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, Box 1051, 751 40 Uppsala, Sweden. Tel: +46-18-65.60.60, Fax: +46-18-65.60.80, E-mail: info@who-umc.org, Internet: http://www.who-umc.org

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The WHO Pharmaceuticals Newsletter provides you with the latest information on the safety of medicines and legal actions taken by regulatory authorities across the world. It also provides signals from the Uppsala Monitoring Centre’s SIGNAL document.

The feature article in this issue gives you an overview of the WHO programme for the monitoring and surveillance of Substandard, Spurious, Falsely labelled, Falsified and Counterfeit (SSFFC) medical products.
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Belimumab

Progressive Multifocal Leukoencephalopathy (PML) reported in patients
Canada. GlaxoSmithKline, in consultation with Health Canada, informed health-care professionals of important new safety information regarding Progressive Multifocal Leukoencephalopathy (PML) reported in patients receiving belimumab (Benlysta™). Belimumab is indicated, in addition to standard therapy, for reducing disease activity in adult patients with active, autoantibody-positive, systemic lupus erythematosus (SLE).

Two cases of PML have been reported spontaneously in adult female patients receiving belimumab out of an estimated post-marketing exposure of over 15,000 SLE patient exposures. Both patients were also receiving mycophenolate mofetil (MMF) and prednisone. One of the patients died.

Health-care providers should consider a diagnosis of PML in any patient on belimumab, presenting with new onset deficits or deterioration in cognition, speech or ocular functions, and/or motor and gait disturbances. Seizures may also occur.

If PML is suspected, the patient should be urgently referred to a neurologist, or other appropriate specialist. Where appropriate, treatment with belimumab and other immunosuppressant therapy should be withheld until PML is excluded.


Caustinerf arsenical and yranicid arsenical

Recommendation to revoke authorisations of use of caustinerf arsenical and yranicid arsenical in dental procedure

Europe. The European Medicines Agency’s (EMA) Committee for Medicinal Products for Human Use (CHMP) has recommended that the marketing authorisations for the dental pastes caustinerf arsenical, yranicid arsenical and associated names be revoked in the EU due to concerns over the risk of genotoxic effects and cell death in tissues around the teeth. The dental pastes, which contain an arsenic-based compound, arsenic trioxide, have been used to remove the damaged nerves in the dental pulp (the inside of the tooth).

In a review of the benefits and risks of these dental products, analyses of data from laboratory and population studies indicate that the arsenic contained in them may pose a risk of genotoxic effects that could increase the risk of cancer. In addition, there have been a small number of cases where arsenic is thought to have leaked into the areas around the teeth, causing parts of the tissue to die, including bone (osteonecrosis).

Post-marketing surveillance of caustinerf arsenical and yranicid arsenical has identified a small number of cases of periodontal necrosis, including 12 cases of osteonecrosis. The majority of cases occurred within 7 days of using the pastes.

During the review, the CHMP considered measures to minimize the risks identified with these products but concluded that restrictions and additional guidance to dentists would not reduce the risks to an acceptable level.

The EMA has concluded that the benefits of caustinerf arsenical, yranicid arsenical and associated products do not outweigh their risks and has recommended that their marketing authorisations in the EU be revoked. Dentists should use other alternative methods available for removing dental pulp.


Cyclizine

Restricted use in children under 6 years of age

Egypt. Egyptian Pharmaceutical Vigilance Center (EPVC) has recommended that cyclizine use in children under six years of age should be restricted. Marketing authorization holders of products containing cyclizine should update the product label to include restrictions of use in children under six years.

Cyclizine is a piperazine derivative with histamine H1-receptor antagonist activity and is indicated in motion sickness. The precise mechanism of action is not well understood. It may have effects directly on the labyrinthine apparatus and on the chemoreceptor trigger zone. Cyclizine exerts a central anticholinergic (anti-muscarinic) action.

Recommendations for Health-care Professionals (HCPs)

1. Cyclizine dose by mouth or by intravenous injection over 3-5 minutes: Child 6-12 years 25 mg up to 3 times daily and Child 12-18 years 50 mg up to 3 times daily.

2. Cyclizine dose by rectum: Child 6-12 years 25 mg up to 3 times daily and Child 12-18
years 50 mg up to 3 times daily.

3. Cyclizine dose by continuous intravenous or sub-cutaneous infusion: Child 6-12 years 75 mg over 24 hours and Child 12-18 years 150 mg over 24 hours.


Dabigatran

Risks as compared to warfarin

USA. The U.S Food and Drug Administration (FDA) recently completed a new study comparing patients on dabigatran (Pradaxa®) to warfarin, for risk of ischaemic or clot-related stroke, bleeding in the brain, major gastrointestinal (GI) bleeding, myocardial infarction (MI), and death. The new study included information from more than 134,000 patients, 65 years or older, and found that among new users of blood-thinning drugs, dabigatran was associated with a lower risk of clot-related strokes, bleeding in the brain, and death, than warfarin. The study also found an increased risk of major gastrointestinal bleeding with use of dabigatran as compared to warfarin. The MI risk was similar for the two drugs.

Importantly, the new study is based on a much larger and older patient population than those used in FDA’s earlier review of post-market data, and employed a more sophisticated analytical method to capture and analyse the events of concern. This study’s findings, except with regard to MI, are consistent with the clinical trial results that provided the basis for dabigatran’s approval. As a result of these latest findings, the FDA still considers dabigatran to have a favourable benefit to risk profile and have made no changes to the current label or recommendations for use.

Patients should not stop taking dabigatran (or warfarin) without first talking with their health-care professionals. Stopping the use of blood-thinning medications such as dabigatran and warfarin can increase the risk of stroke and lead to permanent disability and death. Health-care professionals who prescribe dabigatran should continue to follow the dosing recommendations in the drug label.


Epidural corticosteroid injection

Risk of rare but serious neurologic problems

USA. The FDA is warning that injection of corticosteroids (including methylprednisolone, hydrocortisone, triamcinolone, betamethasone, dexamethasone) into the epidural space of the spine may result in rare but serious adverse events, including loss of vision, stroke, paralysis, and death. The injections are given to treat neck and back pain, and radiating pain in the arms and legs. The effectiveness and safety of epidural administration of corticosteroids have not been established, and FDA has not approved corticosteroids for this use.

FDA is requiring the addition of a Warning to the drug labels of injectable corticosteroids to describe these risks.

FDA will convene an Advisory Committee meeting of external experts in late 2014 to discuss the benefits and risks of epidural corticosteroid injections and to determine if further FDA actions are needed.


Eszopiclone containing sleep aids

Can cause next-day impairment

USA. The FDA has notified health professionals and their medical care organizations of a new warning that the insomnia drug eszopiclone (Lunesta®) can cause next-day impairment of driving and other activities that require alertness. FDA recommends a decreased starting dose of eszopiclone to 1 mg at bedtime. Women and men are equally susceptible to impairment from eszopiclone, so the recommended starting dose of 1 mg is the same for both. FDA approved changes to the eszopiclone (Lunesta®) prescribing information and the patient Medication Guide to include these new recommendations. The drug labels for generic eszopiclone products will also be updated to include these changes.

A study of eszopiclone found that the previously recommended dose of 3 mg can cause impairment to driving skills, memory, and coordination that can last more than 11 hours after receiving an evening dose. Despite these driving and other problems, patients were often unaware they were impaired. The new lower recommended starting dose of 1 mg at bedtime will result in less drug in the blood the next day.

Filgrastim and pegfilgrastim

Risk of Capillary Leak Syndrome (CLS)

Canada. Amgen Canada Inc., in consultation with Health Canada, informed health-care professionals of the risk of Capillary Leak Syndrome (CLS) associated with the granulocyte colony stimulating factors (G-CSF) filgrastim and pegfilgrastim.

Filgrastim (Neupogen®) is associated with a risk of CLS in patients with cancer and in healthy donors. Pegfilgrastim (Neulasta®) is associated with a risk of CLS in patients with cancer.

Cases of CLS have been reported in:

a. patients undergoing chemotherapy who were receiving filgrastim or pegfilgrastim and

b. donors undergoing peripheral blood progenitor cell mobilization who were receiving filgrastim.

CLS can cause circulatory shock and may be fatal. It is associated with hypotension, generalized edema, hypoalbuminemia and hemoconcentration. Episodes can vary in frequency and severity. Should symptoms of CLS be suspected, administration of filgrastim or pegfilgrastim should be stopped and the patient closely monitored. The Product Monographs (Neupogen® and Neulasta®) are being updated to reflect this new safety information.

Filgrastim is indicated to: decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-neoplastic drugs, and for the prevention and treatment of neutropenia, to maintain a normal Absolute Neutrophil Count (ANC) in bone marrow transplant patients and in patients with HIV infection.

Pegfilgrastim is indicated to:

decrease the incidence of infection, as manifested by febrile neutropenia, in patients with non-myeloid malignancies receiving myelosuppressive anti-neoplastic drugs.


Mirtazapine

Association with QT prolongation/Torsades de Pointes

Canada. Merck Canada Inc., in consultation with Health Canada, informed health-care professionals of important new recommendations for mirtazapine (Remeron® / REMERON RD®) regarding post-marketing cases of QT prolongation and torsades de pointes with the use of mirtazapine (REMERON® / REMERON RD®). Most cases occurred in association with drug overdose or in patients with other risk factors for QT prolongation, including concomitant use of QT prolonging medications.

The Product Monograph has been updated to include this information and to advise caution in patients with risk factors such as known cardiovascular disease, family history of QT prolongation and concomitant use of QT prolonging medications. Monitoring of vital signs and cardiac rhythm should be undertaken in the management of mirtazapine overdose.

Serious outcomes including torsades de pointes and death have been reported with mirtazapine overdose. Patients with torsades de pointes may present with dizziness, palpitations, syncope, or seizures. If sustained, torsades de pointes can progress to ventricular fibrillation and sudden cardiac death.

Mirtazapine is indicated for the symptomatic relief of depressive illness.


Meclizine

Restriction of use

Egypt. Based on the Egyptian Pharmaceutical Vigilance Centre (EPVC) assessment study, the Pharmacovigilance Committee recommends:

1. Not to use meclizine in children under two years of age.
2. Allowing the usage under medical supervision only in children from 2-12 years of age.
3. The product label should state this recommendation clearly.

Meclizine is a first-generation antihistamine of the piperazine class. It is structurally and pharmacologically similar to buclizine, cyclizine, and hydroxyzine, but has a shorter half-life of six hours compared to cyclizine and hydroxyzine with about 20 hours.


Temozolomide

Risk of hepatic injury

Canada. Merck Canada Inc., in consultation with Health Canada, informed health-care professionals of new warnings for temozolomide (TEMODAL®) regarding cases of hepatic injury, including
fatal hepatic failure reported post-marketing.

Temozolomide is an antineoplastic agent indicated for the treatment of adult patients with newly diagnosed glioblastoma multiforme concomitantly with radiotherapy and then as maintenance treatment. It is also indicated for treatment of adult patients with glioblastoma multiforme or anaplastic astrocytoma and documented evidence of recurrence or progression after standard therapy.

Cases of hepatic injury, including fatal hepatic failure, have been reported in patients receiving temozolomide. Liver toxicity may occur several weeks after initiation of treatment or after temozolomide discontinuation.

Liver function tests should be performed

- prior to treatment initiation;
- after each treatment cycle;
- midway during the treatment cycle for patients on a 42 day treatment cycle.

For patients with significant liver function abnormalities, the benefits and risks of continuing treatment should be carefully considered.

In total, 44 cases of hepatic injury, including fatal hepatic failure (19 cases) were identified in patients receiving temozolomide from market introduction (19 January 1994) through 15 March 2013.

The temozolomide (Temodal®) product monograph has been revised to include updated information on the risk of hepatic injury and specific recommendations for monitoring of liver function.


Vemurafenib

Association of vemurafenib use with Drug Induced Liver Injury (DILI)

Canada. Hoffmann-La Roche Limited (Roche Canada), in consultation with Health Canada, informed health-care professionals of important new safety information regarding the risk of Drug Induced Liver Injury (DILI) reported with vemurafenib (Zelboraf®).

Vemurafenib is indicated as a monotherapy for the treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma.

DILI, including cases of severe liver injury, has been reported with vemurafenib.

As of September 26, 2013, 63 cases out of an estimated 20,000 patients treated with vemurafenib (Zelboraf®) were identified as having experienced DILI.

There were no reported deaths among the 63 cases of liver injury. There were two severe cases, both reported as hepatic failure; the outcome of one case of severe liver injury was reported as completely resolved with vemurafenib discontinuation while the outcome of the second severe liver injury case is not available at this time.

The Product Monograph (Zelboraf®) will be updated to include appropriate information regarding the risk of DILI and physicians should discuss the currently available information regarding benefits and risks of vemurafenib with their patients.

Prescribers are reminded to monitor transaminases, alkaline phosphatase, and bilirubin before initiation of vemurafenib treatment and monthly during treatment, or as clinically indicated. Liver injury should be managed using dose reduction, temporary interruption, or treatment discontinuation of vemurafenib.

### Hydroxyzine-containing medicines

**Review started**

**Europe.** The European Medicines Agency (EMA) has started a review of hydroxyzine-containing medicines, which have been approved in most EU countries for a variety of uses including anxiety disorders, as premedication before surgery, for relief of pruritus (itching), and for sleep disorders.

The review was requested by the Hungarian medicines agency (GYEMSZI-OGYI) over concerns about the side effects of these medicines on the heart. This followed an examination of the benefits and risks by a marketing authorisation holder for hydroxyzine. Data from drug safety monitoring (pharmacovigilance) and published experimental studies identified a potentially increased risk of alterations of the electrical activity of the heart and arrhythmias (irregular heartbeats). As hydroxyzine-containing medicines are approved in other EU countries, the Hungarian agency decided to trigger an EU-wide review.

The EMA will now review the available data on the benefits and risks of hydroxyzine-containing medicines in all authorized indications, and issue an opinion on the marketing authorisations of these medicines across the EU.

While the review is ongoing, patients should speak to their doctor or pharmacist if they have any questions or concerns.

**Reference:** Press release, EMA, 08 May 2014 ([www.ema.europa.eu](http://www.ema.europa.eu)).

### Ivabradine

**Review started**

**Europe.** The EMA has started a review of the medicine ivabradine (Corlentor/Procoralan®). Ivabradine is used to treat the symptoms of adults with long term stable angina (chest pain due to obstruction in the arteries in the heart) or long term heart failure (when the heart cannot pump enough blood to the rest of the body). The review follows preliminary results from the SIGNIFY study, which was evaluating whether treatment with ivabradine in patients with coronary heart disease reduces the rate of cardiovascular events (such as heart attack) when compared with placebo. Patients in the study received up to 10 mg twice daily, which is higher than the currently authorized maximum daily dose (7.5 mg twice daily), and the results showed a small but significant increase in the combined risk of cardiovascular death or non-fatal heart attack with the medicine in a subgroup of patients who had symptomatic angina (Canadian Cardiovascular Society class II - IV).

The EMA will now evaluate the impact of the data from the SIGNIFY study on the balance of benefits and risks of ivabradine and issue an opinion on whether the marketing authorization should be maintained, varied, suspended or withdrawn across the EU. While the review is ongoing and pending further communication, patients should speak to their doctor or pharmacist if they have any questions or concerns.

**Reference:** Press release, EMA, 08 May 2014 ([www.ema.europa.eu](http://www.ema.europa.eu)).

### Sildenafil

**Clarification on warning about paediatric use for pulmonary arterial hypertension**

**USA.** The FDA clarified its previous recommendation related to prescribing sildenafil (Revatio®) for children with pulmonary arterial hypertension (PAH). Sildenafil is FDA-approved only to treat PAH in adults, not in children; however, health-care professionals must consider whether the benefits of treatment with the drug are likely to outweigh its potential risks for each patient.

FDA revised the sildenafil drug label in August 2012, adding a warning stating that “use of sildenafil, particularly chronic use, is not recommended in children.” This recommendation was based on an observation of increasing mortality with increasing sildenafil doses in a long term clinical trial in paediatric patients with PAH.

The purpose of the August 2012 recommendation was to raise awareness of clinical trial results showing a higher risk of mortality in paediatric patients taking a high dose of sildenafil when compared to paediatric patients taking a low dose. This recommendation was not intended to suggest that sildenafil should never be used in children; however, some health-care professionals have interpreted this information as a contraindication, and have refused to prescribe or administer the drug.

The evidence behind FDAs initial recommendation has not changed; this communication is clarifying the strength of the warning communicated in the sildenafil drug label.

(See WHO Pharmaceuticals Newsletter No.5, 2012 for recommendation against use in children for pulmonary arterial hypertension (PAH) in USA)
**References:** FDA Safety Communication, US FDA, 31 March 2014 ([www.fda.gov](http://www.fda.gov)).

**Tumour necrosis factor alpha inhibitors**

**Risk of tuberculosis**

**UK.** The Medicines and Healthcare Products Regulatory Agency (MHRA) announced that there is an increased risk of tuberculosis, or reactivation of latent tuberculosis, during treatment with tumour necrosis factor alpha (TNF-alpha) inhibitors. Tuberculosis in patients receiving TNF-alpha inhibitors can be life threatening, and deaths from tuberculosis have occurred in these patients. TNF-alpha inhibitors are therefore contraindicated in patients with active tuberculosis or other severe infections. Patients should be screened for tuberculosis before starting treatment with a TNF-alpha inhibitor and be monitored closely for infectious diseases including tuberculosis before, during, and after treatment.

Health-care professionals are advised that:

- TNF-alpha inhibitors are contraindicated in patients with active tuberculosis or other severe infections.
- If latent tuberculosis is diagnosed, start treatment for this infection before treatment with a TNF-alpha inhibitor.

**References:** Drug Safety Update, April 2014 ([www.ema.europa.eu](http://www.ema.europa.eu)).

**Cyproterone acetate and ethinyl estradiol**

**Safety Review: venous thromboembolism**

**Canada.** Cyproterone acetate and ethinyl estradiol are approved in Canada for the treatment of severe acne with accompanying symptoms of androgenisation including excessively oily skin as well as facial and body hair growth, after topical therapy or systemic antibiotic treatments have failed. It is to be used only after other acne treatments have not worked.

Blood clots are a rare but well-known side effect associated with the use of hormonal products containing progestins and estrogens. The risk of blood clot formation is less common in young, healthy, non-pregnant women than in those on hormonal products. Other issues that may increase a woman's chance of developing a clot include older age, smoking, obesity and periods of immobility such as those associated with long distance travel or hospitalization.

To minimize health risk factors, a safety review was initiated to evaluate the currently available information regarding the potential risk of blood clots with cyproterone acetate and ethinyl estradiol (Diane-35®). The review was prompted by a French medicines regulatory agency announcement on January 30th, 2013 indicating its intention to suspend the marketing authorizations for cyproterone acetate and ethinyl estradiol for acne treatment in France within 3 months.

A Health Canada review considered Canadian patient reports, scientific and medical literature, and what is known about the use of this medicine both in Canada and internationally. The current existing strategies to minimize this risk were also considered, including a review of the product information available to health-care professionals and patients.

The major reason for prescribing this medicine is for the treatment of severe acne, but the data also indicate its usage as means of birth control (estimated at 35-40% of prescriptions given by general practitioners and obstetrician/gynaecologists), which is considered an unapproved use of this drug.

The Canada Vigilance database was searched for reports that implicated both cyproterone acetate and ethinyl estradiol products and blood clot related incidence or any report of death.

The review also considered the scientific and medical literature. It was found that the occurrence of blood clots in users of cyproterone acetate and ethinyl estradiol was higher than non-users but similar to some of the hormonal birth control products currently available on the Canadian market. It was concluded that this information does not point to a higher risk of blood clots than what is already known about cyproterone acetate and outlined in the product information.

In Health Canada’s review of the safety of anti-acne medication cyproterone acetate and ethinyl estradiol has found that the drug’s benefits continue to outweigh the risks, when used as authorized.

The current prescribing information for cyproterone acetate and ethinyl estradiol already contains warnings about the risk of blood clots. However, considering the current evidence and discussions that have taken place internationally, Health Canada is adopting a precautionary approach and has updated the prescribing information to provide further clarity regarding this rare but known risk.

**Reference:** Advisories, Warnings and Recalls, Health Canada, 07 April 2014 ([www.hc-sc.gc.ca](http://www.hc-sc.gc.ca)).
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 8 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 on page 29. For information on the UMC Measures of Disproportionate Reporting please refer to WHO Pharmaceuticals Newsletter Issue No. 1, 2014.

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: info@who-umc.org.

Dronedarone and AV block

Dr. Raquel Herrera Comoglio, Argentina

Summary
Dronedarone is an iodine-free analogue of amiodarone, approved for use in atrial fibrillation (AF) since 2009. Its net electrocardiographic manifestations include sinus rate slowing, PR prolongation and mild QTc prolongation with little effect on QRS duration.

The atrioventricular (AV) node conducts the electric impulse generated in the sinoauricular node (P waves) to ventricles. Atrioventricular conduction can be either delayed, intermittent or totally blocked (that is, 1st, 2nd or 3rd degree AV block, respectively). AV block can be caused by pathological conditions or drugs.

On 20 September 2013, 15 reports had been entered into the WHO Global Individual Case Safety Reports (ICSR) Database, VigiBase™ reporting the combination dronedarone and AV block: 14 ICSRs where all but one document dronedarone as the only suspected drug, and one report from literature, an abstract presenting results of ECG monitoring in 70 patients. For these ICSRs, causality assessment globally suggests a possible association between AV block onset and dronedarone, although the role of other concomitant medication cannot be ruled out in six of the patients. No published cases or case series reports were found in a PubMed search with the query “dronedarone AND (AV block OR atrioventricular block)”. Labelled product information does not mention AV block as an adverse effect of dronedarone, and AV block is specifically reported as an adverse effect in only one clinical trial publication. The reported combination “AV block and dronedarone” deserves further investigation and should be considered as a signal.

Introduction
Dronedarone is an amiodarone analogue with structural modifications intended to eliminate the effects of amiodarone on thyroid and pulmonary functions. Dronedarone is iodine-free, less lipophilic than amiodarone, has a much smaller volume of distribution, and has an elimination half-life of about 24 hours, in contrast to amiodarone’s half-life of several weeks. Unlike amiodarone, dronedarone has little effect at thyroid receptors.

Dronedarone’s electrophysiological properties belong to all four Vaughan-Williams classes of antiarrhythmic agents with multiple ion channel blocking, which include inhibiting potassium currents (Class III), sodium currents (Class Ib) and calcium currents (Class IV). It also
AV block can be caused by myocardial ischaemia or infarction, degeneration of the His-Purkinje conduction system, infections, immunological disorders, surgery, congenital disorders and drugs. Beta-blockers, digoxin, verapamil and diltiazem are among the most frequent culprit drugs. Digitalis toxicity causes AV block. Non-cardiovascular drugs, such as rivastigmine, have also been reported as the cause of AV block. Pharmacokinetic (PK) interaction between paroxetine and metoprolol has also been associated with AV block. Pharmacodynamic (PD) interactions between rivastigmine and beta blockers have also been published.

In first degree block there is a delay in conduction of the atrial impulse to the ventricles, usually at the level of the atrioventricular node. In second degree block some P waves are not followed by a QRS complex because of an intermittent failure of conduction between the atria and ventricles. In third degree block there is complete failure of conduction between the atria and ventricles, with complete independence of atrial and ventricular contractions and no relation between P waves and the QRS complexes.4

### Reports in VigiBase

Up to 20 September 2013, 14 Individual Case Safety Reports (ICSRs) and one ICSR reflecting data from literature5 were submitted to the WHO Global ICSR Database, VigiBase™. The ICSRs come from USA (eight), Germany (three), Canada (one), Israel (one), and Spain (one). The main characteristics of these reports in VigiBase are displayed in Table 1.

The ICSRs represent 10 female and four male patients; age was reported in 10 cases and ranged from 28 to 87 years, (seven patients >65 years; four patients 75 years or older). All but two ICSRs were reported as “serious”, one being fatal. Six out of 14 ICSRs do not report the degree of AV block, six report 1st degree AV block and 2nd degree is reported in two cases. The dose of dronedarone was 400 mg twice daily in eight cases, 400 mg without reported frequency in two cases, and not known in four cases.

Nine ICSRs report drug withdrawal: outcome was reported as "recovered" in four cases (two cases recovered the day after the withdrawal of dronedarone), and in one case as "recovering" (case 2). In only one case (with unknown outcome), the dose was reported as "not changed". In case 2, a 28 year old woman with pacemaker presented with AV block 2nd degree Wenckebach and AV block complete and increased pacemaker rhythm 14 days after having started dronedarone therapy. The dose of dronedarone was first reduced and the patient's condition improved; dronedarone was withdrawn 27 days later. After rechallenge, there was no recurrence.
**Table 1. Characteristics of reports in VigiBase™ for Dronedarone and AV-block**

<table>
<thead>
<tr>
<th>Case</th>
<th>Sex/Age</th>
<th>AV block degree</th>
<th>Duration of use</th>
<th>Time to onset</th>
<th>Co-reported adverse drug reactions</th>
<th>Concomitant drugs with potential PD interactions</th>
<th>Dechallenge / Rechallenge</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>F/-</td>
<td>1st degree</td>
<td>10 d</td>
<td>17 d</td>
<td>Acute renal failure, blood creatinine increased, potassium serum increased, diarrhoea</td>
<td>Amlodipin, digoxin</td>
<td>Drug withdrawn/-</td>
<td>Unknown</td>
</tr>
<tr>
<td>2</td>
<td>F/28</td>
<td>2nd degree Wenckebach AV block complet</td>
<td>41 d</td>
<td>14 d</td>
<td>Pacemaker-generated rhythm</td>
<td>-</td>
<td>Drug withdrawn / No recurrence</td>
<td>Recovering</td>
</tr>
<tr>
<td>3</td>
<td>F/73</td>
<td>2nd degree Cardiac</td>
<td>112 d</td>
<td>112 d</td>
<td>Cardiac failure</td>
<td>Lercanidipine, metoprolol</td>
<td>Drug withdrawn/-</td>
<td>Recovered (in a day)</td>
</tr>
<tr>
<td>4</td>
<td>M/-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Bradycardia</td>
<td>Bisoprolol</td>
<td>Unknown</td>
<td>Unknown</td>
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<tr>
<td>5</td>
<td>M/-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Supraventricular extrasystoles</td>
<td>Amiodarone, digoxin</td>
<td>Drug withdrawn/-</td>
<td>Unknown</td>
</tr>
<tr>
<td>6</td>
<td>F/70</td>
<td>-</td>
<td>Start 03/2011</td>
<td>Onset 03/2011</td>
<td>Blood creatinine increased, acute liver disturbance</td>
<td>-</td>
<td>Unknown/-</td>
<td>Died</td>
</tr>
<tr>
<td>7</td>
<td>F/71</td>
<td>-</td>
<td>Start 08/2011</td>
<td>Onset 08/2011</td>
<td>Palpitations</td>
<td>-</td>
<td>Drug withdrawn/-</td>
<td>Recovered</td>
</tr>
<tr>
<td>8</td>
<td>F/-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>Atrial tachycardia</td>
<td>-</td>
<td>Unknown/-</td>
<td>Unknown</td>
</tr>
<tr>
<td>9</td>
<td>M/57</td>
<td>1st degree</td>
<td>-</td>
<td>-</td>
<td>Bradycardia, lethargia, hot flushes, shortness of breath, QT prolonged, supraventricular extrasystoles, intolerance induced, atrial fibrillation</td>
<td>Metoprolol</td>
<td>-/-</td>
<td>Not reported</td>
</tr>
<tr>
<td>10</td>
<td>F/79</td>
<td>1st degree</td>
<td>47 d</td>
<td>-</td>
<td>Sinus bradycardia, oedema peripheral, muscle spasms, dyspnoea, cardiac failure congestive, brain natriuretic peptide increased atrial fibrillation</td>
<td>Carvedilol, atenolol</td>
<td>Drug withdrawn/-</td>
<td>Unknown</td>
</tr>
<tr>
<td>11</td>
<td>F/75</td>
<td>1st degree</td>
<td>7 d</td>
<td>-</td>
<td>Bradycardia, atrial flutter fibrillation</td>
<td>-</td>
<td>Drug withdrawn/-</td>
<td>Recovered</td>
</tr>
<tr>
<td>12</td>
<td>F/67</td>
<td>1st degree</td>
<td>-</td>
<td>1 y 4.5 m</td>
<td>Hyperhydrosis, dyspnoea, tachycardia, atrial fibrillation, palpitations, fatigue, malaise</td>
<td>Pindolol</td>
<td>Dose not changed</td>
<td>Unknown</td>
</tr>
<tr>
<td>13</td>
<td>F/87</td>
<td>1st degree</td>
<td>1 y 5 m</td>
<td>1 y 4 m 21 d</td>
<td>Malaise, atrial fibrillation</td>
<td>Carvedilol</td>
<td>Drug withdrawn/-</td>
<td>Unknown</td>
</tr>
<tr>
<td>14</td>
<td>M/75</td>
<td>-</td>
<td>6 m</td>
<td>6 m</td>
<td>Pacemaker complication (threshold increase of pacemaker with ineffective stimulation)</td>
<td>-</td>
<td>Drug withdrawn/-</td>
<td>Recovered (in a day)</td>
</tr>
<tr>
<td>15</td>
<td>Literature report: sinus bradycardia, AV block 2nd degree, QT prolonged, AF - 4 patients presented with: AV block type II, QT prolongation with sinus bradycardia (unspecified number of patients AV block) in the first 3 days. In other 4 patients, dronedarone was discontinued due to unspecified side effects in the 4 weeks period of follow-up. Causality: associated</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** d = days, m = months, y = year/years, PD = Pharmacodynamic
In all ICSRs except one, dronedarone was the only drug suspected; concomitant medications were reported in 10 cases. Digoxin, beta-blockers, calcium-channel blockers and amiodarone (in one case) are mentioned as previous concomitant medication in seven cases.

In seven cases, time to onset is not reported; although in the fatal case it can be supposed to be shorter than a month because the date of patient’s death was in the same month as the month stated in the duration of use. Time to onset, reported in seven cases, ranges from seven days to one year and five months. Due to inconsistencies in time to onset, case 1 cannot be considered for a possible association of dronedarone and AV block.

The ICSR reflecting data from literature (case 15) contains an abstract of a study in which 70 patients (35 men and 35 women), mean age 67 years, NYHA Class I-III, normal left ventricular ejection fraction, with atrial flutter or paroxysmal or persistent atrial fibrillation, were treated with dronedarone 400 mg twice daily, initiated under or persistent atrial fibrillation, were treated with dronedarone and AV block.

The Auspar “Clinical findings” section includes safety data results of six safety studies. In the study DAFNE, two patients (1%) presented with AV block in the dronedarone group (one patient in the 1200 mg group and one patient in the 1600 mg group), compared with 2 patients (3%) in the placebo group. In the ADONIS study one out of six deaths in the dronedarone group was due to a third degree AV block; AV block is not mentioned among cardiac treatment emerging adverse events (TEAEs). AV block is not mentioned as an adverse effect in the ERATO, EURIDIS, ATHENA or DIONYSOS studies. In the ERATO study, prolongation of PR interval occurred more frequently in the dronedarone group.

The Auspar “Clinical findings” section also includes the safety data results of Bioavailability and Bioequivalence (BA/BE) and PK studies. In 11 BA/BE, PK and interaction studies including 332 healthy volunteers, 44 subjects experienced 1st or 2nd degree AV block, with dronedarone alone (39 cases) or with propranolol (one case), diltiazem (one case) oestrogens (two cases) and grapefruit juice (one case); one AV block was reported as a serious adverse event (SAE), two withdrawals were due to AV block (one being the mentioned SAE). Doses that caused AV block ranged from 400 mg to 2400 mg, but not all are specified. The PR interval was reported as increased in five studies: “at higher doses”, “in all doses”, “with diltiazem”, “in elderly males” and “PR>220 ms”. The studies’ characteristics and number of subjects experiencing AV block are shown in Table 2.

At the www.clinicaltrials.gov website, results from six studies with dronedarone are presented. AV block is not listed as a SAE or AE for the HESTIA, ODYSSEUS or PALLAS studies. AV block first degree is reported as an AE in one subject treated with dabigatran etexilate 150 mg + dronedarone 400 mg two hours later in the Phase I “Drug Interaction Study with dabigatran etexilate and dronedarone in healthy subjects”, (36 healthy volunteers). One patient in the dronedarone group presented with atrioventricular block complete (SAE) in the Phase III Study ATHENA. No patients in the dronedarone group and one patient in the amiodarone group presented with AV block first degree (SAE) in the Phase III study DIONYSOS.

Published articles reporting clinical trials results with dronedarone were also reviewed, although a systematic review was not performed. The article for the EURIDIS and ADONIS trials (828 patients treated with dronedarone and 409 patients with placebo), reported “bradycardia or conduction block” as an adverse event in 22 patients treated with dronedarone (2.7%) and in eight patients with placebo (2%) (p=0.56); and as SAEs in eight patients treated with dronedarone (1%) and in three patients with placebo (0.7%) (p=1.0). The term “Any bradycardia or conduction block event” included complete AV block; serious adverse events included complete AV block, sinus bradycardia, 1st-degree AV block and nodal arrhythmia.

The published results of the ATHENA trial (2,301 patients receiving dronedarone 400 mg twice daily and 2,327 patients receiving placebo) does not specifically mention AV block as an adverse event. In the post-hoc analysis publication, there is no mentioning of AV block as an adverse event. This article highlights that the reduced mortality and cardiovascular hospitalization associated with the use of dronedarone occurs in a subgroup of patients with more extensive cardiovascular disease and who already receive established (secondary) cardiovascular preventive drugs, i.e. β-blockers, statins,
### Table 2. Bioequivalence/bioavailability and PK studies reported in AusPAR for dronedarone hydrochloride with cases of AV block

<table>
<thead>
<tr>
<th>Study</th>
<th>Populations/treatment</th>
<th>Dose</th>
<th>Number of subjects with AV block</th>
</tr>
</thead>
<tbody>
<tr>
<td>GAR3585</td>
<td>24 male healthy volunteers treated with dronedarone</td>
<td>Bioavailabilities of four different formulations at a dose of 800 mg administered orally.</td>
<td>One subject experienced two episodes of 1st degree AV block.</td>
</tr>
<tr>
<td>TDU1657</td>
<td>48 volunteers, 36 treated with dronedarone</td>
<td>25, 50, 100, 200, 400, 500, 600, 700, 800, 1000, 1200 or 1400 mg as a single dose.</td>
<td>One subject (400 mg. dose) had 72 episodes of type II AV block (Wenckebach) on Holter monitor 5.5 hours after administration.</td>
</tr>
<tr>
<td>TDR2395</td>
<td>52 volunteers treated with dronedarone</td>
<td>400, 600 or 800 mg twice daily, or 800, 1200 or 1600 mg once daily. Treatment duration was for 14 days. The comparator was placebo.</td>
<td>Five AV block TEAEs in dronedarone patients and two AV block TEAEs in placebo patients. An increase in PR was seen at higher doses.</td>
</tr>
<tr>
<td>TDR3549</td>
<td>41 volunteers treated with dronedarone</td>
<td>800 mg (n=6), 1000 mg (n=6), 1200 mg (n=7), 1400 mg (n=6), and 1600 mg (n=6), all administered orally, twice daily.</td>
<td>16 AV block: first degree in 15 subjects and 2nd degree in one patient. Prolongation of PR interval was seen in all dose groups.</td>
</tr>
<tr>
<td>POP2769</td>
<td>54 young and elderly healthy volunteers, 52 treated with dronedarone 800 mg/day for 12 days.</td>
<td>800 mg single dose and as a once daily administration, orally, for 12 days.</td>
<td>Two 2nd degree AV block. There was a significant increase in mean PR interval of 9 ms in the elderly male group.</td>
</tr>
<tr>
<td>INT2636</td>
<td>19 volunteers treated with dronedarone</td>
<td>800 mg orally as a single dose, and as once daily for 7 days; and propranolol 40 mg tablets, 80 mg as a single dose and once daily for 14 days.</td>
<td>Two subjects discontinued because of AV block: one subject presented with first degree on dronedarone alone; one subject presented with 2nd degree Wenckebach type AV block on dronedarone plus propranolol.</td>
</tr>
<tr>
<td>INT3353</td>
<td>17 volunteers treated with dronedarone</td>
<td>600 mg twice daily, orally for 14 days, administered orally in the fed state and warfarin 10 mg tablets; 30 mg once daily orally for two single doses (with and without dronedarone coadministration).</td>
<td>One subject presented with 2nd degree AV block.</td>
</tr>
<tr>
<td>INT4074</td>
<td>30 volunteers treated with dronedarone</td>
<td>400, 800, 1200, or 1600 mg once daily oral as two single doses in the fed state. Nifedipine SR 20 mg tablets, 20 mg twice daily for 5 days. Diltiazem SR 240 mg capsules; 240 mg twice daily oral for 5 days.</td>
<td>Three AV blocks were reported as TEAEs; there was a statistically significant increase in PR interval when dronedarone was coadministered with diltiazem.</td>
</tr>
<tr>
<td>INT4442</td>
<td>16 volunteers treated with dronedarone</td>
<td>1200 mg twice daily for 10 days, oral administration in the fed state. Simvastatin 20 mg tablets, 20 mg once daily orally, two single doses. The first dose prior to dronedarone treatment, and the second during dronedarone treatment.</td>
<td>One subject withdrew due to a 1st degree AV block.</td>
</tr>
<tr>
<td>INT4695</td>
<td>21 female volunteers treated with dronedarone</td>
<td>800 mg twice daily for 10 days, oral administration in the fed state. Stediril 30 tablets: ethinylestradiol 0.03 mg and levonorgestrel 0.15 mg, once daily oral administration, two dosing cycles of 21 days.</td>
<td>Two subjects reported AV block during dronedarone treatment, and one out of two was withdrawn.</td>
</tr>
<tr>
<td>INT4886</td>
<td>24 volunteers treated with dronedarone</td>
<td>400 mg as two single doses (fasted and fed), and as a twice daily oral dose (in the fed state) for 10 days and Grapefruit juice, double strength, 300 mL three times daily, orally, during one of the treatment.</td>
<td>One SAE: AV block, and there were two discontinuations, one due to the mentioned AV block. There were five reports of PR&gt;220 ms.</td>
</tr>
</tbody>
</table>
angiotensin converting enzyme inhibitors, and antithrombotic therapy.

An article reporting results from the PALLAS trial does not mention AV block as an adverse effect. There were 13 deaths because of cardiac arrhythmia (2.5%) in the dronedarone group and four deaths (0.8%) in the placebo group, types of arrhythmia are not stated.10

A third of the patients were treated with digoxin, in this subgroup study medication was permanently discontinued prematurely in 21% of patients with dronedarone and in the 11% of patients with placebo, causes are not stated.11

A review article published in 2011 does not mention AV block as a possible adverse effect of dronedarone, but does state that dronedarone slows heart rate and prolongs AV nodal refractoriness and thus can increase the PR interval.11

Discussion

For the analysis of ICSRs retrieved in VigiBase™, as previously stated, case 1 will not be taken into consideration because of inconsistencies in how dates are reported. In six out of the remaining 13 ICSRs, concomitant drugs with potential to prolong PR interval had been administered before the starting of dronedarone's therapy: digoxin (case 5), beta blockers (metoprolol in cases 3 and 9, bisoprolol in case 4, carvedilol in cases 10 and 13, and atenolol in case 10, pindolol in case 12), and calcium channel blockers (lercanidipine in case 3). Besides, amiodarone is mentioned as a concomitant medication in case 5 (together with digoxine). A synergistic effect on atrioventricular conduction is possible; treatment with Class I or III antiarrhythmics such as amiodarone is formally contraindicated with dronedarone. Pharmacodynamic interactions between dronedarone and digoxin, beta blockers and calcium-channel blockers are known: dronedarone (400 mg twice daily) increased digoxin exposure by 2.5-fold by inhibiting P-gp transporter; beta blockers that are metabolized by CYP2D6 can have their exposure increased by dronedarone, and lercanidipine is metabolized by CYP3A4. Cytochrome P450 CYP2D6 is involved in the metabolism of bisoprolol, carvedilol and metoprolol; carvedilol is also substrate of P-gp and CYP3A4 and bisoprolol of CYP3A4. In all these six cases, concomitant medication could play a synergistic effect in AV block, but the role of dronedarone cannot be ruled out due to the time to onset and the PD characteristics of the drug. In two cases, concomitant medication have no potential to cause AV block (cases 2 and 11), and in four cases (including the only fatal case) no concomitant medication was reported. For 13 analysed ICSRs, nine patients (70%) were women: of note, dronedarone's plasma exposure in elderly females was increased in a pharmacokinetic study conducted in healthy subjects. In this study, systemic exposure to dronedarone was increased in the elderly males compared with young males by around 25%, and in elderly females compared with elderly males by around 50%. The PK parameters for dronedarone were increased by around 60% in elderly females compared with elderly males. However, dose adjustments are not formally considered necessary.

2nd and 3rd AV block, which was one of the exclusion criteria in clinical trials EURIDIS,2,7 ADONIS,2,7 ATHENA,2,6 DIONYSOS,2,6 and ERATO2, is a formal contraindication for therapy with dronedarone, except for patients with pacemakers.1-3 No ICSR reports a history of 2nd or 3rd AV block, (but the details for pacemaker indication and implantation were not mentioned for the two patients with pacemaker).

Conclusion

As previously stated, a global analysis of these 13 ICSRs supports an association between dronedarone and AV block, because of biological plausibility, time to onset and dechallenge, although concomitant drugs could have had a contributory or synergistic role. Concerning the case reporting the results of a study performed in 70 patients (although it is not stated how many patients presented with AV block after therapy with dronedarone (one patient would mean 1.43%, two patients 2.86%) and concomitant medication or pathological status are not detailed), it seems to be clear that dronedarone had a role in the onset of AV block due to the time to onset.

No published cases or case series reports for humans were found in a PubMed search with the query “dronedarone AND (AV block OR atrioventricular block)”. Labelled product information does not mention AV block as an adverse effect of dronedarone, although it is stated that decreased AV conduction is one of the electrophysiological effects of dronedarone. In one of the published articles reporting clinical trials results, AV block is mentioned as an adverse effect. Results posted in www.clinicaltrials.gov (six clinical trials) mention AV block as an adverse event or a serious adverse event in two studies.

According to WHO's definition, a signal is “the reported information on a possible causal relation between an adverse effect and a drug, the relationship being previously unknown or incompletely documented”. Taking into account that, on one hand, AV block with dronedarone is not mentioned as an adverse effect in the information addressed to prescribers and is rarely reported in publications of Phase III clinical trial results, and, on the other hand, both PK
clinical trials’ available information and the analysis of the ICSRs in VigiBase provide a rationale for an association between dronedarone and AV block, this combination should be considered as a signal and deserves further investigation.

References


Response from Sanofi

The main safety concern with antiarrhythmics in general, and Class I and III in particular, is the potential proarrhythmic effect. It is universally recognized that the potential proarrhythmia is considerably increased in the presence of structural heart disease, which led to a contraindication for Class I drugs in this subgroup of patients.

Theoretically, dronedarone might share the latter class effect; however, based on clinical experience, dronedarone has a low proarrhythmic effect, nevertheless, close surveillance of proarrhythmic effects has been performed by the Marketing Authorization Holder (MAH) via routine pharmacovigilance, namely in subsequent 6 month Periodic Safety Update Reports (PSURs).

The Risk Management Plan updates coincidence with the release of PSURs, refer to proarrhythmic effects as a potential Pharmacological class effect with emphasis on regular data review by the MAH. From periodic analyses and review of conduction disorders based on the information collected and analysed during the reporting period from submission to last PSUR, no new emerging safety signals were noted. In the Assessment Report to the recently submitted PSUR7 (September 2013), EMA endorsed the MAH conclusion on the topic. From launch of dronedarone to 31 October 2013 the MAH has collected worldwide 7 solicited cases including: atrioventricular block (n =1), atrioventricular block complete (n =2), atrioventricular block second degree (n=2); atrioventricular block first degree (n=2) and 25 unsolicited cases including: atrioventricular block (n=6), atrioventricular block complete (n =6), atrioventricular block second degree (n=4), atrioventricular block first degree (n=9). No consumer case was reported.

Among 32 case reports, 24 cases were serious. The reports concern patients aged between 28 and 90 years (age was not stated in 8 reports). The onset dates was reported in 21 reports, from 1 day to nearly 1 year. In 11 out of 18 reports,
dronedarone was discontinued and the patients were reported as recovered or recovering. No rechallenge was reported. Concomitant drugs which may have contributed to the events onset was reported in 18/32 cases.

Overall, the analysis of the 32 cases (6 cases of atrioventricular block second degree, 11 cases of atrioventricular block first degree, 7 cases of atrioventricular block) and 8 cases of complete atrioventricular block showed that contributive factors such as concomitant drugs and or underlying cardiac disease were reported in all cases; or cases were poorly documented to allow proper medical assessment.

Focusing on eight (8) out of 32 cases were reported as complete atrioventricular block, 3 cases (n=1 solicited, n=2 unsolicited) were reported with fatal outcome in which, alternative explanations and confounding factors were reported:

- In first case, the 78 yearold female patient with a medical history of hypertension and stroke experienced a chest pain and third degree atrioventricular block and cardiogenic shock 4 weeks after starting dronedarone; the most likely cause of death according to the investigator was acute myocardial infarction;
- In the second case, the elderly patient experienced acute liver function impairment NOS and complete atrioventricular block, 5 days after starting dronedarone. She ultimately died from an unknown cause, in addition to the concomitant use of atenolol was reported; and finally,
- In the third case, 77 year old female patient with severe relevant medical history of cardiovascular diseases including cardiac insufficiency (off label use) in addition to the concomitant use of verapamil were reported.
- In the remaining 5 cases reported as complete atrioventricular block, the following confounding might provide alternative explanations:
  - Digoxin was stopped and dronedarone maintained and the patient recovered
  - As the reporter stated, the intrinsic characteristic of patient's heart disease were most likely responsible of the reaction.
  - The patient with already an inserted pacemaker pointing out to heart rhythm/conduction disorders prior to dronedarone. It remained unclear whether the patient had treatment with a beta-blocker.
  - The patient with reoccurrence of the AV-block complete while on different treatment had been given (requirement of placement of a permanent implantable device). Concomitant drugs not reported, patient's heart disease was most likely responsible of the reaction.

- Concurrent effect of hyperkalaemia on heart conduction might be considered as a primary cause. The patient completely recovered following normalization of kalaemia and after discontinuation of dronedarone, carvedilol and spironolactone.

In healthy subjects repeated dose studies, the incidence of first or second degree AV block was similar in dronedarone 800 mg/day (2/102 subjects) and the placebo (1/58 subjects) groups. A higher incidence of first or second degree AV block was observed at dronedarone supratherapeutic doses >800 mg/day (18/72 subjects). All cases of AV block were asymptomatic.

In placebo-controlled clinical trial programme in the pooled population, 1 /989 patients reported AV Block first degree in dronedarone 400mg BID versus none in placebo (n=564 patients)

In others studies (ATHENA study, ANDROMEDA study with patients with severe episode CHF), atrioventricular block were reported with low and similar frequencies between dronedarone and placebo groups

Referring to preclinical data, first degree block was reported in rats, dogs and monkeys. Second degree block was also reported in macaques. Based on the known effect of dronedarone to slow AV-conduction and repolarization prolongation, effects that may increase with dose, the MAH contraindicated the use of dronedarone in patients with first and second degree atrioventricular block (except when used in conjunction with a functioning pacemaker). In addition, information on this potential risk when dronedarone is coadministered with Calcium antagonists was provided in the label.

Furthermore, it is clearly stated in dronedarone label (precaution section) that, proarrhythmic effects may occur in particular situations such as concomitant use with drugs favoring arrhythmia and/or electrolytic disorders.

Based on available up-to-date information the MAH concludes that when dronedarone used as recommended, the cumulative weighted evidence is insufficient to support causal association between dronedarone and AV Block, however with doses of dronedarone above 800mg/Day (i.e. per phase 1 repeated dose study) or when used in a setting of interaction, the risk of AV Block may increase.
Ustekinumab and Vasculitis

Signal from the Uppsala Monitoring Centre

Summary

Ustekinumab is a relatively new monoclonal antibody that prevents the binding of IL-12 and IL-23 to their respective receptors. Since its introduction on the clinical market, in late 2008, it has been licensed for the treatment of plaque psoriasis, but was recently further approved for the indication psoriatic arthritis.

Clinical experience with ustekinumab appears limited, perhaps reflecting the restricted indication for use until recently. No incidences of serious hypersensitivity reactions were recorded during clinical trials for either of the approved indications. However, cases of anaphylaxis and angioedema have occurred post marketing. A case series of eight reports on the association of ustekinumab and vasculitis, reported from five different countries to the WHO Global Individual Case Safety Report Database, VigiBase™ has been assessed. The association has been statistically disproportionately reported and current information supports a signal on the risk of vasculitis with ustekinumab.

Introduction

Ustekinumab is described as a fully human IgG1κ monoclonal antibody to interleukin (IL)-12 and 23, binding to the shared p40 protein subunit of the corresponding human cytokines. Ustekinumab is a relatively new monoclonal antibody that prevents the binding of IL-12 and IL-23 to their respective receptors. Since its introduction on the clinical market, in late 2008, it has been licensed for the treatment of plaque psoriasis, but was recently further approved for the indication psoriatic arthritis.

Vasculitis is a condition involving an inflammatory reaction damaging the wall of blood vessels that can lead to subsequent ischaemic damage of organs supplied by the blood vessels affected. It can be a primary manifestation of disease, e.g. as in Henoch Schönlein purpura, or a secondary manifestation of other conditions as seen with malignancies or with drug induced vasculitis. The underlying pathophysiological mechanism is considered at least partly immune mediated, as a response to an antigen in the context of an immune complex disease. Antineutrophil cytoplasmic antibodies (ANCA) have been associated with small vessel vasculitis as in Wegener granulomatosis or in drug induced vasculitis, e.g. by antithyroid drugs. The prevalence of drug induced vasculitis is unclear and drugs associated with it besides antithyroid drugs are antibiotics such as minocycline, TNF-α inhibitors such as adalimumab, etanercept and infliximab, and other medicines such as clozapine, allopurinol and others. Drug induced vasculitis often manifests in the skin and the subcutis but can affect also other organs.

Reports in VigiBase

Nine cases of vasculitis with ustekinumab were reported to the WHO Global Individual Case Safety Report (ICSR) Database, VigiBase™ between late 2010 to mid 2013; the association was detected as disproportionally reported with an IC value of 1.21 (IC025 0.12). Upon review, two of the cases were identified as duplicates, therefore only the most informative version was included in the case series of eight unique ICSRs. The cases originate from United Kingdom, United States, Canada, Spain and Greece: seven spontaneous reports and one report from a study. Among the spontaneous reports, six other approved IL-12/23 antibodies indicated in the treatment of adult psoriasis and PsA patients in the US or EU, although new candidates are under study. In population-based studies, the incidence of psoriasis in adults has been estimated to range between 78.9-230/100,000 person-years, the occurrence varying with geographic region and age. Considering the restricted indication for which ustekinumab has been licensed until recently, clinical experience of the antibody is somewhat limited. In clinical trials on psoriasis patients, no cases of serious hypersensitivity, e.g. anaphylaxis or serum sickness-like reactions, were observed. Also based on the available phase III clinical trials data on short term safety (52 weeks) of ustekinumab in PsA patients, there are no reported incidences of serious hypersensitivity reactions.

Vasculitis is a condition involving an inflammatory reaction damaging the wall of blood vessels that can lead to subsequent ischaemic damage of organs supplied by the blood vessels affected. It can be a primary manifestation of disease, e.g. as in Henoch Schönlein purpura, or a secondary manifestation of other conditions as seen with malignancies or with drug induced vasculitis. The underlying pathophysiological mechanism is considered at least partly immune mediated, as a response to an antigen in the context of an immune complex disease. Antineutrophil cytoplasmic antibodies (ANCA) have been associated with small vessel vasculitis as in Wegener granulomatosis or in drug induced vasculitis, e.g. by antithyroid drugs. The prevalence of drug induced vasculitis is unclear and drugs associated with it besides antithyroid drugs are antibiotics such as minocycline, TNF-α inhibitors such as adalimumab, etanercept and infliximab, and other medicines such as clozapine, allopurinol and others. Drug induced vasculitis often manifests in the skin and the subcutis but can affect also other organs.
were reported by a physician or other health professional, while one was from the literature. The demographics of this case series are presented in Table 1 and further described below.

The age span of the patients ranges between 29 to 64 years and the gender distribution is dominated by females (7/8 subjects). Ustekinumab is the single suspected drug in six cases, concomitant medication being reported in four of these. The remaining two cases contained at least one other co-suspected drug, respectively.

Psoriasis was specified as the indication for treatment in all eight ICSRs. The reaction was further specified as cutaneous vasculitis in two reports and leukocytoclastic vasculitis in two, with no additional description in the remaining four. Time-to-onset information including dates for start of ustekinumab treatment and onset of vasculitis was provided in four cases. However, narrative information presented estimates for the timeliness of the reaction in one additional case, with recurring vasculitis "one week after 3rd and 4th dose" of ustekinumab therapy. Considering the dose regimen of ustekinumab therapy starting as subcutaneous injections at weeks 4, 16 and 28, the time to onset may be estimated to 119–203 days for the reflected case. Dechallenge of ustekinumab was reported in three cases, one of which having records of reaction abating and a second having outcome recovering at the time of reporting. Two cases of negative rechallenge were also reported, one of which in association with a medication error related problem (incorrect storage of drug). The overall outcomes were recovered (or recovering) in four, not recovered in one, unknown in one and not reported in two cases. No fatalities were reported.

Table 1. Characteristics of ICSRs in VigiBaseTM indicating vasculitis during treatment with ustekinumab

<table>
<thead>
<tr>
<th>ICSR</th>
<th>Country</th>
<th>Age/Gender</th>
<th>Other suspected (S) or concomitant</th>
<th>Reactions (WHO-ART preferred terms)</th>
<th>Time to onset (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Greece</td>
<td>37/F</td>
<td>-</td>
<td>Vasculitis</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>United Kingdom</td>
<td>44/F</td>
<td>Ramipril (C)</td>
<td>Vasculitis, abdominal pain, arthritis, haematuria</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>United States</td>
<td>-/M</td>
<td>Indometacin (C), omeprazole (C)</td>
<td>Vasculitis, medicine ineffective</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>Canada</td>
<td>-/F</td>
<td>Cilazapril (C), metformin (C), amoxicillin</td>
<td>Vasculitis</td>
<td>-</td>
</tr>
<tr>
<td>5</td>
<td>Spain</td>
<td>29/F</td>
<td>Infliximab (S), acitretin (C), ciclosporin (C), methotrexate (C), etanercept (C), adalimumab (C)</td>
<td>Vasculitis</td>
<td>49</td>
</tr>
<tr>
<td>6</td>
<td>Canada</td>
<td>-/F</td>
<td>-</td>
<td>Vasculitis, antinuclear factor test positive, complement factor abnormality</td>
<td>-</td>
</tr>
<tr>
<td>(7)*</td>
<td>United Kingdom</td>
<td>64/F</td>
<td>-</td>
<td>Vasculitis, somnolence, malaise, tachycardia, hypotension, respiratory depression, diarrhoea, rash, pruritus</td>
<td>877</td>
</tr>
<tr>
<td>8*</td>
<td>United Kingdom</td>
<td>64/F</td>
<td>Levothyroxine (C)</td>
<td>Vasculitis, somnolence, medication error related problems, abdominal pain, rash, dyspnoea, creatinine clearance decreased, c-reactive protein increased, injection site rash, serum sickness, LE rash</td>
<td>866</td>
</tr>
<tr>
<td>9</td>
<td>United States</td>
<td>58/F</td>
<td>Amoxicillin (S), etanercept (S), fexofenadine (C), glipizide (C), alprazolam (C), venlafaxine (C), lisinopril (C), metformin (C), salbutamol (C), fluticasone propionate/salmeterol xinafoate</td>
<td>Vasculitis</td>
<td>10</td>
</tr>
</tbody>
</table>

*Asterisk indicates duplicates; ICSR in brackets has been excluded
**Literature and Labelling**

To date, we have not found any case reports or other publications on ustekinumab and vasculitis in the literature.

Serious hypersensitivity reactions, including anaphylaxis and angioedema, have been observed during post-marketing and are labelled as rare (≥ 1/10,000 to < 1/1,000). Rash and urticaria have been documented to occur in <1% of patients during the controlled periods of clinical studies and are labelled as uncommon in the EU.

Data on immunogenicity from clinical trials estimated 6% of patients on ustekinumab to have developed antibodies to the agent. The detection of antibodies against ustekinumab was not apparently associated with hypersensitivity reactions. Agents from the therapeutically related class TNF-α inhibitors, e.g. the monoclonal antibodies adalimumab, etanercept and infliximab, have been labelled with immunologic reactions including cutaneous and/or systemic vasculitis. Repeated treatment with these agents has been observed to lead to the development of autoantibodies including antinuclear antibodies and ANCA, with the manifestation of clinical vasculitis in rare instances.

**Discussion and Conclusion**

The presented case series of eight ICSRs on the association of ustekinumab and vasculitis comprise a relatively small but noteworthy first signal on the occurrence of a potentially serious safety issue. Ustekinumab has been associated with vasculitis as the only suspected drug in six cases from four reporting countries, all reported to have been used for a licensed indication. The potential for co-suspected drugs to affect the causality assessments were found only in two cases, consisting of TNF-α inhibitors and penicillin. The positive antinuclear factor test reported in case number 6 with ustekinumab as the single reported drug indicates the possibility of a similar mechanism of induction of vasculitis by this agent. Being the only IL-12/23 monoclonal antibody approved on the clinical market for the indications psoriasis and PsA, the assessment of a drug-class effect is however unattainable at this point.

In clinical trials, the presence of antibodies against ustekinumab as measured in psoriasis and PsA patients ranged from 3.8% to 6%. The majority of patients presenting antibodies to ustekinumab were found having neutralizing such of low titer. Another immunologically related reaction of interest is serum sickness, having no records of reported incidences during clinical trials with ustekinumab in psoriasis or in PsA patients. If yet rare, there are reported incidences of serum sickness (PT serum sickness) associated with ustekinumab treatment reported to VigiBase, one of which is represented by case number 8) in the series reflected above. The referred ICSR does however indicate that a medication error related problem occurred (primary source stating suspected incorrect storage of drug), which may explain the unexpectedly long time-to-onset (866 days) and negative rechallenge when therapy was resumed.

The reaction vasculitis has been reported with related clinical manifestations, such as arthritis, haematuria, abdominal pain or confirmatory biopsy findings by laboratory data in cases 1 and 2. Increased anti-DNA antibody titer and hypocomplementemia were also recorded, if yet in an antinuclear antibody positive patient, having previous medical history of systemic lupus erythematosus. Observations of decreased creatinine clearance, increased C-reactive protein, serum-sickness and lupus erythematosus were reported in the case of suspected administration with incorrectly stored drug.

In contrast to the idiopathic reaction, drug-induced vasculitis has been observed to have a milder course in terms of organ involvement and time-to-onset, which is consistent with the reported findings mostly involving cutaneous reactions. Considering the compiled available information on the association of ustekinumab and vasculitis, there is support for a signal.

**References**

Response from Janssen

Methods

The Marketing Authorization Holder (MAH) of ustekinumab (Stelara®) performed a comprehensive search of the Global Medical Safety Database using the MedDRA SMQ for Vasculitis (narrow) to identify all solicited and unsolicited cases of vasculitis including cases from clinical trials, spontaneous reports, and postmarketing studies reported through 15 October 2013.

Results

The search identified 20 cases, which included 7 of the 8 unique cases referenced in the WHO report. The eighth case (ICSR No 5) was not included in the MAH Safety Database and was added resulting in a total of 21 cases. Of these 21 cases, 1 case was excluded due to duplication and another case was excluded as the event occurred before the treatment with ustekinumab. Thus 19 cases were included in the analysis. Case characteristics of these 19 cases are provided in Table 1:

A review of these 19 cases (see Table 2) showed that in 2 cases, vasculitis was assessed by the reporter as unrelated to treatment with ustekinumab; in 3 cases, the information reported was very limited and inadequate for medical assessment; and in 11 cases, the patients had one or more confounding factors, plausible alternative explanations that could have contributed to the event of vasculitis, or clinical features not typical for a diagnosis of vasculitis. The remaining 3 cases of interest are discussed below.

Case 1

Was reported by a 48-year-old female (weight 345 lbs), ex-smoker who initiated ustekinumab (dose, date unspecified) for psoriasis. Approximately 2 months after starting ustekinumab, she stated that she was diagnosed with “Widners vasculitis” (possibly implying Wegener’s granulomatosis) with symptoms of blurred vision, selective memory, painful joints, and difficulty with walking. Treatment with ustekinumab was discontinued 4 months after initiation for complaints of “feeling bad” and “coughs with blood.” She was treated in the intensive care unit and was discharged after 2 weeks. Treatment included kidney dialysis every other day for 2 months. Outcome of the treatment could not be received. MAH Comment: While the reported events of blurred vision, selective memory, painful joints, feeling bad, and haemoptysis with reported vasculitis may resemble Wegener’s granulomatosis, the diagnosis was not confirmed medically with biopsy and cytoplasmic anti-neutrophil cytoplasmic antibody (cANCA) results. In the absence of information on medical history, concomitant medications, comorbidities, and corrective treatments, a definite causal relationship to the treatment with ustekinumab cannot be established. Wegener’s granulomatosis is an autoimmune disorder and generally not viewed as a drug-induced disease. Further, it is unclear if the obesity (345 lbs) in this patient was associated with other comorbidities such as diabetes, hypertension,
atherosclerosis, renal disorders, and if the medical evaluation included glomerulonephritis, sarcoidosis, lymphomatoid granulomatosis, NK/T-cell lymphoma, systemic lupus erythematosus etc. as part of the differential diagnosis.

Case 2

A 58-year-old female (weight 169 lbs) with a history of hysterectomy, hypersensitivity to calcipotriol, penicillin, and sulfacetamide was treated with ustekinumab 45 mg for psoriasis. Concomitant medications included methotrexate, clobetasol, conjugated estrogens, tolterodine, and folic acid. After the first injection, she experienced a vasculitic-like rash (with numerous guttate papules) on the left chest, left arm, and left lower extremity, which turned into a severe vasculitic eruption after the second injection. The treating physician stated that a biopsy was not performed and the appearance on photos was vasculitis. Ustekinumab was discontinued. Corrective treatment included ciprofloxacin and the eruptions resolved 2 months later. MAH Comment: While vasculitis could be diagnosed by its clinical signs and symptoms, a definitive diagnosis of vasculitis could not be affirmed based on the available information without the results of biopsy and/or ANCA antibodies. The unilateral presentation of vasculitic-like rash reported in this patient is uncharacteristic of drug-induced vasculitis.

Case 3

WHO ICSR No 1) described a 37-year-old female treated with ustekinumab 45 mg for psoriasis. She experienced 2 episodes of pruritic bullous rash on lower extremities 1 week after the third and 1 week after the fourth dose, which was diagnosed as "medicinal vasculitis" based on biopsy. The patient recovered "1 week later." No other information was reported. MAH Comment: There is insufficient information on medical history and concomitant medications available to make an adequate assessment of a drug-event relationship.

Conclusion

The safety profile of ustekinumab has been well established since its approval 5 years ago. An evaluation of the reported cases does not support vasculitis as an adverse drug reaction related to the treatment with ustekinumab. The biologic plausibility and role of anti-IL-12/23 monoclonal antibodies in the pathogenesis of different types of vasculitis is not fully understood. The MAH continues to monitor vasculitis through routine pharmacovigilance activities.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>6</td>
</tr>
<tr>
<td>Female</td>
<td>12</td>
</tr>
<tr>
<td>Not reported</td>
<td>1</td>
</tr>
<tr>
<td>Age Group (years)</td>
<td></td>
</tr>
<tr>
<td>≤17</td>
<td>0</td>
</tr>
<tr>
<td>18 to 35</td>
<td>3</td>
</tr>
<tr>
<td>36 to 50</td>
<td>5</td>
</tr>
<tr>
<td>51 to 64</td>
<td>7</td>
</tr>
<tr>
<td>≥65</td>
<td>1</td>
</tr>
<tr>
<td>Not reported</td>
<td>3</td>
</tr>
<tr>
<td>Indication</td>
<td></td>
</tr>
<tr>
<td>Psoriasis</td>
<td>13</td>
</tr>
<tr>
<td>Psoriatic arthropathy, pustular psoriasis</td>
<td>1</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>1</td>
</tr>
<tr>
<td>Not reported</td>
<td>4</td>
</tr>
</tbody>
</table>

Table 1: Characteristics of Reported Cases of Vasculitis

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Number of Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td></td>
</tr>
<tr>
<td>45 mg</td>
<td>5</td>
</tr>
<tr>
<td>90 mg</td>
<td>4</td>
</tr>
<tr>
<td>90 mg every 8 weeks</td>
<td>1</td>
</tr>
<tr>
<td>Not reported</td>
<td>9</td>
</tr>
<tr>
<td>Latency From the First Dose</td>
<td></td>
</tr>
<tr>
<td>1 month or less</td>
<td>3</td>
</tr>
<tr>
<td>&gt;1 to 3 months</td>
<td>5</td>
</tr>
<tr>
<td>&gt;3 to 6 months</td>
<td>1</td>
</tr>
<tr>
<td>&gt;6 months to 1 year</td>
<td>2</td>
</tr>
<tr>
<td>&gt;1 to 2 years</td>
<td>2</td>
</tr>
<tr>
<td>&gt;2 years</td>
<td>1</td>
</tr>
<tr>
<td>Not reported</td>
<td>5</td>
</tr>
</tbody>
</table>
**Summary**

Vemurafenib is a low molecular weight, orally available, inhibitor of BRAF serine-threonine kinase (a member of the Raf kinase family of growth signal transduction protein kinases). It is one of the medications widely known as tyrosine kinase inhibitors (TKIs) but should be referred to as protein kinase inhibitors (PKIs). Vemurafenib is indicated in monotherapy for the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma.

In the WHO Global Individual Case Safety Report (ICSR) Database, VigiBase there are currently (3 September 2013) 25 ICSRs of renal failure acute (ARF) in association with vemurafenib. In addition, there are 16 ICSRs of renal failure chronic (CRF) in association with vemurafenib, both combinations with a positive IC value. There is also one ICSR of renal failure aggravated. After elimination of duplicates, there are 38 ICSRs of renal failure. Vemurafenib was the only drug suspected in all but three cases. Time to onset was reported in 14 cases and ranged from three days to six months. The six reports with a time to onset within a month are suggestive of a drug-induced effect. Patients were reported as recovered or recovering in 12 cases, not recovered in seven cases and the outcome was fatal in two ICSRs.

The cases reported as recovered or recovering together with the two cases of rechallenge are highly suggestive of a drug-induced effect.

In conclusion, although renal failure may have other possible causes in this series of patients, the use of vemurafenib appears the most likely reason.

**Introduction**

Vemurafenib is a low molecular weight, orally available, inhibitor of BRAF serine-threonine kinase (a member of the Raf kinase family of growth signal transduction protein kinases). Mutations in the BRAF gene which substitute the valine at amino acid position 600 result in constitutively activated BRAF proteins, which can cause cell proliferation in the absence of growth factors that would normally be required for proliferation. Before taking vemurafenib, patients must have BRAF V600 mutation-positive tumour status confirmed by a validated test. It is one of the medications widely known as tyrosine kinase inhibitors (TKIs) but should be referred to as protein kinase inhibitors (PKIs). Vemurafenib is indicated in monotherapy for the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma.
inhibitors (TKIs) but should be referred to as protein kinase inhibitors because although the earliest drugs in this class were TKIs, they can now be further categorized based upon the amino acid that they phosphorylate: serine, threonine or tyrosine. Vemurafenib is indicated in monotherapy for the treatment of adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma. The most common adverse drug reactions (ADR) reported with vemurafenib (>30%) reported with vemurafenib include arthralgia, fatigue, rash, photosensitivity reaction, nausea, alopecia and pruritus. Cutaneous squamous cell carcinoma (CuSCC) was very commonly reported and was most commonly treated by local excision. There are warnings in the product information concerning the possible occurrence of severe hypersensitivity and dermatological reactions, QT prolongation, serious ophthalmologic reactions, new primary melanomas, liver laboratory abnormalities and mild to severe photosensitivity.

Renal failure is a reduction or suppression of the excretory function of the kidney, characterized by a decrease in creatinine clearance. Renal failure is demonstrated by an increase in serum creatinine above 150 mmol/L, or reduction in creatinine clearance below 50 ml/min per 1.73 m² of body surface. Age, sex, weight and whether the patient is pregnant should be considered in determining abnormality of levels of serum creatinine or creatinine clearance. The presenting symptoms of drug-induced renal failure are the same as those for renal failure due to other causes. Drugs can cause renal failure, which may be acute (developing within hours or days), subacute (within weeks), or chronic (within months or years); they may also exacerbate pre-existing renal failure. Whenever possible in reporting a suspected adverse drug reaction, the pre-existing level of renal function should be included in addition to the actual change in function.

The cause of acute renal failure (ARF) can be characterised based on where the injury has occurred. Pre-renal causes include hypovolaemia, dehydration due to vomiting, diarrhoea, sweating or fever, poor intake of fluids, medications such as diuretics and abnormal blood flow due to obstruction. Renal causes include sepsis, medications such as NSAIDs, antibiotics such as aminoglycosides, lithium and iodine, rhabdomyolysis, multiple myeloma and glomerulonephritis. Post-renal causes include obstruction of the bladder or the ureters, prostatic hypertrophy or prostate cancer, abdominal tumours or kidney stones. The most common causes of chronic renal failure (CRF) are poorly controlled diabetes, poorly controlled hypertension and chronic glomerulonephritis. Other causes include polycystic kidney disease, reflux nephropathy, kidney stones and prostate disease.

Reports in VigiBase
As of 3 September 2013 there were 25 Individual Case Safety Reports (ICSRs) of ARF in association with vemurafenib in the WHO Global ICSR Database, VigiBase™. The association has an IC value of 1.30 with an IC₀₂₅ value of 0.66. In addition there are 16 ICSRs of CRF in association with vemurafenib. The association has an IC value of 1.08 with an IC₀₂₅ value of 0.28. There is also one ICSR of renal failure aggravated (IC 0.83, IC₀₂₅ -2.97).

The cases can be analysed together. There are pairs of duplicates in the ARF and in the CRF series (Table 1). After elimination of duplicates, there are 38 cases. The cases were submitted from the United States (20 cases), Germany (four), Australia (three), Canada and Austria (two cases each), Belgium, Greece, Italy, the Netherlands, Sweden, Switzerland and the United Kingdom (all one each). The patients ranged in age from 38 to 89 years. The gender distribution was 22 males, 13 females and 3 not specified.

Vemurafenib was the only drug suspected in all 38 cases except three. In these three cases, there was one other suspected drug: ibuprofen, iodine and piperacillin/ tazobactam. Concomitant drugs were reported in 24 cases and included antihypertensive drugs (14 cases), proton pump inhibitors (nine), pain management drugs (10), hypolipidaemics (seven), and drugs for the treatment of diabetes, constipation and infection (five each). There was also use of allopurinol and corticosteroids (five cases each).

Time to onset was reported in 14 of the 38 ICSRs. It ranged from three days to six months. The outcome was stated in 21 reports. The patients were reported as recovered or recovering in 12 cases, not recovered in seven cases and the outcome was fatal in the remaining two reports. The reason for death in one case was renal failure, hepatic failure and sepsis while in the other case, renal failure was stated to be contributory to the death. In another case in which the patient had not recovered from renal failure, the patient died, with the cause of death given as respiratory arrest. In the ICSRs were the outcome was reported as recovered or recovering, there was a positive dechallenge in three cases. In one of these cases, there was a negative rechallenge in that the reaction did not recur when the drug was re-introduced. In five other cases, a positive dechallenge could not be confirmed to a lack of detail but appeared likely and in another three cases, recovery followed withdrawal but onset was also after drug withdrawal. In the cases where the patients had not recovered, the drug was
withdrawn in three cases, continued in one case and the dose was reduced in one case. In the remaining two cases, the patient recovered with drug withdrawal but the reaction recurred on rechallenge and the patient had not recovered from that episode.

Other reactions were described in 31 of the reports. These reactions included skin reactions, abnormal liver function, nausea, diarrhoea, joint problems, dehydration and cardiac failure, vomiting and infection. Many of these reactions may have caused or made a contribution to the cause of the ARF.

**Literature and Labelling**

The product literature does not refer to renal failure or any other renal reaction. There is a warning in the product information regarding renal impairment which indicates that no adjustment to the starting dose is needed for patients with mild or moderate renal impairment. There are only limited data available in patients with severe renal impairment. Vemurafenib should be used with caution in patients with severe renal impairment and patients should be closely monitored. There are no reports in the literature of renal failure in association with vemurafenib. There is, however, an isolated report of renal failure in a patient taking vemurafenib. In a Phase II trial of the efficacy of the drug in 132 patients, one patient died owing to rapid progression of melanoma and ARF, possibly related to the study drug. A recent review of the on-target toxicities of TKIs noted that renal failure is an effect of the TKIs bosutinib, dasatinib, erlotinib, imatinib, nilotinib, sorafenib and sunitinib.

**Discussion and Conclusion**

Case reports in VigiBase suggest that there is a signal for the association of vemurafenib and renal failure.

There are 23 reports of ARF, 14 reports of CRF and one report of renal failure aggravated with both ARF and CRF described in one report. There are some issues in terminology with the reports of CRF. In MedDRA, there are separate preferred terms (PTs) for ARF, CRF and renal failure (RF). In WHO-ART, however, RF is an included term with CRF in the PTCRF. This means that reports of CRF may be renal failure without further qualification. Vemurafenib was the only drug suspected in all 38 cases except three. In these three cases, there was one other suspected drug: ibuprofen, iodine and piperacillin/tazobactam.

Time to onset was reported in 14 of the reports and ranged from two days to six months. The six reports with a time to onset within a month are suggestive of a drug-induced effect. The outcome was stated in 21 reports. The patients were reported as recovered or recovering in 12 cases, not recovered in six cases and the outcome was fatal in two reports. The cases of recovery or recovering on drug withdrawal and the case of recurrence of renal failure on rechallenge are highly suggestive of a drug-induced effect.

Concomitant drugs were reported in 23 cases and included drugs used in a patient population which might be at risk of renal failure due to the presence of hypertension, diabetes and infection. There were also a number of concomitant reactions that may have caused or made a contribution to the cause of the renal failure. It is also possible that the underlying disease may have been responsible in some cases.

There are no reports in the literature of renal failure in association with vemurafenib. There is, however, an isolated report of renal failure in a patient taking vemurafenib, and a recent review of the on-target toxicities of TKIs noted that renal failure is an effect of the TKIs bosutinib, dasatinib, erlotinib, imatinib, nilotinib, sorafenib and sunitinib. In conclusion, although renal failure may have other possible causes in this series of patients, the use of vemurafenib appears the most likely reason.

**References**


Table 1. Case overview of ICSRs in VigiBase™ of renal failure in association with vemurafenib

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/Gender</th>
<th>Other suspected (S) or concomitant (C) drugs</th>
<th>Reactions (WHO-ART preferred term)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-/M</td>
<td>Ibuprofen (S)</td>
<td>Renal failure acute, renal function abnormal, liver function abnormal, arthralgia</td>
<td>Unknown</td>
</tr>
<tr>
<td>2</td>
<td>66/M</td>
<td>Tamsulosin, paracetamol (C)</td>
<td>Renal failure acute, anorexia, diarrhoea, tremor, fever</td>
<td>Recovered</td>
</tr>
<tr>
<td>3</td>
<td>-/F</td>
<td>Ondansetron, lisonopril, promethazine, calcium carbonate, paracetamol/ hydrocodone, vitamins/minerals, chlortalidone/atenolol (all C)</td>
<td>Renal failure acute hypotensive, nausea, dehydration, vomiting</td>
<td>Recovered</td>
</tr>
<tr>
<td>4</td>
<td>-/F</td>
<td>None</td>
<td>Renal failure acute, nausea, diarrhea, vomiting</td>
<td>Unknown</td>
</tr>
<tr>
<td>5</td>
<td>-/F</td>
<td>None</td>
<td>Renal failure acute, cardiac failure</td>
<td>Unknown</td>
</tr>
<tr>
<td>6</td>
<td>63/M</td>
<td>Oxycodone, allopurinol, simvastatin, nifedipine, temazepam, sodium bicarbonate/potassium chloride/sodium chloride/Macrogol, paracetamol (all C)</td>
<td>Renal failure acute</td>
<td>Not recovered</td>
</tr>
<tr>
<td>7</td>
<td>61/M</td>
<td>Spironolactone, codeine phosphate/ paracetamol, zopiclone, dexamethasone (all C)</td>
<td>Renal failure acute, creatinine clearance decreased, renal function abnormal, oedema, pleural effusion, respiratory arrest, urea blood increased, cardiac failure</td>
<td>Not recovered</td>
</tr>
<tr>
<td>8</td>
<td>-/F</td>
<td>Potassium, zopiclone, oxycodone, ondansetron, aperpitant, dexamethasone, phytomenadione, escitalopram, warfarin, temozolomide, nystatin (all C)</td>
<td>Renal failure acute, rash, diarrhoea, dehydration, metastases nos</td>
<td>Recovered</td>
</tr>
<tr>
<td>9</td>
<td>72/M</td>
<td>Propylene glycol, allopurinol, felodopine, metolazone, metoprolol (all C)</td>
<td>Renal failure acute</td>
<td>Not recovered</td>
</tr>
<tr>
<td>10</td>
<td>52/M</td>
<td>Olmesartan (C)</td>
<td>Renal failure acute</td>
<td>Recovered</td>
</tr>
<tr>
<td>11#</td>
<td>62/M</td>
<td>Methylprednisolone, ciprofloxacin (both C)</td>
<td>Renal failure acute, infection</td>
<td>Not recovered</td>
</tr>
<tr>
<td>12</td>
<td>54/F</td>
<td>None</td>
<td>Renal failure acute, rash maculo-papular, drug eruption, arthralgia, angioedema</td>
<td>Unknown</td>
</tr>
<tr>
<td>13*</td>
<td>64/F</td>
<td>None</td>
<td>Renal failure acute, hypovolaemia, appetite decreased, systemic inflammatory response syndrome, rash, rash erythematous, chest discomfort</td>
<td>Recovered</td>
</tr>
<tr>
<td>14</td>
<td>57/M</td>
<td>Propranolol, omeprazole, sertraline, perindopril, vardenafil (all C)</td>
<td>Renal failure acute, dehydration</td>
<td>Unknown</td>
</tr>
<tr>
<td>15</td>
<td>63/M</td>
<td>Iodine (S), Simvastatin, oxycodone, tamsulosin, metformin, lactulose, levothyroxine, rosuvastatin, lanosproazole (all C)</td>
<td>Renal failure acute, ventricular dysfunction, hypokinesia</td>
<td>Recovered</td>
</tr>
<tr>
<td>16*</td>
<td>64/F</td>
<td>None</td>
<td>Renal failure acute, renal failure#, hypophagia, systemic inflammatory response syndrome, rash erythematous, chest discomfort, hypovolaemia</td>
<td>Recovered</td>
</tr>
<tr>
<td>17#</td>
<td>62/M</td>
<td>Methylprednisolone, ciprofloxacin (both C)</td>
<td>Renal failure acute, infection</td>
<td>Not recovered</td>
</tr>
<tr>
<td>18</td>
<td>73/F</td>
<td>Meropenem (C )</td>
<td>Renal failure acute</td>
<td>Recovered</td>
</tr>
<tr>
<td>19</td>
<td>73/M</td>
<td>None</td>
<td>Renal failure acute, lung oedema, cardiac failure</td>
<td>Recovered</td>
</tr>
<tr>
<td>20</td>
<td>70/M</td>
<td>Pioglitazone, metformin, dimenhydrinate, senna alexandrina, metoclopramide, diphenhydramine, menthol/zinc oxide, magnesium oxide, sodium polystyrene sulfonate, hydrocortisone, iron, ergocalciferol, pantoprazole, atorvastatin, acarboside, irbesartan, (all C)</td>
<td>Renal failure acute, creatinine clearance decreased, sunburn, constipation, weight decrease, appetite decreased, asthena, nausea, vomiting, alopecia, hyperkalaemia, rash, urinary tract infection</td>
<td>Unknown</td>
</tr>
<tr>
<td>21</td>
<td>75/M</td>
<td>None</td>
<td>Renal failure acute, diarrhoea, sloughing of skin</td>
<td>Unknown</td>
</tr>
<tr>
<td>22</td>
<td>-/-</td>
<td>None</td>
<td>Renal failure acute, rash, dehydration, hypotension</td>
<td>Recovering</td>
</tr>
<tr>
<td>Case</td>
<td>Age/Gender</td>
<td>Other suspected (S) or concomitant (C) drugs</td>
<td>Reactions (WHO-ART preferred term)</td>
<td>Outcome</td>
</tr>
<tr>
<td>------</td>
<td>------------</td>
<td>---------------------------------------------</td>
<td>----------------------------------</td>
<td>---------</td>
</tr>
<tr>
<td>23</td>
<td>-/M</td>
<td>Milrinone (C)</td>
<td>Renal failure acute, congestive heart failure, pneumonia</td>
<td>Unknown</td>
</tr>
<tr>
<td>24</td>
<td>-/M</td>
<td>Timolol, Metamizole, Fentanyl, Finasteride, Candesartan, Sodium bicarbonate/Potassium</td>
<td>Renal failure acute, pancreatitis, cholecystitis</td>
<td>Unknown</td>
</tr>
<tr>
<td>25</td>
<td>66/M</td>
<td>Spironolactone, paroxetine, lisinopril, furosemide, carvedilol, atorvastatin,</td>
<td>Renal failure acute, congestive heart failure, pneumonia</td>
<td>Recovered</td>
</tr>
<tr>
<td>26</td>
<td>-/F</td>
<td>Piperacillin/tazobactam (S) 23 concomitant drugs including allopurinol, antibiotics, anticoagulants, antidiabetics, antihypertensives, proton pump inhibitors and hypolipidaemics</td>
<td>Renal failure chronic, cardiac arrest, respiratory arrest and 28 other reactions terms</td>
<td>Not recovered but died as an outcome of respiratory arrest</td>
</tr>
<tr>
<td>27</td>
<td>-/M</td>
<td>None</td>
<td>Renal failure##, lymphoedema</td>
<td>Unknown</td>
</tr>
<tr>
<td>28</td>
<td>-/F</td>
<td>None</td>
<td>Renal failure##, fatigue, rash</td>
<td>Recovering</td>
</tr>
<tr>
<td>29</td>
<td>-/M</td>
<td>None</td>
<td>Renal failure##, creatine blood increased</td>
<td>Unknown</td>
</tr>
<tr>
<td>30</td>
<td>-/-</td>
<td>None</td>
<td>Renal failure##, arthralgia, rash maculopapular, keratocanthoma, alkaline phosphatase serum increased, photosensitivity reaction, cholestasis intrahepatic, erythema, asthenia, keratosis</td>
<td>Unknown</td>
</tr>
<tr>
<td>31</td>
<td>38/F</td>
<td>Prednisolone, tamsulosin, ranitidine, pregabalin, sodium bicarbonate/ potassium chloride/sodium chloride/ Macrogol, enoxaparin (all C)</td>
<td>Renal failure##, myalgia, leg pain</td>
<td>Not recovered</td>
</tr>
<tr>
<td>32</td>
<td>56/M</td>
<td>Allopurinol, naproxen, celecoxib, paracetamol (all C)</td>
<td>Renal failure##, joint pain, uric acid blood increased, bone pain, muscle ache, nausea, headache, hypotension, paraesthesia, itching, sunburn, blood sugar increased, blisters, rash</td>
<td>Unknown</td>
</tr>
<tr>
<td>33</td>
<td>-/F</td>
<td>Clonidine, omeprazole, potassium, valaciclovir, glibizide, doxusate, valsartan/amlopidine, metoprolol, hydrochlorothiazide, metformin (all C)</td>
<td>Renal failure##, arthralgia, pyrexia, diarrhoea, rash, pancreatitis</td>
<td>Unknown</td>
</tr>
<tr>
<td>34**</td>
<td>44/F</td>
<td>Citric acid/potassium bicarbonate/ potassium citrate, colecalciferol, pantoprazole, sitaglpitin, metformin, hydrochlorothiazide, ramipril, dexamethasone, valproic acid (all C)</td>
<td>Renal failure##</td>
<td>Not recovered</td>
</tr>
<tr>
<td>35</td>
<td>57/M</td>
<td>Imipenem, amoxicillin sodium/ clavulanate potassium, ramipril, pantoprazole (all C)</td>
<td>Renal failure##, sepsis, hepatic failure</td>
<td>Died from renal failure, sepsis and hepatic failure</td>
</tr>
<tr>
<td>36**</td>
<td>44/F</td>
<td>Hydrochlorothiazide, valproic acid, sitaglpitin, potassium, metformin, ramipril, dexamethasone, ergocalciferol, pantoprazole (all C)</td>
<td>Renal failure##</td>
<td>Not recovered</td>
</tr>
<tr>
<td>37</td>
<td>89/M</td>
<td>None</td>
<td>Renal failure##, sepsis</td>
<td>Died – reaction may be contributory</td>
</tr>
<tr>
<td>38</td>
<td>75/M</td>
<td>Simvastatin, lisinopril, codeine phosphate/paracetamol, codeine, allopurinol, prazosin, metoprolol, acetylsalicylic acid, furosemide, irbesartan (all C)</td>
<td>Renal failure chronic, rash, diarrhoea, nausea</td>
<td>Unknown</td>
</tr>
<tr>
<td>39</td>
<td>74/F</td>
<td>Lovastatin, nadolol, hydrochlorothiazide (all C)</td>
<td>Renal failure##, laboratory test false, hepatic function abnormal, hyponatraemia, QT prolonged</td>
<td>Recovered</td>
</tr>
<tr>
<td>40</td>
<td>-/-</td>
<td>None</td>
<td>Renal failure##</td>
<td>Unknown</td>
</tr>
<tr>
<td>41</td>
<td>81/-</td>
<td>Pantoprazole, metoprolol, acetylsalicylic acid, amlopidine, molsidomine (all C)</td>
<td>Renal failure aggravated, rash, liver function tests abnormal nos</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

#cases 11 and 17 are duplicates, *cases 13 and 16 are duplicates, ##included term, **cases 34 and 36 are duplicates
Response from Roche

Thank you for the opportunity to provide our comments on your article, acute renal failure with vemurafenib.

Roche already completed an assessment of this adverse event on 15 October 2013. This signal was detected internally during the company’s review of Serious Unlisted Related (SUR) listings last July. In the SUR listing review, the number of renal events was raised as a concern as well as a literature abstract1 that reported the deterioration of renal function in a group of patients receiving vemurafenib. In September of this year, the Pharmacovigilance Risk Assessment Committee (PRAC) also requested Roche to review cases of acute renal failure and to look into the role of dehydration to identify plausible mechanisms, groups at risk, and the role of other factors in the occurrence of this event.

A cumulative review of vemurafenib cases entered in the Roche global drug safety database until 25 June 2013 was undertaken using the broad MedDRA SMQ for acute renal failure (ARF) which includes preferred terms of renal failure, renal impairment, clinical manifestations of oedema, decreased urine output, and abnormal laboratory findings of creatinine and blood urea among others. Data from preclinical studies, clinical trials, epidemiologic studies and the published literature were also reviewed.

There were 156 cases retrieved from the search of which 93 case reports were confirmed to include significant acute kidney injury (AKI) or acute renal failure. In 8 of the 93 cases, ARF was caused secondary to drug reaction with eosinophilia and systemic symptoms (DRESS), which is a labelled event. The majority, 49 out of the 93 cases, presented with alternative risk factors other than vemurafenib treatment: 19 cases (20.4%) occurred in association with adverse events of nausea, vomiting, diarrhoea or dehydration and in three cases (3.2%) due to aggravation of pre-existing dehydration. The remaining 36 cases presented with insufficient information.

Using a recent population-based study2 which estimated the incidence of acute renal failure per the RIFLE classification including all severity levels of risk: injury, failure, loss of kidney function, end-stage renal disease among patients with cancer by type, we compared the number of cases retrieved from our search. In that study, the incidence of all severity grades of RIFLE combined was 4.5% among melanoma patients with a baseline creatinine measurement and 1.6% among melanoma patients without a baseline creatinine measurement. Based on an estimated cumulative exposure of 19,926 vemurafenib patients and the 156 cases identified from the broad SMQ of Acute Renal Failure (includes terms of non-confirmed events of ARF such as increased creatinine), a conservative reporting rate of AKI/ARF for vemurafenib is 0.8% (156/19,926), lower than the rate of ARF for metastatic melanoma patients cited in the above literature (1.6% - 4.5%).

In addition, laboratory results from the pivotal randomized phase III trial, NO25026 (BRIM3) showed that there is no difference between arms (vemurafenib versus dacarbazine) in higher grades (3 + 4) of creatinine increase. This finding supports that vemurafenib is not directly nephrotoxic.

After this review of the available clinical data, a direct nephrotoxic effect of vemurafenib cannot be established. Although cases of dehydration (caused by nausea, vomiting, or diarrhoea, which are labelled events for vemurafenib) were identified to precede the AKI/ARF, the small number of these cases seen during this assessment within the context of the terminally ill patient population, a causal relationship cannot be established. Roche concluded that vemurafenib is not causally associated with ARF. Roche continues to closely monitor the events of AKI/ARF and related event of dehydration.

Reference:
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.
The surveillance and monitoring of Substandard, Spurious, Falsely labelled, Falsified and Counterfeit (SSFFC) medical products

It is now widely and openly recognized by both the public and private sectors that the existence of Substandard, Spurious, Falsely labelled, Falsified and Counterfeit (SSFFC) medical products impedes social and economic development. They cause harm to patients, damage economies, and undermine confidence in medicines, health-care professionals and the reliability of our supply chains. They also undermine our progress in achieving the challenging Millennium Development Goals.

A number of World Health Assembly (WHA) resolutions have drawn attention to the issue and called for international collaboration in tackling the problem. The latest of these was WHA resolution 65.19 adopted by Member States in 2012. After careful negotiation the resolution called for the establishment of a new Member State Mechanism to address SSFFC medical products.

It was an important step which led to the agreement of an eight point work plan, endorsed by the WHA in 2014. The work plan calls for strengthening of regulatory authorities and quality control laboratories, greater collaboration and co-operation amongst National agencies, awareness raising, sharing information, engagement with stakeholders, improving access to medicines and the surveillance and monitoring of SSFFC medical products.

It is the last of these which will really improve our understanding of the true scope, scale, extent and most importantly harm caused by SSFFC medical products. Despite numerous successful initiatives at National and Regional levels, training, awareness raising and market surveys we still do not have an accurate assessment of the true risk these products represent or the extent of the problem. Decisions to invest in strengthening Regulatory authorities and supply chains need to be based on validated evidence, which at present is scarce.

WHO had operated a rapid alert system concerning what was then known as counterfeit medicines in the Western Pacific Region, but the system was under-used. Building upon the knowledge gained and lessons learned from that system and other local initiatives WHO developed a new rapid alert system with the objective of encouraging Member States to report incidents of suspected and confirmed SSFFC’s in a more systematic and structured format.

Following a period of consultation and research a new reporting system was developed. It uses an electronic form with a number of optional and mandatory questions which was piloted by 10 Member States in September 2012 to January 2013. The Countries participating in the pilot study were Cambodia, Croatia, Georgia, Indonesia, Kyrgyzstan, Malaysia, Philippines, Russian Federation, Ukraine, and Vietnam. The pilot study tested the system and highlighted a number of improvements that were carried out.

The rapid alert form is available at the moment in English and French and will soon be available in other languages. Focal points from National Medicines Regulatory Agencies are trained in the use of the form which is sent to rapidalert@who.int. On receipt the sender will receive an automatic acknowledgement and Safety and Vigilance (SAV) personnel at WHO, Geneva will receive a warning that a new alert has arrived. The rapid alert form will be automatically translated and downloaded to a database where it will be compared against existing reports to identify any matches.

If the report indicates adverse reactions have occurred WHO will be in touch with the originator for some further detail and within 24 hours; if there is no indication suggesting an obvious adverse reaction, a response from WHO will be received within 72 hours.

WHO will contact the originator of the report to establish and clarify the facts and seek photographs and any results of laboratory analysis.

There are two principle benefits to this system. The first is the immediate operational benefit. Incidents can be linked automatically and immediately upon receipt. Laboratory assistance can be facilitated in emergency cases, technical support can be provided when requested and where necessary International Drug Alerts published.

The second benefit is that a validated body of reliable evidence is being accumulated upon which evidence-based policy can be recommended. The products most affected can be identified, vulnerabilities in the supply chain established and a more accurate assessment of the scope, scale, extent and harm caused by SSFFC medical products provided to Member States.
Workshops to train National focal points commenced in July 2013. Three day workshops have taken place in China, Nigeria, Switzerland, United Republic of Tanzania, Tunisia, and Turkey. 80 Member States are now trained and over 200 personnel have attended. The workshops comprises of four or five exercises involving real and recent incidents involving SSFFC, at the end of each incident the focal points report the case using the rapid alert form and send it to WHO. The attendees at the workshop include regulators, pharmacovigilance specialists and where possible, laboratory personnel. An additional workshop was conducted in Geneva attended by most UN and non-governmental procurers of medical products. The database has received reports of the first 340 products, involving all of the top level therapeutic categories. Antibiotics and antimalarial medicines are frequently reported and have resulted in a number of published drug alerts.

Some of the reports prove to be substandard medicines, others falsified. Expensive oncology products through to aspirin and paracetamol are reported. Innovator and generic medicines are almost equally reported and most are found in pharmacies, hospitals and clinics around the world. A number of reports have involved fatalities and other unexpected adverse reactions, but most products just fail to treat the disease for which they were intended. Trends and vulnerabilities are beginning to emerge and once the system is more widely rolled out and the number of reports increased WHO will begin to publish data. In the meantime focal points are encouraged to report early. Sometimes the product will already exist in the database and countries can be put in touch with each other quickly.

This system does not replace pharmacovigilance reporting in any way, but there is some overlap. Incidents involving SSFFC products are extremely difficult to identify, particularly if there is no obvious adverse reaction, but just a lack of effect. WHO SAV group is working closely with the WHO Collaborating Centre in Uppsala to develop methodologies to identify these very hard to detect signals.

Pharmacovigilance can be a key tool in identifying SSFFC medical products in our supply chains, we need to develop early warning systems which will help us to minimize the risks from these products.

It is through accurate reporting and subsequent analysis that we can truly understand SSFFC medical products and put in place proportionate measures to prevent, detect and respond to them.

We all know that the pharmaceutical market is a global one. What is produced in one part of the world can have an impact on the other side of the world. Regional approaches to tackling the issue are strongly encouraged by WHO, but there is also a need for global oversight of incidents. Already in the last 12 months positive outcomes for patients have been achieved through linking cases and sharing information rapidly on an inter-regional basis.

New and innovative approaches are required to mitigate the risks from SSFFC and improve our vigilance and post-market surveillance, pharmacovigilance represents one of those approaches.

The system is continuously being refined and improved and plans to enable reporting through a secure web portal will also be developed, together with photo libraries and lists of confirmed SSFFC products. Any further enquiries or information concerning the system or matters relating to SSFFC medical products should be sent to rapidalert@who.int.