thrombocytopenia associated with agomelatine from seven different countries were available for assessment in the WHO Global Individual Case Safety Report (ICSR) Database, VigiBase®. The pattern of time to onset of the reports was consistent with thrombocytopenia. Although in some cases there were concomitant drugs that may affect the platelet homeostasis, the analysis of the case reports suggests there is cause for further investigation. Agomelatine and thrombocytopenia was placed under monitoring by Lareb in 2011, and in 2013 the EMA requested the marketing authorization holder (MAH) to keep agomelatine and thrombocytopenic purpura under close monitoring.

Introduction
Agomelatine, the first melatonergic antidepressant, was designed to improve depressed states by resynchronizing perturbed biological rhythms. Its ‘synergistic’ agonist properties at melatonin receptors (MT1/MT2) plus antagonist properties at 5-hydroxytryptamine 2C (5-HT2C) receptors account for its beneficial influence on depressed states.\(^1\) The 5-HT2C receptor inhibits the release of norepinephrine and dopamine. By antagonizing the 5-HT2C receptor, agomelatine disrupts the previous inhibition effect, resulting in the release of norepinephrine and dopamine and increasing their extracellular levels. Drugs that inhibit or induce the cytochrome P450 isoenzyme CYP1A2 have the potential to interact with agomelatine.\(^2\)

Since 2009 agomelatine has centralized marketing authorization in the European Union by the EMA for the treatment of major depressive disorders in patients over 18 years in a dosage of 25-50 mg orally once daily. It is also marketed in Australia and Latin American countries but is not approved in the USA. The development for the US market was discontinued in October 2011, when the negative results of phase III clinical trials (randomized, double-blind, placebo-controlled studies) became available.\(^3\) The most common adverse effects that occur within the first few weeks of agomelatine treatment are transient
nausea and dizziness, which are usually mild or moderate. Other gastrointestinal disturbances, headache, somnolence, insomnia, migraine, hyperhidrosis, back pain and fatigue are also reported as being common adverse effects.\(^4\)

Thrombocytopenia is a decrease in the number of circulating platelets below 150,000/mcL, potentially resulting in abnormal coagulation and manifesting as a bleeding diathesis. Causes of thrombocytopenia are varied, and can be either endogenous or exogenous. It can arise from decreased platelet production (as in congenital or acquired thrombocytopenia, e.g. bone marrow infiltration)), platelet sequestration (as in splenomegaly), secondary to platelet loss, as from massive blood loss (e.g. consumptive or dilutional) or increased platelet destruction by immune or non-immune mechanisms; with all these conditions occurring in combination in certain disease settings. Common precipitating factors include drugs, infections, trauma, neoplasms, and vasculitis. Immune-mediated thrombocytopenia, also called idiopathic thrombocytopenia (ITP), and thrombotic thrombocytopenic purpura (TTP) are the major types of thrombocytopenic disorders. ITP is the autoimmune destruction of platelets and is managed with immunosuppression, while TTP is the microvascular consumption of platelets and can be associated with anemia, renal failure and fever. It is a medical emergency and is managed with plasma exchange. Due to the short life span of platelets, clinical symptoms of thrombocytopenia can develop quickly, resulting in bleeding emergencies. Spontaneous bleeding is usually associated with platelet counts less than 50,000/mcL.\(^5\)

Reports in VigiBase®

As of 21 May 2014, there were 14 ICSRs of thrombocytopenia (WHO-ART preferred term) in association with agomelatine in the WHO Global ICSR Database, VigiBase®. The related term thrombocytopenic purpura was also searched for in VigiBase® but there were no reports of this association.

Two duplicates were excluded and the remaining 12 reports are summarized in Table 1. The reports were submitted from seven countries; six cases from Germany and one from Australia, Belgium, Italy, Netherlands, Portugal and Switzerland. The age of the patients was reported in all 12 cases and ranged from 18 to 87 years with a median age of 46 years. Gender was equally distributed.

Duration of exposure to agomelatine ranged from 10 days to 9 months. Four reports did not provide this information. Time to onset ranged from 6 days to approximately 10 months with an average of 77 days. Agomelatine was considered the only suspected drug in 10 cases and in four of them it was the only reported drug. Concomitant drugs for which the UK Summary of Product Characteristics (UK SPC) and Micromedex list ‘thrombocytopenia’ are included in six cases (cases 1, 2, 4, 5, 7 and 10). In three cases (cases 2, 3 and 5) the patient had a medical history of thrombocytopenia, and in two of these cases (cases 3 and 5) the reported term was thrombocytopenia aggravated.

Three cases (cases 6, 10 and 12) reported a positive dechallenge, while in four cases (cases 1, 2, 3 and 7) there was a negative dechallenge. No fatal cases were reported. In case 7 the reporter stated a non-serious thrombocytopenia related to agomelatine while in cases 8 and 5 the reporters assessed the role of agomelatine in thrombocytopenia as rather unlikely. In cases 4 and 8 the patients were recovering even though the agomelatine treatment was maintained (in case 8 the treatment was interrupted but then reintroduced after a couple days). In case 5 the agomelatine dose was not changed and the patient did not recover but the sender stated that, according to the oncologist, the role of agomelatine was rather unlikely, as the worsening of thrombocytopenia could be the natural evolution of the idiopathic thrombocytopenia (natural variation between 30,000 and 150,000), or the consequence of cortisone dose decrease.

Literature and Labelling

Thrombocytopenia is not listed among undesirable effects in the UKSPC for agomelatine.\(^6\) Many agomelatine placebo-controlled and active comparator trials have been published, in which the most common adverse effects reported were headache, dizziness, somnolence, diarrhoea, nausea, sedation, fatigue and insomnia.\(^5\) There are no published cases of agomelatine and thrombocytopenia or thrombocytopenic purpura in the literature. In March 2011 the Netherlands Pharmacovigilance Centre Lareb published an overview on 39 received reports related to the use of agomelatine. These reports contained a total of 93 possible adverse drug reactions including two cases of thrombocytopenia. In the overview they said that thrombocytopenia will be monitored, and possibly analysed in the future.\(^7\) In September 2013 the EMA also presented an overview of agomelatine, including two cases of thrombocytopenic purpura. In both cases positive dechallenges were reported but overall the evidence was not considered sufficient to conclude that there was an association. The MAH was requested to keep agomelatine and thrombocytopenic purpura under close monitoring.\(^8\)
Discussion and Conclusion

As of May 2014, there were 12 cases of thrombocytopenia associated with agomelatine from seven different countries in VigiBase®. Agomelatine was considered the only suspected drug in 10 cases and in four of them it was the only reported drug. In three cases positive dechallenges were stated. The time to onset of the reports in VigiBase® was consistent with literature data: onset of non-immune thrombocytopenia is generally slow, often several weeks, while the mean delay in onset of immune-mediated thrombocytopenia in individual patients ranges from hours to several years.9

Recent studies have demonstrated the direct interaction of melatonin with platelets: at physiological concentration it promotes platelet aggregation; on the other hand, at pharmacological doses a possible mechanism of toxicity on platelet was pointed out.10,11 In 2013, Girish et al attributed to melatonin, at pharmacological doses, a significant increase of generation of intracellular reactive oxygen species (ROS) and Ca2+, facilitating mitochondrial membrane depolarization, cytochrome c release, caspase activation, protein phosphorylation and phosphatidylserine externalization. According to the authors, the elevated rate of platelet apoptosis has far-reaching consequences including thrombocytopenia.11

Although there was a negative IC value (-1.25 (IC25=0.39) as well as confounding concomitant drugs or medical history in some of the cases, the reports in VigiBase® altogether and the current published studies related to melatonin suggest that agomelatine, by its melatonergic activity, may play a contributory role in the development of thrombocytopenia.

Table 1. Characteristics of reports in VigiBase® for agomelatine

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/ Sex</th>
<th>Other suspected (S) or concomitant (C) drugs</th>
<th>Daily dose (mg)</th>
<th>Duration of treatment</th>
<th>Time to onset</th>
<th>Reactions (WHO-ART preferred terms)</th>
<th>Outcome</th>
<th>Reporter qualification</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>41/M</td>
<td>Atorvastatin, carbamazepine*, diazepam, redoxin, zolpidem (all C)</td>
<td>50</td>
<td>128 days</td>
<td>121 days</td>
<td>Myalgia, anorexia, rash erythematosus, fever, hepatic function abnormal, thrombocytopenia</td>
<td>Not recovered</td>
<td>Pharmacist</td>
</tr>
<tr>
<td>2</td>
<td>87/M</td>
<td>Acetylsalicylic acid*, bumetamide, levodopa/ benzodopa hydrochloride, perindopril*, primidone, repaglinide, simvastatin, sotalol, trazodone (all C)</td>
<td>25</td>
<td>10 days</td>
<td>6 days</td>
<td>Anaemia, thrombocytopenia, leucopenia</td>
<td>Not recovered</td>
<td>Physician</td>
</tr>
<tr>
<td>3</td>
<td>49/M</td>
<td>-</td>
<td>25</td>
<td>67 days</td>
<td>39 days</td>
<td>Impotence, thrombocytopenia</td>
<td>Not recovered</td>
<td>Physician</td>
</tr>
<tr>
<td>4</td>
<td>27/M</td>
<td>Corticosteroids, etoricoxib* (all C)</td>
<td>25</td>
<td>Treatment continued</td>
<td>~300 days</td>
<td>Thrombocytopenia</td>
<td>Recovering</td>
<td>Physician</td>
</tr>
<tr>
<td>5</td>
<td>48/M</td>
<td>Budesonide, cortisone, furoterol, hydrochlorothiazide*, lisinopril*, verapamil (all C)</td>
<td>25</td>
<td>Treatment continued</td>
<td>26 days</td>
<td>Thrombocytopenia</td>
<td>Not recovered</td>
<td>Physician</td>
</tr>
<tr>
<td>6</td>
<td>40/F</td>
<td>-</td>
<td>25</td>
<td>60 days</td>
<td>60 days</td>
<td>Thrombocytopenia, fever, leucopenia</td>
<td>Recovered</td>
<td>Physician</td>
</tr>
<tr>
<td>7</td>
<td>44/F</td>
<td>Cefuroxime*, levotyroxine sodium/potassium iodide, metaminizole, omeprazole (all C)</td>
<td>25</td>
<td>24 days</td>
<td>22 days</td>
<td>Thrombocytopenia</td>
<td>Not recovered</td>
<td>Physician</td>
</tr>
<tr>
<td>8</td>
<td>18/F</td>
<td>-</td>
<td>25</td>
<td>Treatment continued</td>
<td>~59 days</td>
<td>Thrombocytopenia</td>
<td>Recovering</td>
<td>Physician</td>
</tr>
<tr>
<td>9</td>
<td>65/F</td>
<td>-</td>
<td>25</td>
<td>-</td>
<td>13 days</td>
<td>Thrombocytopenia</td>
<td>Not recovered</td>
<td>Physician</td>
</tr>
<tr>
<td>10</td>
<td>76/M</td>
<td>Acetylsalicylic acid* (S)</td>
<td>25</td>
<td>85 days</td>
<td>85 days</td>
<td>Thrombocytopenia</td>
<td>Recovering</td>
<td>Physician</td>
</tr>
<tr>
<td>11</td>
<td>52/F</td>
<td>Bisoprolol (C)</td>
<td>25</td>
<td>~270 days</td>
<td>~150 days</td>
<td>Medication error, influenza-like symptoms, haematoma, fall, thrombocytopenia</td>
<td>Recovering</td>
<td>Physician</td>
</tr>
<tr>
<td>12</td>
<td>23/M</td>
<td>Budesonide, desloratadine, sodium bicarbonate/ potassium chloride/ sodium chloride/macrogol, triamcinolone (all C)</td>
<td>50</td>
<td>42 days</td>
<td>42 days</td>
<td>Thrombocytopenia</td>
<td>Recovering</td>
<td>Pharmacist</td>
</tr>
</tbody>
</table>

*Drugs marked in bold are known to cause thrombocytopenia
Response from Servier

Regarding the signal “Thrombocytopenia”, all sources were considered and are presented thereafter:

Pharmacology

Agomelatine is a naphthalene derivative (1) that retains a similar binding affinity as melatonin but possesses both melatonin agonist and 5-HT2C antagonist properties (2, 3).

At physiological and pharmacological concentrations, melatonin displays antioxidant and direct reactive oxygen species (ROS) scavenger effects (4), as well as antiapoptotic effects or proapoptotic cell actions (5).

In the study performed by Girish et al (6), melatonin was found to trigger platelet apoptosis at a concentration-range 10-100μM. These concentrations are in agreement with in vivo melatonin tissue-levels, reaching micromolar concentrations (7), however, more than 10 times higher than plasma levels of agomelatine after oral administration of the highest daily therapeutic dose 50mg of agomelatine in patients (internal data).

Thereby, agomelatine, although acting as MT1/MT2 melatonergic receptors agonist, is not expected to play a contributory role in the development of thrombocytopenia.

Toxicology

Agomelatine was tested in a number of toxicity studies in rats and monkeys with daily oral administrations over 4, 13, 26 and 52 weeks at doses ranging from 25 to 750mg/kg/day in rats and from 60 to 720mg/kg/day in monkeys. A 4-week study via intravenous route (2 to 60 mg/kg/day) was also performed in each of these species. In all these studies, platelet counts were quantified, either as a terminal measurement or regularly over the course of the studies. In addition, daily clinical observations were performed in all animals and histology was performed for various tissues, including those which could reflect a platelet disorder, namely bone marrow and spleen.

Over this comprehensive toxicology program, in any of the studies and any of the treated animals, no clinical sign suggesting a platelet disorder (e.g. purpura, petechia, spontaneous bleeding, haemorrhages), no quantitative anomaly in platelet counts or volumes (when measured), no salient spleen weight variation and no histological finding on bone marrow or spleen were detected.

A special study in juvenile rats was performed with agomelatine, with oral daily administration for 10

References


weeks starting 7 days postpartum (5-150 mg/kg/day), and again, there was no indication for an effect of the drug on platelets.

A 4-week special study was performed in the rat with melatonin at 250 and 750 mg/kg, and no decrease in platelets was observed at any dose.

Therefore, the lack of any toxicological effect for agomelatine or melatonin regarding platelet counts and related data supports a lack of contributory role of agomelatine in the development of thrombocytopenia.

**Clinical trial data**

In the agomelatine development program, 14377 patients were included: 8693 on agomelatine, 1886 on placebo (and 3798 on comparators). The incidence of emergent Thrombocytopenia or related events was similar in the agomelatine and placebo groups, 0.09% and 0.11% respectively. In the overall development, 3.10% of patients exposed to agomelatine presented at least one value of platelet lower than 150 G/L versus 4.04% in patients exposed to placebo.

**Postmarketing data**

Search was performed on the following preferred terms: thrombocytopenia, Immune Thrombocytopenic purpura and platelet count decreased.

From Market Authorisation (19-FEB-2009) up to 25-AUG-2014, 30 cases were reported (including the 12 cases mentioned by Uppsala): 16 Thrombocytopenia, 2 Immune Thrombocytopenic purpura and 12 Platelet count decreased. i.e. an overall reported incidence of 2.1 / 100 000 patient-years.

Analysis of the 30 cases is displayed thereafter:

<table>
<thead>
<tr>
<th>Clinical signs associated 6/30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Purpura: 3</td>
</tr>
<tr>
<td>Gastrointestinal bleeding: 1</td>
</tr>
<tr>
<td>(associated with purpura)</td>
</tr>
<tr>
<td>Haematoma: 1</td>
</tr>
<tr>
<td>Epistaxis: 1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Causality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doubtful: 30</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dechallenge / Rechallenge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive dechallenge: 13</td>
</tr>
<tr>
<td>No positive rechallenge</td>
</tr>
<tr>
<td>Recovered/Recovering under treat- ment: 3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Alternative explanation 27/30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relevant medical history (11/30):</td>
</tr>
<tr>
<td>Thrombocytopenia, auto immune thrombocytopenia (9)</td>
</tr>
<tr>
<td>Systemic lupus erythematosus (1)</td>
</tr>
<tr>
<td>Cancer (1)</td>
</tr>
<tr>
<td>Alcohol abuse (1)</td>
</tr>
<tr>
<td>Relevant context (16/30): Infection (4)</td>
</tr>
<tr>
<td>Myelodysplastic syndrome, Hypergammaglobulinemia, Chronic myelomonocytic leukaemia (4)</td>
</tr>
<tr>
<td>Splenomegaly, Hepatitis (4)</td>
</tr>
<tr>
<td>Probable laboratory error (2)</td>
</tr>
<tr>
<td>Concomitant drugs (16/30): Antibiot-</td>
</tr>
</tbody>
</table>

Three cases did not present alternative causes, that is absence of relevant medical history, context or concomitant drugs likely to induce thrombocytopenia

- One patient (case 12 in the signal) experienced thrombocytopenia 42 days after starting valdoxan, platelet value decreased again after valdoxan withdrawal, and patient recovered one month later.
- One patient (case 8 in the signal) experienced platelet decrease around 90 G/L about 2 months after starting valdoxan. Patient was recovering albeit valdoxan dosage was increased.
- In the remaining case (case 9 in the signal), patient’s presented low platelet value (140 G/L) before valdoxan treatment, no investigation was performed and action taken regarding valdoxan was unknown.

In conclusion, review of postmarketing did not raise new safety concerns:
- Low incidence of events: 2.1/100 000 PY,
- No cases with a “likely” or “possible” causality assessment
- In 90% of the cases, confounding factors such as relevant medical history and/or relevant context and/or concomitant treatment(s) known to induce such events were present.

Conclusion
There is no pharmacological data or toxicological data in favour of deleterious actions of agomelatine on platelet functions. Additionally, no safety concern regarding “Thrombocytopenia” was raised with agomelatine from clinical data or post-marketing surveillance
Thus the signal “Thrombocytopenia” was refuted and closed. This event will remain under close monitoring.

References

Dronedarone and ventricular arrhythmia

Dr. Mónica Tarapués, Ecuador/Spain

Summary
Dronedarone is a new antiarrhythmic drug indicated for the treatment of persistent or paroxysmal atrial fibrillation as well as for restoring the normal sinus rhythm after cardioversion. Alteration to cardiac rhythm is not mentioned as an expected adverse reaction either in the EMA or the US FDA summary of product characteristics. In the WHO Global Database, VigiBase®, there are, as of May 2014, four cases of ventricular arrhythmia in association with dronedarone use. This finding led to an in-depth search and 29 cases of ventricular fibrillation with dronedarone use were also found in VigiBase®. The total of 33 ICSRs were submitted from the United States, Germany and Canada. Some cases have potential risk factors for ventricular arrhythmia. Despite potential confounders 10 patients recovered fully or partially after dronedarone withdrawal. As a multichannel blocker that meets the criteria of all Vaughan Williams antiarrhythmic drug classes: inhibition of the rapid Na⁺ current (class I), α and β adrenergic receptor inhibition (class II), inhibiting of K⁺ currents (class III) and blocking of slow Ca²⁺ currents (class IV). It was launched as a safer option than amiodarone, especially due to its apparent lack of toxicity in skin, lungs and thyroid. A better tolerability is suggested because dronedarone has a less lipophilic characteristic, thus a short plasma half-life is the main feature that would reduce the organ toxicity.

In the summary of the product characteristics of dronedarone, the most common adverse reactions (experienced by at least 10% of the patients) include gastrointestinal disorders such as diarrhoea, nausea, vomiting, abdominal pain and dysgeusia, cardiac disorders such as congestive heart failure and bradycardia, skin disorders such as rashes and pruritus, general disorders such as fatigue and asthenia, and liver function test abnormalities.

The term “ventricular arrhythmia” incorporates a wide spectrum of abnormal cardiac rhythms, such as: premature ventricular complex, sustained monomorphic ventricular tachycardia, polymorphic
ventricular tachycardia, and ventricular fibrillation. Ventricular arrhythmias can occur in individuals with or without cardiac disorders. Monomorphic ventricular tachycardia could lead to sudden cardiac death if it degenerates into polymorphic ventricular tachycardia or ventricular fibrillation. These arrhythmias have a great deal of overlap between clinical presentations and severity. Ventricular arrhythmias occur predominantly in patients with structural heart disease and ischemic cardiac disease, although it can occur in patients with congenital cardiac disorders (associated with surgical scar), electrolyte imbalances and inherited or acquired channelopathies.

Statistical disproportional reporting has been observed in the WHO Global ICSRs Database, VigiBase® for ventricular arrhythmia associated with dronedarone treatment.

Reports in VigiBase®
As of 19 May 2014, there were four ICSRs in VigiBase® that described ventricular arrhythmia associated with dronedarone use. In addition there were 29 ICSRs of ventricular fibrillation, 89 cases of ventricular tachycardia and 62 of cardiac arrest.

The four cases reported with ventricular arrhythmia were submitted from two countries: Germany (three cases) and United States (one case); all the cases were sent by physicians. These ICSRs involved three men and one woman. In one case the patient was described as an adult, and in the other cases the patients were >70 years old. Sudden death and ventricular tachycardia were found as co-reported terms. The four cases are described in Table 1.

Regarding outcome, “recovered” was reported in two patients. In another case the outcome was reported as “unknown”, and in the last one outcome was reported as “died”. Information regarding other potential risk factors such as baseline conditions, electrolyte abnormalities or cardiac disorders was lacking. Dronedarone was the only suspected drug in all the cases. The time to onset was available in 22 cases; it ranged from the same day the drug was started to 446 days, with a mean value of 81 days. In seven cases the dronedarone use was off-label. Other suspected drugs were; amiodarone, metoprolol, levofloxacin, amoxicillin, mexiletine, theophylline, ethanol and quetiapine (one case each). Concomitant drugs with potential cardiac risk such as β-blockers were reported in 12 cases (metoprolol [7], carvedilol [2], bisoprolol [2], atenolol [1]), calcium antagonists in four cases (diltiazem [3] non specific [1]) and digitalis derivates in five cases. Causality was assessed as possibly related to dronedarone in four cases, unknown in 24 cases and unclassified in one case.

In 21 ICSRs relevant medical information was available. The most frequent co-morbidities identified were heart failure (9 cases), cardiomyopathy (11), coronary artery disease (3), hypertension (6), type 2 diabetes mellitus (4) and chronic kidney disease (4). In eight patients abnormal heart rhythms were found (tachyarrhythmia, tachycardia-bradycardia syndrome, or premature ventricular contractions). In addition, nine patients were pacemaker or implantable cardioverter defibrillator users.

In 22 ICSRs dronedarone was the only suspected drug. Time to onset was available in 22 cases; it ranged from the same day the drug was started to 446 days, with a mean value of 81 days. In seven cases the dronedarone use was off-label. Other suspected drugs were; amiodarone, metoprolol, levofloxacin, amoxicillin, mexiletine, theophylline, ethanol and quetiapine (one case each). Concomitant drugs with potential cardiac risk such as β-blockers were reported in 12 cases (metoprolol [7], carvedilol [2], bisoprolol [2], atenolol [1]), calcium antagonists in four cases (diltiazem [3] non specific [1]) and digitalis derivates in five cases. Causality was assessed as possibly related to dronedarone in four cases, unknown in 24 cases and unclassified in one case.

Literature and Labelling
Dronedarone is considered a second line treatment; it should only be prescribed after non-response of alternative treatment options. Ventricular arrhythmia or arrhythmia is not mentioned in either the EMA or the US SPCs of dronedarone. Regarding cardiac adverse drug reactions, congestive heart failure and bradycardia are described, as well as QTc Bazett prolonged (>450 msec in male, >470 msec in female). In the warning and precautions section, it is mentioned
that proarrhythmic effects may occur in particular situations such as concomitant use with medicinal products that favour arrhythmia and/or electrolytic disorders. Furthermore, potential interactions between dronedarone and other proarrhythmic drugs are mentioned, especially with β-blocker drugs, calcium antagonists and digoxin.

A restricted use of dronedarone is strongly recommended; especially, dronedarone should not be prescribed in patients with permanent atrial fibrillation, heart failure or left ventricular systolic dysfunction (impairment of the left side of the heart). Its use is also contraindicated in patients with second- or third-degree complete bundle branch block, sinus node dysfunction and atrial conduction defects.1

In patients treated with amiodarone, bradycardia is the most common cardiac event. However amiodarone has been associated (less frequently) with arrhythmias, conduction disturbances and cardiac arrest events. Dronedarone as antiarrhythmic drug class III and derivate of amiodarone, might have some proarrhythmic action. There is evidence that the inhibition of potassium currents appears to trigger early after depolarizations (EAD) in animals. These EADs may trigger another action potential and promote triggered activity; therefore it might induce reentry and lead to proarrhythmic events.3,4

The ANDROMEDA trial was early stopped early due to a high mortality rate (25 patients in the dronedarone group vs. 12 in the placebo group [HR 2.13: 95%CI 1.07-4.25; p=0.03). In this trial, most deaths were due to worsening of heart failure, however deaths due to dysrhythmia or sudden death were also observed in the dronedarone group. It was difficult to draw definitive conclusions regarding cardiac safety of dronedarone because of the presence of potential confounding factors such as severe heart failure and left ventricular systolic dysfunction. Later, in the ATHENA study, the most successful and largest trial, there was no difference in death from any cause in both groups.4

Moreover, in 2012 the proarrhythmic potential of dronedarone was analyzed in a review of the FDA adverse event reporting system (FAERS) database. In this study, several reports with ventricular arrhythmias or cardiac arrest, as well as torsade de pointes were found.5 The authors concluded that further investigation regarding this issue is necessary.5

**Discussion and Conclusion**

In our assessment, four cases of ventricular arrhythmia and 29 cases of ventricular fibrillation were found, a total of 33 cases. Potential risks for ventricular arrhythmia were described in 26 out of 33 cases. It is important to bear in mind that there were patients with more than one risk factor, e.g. four patients had both heart failure and cardiac arrest events. Dronedarone was an off-label use (ventricular arrhythmia). These findings highlight the potential impact of an inappropriate use of dronedarone.

A potential interaction should be taken into consideration. Dronedarone has a warning for concomitant use of β-blockers, calcium antagonists or digoxin. It is recommended to reduce the dose of these drugs especially for increased risk of toxicity. On the other hand, as the washout period was not enough to eliminate arrhythmic events associated with other antiarrhythmic drugs, a residual effect of amiodarone, sotalol or flecainide could be another explanation.

Even though the association of dronedarone and ventricular arrhythmias did not reach statistical difference [IC value 1.38; IC<sub>025</sub> -0.36], the association of dronedarone and ventricular fibrillation caught our attention due to its statistically significant IC value [IC 3.10; IC<sub>025</sub> 2.53], thus these combinations stand out against the background of the database. Altogether 33 ICSRs showed a plausible temporal sequence.

In 24 ICSRs, information regarding time to onset was available, and extending up to 446 days, but it is important to mention that time to onset in 16 out of the 24 ICSRs that has this information recorded was 2,5 months or less. In addition, in eleven patients a full or partial recovery was observed after dronedarone withdrawal (positive dechallenges). Moreover in two cases (case 2, table 1 and case 17, table 2) dronedarone was not immediately stopped when the events of ventricular arrhythmia and ventricular fibrillation occurred and the patients developed the same events again while still on the medication. When the drug was removed, the patients both recovered.

Some of the potential risk factors described in the ICSRs by themselves could contribute to the occurrence of ventricular arrhythmia; nevertheless the inadequate use of dronedarone together with some cardiac risk factors could increase the proarrhythmic risk, and finally the occurrence of serious ventricular arrhythmias.

Also, in a few patients QT interval prolongation was co-reported. This is a known adverse reaction of dronedarone, but it is important to highlight that persistent QT prolongation could lead to torsade de pointes. This serious and sometimes
fatal reaction is already known for other antiarrhythmic drugs, and further studies are necessary in order to elucidate the potential risk of torsade de pointes and dronedarone.

In conclusion, dronedarone, like other antiarrhythmic drugs, might have a potential arrhythmogenic risk. This risk is an inherent characteristic associated with its multichannel activity. Clinicians should be aware of the cardiac adverse reactions observed with its use in clinical practice. We consider ventricular arrhythmias such as ventricular fibrillation in patients taking dronedarone as a signal because as an antiarrhythmic drug its inhibitory action on potassium channels might explain the arrhythmic events. There are also consistent reports of positive dechallenges in VigiBase®. The cardiac baseline condition of the patients and the concomitant medication can act as inevitable confounders, which is to be expected according to the indication for treatment with dronedarone. Further studies are needed to confirm these findings.

Table 1. Characteristics of four reports for dronedarone and ventricular arrhythmia in VigiBase®

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/ Sex</th>
<th>Medical history</th>
<th>Suspected (S) and concomitant (C) drugs</th>
<th>Time to onset</th>
<th>Indication</th>
<th>Action Drug</th>
<th>ADR terms (WHO-ART)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Adult/M</td>
<td>Implanted cardioverter defibrillator user</td>
<td>Dronedarone (S) Sotalol, flecainide (both C)</td>
<td>-</td>
<td>Ventricular arrhythmia</td>
<td>Withdrawn</td>
<td>Arrhythmia ventricular, of-label use, Pacing threshold decreased*</td>
<td>Unknown</td>
</tr>
<tr>
<td>2</td>
<td>76/M</td>
<td>Hypertension, electrical cardioversion</td>
<td>Dronedarone (S) Ramipril, hydrochlorothiazide, phenprocoumon, tamsulosin (all C)</td>
<td>17 days to first recorded episode</td>
<td>Atrial fibrillation</td>
<td>Withdrawn after recurring episodes</td>
<td>Arrhythmia ventricular, tachycardia ventricular</td>
<td>Recovered</td>
</tr>
<tr>
<td>3</td>
<td>71/F</td>
<td>Type 2 diabetes Mellitus</td>
<td>Dronedarone (S) Simvastatin, candesartan, metoprolol, phenprocoumon (all C)</td>
<td>-</td>
<td>Cardiac ablation</td>
<td>Unknown</td>
<td>Arrhythmia ventricular</td>
<td>Recovered</td>
</tr>
<tr>
<td>4</td>
<td>75/M</td>
<td>Merkel cell carcinoma previously in chemotherapy</td>
<td>Dronedarone (S) Betablocking agents, ceftriaxone, paracetamol, enoxaparin, oxycodone, vancomycin (all C)</td>
<td>21 days</td>
<td>Atrial flutter</td>
<td>Dose not changed</td>
<td>Arrhythmia ventricular, sudden death</td>
<td>Died</td>
</tr>
</tbody>
</table>

*term in MedDRA
Table 2. Characteristics of 29 reports for dronedarone and ventricular fibrillation in VigiBase®

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/ Sex</th>
<th>Medical history</th>
<th>Suspected (S) and concomitant (C) drugs</th>
<th>Time to onset</th>
<th>Indication</th>
<th>Action Drug</th>
<th>ADR terms (WHO-ART)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>68/M</td>
<td>Dilated cardiomyopathy, left BBB, HF with ejection fraction decreased, tachy-arhythmia absoluta, atrial fibrillation, coronary sclerosis, hyperthyroidism, nodular goiter</td>
<td>Dronedarone (S) Digoxin, phenprocoumon, ramipril, acetylsalicylic acid, fluoxetine, enoxaparin, spironolactone, bisoprolol, simvastatin, furosemide (all C)</td>
<td>0 days</td>
<td>Cardiac arrhythmia</td>
<td>Withdrawn</td>
<td>Fibrillation ventricular</td>
<td>Recovered</td>
</tr>
<tr>
<td>2</td>
<td>87/M</td>
<td>CKD, tuberculosis, COPD, osteoarthritis, pacemaker user (biventricular), dyslipidemia, T2DM, ischemic cardiomyopathy, hypertension, HF, chronic atrial fibrillation, coronary artery bypass</td>
<td>Dronedarone, mexiletine, amidarone (all S) Guaiifenisin, digoxin, warfarin, prednisone, simvastatin, mometasone, furosemide, macrogol, metoprolol, glibenclamide, calcium carbonate, diazepam, spironolactone, colchicine, allopurinol, zolpidem (all C)</td>
<td>0 days</td>
<td>Ventricular tachycardia</td>
<td>N/A</td>
<td>Fibrillation ventricular, tachycardia ventricular, QT prolonged, cardiac arrest, off-label use</td>
<td>Died</td>
</tr>
<tr>
<td>3</td>
<td>55/F</td>
<td>Valvular heart disease, cardiomyopathy</td>
<td>Dronedarone (S)</td>
<td>-</td>
<td>Atrial fibrillation</td>
<td>Withdrawn</td>
<td>Fibrillation ventricular, torsade de pointes, QT prolonged, cardiac arrest, heart valve disorders, fibrillation atrial, hemothorax, thrombocytopenia, fall, anaemia</td>
<td>Recovered</td>
</tr>
<tr>
<td>4</td>
<td>-/-</td>
<td>-</td>
<td>Dronedarone (S)</td>
<td>6 days</td>
<td>Atrial fibrillation</td>
<td>Unknown</td>
<td>Fibrillation ventricular</td>
<td>Unknown</td>
</tr>
<tr>
<td>5</td>
<td>71/M</td>
<td>Alcohol use, left ventricular dysfunction, cardiomyopathy</td>
<td>Dronedarone (S) Gabapentin, metoprolol, lisinopril, folic acid, warfarin, calcium channel blockers (all C)</td>
<td>111 days</td>
<td>Atrial fibrillation</td>
<td>Withdrawn</td>
<td>Fibrillation ventricular, encephalopathy anoxic</td>
<td>Died</td>
</tr>
<tr>
<td>6</td>
<td>68/M</td>
<td>Hypertension, coronary artery disease, mitral regurgitation, dilated cardiomyopathy</td>
<td>Dronedarone (S) Furosemide, lisinopril, carvedilol (all C)</td>
<td>31 days</td>
<td>Atrial fibrillation</td>
<td>Withdrawn</td>
<td>Fibrillation ventricular, QT prolonged</td>
<td>Recovered</td>
</tr>
<tr>
<td>No</td>
<td>Sex</td>
<td>Age</td>
<td>Event</td>
<td>Drug(s)</td>
<td>Duration</td>
<td>Cause of Event</td>
<td>Outcome</td>
<td>Result</td>
</tr>
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<tr>
<td>7</td>
<td>74/M</td>
<td>74</td>
<td>Ventricular fibrillation</td>
<td>Dronedarone (S) Bisoprolol, acetylsalicylic acid, atorvastatin, warfarin, furosemide, candesartan (all C)</td>
<td>unknown</td>
<td>Fibrillation ventricular, breath shortness, cardiac failure, condition aggravated, intolerance induced, off-label use</td>
<td>unknown</td>
<td>unknown</td>
</tr>
<tr>
<td>8</td>
<td>54/M</td>
<td>54</td>
<td>Ventricular arrhythmia</td>
<td>Dronedarone (S)</td>
<td>4 days</td>
<td>Withdrawn</td>
<td>Fibrillation ventricular, implantable defibrillator malfunction*, off-label use</td>
<td>Recovered</td>
</tr>
<tr>
<td>9</td>
<td>65/M</td>
<td>65</td>
<td>Atrial fibrillation at arrhythmia absoluta, sick sinus syndrome moderate adipositas, hypertension with left ventricular hypertrophy, dilated cardiomyopathy, HF NYHA II, ventricular septal defect, pacemaker user</td>
<td>Dronedarone (S) Phenprocoumon (C)</td>
<td>unknown</td>
<td>Atrial fibrillation</td>
<td>died</td>
<td>died</td>
</tr>
<tr>
<td>10</td>
<td>36/M</td>
<td>36</td>
<td>Atrial fibrillation</td>
<td>Dronedarone, ethanol (both S) Atorvastatin, potassium, warfarin, iron, furosemide (all C)</td>
<td>159 days</td>
<td>Atrial fibrillation</td>
<td>withdrawn</td>
<td>fibrillation ventricular, tachycardia ventricular, QT prolonged, cardiac arrest, hypokalaemia</td>
</tr>
<tr>
<td>11</td>
<td>78/M</td>
<td>78</td>
<td>Melanoma, HF, asthma</td>
<td>Dronedarone (S) Digitoxin (C)</td>
<td>6 days</td>
<td>Atrial fibrillation</td>
<td>withdrawn</td>
<td>fibrillation ventricular, resuscitation*</td>
</tr>
<tr>
<td>12</td>
<td>25/M</td>
<td>25</td>
<td>Atrial fibrillation</td>
<td>Dronedarone (S) Digoxin, escitalopram, furosemide, sildenafil, lorazepam, multivitamins with minerals, diphenydramine, metoprolol, paracetamol/ hydrocodone, epoprostenol (all C)</td>
<td>unknown</td>
<td>Atrial fibrillation</td>
<td>withdrawn</td>
<td>fibrillation ventricular, tachycardia ventricular, collapse transient, right BBB*</td>
</tr>
<tr>
<td>No.</td>
<td>Gender</td>
<td>Condition(s)</td>
<td>Drug(s)</td>
<td>Duration</td>
<td>Event(s)</td>
<td>Outcome</td>
<td></td>
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</tr>
<tr>
<td>13</td>
<td>69/M</td>
<td>Carotid arteriosclerosis, hyperkalemia, acute renal failure, colon carcinoma, transit ischemic attack, aortic sclerosis, anemia, steroid</td>
<td>Dronedarone, theophylline (both S), Prednisolone (C)</td>
<td>~186 days</td>
<td>Extrasystoles</td>
<td>Recovering</td>
<td></td>
<td></td>
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<tr>
<td>14</td>
<td>25/M</td>
<td>-</td>
<td>Dronedarone (S) Metoprolol (C)</td>
<td>Within a month</td>
<td>Ventricular fibrillation</td>
<td>Recovered</td>
<td></td>
<td></td>
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<tr>
<td>15</td>
<td>46/F</td>
<td>Hypothyroidism, T2DM, muscular dystrophy, atrial fibrillation, atrial tachycardia</td>
<td>Dronedarone (S) Enoxaparin, metoprolol, metformin, warfarin, thyroid therapy, ibuprofen, paracetamol (all C)</td>
<td>2 days</td>
<td>Atrial fibrillation</td>
<td>N/A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>49/F</td>
<td>Implantable cardioverter defibrillator user</td>
<td>Dronedarone (S)</td>
<td>28 days</td>
<td>Atrial fibrillation</td>
<td>Unknown</td>
<td></td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>59/F</td>
<td>Dilated cardiomyopathy, thyrotoxicosis, lung cancer, hypertension, HF NYHA II-III, implantable cardioverter defibrillator user</td>
<td>Dronedarone (S) Furosemide, ezetimibe, sertraline, carvedilol, iron, valsartan, eplerenone, acetyl-salicylic acid, linum usitatissimum (all C)</td>
<td>2.5 months to first recorded episode</td>
<td>Ventricular arrhythmia</td>
<td>Withdrawn after second episode</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>50/M</td>
<td>HF, implantable cardioverter defibrillator user</td>
<td>Dronedarone (S)</td>
<td>14 days</td>
<td>Atrial flutter</td>
<td>Recovered</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>Age</td>
<td>Gender</td>
<td>Underlying Disease(s)</td>
<td>Medication(s)</td>
<td>Duration</td>
<td>Adverse Event(s)</td>
<td>Outcome</td>
<td></td>
</tr>
<tr>
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<td></td>
</tr>
<tr>
<td>19</td>
<td>59/F</td>
<td>Hypertension, obesity, HF, CKD stage III</td>
<td>Dronedarone (S) Diltiazem, spironolactone, ramipril, simvastatin, furosemide (all C)</td>
<td>Atrial fibrillation</td>
<td>Withdrewn</td>
<td>Fibrillation ventricular, tachycardia ventricular, QT prolonged, cardiac arrest, hypoxic-ischaemic encephalopathy*</td>
<td>Died</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>88/F</td>
<td>Congestive HF, CKD, COPD, coronary artery disease, T2DM, hyperlipidemia, hypothyroidism, gastroesophageal reflux disease</td>
<td>Dronedarone, levofloxacin (both S) Diltiazem, digoxin, glyceryl trinitrate, salbutamol, clopidogrel, clostaol (total 29 medical products, all C)</td>
<td>Atrial fibrillation</td>
<td>N/A</td>
<td>Fibrillation ventricular, tachycardia ventricular, torsade de pointes</td>
<td>Died</td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>77/F</td>
<td>Tachycardia-bradycardia syndrome, pacemaker user (dual chamber), dilated cardiomyopathy with ejection fraction 69%, asthma, obesity</td>
<td>Dronedarone (S) Calcium, docusate, diltiazem, ergocalciferol, levosibutamol, alendronic acid, estradiol, vitamins, flutocsaone, atorvastatin, levothyroxine, furosemide (all C)</td>
<td>Atrial fibrillation</td>
<td>446 days</td>
<td>Withdrewn</td>
<td>Fibrillation ventricular, torsade de pointes, QT pro-longed, cardiac arrest</td>
<td>Recovered</td>
</tr>
<tr>
<td>22</td>
<td>80/M</td>
<td>-</td>
<td>Dronedarone, quetiapine (both S) Acetylsalicylic acid, warfarin (both C)</td>
<td>Atrial fibrillation</td>
<td>128 days</td>
<td>Withdrewn</td>
<td>Fibrillation ventricular, QT pro-longed, hypertension, drug interaction, haematuria</td>
<td>Recovering</td>
</tr>
<tr>
<td>23</td>
<td>67/M</td>
<td>Previous episodes of ventricular arrhythmia, cardiac ablation, bronchitis, ischemic heart disease</td>
<td>Dronedarone, amoxicillin (both S) Metoprolol, rosuvastatin, clopidogrel, ubidecarenone, famotidine, warfarin, enoxapar in (all C)</td>
<td>Ventricular fibrillation</td>
<td>Continued</td>
<td>Fibrillation ventricular, anxiety, extrasystoles, dyspepsia, tachycardia, off-label use</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>79/M</td>
<td>Tachycardia-bradycardia syndrome, sick sinus syndrome, CKD, hypertension, T2DM, coronary artery disease, previous myocardial infarction</td>
<td>Dronedarone (S) Isosorbide mononitrate, lisinopril, simvastatin, metoprolol, vitamins, acetylsalicylic acid, cimetidine, furosemide, insulin (all C)</td>
<td>Atrial fibrillation</td>
<td>Withdrewn</td>
<td>Fibrillation ventricular, torsade de pointes, QT prolonged</td>
<td>Recovered</td>
<td></td>
</tr>
<tr>
<td>Patient</td>
<td>Age</td>
<td>Sex</td>
<td>Previous episodes of premature ventricular contractions, bifascicular block, normal left ventricular function</td>
<td>Treatment</td>
<td>Duration</td>
<td>Outcome</td>
<td>Reason for withdrawal</td>
<td>Tertiary reasons</td>
</tr>
<tr>
<td>---------</td>
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<tr>
<td>25</td>
<td>73</td>
<td>M</td>
<td>Dronedarone, metoprolol (both S) Zolpidem, digoxin, iron, acetaminophen (all C)</td>
<td>Withdrawn</td>
<td>144 days</td>
<td>Fibrillation ventricular</td>
<td>Died</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>51</td>
<td>M</td>
<td>Dronedarone (S) Antipropulsives, warfarin (both C)</td>
<td>Withdrawn</td>
<td>46 days</td>
<td>Atrial fibrillation</td>
<td>Died</td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>58</td>
<td>F</td>
<td>Dronedarone (S) Atenolol, hydrochlorothiazide/triamterene, furosemide, tranylcypromine, quinapril, warfarin (all C)</td>
<td>N/A</td>
<td>36 days</td>
<td>Fibrillation ventricular and ventricular arrhythmia</td>
<td>Died</td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>72</td>
<td>F</td>
<td>Dronedarone (S)</td>
<td>Withdrawn</td>
<td>190 days</td>
<td>Fibrillation ventricular, torsade de pointes, QT prolongation, tachycardia ventricular</td>
<td>No effect observed</td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>70</td>
<td>M</td>
<td>Dronedarone (S) Omeprazol, rosuvastatin, warfarin, acetaminophen (all C)</td>
<td>N/A</td>
<td></td>
<td>Fibrillation ventricular, myocardial infarction</td>
<td>Died</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BBB - bundle branch block, HF - Heart failure, CKD - chronic kidney disease, COPD - chronic obstructive pulmonary disease, T2DM - type 2 diabetes mellitus, N/A - not applicable *terms in MedDRA

References
5. Shantsila E, Watson T, Lip GY. Drug-induced


Response from Sanofi

The main safety concern with antiarrhythmics particularly with Class I and III, is the potential proarrhythmic effect. The pharmacological action of dronedarone may induce a moderate QTc Bazett prolongation (about 10 msec), related to prolonged repolarisation linked to the therapeutic effect of dronedarone and does not reflect toxicity. Follow up, including ECG (electrocardiogram), is recommended during treatment. If QTc Bazett interval is ≥500 milliseconds, dronedarone should be stopped. Based on clinical experience, dronedarone has a low proarrhythmic effect. However, proarrhythmic effects may occur in particular situations such as concomitant use with medications favouring arrhythmia and/or electrolytic disorders. That information is translated into the contraindications and precautions for use of dronedarone Product Information worldwide.

After the early termination of the PALLAS study due to excess of cardiovascular events in the dronedarone group, the use in permanent AF patients was contraindicated and serial ECGs were recommended, additional risk minimisation measures were implemented in the Risk Management Plan.

Close surveillance of proarrhythmic effects ventricular arrhythmia (NOS) and cardiac death cases has been performed via routine pharmacovigilance, namely in Periodic Safety Update Reports (PSURs). From periodic analyses and review of such cases and based on the information collected from product launch to last PSUR (31 July 2013), no new safety information with regards this topic was raised. The EMA endorsed this conclusion in its assessment of the last submitted PSUR.

From launch to 31 July 2014 the MAH has collected worldwide 227 cases referring to ventricular tachyarrhythmia using the standardized MedDRA query version 17.0 “Ventricular tachyarrhythmia_Narrow”, and 60 cases referring to cardiac or cardio-respiratory Arrest.

Overall, the review and analysis of all the cases of ventricular tachycardia, torsade de pointes and cardiac arrest showed that contributive factors such as concomitant drugs and or underlying cardiac disease were reported; or cases were poorly documented to allow proper medical assessment.

Focusing on the cases reported in the publication, the safety database retrieved 11 cases of ventricular arrhythmia/tachyarrhythmia and 40 cases of ventricular fibrillation, they are analyzed below:

Ventricular arrhythmia(VA)/ tachyarrhythmia cases(n=11):

They originated from Germany (n=4), United States (n=3), France (n=2), Italy and Sweden (n=1 each), involved 7 men and 4 women. One case was solicited and 10 were unsolicited. Two patients were <65 years, unknown age (n=1), elderly >70 years (n=8), (mean 71.7 years). Time to onset was available in 4 cases, all but 1 within 1 month. Outcome was favorable (n=5), all after dronedarone discontinuation; unknown (n=5), fatal (n=1). Ventricular tachycardia was co-reported in 3 cases, sudden death and cardiac arrest in 1 case each.

Among 9 documented cases, in all reported concomitant treatments with potential cardiac effects, and 8 relevant medical history/concomitant diseases, and information on electrolyte abnormalities, thyroid status, was missing in all but 1 case.

- In the case of sudden death, the death is likely resulting from a malignant ventricular arrhythmia given the patient’s carcinoma, the instantaneous nature of death and recent arrhythmias.
- In the case of cardiac arrest, concomitant use of amiodarone by error was reported, the patient recovered while dronedarone was pursued.

Concerning ventricular fibrillation(VF) cases(n=40)

They originated from mainly from United States (n=25) and Germany (n=5), involved 30 men, 8 women (unknown gender in 2 cases). Nine cases were solicited and 31 were unsolicited. Seventeen patients were <65 years, elderly (n=11), elderly >75 years(n=9), and unknown(n=3), (mean 64.2 years). Time to onset was available in 25 cases, from few hours to 8.5 months and within 1 month in 13 cases. Outcome was recovered/recovering (n=21) (following dronedarone withdrawal (n=14), pursued(n=4); not applicable (n=2), and unknown (n=1)); unknown(n=3); and fatal(n=16). Ventricular tachycardia was co-reported (n=9), torsade de pointes (n=5); cardiac arrest(n=6), and sudden death(n=4).
Among 40 cases, in 39 cases relevant medical history/comorbidities were reported mainly, including heart failure; Concomitant treatments were documented in 35 cases and included at least 1 drug (up to 6) with potential cardiac effects (n=30). Information on electrolyte, thyroid status was missing in most cases. In 9 cases, other suspect drugs were reported.

- Ventricular fibrillation with fatal outcome cases (n=16) (including sudden death, cardiac arrest or torsade de pointes cases), all documented cases reported multiple advanced diseases, with additional rhythm disorders, furthermore, concomitant treatments with potential cardiac effects were reported in most cases; additionally specific context was reported in 3 cases (possible acute ischemia, status post cardiac ablation, severe diarrhea leading to electrolytes depletion and 2 were reported in CHF patients study
- Ventricular fibrillation cases with co-reported of cardiac arrest (3), dronedarone had been discontinued 3 days before onset (n=1), hypokalaemia (n=2), in addition to underlying cardiac pathologies (n=1). All without fatal outcome

In the AF/ALF population, dronedarone 400mg BID significantly reduced the risk of sudden death by 50.8% (RR= 0.492, 95% CI [0.281; 0.861], p=0.0118). The DIONYSOS study shows that, at the 400mg BID dose, dronedarone has less effect on QTc-interval prolongation than amiodarone (600mg od for 28 days followed by 200mg od). Based on the cumulative review of ventricular arrhythmia (NOS) including cardiac death, no direct effect of dronedarone leading to ventricular arrhythmia could be confirmed. Indeed, the clinical context and the underlying condition of these patients provided more plausible other alternative explanations in all documented cases. The MAH, will continue to closely monitor this topic, and signal detection analyses will be regularly assessed as part of the PSUR.

Dronedarone and vision abnormal
Dr. Ian Boyd, Australia

Summary
Dronedarone has been shown to prevent atrial fibrillation or restore normal sinus rhythm depending on the model used. It is indicated for the maintenance of sinus rhythm after successful cardioversion in adult clinically stable patients with paroxysmal or persistent atrial fibrillation. In the WHO Global ICSR Database, VigiBase®, there are as of January 2014, 35 reports of vision abnormal in association with dronedarone. The association has an IC value (IC_{0.25} value) of -0.27 (-0.77). The ICSRs are submitted from the United States, Germany, United Kingdom, Sweden, Canada and Italy. Although there are some reports in which other vision disorders and/or the use of amiodarone may have been a cause of abnormal vision, the observation of recovery after dechallenge together with a few reports of reasonable time to onset is supportive of a signal.

Introduction
Dronedarone has been shown to prevent atrial fibrillation (AF) or restore normal sinus rhythm depending on the model used. The drug can also prevent ventricular tachycardia and ventricular fibrillation in several animal models. These effects most likely result from its electrophysiological properties belonging to all four Vaughan-Williams classes. Dronedarone is a multichannel blocker inhibiting the potassium currents and thus prolonging cardiac action potential and refractory periods. It also inhibits the sodium currents and the calcium currents. It also non-competitively antagonises adrenergic activities. It is indicated for the maintenance of sinus rhythm after successful cardioversion in adult clinically stable patients with paroxysmal or persistent atrial fibrillation. The most common adverse reactions (experienced by at least 10% of the patients) include gastrointestinal disorders such as diarrhoea, nausea, vomiting, abdominal pains and dysgeusia, cardiac disorders such as congestive heart failure and bradycardia, skin disorders such as rashes and pruritus, general disorders such as fatigue and asthenia and liver function test abnormalities. Vision abnormal is a non-specific term which refers to a change, usually a deterioration, in visual function or perception. In WHO-ART, vision
abnormal is a preferred term (PT) which encompasses many included terms (ITs) consisting of amblyopia (reduced vision in an apparently normal eye), asthenopia (eye strain), depth perception difficulty, metaporphopsia (a specific type of distorted vision), refractive error, tired eye, vision abnormal, vision abnormal aggravated, vision blurred, vision decreased, visual acuity alteration, visual disturbance and visual impairment.

**Reports in VigiBase®**

After the elimination of duplicates, as of January 2014 there are 35 ICSRs of vision abnormal in association with dronedarone in the WHO Global ICSR Database, VigiBase® (Table 1). The association has an IC value of -0.27 with an IC\textsubscript{0.05} value of -0.77. The ICSRs were submitted from the United States (22 cases), Germany (seven cases), United Kingdom, Sweden (two each) and Canada and Italy (one each). The patients ranged in age from 51 to 83 years with a median of 70 years in the 30 cases which provided this information. The gender distribution was 16 males and 19 females. Case 1 is a combination of three reports (triplicate), Case 2 is a combination of two reports (duplicate) and Case 4 is another combination of three reports (triplicate) reports.

Dronedarone was the only suspected drug in 23 of the reports. There were other suspected drugs in eleven cases. Amiodarone was another suspected drug in five cases, dabigatran was suspected in two cases, estrogen and metoprolol suspected in one case each, both silodosin and warfarin in another case, and sotalol, digoxin and bisoprolol in the remaining case. Amiodarone is a well known cause of visual disturbance and is a probable cause in the five cases where it is a suspected drug. The final case involved a suspected interaction between dronedarone and phenprocoumon.

Concomitant drugs were reported in the majority of these cases. These indicated a patient population with considerable morbidity and included use of antihypertensives, anticoagulants, hypcholesterolaemic drugs, acetylsalicylic acid, antidiabetic drugs, diuretics and thyroxine. Dronedarone was reported to have been administered orally, as expected, in the cases which provided this information.

Time to onset was reported in seven of the reports. It ranged from the same day the drug was started (in three cases) to about seven months.

The outcome was stated in 19 reports. The patients were reported as recovered or recovering in 15 cases and not recovered in the other four cases. In the cases in which the patient was reported as recovered, the drug was reported to have been withdrawn in 12 cases and continued in the other three cases. In the four cases in which the patient was reported as not recovered, the drug was withdrawn in one case, continued in two cases and the fate of the drug was unknown in the remaining case.

Other reactions were described in the reports. Neurological reactions include headache, hypoesthesia, agitation, dizziness and nervousness; cardiovascular reactions, particularly AF; gastrointestinal reactions such as diarrhoea and nausea; respiratory reactions particularly dyspnoea; musculoskeletal reactions and skin reactions. There were also cases where other vision disorders were present including blindness and eye deposits.

**Literature and Labelling**

The product literature does not refer to vision abnormal. There are no reports of vision abnormal in association with dronedarone in the literature. There is, however, an isolated report of blurred vision in the DIONYSOS trial which compared the efficacy and safety of amiodarone and dronedarone in patients with persistent AF. In this trial, there was a report of blurred vision in one of 249 patients taking dronedarone as well as a report of blurred vision in one of 255 patients taking amiodarone.

**Discussion and Conclusion**

Case reports in VigiBase® suggest that there is a signal for the association of dronedarone and vision abnormal. Dronedarone was the only suspected drug in 23 of the 35 reports of vision abnormal. There were other suspected drugs in 11 cases. Amiodarone was another suspected drug in five cases, dabigatran was suspected in two cases, oestrogen and metoprolol suspected in one case each, both silodosin and warfarin in another case, and sotalol, digoxin and bisoprolol in the remaining case. The final case involved a suspected interaction between dronedarone and phenprocoumon. Amiodarone is a well known cause of visual disturbance and is a probable cause in the five cases where it is a suspected drug. Digoxin is also a well known cause of chromatopsia and blurred vision. The use of dabigatran with dronedarone is contraindicated and there may have been an interaction in these two cases.

Time to onset is reasonably suggestive of a signal. In the seven reports in which time to onset was reported, it ranged from the same day the drug was started (in three cases) to about seven months. Dechallenge is also suggestive of a signal. The outcome was stated in 19 reports. The patients were reported as recovered or recovering in 15 cases and not recovered in the other four
cases. In the cases in which the patient was reported as recovered, the drug was reported to have been withdrawn in 12 cases and continued in the other three cases. In the four cases in which the patient was reported as not recovered, the drug was withdrawn in one case, continued in two cases and the fate of the drug was unknown in the remaining case.

There are a number of reports in which other vision disorders may have been a cause of abnormal vision. These include two reports of eye deposits in which amiodarone is a likely cause, one report of photophobia and one report of retinal vein thrombosis in which amiodarone was also suspected. Two other cases had blindness as well as other visual problems, glaucoma was also reported in two cases and a further two reports described chromatopsia with digoxin as a likely cause in one case and a number of other vision disorders as a likely cause in the other case.

Another report described a vitreous haemorrhage which is a likely cause of abnormal vision and a further report describes oscillopsia which is also a form of abnormal vision.

Leaving aside all the cases in which amiodarone or another vision disorder may have been responsible for abnormal vision (the 13 shaded cases in Table 1), there are 22 remaining cases. Of these, the outcome was stated in 13 cases. Recovery was documented in 11 cases for which the drug was withdrawn in nine of these. The patients in the other two cases had not recovered but the drug was continued. This number of dechallenges in cases which have no other obvious cause supports the possibility of a signal.

Table 1. Case overview of reports in VigiBase® of vision abnormal in association with dronedarone

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/Sex</th>
<th>Other suspected (S), concomitant (C) or interacting (I) drugs</th>
<th>Reactions WHO-ART/MedDRA</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>71/M</td>
<td>Sotalol, digoxin, bisoprolol (all S) Allopurinol, atorvastatin, candesartan, doxazosin, finasteride, metformin, omega-3-acid ethyl ester, potassium bicarbonate/sodium alginate, spironolactone, warfarin (all C)</td>
<td>Chromatopsia, bradycardia, diarrohoea, hypotension, prothrombin decreased, therapeutic response increased, renal failure acute, vision abnormal, abdominal pain, azotaemia, creatinine clearance decreased, dizziness, drug interaction, hypertenaemia, oedema, oliguria, urine abnormal</td>
<td>Unknown</td>
</tr>
<tr>
<td>2</td>
<td>74/M</td>
<td>None</td>
<td>Chromatopsia, vision abnormal, eye pain, optic atrophy, papilloedema, photopsia, pupillary reflex impaired, scotoma, visual field defect, vitreous floaters, EEG abnormal, blindness colour, blindness, optic neuritis, headache</td>
<td>Recovering</td>
</tr>
<tr>
<td>3</td>
<td>74/F</td>
<td>Amiodarone (S) Amiodarone, carvedilol, fish oil, furosemide, hydralazine, Ubidecarenone, warfarin (all C)</td>
<td>Photophobia, vision abnormal, ataxia, colon carcinoma, condition aggravated, confusion, fibrillation atrial, gait abnormal, hypoaesthesia, hypotension, muscle weakness, nervousness, pneumonia, purpura, rash, skin discoloration, tremor, pain in extremity</td>
<td>Not recovered</td>
</tr>
<tr>
<td>4</td>
<td>83/M</td>
<td>Amiodarone (S)</td>
<td>Vision abnormal, skin exfoliation, photo-sensitivity reaction, rash psoriasis, deposit eye</td>
<td>Unknown</td>
</tr>
<tr>
<td>5</td>
<td>68/M</td>
<td>Levothyroxine, rivaroxaban (both C)</td>
<td>Vision abnormal, hearing decreased</td>
<td>Unknown</td>
</tr>
<tr>
<td>6</td>
<td>51/M</td>
<td>None</td>
<td>Vision abnormal, alcohol problem, coma hepatic, diarrhoea, fatigue, headache, hyperammonaemia, hypoaesthesia, liver fatty, sweating increased, urinary incontinence, weight decrease, rigors</td>
<td>Unknown</td>
</tr>
<tr>
<td>7</td>
<td>64/M</td>
<td>None</td>
<td>Vision abnormal, headache, hepatic enzymes increased</td>
<td>Recovered</td>
</tr>
<tr>
<td>8</td>
<td>80/F</td>
<td>Lercanidipine, metoprolol, phenprocoumon, pravastatin (all C)</td>
<td>Vision abnormal, hypoaesthesia, polyneuropathy</td>
<td>Recovered with sequelae</td>
</tr>
<tr>
<td>9</td>
<td>58/F</td>
<td>Estrogen nos (S) Acetylsalicylic acid, salbutamol (both C)</td>
<td>Vision abnormal, allergic reaction, chest pain, diarrhoea, dyspnoea, insomnia, oedema peripheral, rash, thrombosis, weight increase</td>
<td>Unknown</td>
</tr>
<tr>
<td>10</td>
<td>82/F</td>
<td>Dabigatran (S) Diltiazem, simvastatin (both C)</td>
<td>Vision abnormal, dizziness</td>
<td>Unknown</td>
</tr>
<tr>
<td>11</td>
<td>77/F</td>
<td>Atenolol, lisinopril, nifedipine, warfarin (all C)</td>
<td>Vision abnormal, bradycardia, chest pain, fibrillation atrial, glaucoma, headache</td>
<td>Recovered</td>
</tr>
<tr>
<td>No.</td>
<td>Gender</td>
<td>Medication (S/C/I)</td>
<td>Symptoms</td>
<td>Outcome</td>
</tr>
<tr>
<td>-----</td>
<td>--------</td>
<td>--------------------</td>
<td>----------</td>
<td>---------</td>
</tr>
<tr>
<td>12</td>
<td>-/M</td>
<td>Dabigatran (S)</td>
<td>Vision abnormal, arthralgia</td>
<td>Not recovered</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Terazosin (C)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>75/F</td>
<td>Atorvastatin, clopidogrel, glibenclamide, insulin glargine, lansoprazole, levoflaxine, potassium, valsartan (all C)</td>
<td>Vision abnormal, blindness, condition aggravated, constipation, fibrillation atrial, halo vision</td>
<td>Unknown</td>
</tr>
<tr>
<td>14</td>
<td>68/F</td>
<td>Amiodarone (S)</td>
<td>Vision abnormal, thrombosis retinal vein, agitation, fibrillation atrial, sleep disorder, thyroid disorder, product label issue</td>
<td>Unknown</td>
</tr>
<tr>
<td>15</td>
<td>82/F</td>
<td>Carvedilol, clopidogrel, esomeprazole, gabapentin, insulin, insulin glargine, insulin lispro, levoflaxine, lisinopril, warfarin (all C)</td>
<td>Vision abnormal, fatigue, flatulence, pain, speech disorder, thrombosis coronary</td>
<td>Unknown</td>
</tr>
<tr>
<td>16</td>
<td>-/F</td>
<td>None</td>
<td>Vision abnormal, diarrhoea</td>
<td>Unknown</td>
</tr>
<tr>
<td>17</td>
<td>70/F</td>
<td>Dronedarone, phenprocoumon (both I) Bisoprolol, hydrochlorothiazide/triamterene, ramipril (all C)</td>
<td>Vision abnormal, vitreous haemorrhage, drug interaction, prothrombin decreased</td>
<td>Recovering</td>
</tr>
<tr>
<td>18</td>
<td>65/F</td>
<td>Acetylsalicylic acid, alprazolam, atorvastatin, colecalciferol/calcium carbonate, fish oil, risedronic acid, rosuvastatin, vitamins nos/minerals nos (all C)</td>
<td>Vision abnormal, blepharospasm, eye abnormality, eye pain, arrhythmia, depression, fibrillation atrial, hyperglycaemia, pulmonary disorders, rash erythematous, sleep disorder, wheezing, angle closure glaucoma, tension headache</td>
<td>Not recovered</td>
</tr>
<tr>
<td>19</td>
<td>70/M</td>
<td>Atorvastatin, bisoprolol (both C)</td>
<td>Vision abnormal, agitation, fibrillation atrial, tachycardia supraventricular</td>
<td>Unknown</td>
</tr>
<tr>
<td>20</td>
<td>79/F</td>
<td>Adalimumab, metoprolol, warfarin, verapamil (all C)</td>
<td>Vision abnormal, abdominal pain, dyspepsia, headache, skeletal pain, urinary incontinence</td>
<td>Recovered</td>
</tr>
<tr>
<td>21</td>
<td>80/F</td>
<td>None</td>
<td>Vision abnormal, abdominal pain, tinnitus</td>
<td>Recovered</td>
</tr>
<tr>
<td>22</td>
<td>70/F</td>
<td>Atenolol, diltiazem, levoflaxine, warfarin (all C)</td>
<td>Vision abnormal, drug level decreased, prothrombin decreased</td>
<td>Recovering</td>
</tr>
<tr>
<td>23</td>
<td>68/F</td>
<td>Acetylsalicylic acid, atorvastatin, heparin, nebivolol, pantoprazole, valsartan, zinc, drug name/s under assessment (all C)</td>
<td>Vision abnormal, anxiety, dizziness, dyspnoea, gait abnormal, hallucination, medication error</td>
<td>Recovered</td>
</tr>
<tr>
<td>24</td>
<td>61/F</td>
<td>None</td>
<td>Vision abnormal, agitation, diarrhoea, fibrillation atrial, nausea, nervousness, oedema, skin disorder</td>
<td>Not recovered</td>
</tr>
<tr>
<td>25</td>
<td>68/M</td>
<td>Digoxin, glipizide, lisinopril, metoprolol, nicotinic acid, simvastatin, warfarin, vitamin b complex (all C)</td>
<td>Vision abnormal, confusion, fibrillation atrial, neuropathy peripheral, oedema peripheral, weight decrease</td>
<td>Recovered</td>
</tr>
<tr>
<td>26</td>
<td>60/F</td>
<td>Metoprolol (S) Acetylsalicylic acid, enalapril, pravastatin, warfarin (all C)</td>
<td>Vision abnormal, cardiac failure, depersonalization, dizziness, dyspnoea, dysuria, hypertension, nausea, oedema peripheral, renal failure chronic</td>
<td>Recovered</td>
</tr>
<tr>
<td>27</td>
<td>78/M</td>
<td>Silodosin, warfarin (both S)</td>
<td>Vision abnormal, drug interaction</td>
<td>Unknown</td>
</tr>
<tr>
<td>28</td>
<td>70/F</td>
<td>None</td>
<td>Vision abnormal, blindness, ocular haemorrhage, abdomen enlarged, cerebrovascular disorder, dyspnoea, fatigue, fibrillation atrial, myalgia, nausea, sleep disorder, weight increase, hemianopia homonymous, quality of life decreased</td>
<td>Unknown</td>
</tr>
<tr>
<td>29</td>
<td>-/M</td>
<td>Amiodarone (S)</td>
<td>Vision abnormal, arrhythmia, coughing, confusion, depression, dyspnoea, emotional lability, fatigue, fibrillation atrial, GI haemorrhage, headache, hypoaeesthesia, myalgia, muscle weakness, nervousness, paraesthesia, photosensitivity reaction, pleural effusion, rigors, sleep disorder, tremor, blood count abnormal, product quality issue</td>
<td>Unknown</td>
</tr>
<tr>
<td>No.</td>
<td>Age</td>
<td>Gender</td>
<td>Medications</td>
<td>Adverse Reactions</td>
</tr>
<tr>
<td>-----</td>
<td>-----</td>
<td>--------</td>
<td>-----------------------------------------------</td>
<td>--------------------------------------------------------</td>
</tr>
<tr>
<td>30</td>
<td>58/F</td>
<td>Vision abnormal, abdominal pain, depression, headache, lacrimation abnormal</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>75/F</td>
<td>Metoprolol, phenprocoumon, pravastatin, ramipril (all C)</td>
<td>Vision abnormal, oscillopsia</td>
<td>Recovered</td>
</tr>
<tr>
<td>32</td>
<td>79/F</td>
<td>Acetylsaliclyc acid, amlodipine, clonidine, glipizide, glyceryl trinitrate, insulin, isosorbide dinitrate, labetalol, lansoprazole, methyldopa, phenobarbital/atropine sulfate/hyoscine hydrobromide/hyoscyamine sulphate (all C)</td>
<td>Vision abnormal, hallucination</td>
<td>Recovered</td>
</tr>
<tr>
<td>33</td>
<td>76/M</td>
<td>Amiodarone (S) Benazepril hydrochloride/amlodipine besylate, clopidogrel, lovastatin, nicotinic acid (all C)</td>
<td>Vision abnormal, blindness temporary, corneal deposits</td>
<td>Unknown</td>
</tr>
<tr>
<td>34</td>
<td>73/M</td>
<td>Digoxin, fish oil, glyceryl trinitrate, hydrochlorothiazide/lisinopril, metformin, metoprolol, rosuvastatin, tadalafil, testosterone, warfarin, vitamins nos (all C)</td>
<td>Vision abnormal, cardiac failure, dyspnoea, oedema, weight increase</td>
<td>Recovered</td>
</tr>
<tr>
<td>35</td>
<td>51/M</td>
<td>Acetylsaliclyc acid, beta blocking agents, simvastatin (all C)</td>
<td>Vision abnormal, arrhythmia, leg pain, myalgia</td>
<td>Recovered</td>
</tr>
</tbody>
</table>

**References**


**Response from Sanofi**

Dronedarone is similar to amiodarone in its molecular structure with an important difference consisting in the presence of methylsulfonamide group to reduce solubility in fats (lipophilicity) and thus reduce neurotoxic effects. As dronedarone might theoretically share the latter class effect, close surveillance of neuropathy ADRs including optic neuropathy has been performed since launch by the MAH via routine pharmacovigilance, namely in subsequent 6-month PSURs and as a potential pharmacological class effect in the Risk Management Plan updates. Periodic analyses of the cases did not confirm an evidence of a causal link between dronedarone and neurologic disorders including neuropathy not otherwise specified (NOS) or optic neuropathy (using MedDRA standardized query "Optic nerve disorders_Broad+Narrow"). This conclusion was endorsed by EMA in the Assessment Report to the most recently submitted PSUR7 (September 2013).

From launch of dronedarone to 31 January 2014, a total of 115 cases (3 solicited and 112 unsolicited: 62 medically confirmed and 50 consumer; 70 serious and 45 nonserious) pertaining to the HLGT “vision disorders” were collected worldwide. They referred to 137 reactions mainly coded with the following MedDRA preferred terms: visual impairment (n=49), vision blurred (n=46) or visual acuity reduced (n=11), concerned 55 women and 51 men (unspecified in 9 cases), aged between 43 and 90 years (median: 72 years; unspecified in 22 cases). Onset dates were available in 37 out of 65 medically confirmed cases (a few hours-2.3 years).

In 40 out of 115 cases, dronedarone was withdrawn, leading to favorable outcome in 26 cases, but information on corrective treatment, if any, was missing in all but 1 case where
Concerning the 62 unsolicited medically confirmed cases:

• In 1 case, dronedarone rechallenge was negative.
• In 29 cases, the case documentation elements were not sufficient to allow drawing a clear conclusion.
• In 10 cases, treatment with amiodarone provides a more likely explanation.
• In 4 cases, treatment with digoxin provides a more likely explanation.
• In 4 cases, the patient’s underlying condition provides a plausible alternative explanation: medical history of abnormal vision NOS (n=1), multiple risk factors potentially inducing ischemic optic neuropathy, retinal detachment and macular edema (n=1), optic neuritis since amiodarone therapy in a patient with multiple risk factors including among other recent treatment for metastatic breast cancer (n=1), hypertension in a patient experiencing “flickering in the eyes” (n=1).
• In 4 cases, visual disturbances occurred in a specific context that explains its occurrence: vitreous hemorrhage with increased PT under VKA therapy (n=1), occipitotemporal infarction in a patient with multiple risk factors (TIA, cerebral infarction) (n=1), syncope and dehydration in 1 case of “vision blackout” (coded transient blindness), very recent TIA in a patient with contributive underlying condition and concomitant treatments (n=1).
• In 1 case, concomitant silodosin provides a more likely explanation.
• In 1 case, the patient’s medical history was relevant for severe coronary artery disease, vascular disease, diabetes and hypertension, and concomitant treatments included clonazepam, lamotrigine and metoprolol.
• In 1 case, the patient, with unknown medical history, had normal ophthalmological investigation NOS and concomitant treatment with venlafaxine.
• In 1 case of optic nerve atrophy and papilloedema, missing information on neurological and ophthalmological investigation results at baseline did not allow a proper medical assessment. Furthermore, poor blood flow causing ischemic optic neuropathy may have contributed to the development of optic atrophy that may be secondary to prolonged papilloedema.
• In the following 6 cases, vision disorder were associated with others events:
  - Context of congestive heart failure in a patient with glaucoma and diabetes mellitus, and relevant concomitant digoxin (n=1).
  - Face and lips edema, in a patient with diabetes mellitus (n=1).
  - Hallucinations in a patient with diabetes mellitus, coronary heart disease and hypertension concomitantly treated with phenobarbital, clonidine and methyldopa (n=1).
  - Dizziness and headache in a patient with digoxin therapy, diabetes, hypertension, concomitantly treated with hydrocodone, carvedilol and pantoprazole (n=1).
  - Balance disorder, dizziness and fatigue in a patient with hypothyroidism, and concomitant treatments relevant for nebivolol, omeprazole, and primidone (n=1).
  - Headache in a patient with hypertension and concomitant treatments for hydrochlorothiazide (n=1).

Concerning the 50 consumer cases, ophthalmic investigations results were performed in 4 cases and without findings. Overall, the case documentation elements were not sufficient to allow drawing a clear conclusion. Moreover alternative explanations or confounding factors were reported in most of the cases.

In context of pharmacovigilance activities to assess the risk of optic neuritis, peripheral neuropathy, and muscular disorders in patients treated with dronedarone compared with amiodarone and other antiarrhythmics, an epidemiology study (DRONE C06714) was performed by MAH using the MarketScan database. The results showed no evidence that dronedarone was associated with significantly higher risks of optic neuritis, peripheral neuropathy compared to other antiarrhythmics. Final report was submitted in the previous RMP version 9.

In placebo-controlled clinical trial program in the pooled population, vision disorders were reported in 1.3% of patients in dronedarone and 1.1% of patients in placebo groups. Incidence of vision blurred was 0.6% in both treatment groups.

In the DIONYSOS study, no differences concerning vision disorders were observed. A trend towards less photophobia and blurred vision was observed in the dronedarone compared to the amiodarone group.

In Pallas study, peripheral neuropathies, including optic neuropathy were reported in 0.4% in the
dronedarone group, versus 0.2% in the placebo group. Vision blurred was reported in 1 patient in each group (< 0.1%).

Based on available up-to-date information the MAH concludes that there is insufficient evidence to support a causal association between dronedarone and vision abnormal. The MAH will continue to monitor this topic in the next PSUR.
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®.
16th International Conference of Drug Regulatory Authorities (ICDRA) and its recommendations

As featured in WHO Drug Information Vol. 28, No.3, 2014

The 16th International Conference of Drug Regulatory Authorities (ICDRA) was held in Rio de Janeiro, Brazil, on 26–29 August 2014. The conference was hosted by the Brazilian Health Surveillance Agency ANVISA, in collaboration with WHO. The recommendations are set out on the following pages.

Government officials and regulators from more than 100 WHO Member States came together at this year’s ICDRA to discuss current challenges and strengthen collaboration. The ICDRA conferences, held every two years, have become a well-established forum for regulatory authorities, WHO and interested stakeholders to determine priorities for action in regulation of medical products.

A pre-conference titled “Ensuring Quality and Safety of Biosimilars for Patients Worldwide” was held on 24–25 August at the same venue. The ICDRA pre-conferences are open to participants from regulatory authorities, industry, academia and nongovernmental and international organizations.

►WHO. International Conference of Drug Regulatory Authorities [web site]: http://www.who.int/medicines/icdra (includes links to recommendations and presentations of past ICDRA conferences)
►16th ICDRA official web site: http://www.icdra.com.br

16th ICDRA sessions (recommendations, see pages 37–45)

| Plenary 3 | The role of drug regulatory authorities in national health systems |
| Plenary 4 | Strengthening regulatory systems for medical products |
| Plenary 5 | Regulators’ role in access/availability (shortages etc.) |
| Plenary 6 | New trends in regulating medical devices |
| Workshop A | Best practices in pharmacovigilance |
| Workshop B | How to ensure the safety of traditional and complementary medicines in national healthcare systems |
| Workshop C | Regulatory models for minimizing risks in blood and blood products |
| Workshop D | Approaches to educating regulators to meet country needs |
| Workshop E | Challenges of vaccine safety regulation and safety monitoring |
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16th ICDRA recommendations

Plenary 3

The role of drug regulatory authorities in national health systems

Strengthen the role of national regulatory authorities (NRAs) in public health protection and promotion, establishing the necessary governance and legal frameworks that will support NRAs in the exercise of this role, and establishing mechanisms to ensure effective linkages within the health, science/technology and industrial sectors, and with civil society, in order to contribute to universal health coverage.

Strengthen the capacity of NRAs to assess and monitor the quality, safety and efficacy of medicines and medical products, ensuring effective implementation of core regulatory functions to support product registration and market authorization, as well as post-marketing surveillance, to monitor the use of the products in health services and during the complete product life cycle.

Recognize the role of the NRA in supporting innovation and ensuring access to medical products in health systems and services by supporting regulatory processes that result in the introduction of safe new innovative medical products within health services, that guide the safe use of medical products in public health emergencies, and – in collaboration with other stakeholders – address shortages of essential medicines.

Plenary 4

Strengthening regulatory systems for medical products

Recognize that effective regulatory systems are an essential component of health system strengthening that contribute to better public health outcomes; that regulators are an essential part of the health workforce; and that inefficient regulatory systems themselves can be a barrier to access safe, effective and quality medical products.

Strengthen WHO’s role in strengthening regulatory systems for medical products from a public health perspective, and in supporting national drug regulatory authorities and relevant regional bodies in this area, and in particular in developing countries.

Support the development and strengthening of national regulatory systems through the assessment of regulatory functions and system performance with WHO support, and the development and implementation of institutional development plans that will protect and promote health at the national level, and will pool and leverage regulatory capacity regionally and globally to promote access to quality, safe and efficacious and affordable medical products.

Promote the greater participation of national regulatory authorities in existing international and regional initiatives and networks for collaboration and cooperation in accordance with WHO principles and guidelines, and increase support for and recognition of the significant role of the International Conference of Drug Regulatory Authorities in promoting the exchange of information and collaborative approaches among drug regulatory authorities, and as a resource to facilitate further development of regulatory cooperation and coherence.
Plenary 5

Regulators’ role in access/availability (shortages etc.)

**Member States**
Explore the possibilities to promote convergence and harmonization of regulatory processes, and use joint and collaborative assessments as appropriate (with neighbouring countries or between authorities with common interest in certain products), in order to facilitate registration of medical products and increase efficiency.

Design and implement fast-track and/or abbreviated registration processes for medical products that have already undergone rigorous evaluation in other countries e.g. by using the Collaborative procedure between national regulatory authorities in user countries and the WHO Prequalification programme for vaccines and medicines for priority diseases.

Share experiences in design of special procedures for registration of products in case of emergencies or structural shortages, and for parallel importation.

**WHO and Member States**
WHO and countries should:
- collaborate in setting up a global monitoring system on medicines shortages;
- identify medicines vulnerable to supply interruption; and
- share experience in preventing and managing shortages.

► **To respond to the Ebola virus disease (EVD) public health emergency of international concern, the following recommendations are made.**

**Member States**
Ensure there are emergency use regulatory pathways in place;
ensure there is rapid and proactive cooperation and collaboration between regulators, and also with WHO, to help accelerate development and evaluation of investigational treatments and vaccines; and drive innovative clinical trial design for situations like the current EVD emergency where traditional clinical trial designs may not be feasible.

**WHO**
Rapidly provide scientific information on the potential therapies and vaccines for EVD, and ensure the information is regularly updated;
establish and lead a network of regulators globally to address the response to EVD; and facilitate collaborations between regulators in countries where products are being developed and those in countries where the products will be evaluated and, if found safe, used.

Plenary 6

New trends in regulating medical devices

**WHO**
Continue and further strengthen international convergence/harmonization initiatives and normative work for medical devices, including IVDs, to support regulatory convergence in different jurisdictions.
Support low- and middle-income countries (LMIC) to strengthen their regulations of medical devices, including IVDs, through provision of regulatory mechanisms that balance pre-and post-market regulatory oversight according to the risk level of the device.
Workshop A

Best practices in pharmacovigilance

Member States
Implement Pharmacovigilance (PV) as an integrated service that informs and improves health-systems, health resources and health-care delivery;
integrate PV within a regulatory framework to ensure accountability and best practices in the way medicinal products are handled throughout their life cycle;
embrace robust tools and methods for risk-based PV, to collect, manage and exploit PV information, including the detection of irrational use and quality-related aspects;
engage all relevant stakeholders (patients, industry, authority, academia, health professionals and others) to develop and implement comprehensive PV plans; and
in order to participate in a global PV community, be the beneficiary and the benefactor of PV information.

WHO
Promote PV as an overarching integrated service that informs public health programmes and supports regulatory decisions;
maintain and convene the global PV network and database, and support the global exchange of PV information across Member States;
facilitate PV convergence and alignment across Member States, to allow consistent and comparable PV practices, optimal information exchange and learning; and
develop and support the adoption of international norms, standards and tools to promote risk-based PV and for the full scope of PV (irrational use, medication errors, quality-related aspects).

Workshop B

How to ensure the safety of traditional and complementary medicines in national healthcare systems

Member States
Establish, strengthen and implement an effective regulation of providers of herbal medicines in respect of their qualification, in order to ensure the safety and quality of their practices;
establish, strengthen and effectively enforce regulations on herbal medicines;
strengthen capacity-building efforts for providers, manufactures and regulators of herbal medicines in order to improve their capacity and expertise regarding assurance of safety and quality of herbal medicines; and
include safety monitoring on herbal medicines in pharmacovigilance systems and promote the awareness of consumers/patients on safety aspects of herbal medicines.

WHO
Provide technical support to Member States in the implementation of the latest World Health Assembly resolution on traditional medicine (WHA67.18) and the WHO Traditional Medicine Strategy: 2014-2023, in particular regarding the safety of herbal medicines and of traditional and complementary medicine practices.
Continue to provide technical support to Member States in:
strengthening national capacity for regulation of herbal medicines in ensuring the safety and quality of herbal medicines; and
sharing information regarding the safety of herbal medicines through global networking and relevant tools, including the networks of the International Regulatory Cooperation for Herbal Medicines (IRCH) and of the National Centres participating in the WHO International Drug Monitoring Programme.
Workshop C

Regulatory models for minimizing risks in blood and blood products

Member States
Member States are encouraged to add whole blood and blood components (red blood cells, platelets and fresh frozen plasma) to their national lists of essential medicines consistent with their inclusion in 2013 on the WHO Model List of Essential Medicines.

Member States are encouraged to establish regulation of whole blood and blood components on the model of biological therapeutics* in order to:
   - protect the health and safety of blood donors; and
   - assure the quality, safety, efficacy and availability of blood for transfusion, and of plasma for further manufacturing to make essential derivatives.

Member States are encouraged to establish regulation of whole blood, blood components and plasma derivatives within the national regulatory authority, including:
   - appropriate risk-based selection and quality assurance of test kits for donor screening; and
   - assuring bidirectional traceability of blood components between donors and patients as a foundation of haemovigilance.

Member States are encouraged to adopt internationally recognized standards for blood collection and processing as an essential element of blood regulation.

National standards for blood collection, processing and testing should be established and enforced by the national regulatory authority.

WHO
At the request of Member States, WHO should provide assistance on:
   - capacity-building for national blood systems including a national regulatory authority;
   - establishment of appropriate legal frameworks for blood regulation and strategies for their implementation.

Workshop D

Approaches to educating regulators to meet country needs

WHO
Expedite coordination, development and launching of a global regulatory science curriculum; and develop and publish an inventory of accredited training centres and other training initiatives including specific areas of competency.

Workshop E

Challenges of vaccine safety regulation and safety monitoring

Member States
Vaccine safety concerns need to be addressed on an individual basis, and regulatory action should be tailored to the clinical setting as well as to the safety issue, the disease, and the strength of the evidence available.

A combined effort by national regulatory authorities to support WHO in setting appropriate monitoring systems for vaccines worldwide is encouraged, especially in relation to newer vaccines.

* The wording reflects recommendations as proposed and agreed during the conference; one comment was subsequently received.
WHO

Multi-country collaboration on surveillance and monitoring of vaccine safety concerns should be actively pursued, to maximize the use of resources and public health protection, under the WHO umbrella.

WHO efforts to enhance maternal immunization efforts are commended and should continue with support from all stakeholders.

**Member States and WHO**

Pharmacovigilance data from multiple sources should be considered, with special emphasis and continued efforts to harmonize reporting and collection of safety data.

Efforts to raise the quality and quantity of relevant data on vaccines use during pregnancy should continue.

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**Workshop F**

**Collaboration for ensuring the quality and safety of active pharmaceutical ingredients (APIs)**

At the request of Member States, WHO and Member States (well-resourced national regulatory authorities) should establish a system of targeted capacity-building for ensuring the quality and safety of APIs:

- focusing on the needs and obligations of producing countries and user countries;
- emphasizing practical skills development through:
  - twinning and staff placements;
  - sustainable training approaches based on defined competencies (e.g., through a network of Centers of Excellence); and
  - observed/collaborative/joint inspections.

Member States should establish transparent regulatory systems, based on internationally agreed-upon standards, that will assure quality and safety of APIs produced and used in, and/or exported from their borders, ensuring that:

- APIs and their intermediates are manufactured by regulated manufacturers; and
- API suppliers and brokers are regulated.

WHO and Member States should support and encourage the use of work-sharing mechanisms for ensuring the quality and safety of APIs, e.g. WHO Prequalification of APIs, Certificates of Suitability of the European Pharmacopoeia (CEP), the International Generic Drug Regulators Pilot (IGDRP), etc.

WHO should facilitate establishment of guidance on good/risk-based regulatory practice, including identification and use of available regulatory expertise to facilitate local regulatory decisions.

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**Workshop G**

**Preventing and reducing the risk to public health from substandard/spurious/falsely-labelled/falsified/counterfeit (SSFFC) medical products**

▷ **With a view to reducing the risks to public health from SSFFC medical products, all Member States are strongly encouraged to:**

- participate in the WHO Member State Mechanism on SSFFC medical products, including implementation of the agreed work plan;
- in particular, to participate in on line working groups both to:
  - establish recommendations to detect and deal with actions, activities and behaviours that result in SSFFC medical products, and
  - establish activities that fall outside of the mandate of the Member State Mechanism.

Within the framework of the Member State Mechanism, WHO should continue to provide support and build capacity in low-income countries to tackle SSFFC medical products.
Prevention
National medicines regulatory authorities (NMRAs) are encouraged to develop a specific strategy to combat SSFFC medical products tailored to their national and regional needs, including but not restricted to:
- target awareness campaigns for specific stakeholders; and
- strengthening networks of key stakeholders to enable more effective collaboration, cooperation and communication.
NMRAs utilizing track, trace and authentication technologies should share knowledge and experience with a view to strengthening supply chain integrity.
WHO and Member States should undertake research into the root causes of SSFFC medical products, including the scope, scale and harm caused to public health, health systems and Member States.

Detection
All NMRAs should have access to field testing equipment and/or Quality Control Laboratories; all NMRAs are encouraged to carry out risk-based post market surveillance and market surveys; and all NMRAs are encouraged to ensure sustainable pharmacovigilance reporting systems from healthcare professionals and the public, specifically including the lack of efficacy of a medical product.

Response
All NMRAs are encouraged to have developed procedures to respond to suspected SSFFC medical products, with particular attention to quarantine, seizure, sampling, analysis, recall, investigation, enforcement, information-sharing and collaborating with stakeholders.
All NMRAs are encouraged to share information concerning incidents involving suspected SSFFC medical products with sub-regional and regional regulatory networks and WHO through rapid alert systems.
In order to protect public health, all NMRAs should increase knowledge and understanding and influence evidence-based policy and resource allocation.

Workshop H
Biosimilars
1. Ensure regulatory oversight throughout the life cycle of biotherapeutic products, including similar biotherapeutic products, (SBP) to assure quality, efficacy and safety of these products

Member States
Clearly define regulatory pathways for biotherapeutic products, including biosimilars, and make this information transparent and easily available (e.g. through a web site).
Implement regulatory standards for approval of biological products that are aligned with WHO standards.
Strengthen regulatory functions, in particular clinical evaluation and PV, including proactive collection of PV data.

WHO
Update norms, standards, and tools to facilitate further development of expertise for regulatory evaluation of biologicals.
Nomenclature for similar biotherapeutics is a complex issue for which there is no consensus yet; this is under discussion with the WHO INN Expert group, and a consultation with all Member States and stakeholders is under way.

2. Improve efficiency of regulatory evaluation of biotherapeutic products, including SBP, in order to improve access to products of assured quality, safety and efficacy

Member States
Make effort to reduce time for evaluation without compromising quality of the review, in particular review
time for the purpose of licensing or clinical trial approval.

Facilitate the development and licensing of innovative molecules which could serve as reference products in the development of biosimilars.

Develop information and/or work-sharing with other regulators for SBP (e.g. recognition of other NMRAs’ conclusions; work-sharing in sub-regional or regional networks).

**WHO**

Continually update information regarding WHO standards for biologicals through regional and/or inter-regional networks and initiatives.

### 3. WHO guidelines on biotherapeutic products and on SBP

**Member States**

Implement existing WHO guidelines and subsequent updates in full, and monitor levels of implementation over time.

If national standards differ from WHO standards, inform WHO of the rationale for this situation.

**WHO**

Amend Guidelines on evaluation of SBP by providing additional information on:
- extrapolation of indication;
- special considerations for evaluation of monoclonal antibodies;
- acceptance criteria and evaluation of reference biotherapeutic products (RBP) including the reliance on reference agencies;
- the design, conduct and interpretation of data for comparability exercise.

Facilitate implementation of existing guidelines on SBP (adopted in 2009), and subsequent updates, and on biotherapeutic products made by recombinant DNA technology (adopted in 2013).

Develop e-learning tools for different levels (e.g. basic, advanced).

Prepare case studies for illustrating practical application of guiding principles to different scenarios, e.g. mimic the real situation.

Make all materials from implementation workshop (i.e. lectures, discussions, and case studies) available to all regulators.

Develop criteria and/or tool for assessing implementation level of WHO written standards (guidelines) into regulatory practice.

### 4. Collaboration between regulators and other relevant stakeholders

**Member States**

Involve all relevant stakeholders (e.g. manufacturers, academia, health care providers, patient associations) during development of national regulatory requirements and create opportunities for regular feedback on regulatory practices.

Develop national initiatives for better access to biotherapeutic products, including SBPs; such initiatives may include considerations on intellectual property issues, interchangeability, and substitutability. *

Develop programmes to educate all relevant stakeholders on the nature and intended use of biosimilars, and define the role of each stakeholder in improving access to biotherapeutic products, including biosimilars. *

**WHO**

Provide a forum for information-sharing on collaborative efforts that leads to better access.

* Reflects recommendations as proposed and to which no objections were made at the time of adoption, but which do not necessarily represent consensus since some regulators expressed different views during the meeting.
**5. Regulatory convergence as a tool to increase global access to SBPs of quality, safety, and efficacy**

**Member States**
Make effort to align national regulatory requirements with WHO guiding principles for biotherapeutic products, including SBP.
Define terminology for naming SBP that enables clear identification of the evaluation pathway. *
Use the term “biosimilar” for products that were demonstrated as similar through an evaluation that is in line with the biosimilar pathway as described in WHO Guidelines on evaluation of similar biotherapeutic products, only.

**WHO**
Develop tools to measure progress in regulatory convergence.

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**Workshop I**

**Current status and future vision of regulating advanced therapies**

Products containing genetically modified viable cells should be considered cell therapy medicinal products. They are biological medicinal products.
Products containing viable cells which are used in transfusion medicine (e.g. thrombocyte, erythrocyte, granulocyte concentrates) or for haematopoietic reconstitution are not considered cell therapy medicinal products.

**Member States**
Member States are encouraged to develop regulatory expertise for cell therapy medicinal products appropriate for the specific nature of these products. In this regard it is recommended to:
- share regulatory experiences among national regulatory authorities to allow appropriate regulatory responses; and
- promote information-sharing between academia, industry and national regulatory authorities on newest technologies including stem cell therapies.

Development of cell therapy medicinal products in clinical trials should be facilitated prior to standard clinical use after authorization by a national regulatory authority.

Experimental product testing by the developer should be established and enforced by the national regulatory authority.

**WHO**
WHO should consider developing guidance on manufacture, non-clinical and clinical aspects of cell therapy medicinal products, taking into account existing guidelines, points to consider and recommendations, with the collaboration of leading regulatory authorities.
At the request of Member States, WHO should organize the provision of assistance on capacity-building for the regulation of cell therapy medicinal products.
WHO should foster international collaboration between regulatory authorities regarding information-sharing to protect patients and the public from the risks of unauthorized cell therapy medicinal products.

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**Workshop J**

**Managing decentralized Good Manufacturing Practice (GMP) systems**

It is recommended that Member States, whatever their organizational model is in the field of GMP inspections,
should ensure that all inspections are done in a consistent manner and that inter-inspector variability is measured and managed.

It is recommended that Member States, when interacting with other Member States in the field of GMP inspections, make sure that any international inspection is notified well in advance to the national inspectorate on whose territory the inspection will take place, with the aim of allowing inspectors from that country to observe the inspection, thus serving the ultimate goal of creating mutual trust and recognition between inspectorates.

Workshop K

Current challenges and transparency in clinical trials regulation

Member States
Increase the transparency of processes, and work towards consistency of approaches to transparency for clinical trial review and approvals across countries.
Increase collaboration and cooperation to build capacity of regulatory authorities for oversight of clinical trials;
Ensure that appropriate regulatory pathways are in place to provide rapid but effective regulatory oversight of products to be used in public health emergencies;
Rarely use domestic clinical trials to generate local data but use extrapolation instead; where justified, the regulator should define the scientific question to be answered in domestic studies.

WHO
Support countries in developing consistent approaches to transparency for clinical trial reviews and approvals.
Strengthen platforms to support capacity-building initiatives for regulatory oversight of clinical trials.
Facilitate joint reviews of multi-country clinical trial approvals.
Establish guidelines on regulatory pathways for products to be used in public health emergencies.

Workshop L

Current topics and future developments

Member States
Promote innovative approaches to enhancing quicker access of medicinal products, without compromising safety;
Future-proof regulatory approaches and gain insight into newer emerging products through horizon-scanning; interact with stakeholders and collaborate;
With other national regulatory authorities, garner support for appropriate resources and funding to be better prepared in tackling the safety, quality and efficacy of these emerging products.
Member States are encouraged to engage in multilateral cooperative networks with other regulators, which will facilitate information-sharing and provide mutual benefit for participants; and
Member States are encouraged to join or draw benefits from multinational initiatives aimed at sharing best practices and expertise, achieving regulatory convergence of requirements as well as work-sharing, e.g. the International Generic Drug Regulators Pilot (IGDRP), the International Medical Device Regulators Forum (IMDRF) and the International Pharmaceutical Regulators Forum (IPRF).

WHO
Support NMRAs in decision-making by provision of models for regulatory information-sharing and collaboration, including suitable IT instruments/tools.
Expand existing WHO collaborative procedures for information-sharing.