WHO PHARMACEUTICALS NEWSLETTER

Prepared in collaboration with the
WHO Collaborating Centre for
International Drug Monitoring,
Uppsala, Sweden

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:

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This Newsletter is also available on our Internet website:
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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

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Regulatory Matters

Safety of Medicines

Signal

Azathioprine

Cytomegalovirus reactivation

Australia. The Therapeutic Goods administration (TGA) has warned about the risk of Cytomegalovirus reactivation associated with the use of Azathioprine**.**

Information about the risk of cytomegalovirus reactivation in patients with inflammatory bowel disease has been added to the Product Information for Azathioprine.

Azathioprine is used as an immunosuppressant antimetabolite. It can be used alone or in combination with corticosteroids and/or other immunosuppressive drugs and procedures.

The oral use of Azathioprine has been reported to be associated with Cytomegalovirus (CMV) which is a common viral infection that normally remains dormant until reactivated when T-lymphocyte mediated immunity is compromised. CMV viraemia can lead to secondary haemophagocytic syndrome.

TGA now advises that CMV viraemia resulting in severe pneumonitis and haemophagocytic syndrome in patients with inflammatory bowel disease has been reported in the literature. It recommends that caution be exercised and specialist literature consulted when assessing the risk of CMV reactivation and inflammatory bowel disease deterioration.

Four cases of CMV reactivation and/or haemophagocytic syndrome associated with azathioprine have been reported to the TGA since 1992.

Reference: Medicine Safety Update. June 2014. (www.tga.gov.au)

Docetaxel

Risk of alcohol intoxication

USA. The US Food and Drug Administration (FDA) is warning that the intravenous chemotherapy drug docetaxel contains ethanol, also known as alcohol, which may cause patients to experience intoxication or feel drunk during and after treatment. FDA is revising the labels of all docetaxel drug products to warn about this risk.

Docetaxel is a prescription chemotherapy drug used to treat different kinds of cancer, including cancers of the breast, prostate, stomach, head and neck cancers, and non-small-cell lung cancer.

Health-care professionals should consider the alcohol content of docetaxel when prescribing or administering the drug to patients, particularly in those whom alcohol intake should be avoided or minimized and when using it in conjunction with other medications.

Reference: FDA Safety Communications, US FDA, 20 June 2014. (www.fda.gov)

Etonogestrel/ethinyl estradiol slow release vaginal ring

New usage restrictions

Canada. Health Canada has endorsed important safety information on etonogestrel /ethinyl estradiol slow release vaginal ring (NUVARING®). New contraindications include the following:

- Etonogestrel /ethinyl estradiol should not be used by women who smoke (if over age 35), or who have severe or multpile risk factors for thrombosis, including: vulvular heart disease with complications, hypertension, severe dyslipoproteinemia, abnormality in proteins that regulate coagulation, diabetes mellitus with vascular involvement, or major surgery with prolonged immobilization.
- Etonogestrel /ethinyl estradiol should NOT be used by women who have experienced migraines with focal neurological symptoms, or pancreatitis associated with severe hypertriglyceridemia.
- Prescribers should consider the above new contraindications when discussing treatment options with their patients.

Reference: Health Canada, Important Safety Information, July 31, 2014. (www.canada.gc.ca)

Lidocaine Viscous

Should not be used to treat teething pain

USA. The US Food and Drug Administration (FDA) notified health professionals, their provider organizations and caregivers for infants, that prescription oral viscous lidocaine 2% solution should not be used to treat infants and children with teething pain. FDA is requiring a Boxed Warning to be added to the prescribing information (label) to highlight this information. Oral viscous lidocaine solution is not approved to treat teething pain, use in infants and young children can cause serious harm, including death.

Topical pain relievers and medications that are rubbed on the gums are not necessary or even useful because they wash out of the baby's mouth within minutes. When too much viscous lidocaine is given to infants and young children or they accidentally swallow too much, it can result in seizures, severe brain injury, and problems with the heart. Cases of overdose due to wrong

dosing or accidental ingestion have resulted in infants and children being hospitalized or dying.

In 2014, FDA reviewed 22 case reports of serious adverse reactions, including deaths, in infants and young children 5 months to 3.5 years of age who were given oral viscous lidocaine 2 percent solution for the treatment of mouth pain, including teething and stomatitis, or who had accidental ingestions.

Health care professionals should not prescribe or recommend this product for teething pain. Parents and caregivers should follow the American Academy of Pediatrics' recommendations for treating teething pain which includes the following:

- Use a teething ring chilled in the refrigerator (not frozen).
- Gently rub or massage the child's gums with your finger to relieve the symptoms.

FDA is also encouraging parents and caregivers not to use topical medications for teething pain that are available over the counter (OTC) because some of them can be harmful. FDA recommends following the American Academy of Pediatrics' recommendations to help lessen teething pain.

Reference: FDA Safety Communications, US FDA, 26 June 2014 (www.fda.gov).

Methadone (Oral)

Safety issues associated with high povidone content

Europe. The Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) 1 has endorsed by consensus the recommendation to suspend the marketing authorisation of methadone oral (by mouth) solutions containing high molecular weight povidone. These products will remain suspended until they have been reformulated. Additionally, the CMDh agreed that methadone tablets that contain low molecular weight povidone should remain on the market with changes to the product information.

Methadone is used in rehabilitation programs to prevent or reduce withdrawal symptoms in patients dependent on opioids such as heroin. Some oral formulations of methadone also contain the additive povidone, which is available in different molecular weights. While these medicines are intended for oral use only, some patients may misuse oral methadone formulations by injecting them into a vein. If a medicine containing high molecular weight povidone (known as K90) is misused in this way, the povidone is not excreted from the body and accumulates inside the cells of vital organs, which may cause serious harm.

The safety of oral methadone medicines containing povidone was reviewed by the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC), following reports of serious adverse events in former or current drug abusers in Norway, which led to the suspension of methadone oral solutions containing povidone K90 from the Norwegian market.

The PRAC concluded that risk minimisation measures would be insufficient to mitigate the risks with oral solutions containing high molecular weight povidone, and therefore recommended that these products should be suspended. They will need to be appropriately reformulated before being reintroduced in the European market.

For methadone tablets containing povidone of lower molecular weight (e.g. K25 and K30), the available data showed that this kind of povidone is excreted from the body and does not accumulate inside the cells as high molecular weight povidone does. Therefore, these products will remain in the market and changes will be made to the product information (SmPC and package leaflet) to reinforce the message that tablets are for oral administration only and must not be taken in any other way.

As the PRAC recommendation was endorsed by consensus by the CMDh, it will now be implemented in all EU Member States where these medicines are marketed, according to an agreed timetable.

Reference*:* Press Release, EMA, 24 June 2014 (www.ema.europa.eu)

Ondansetron

New dosing restrictions

Canada. Health Canada has informed health-care professionals the new safety information regarding the dosage and administration of intravenous ondansetron in geriatrics (>65 years of age).

In geriatrics, ondansetron (Zofran ®) is indicated for the prevention of nausea and vomiting associated with emetogenic chemotherapy.

New dosing restrictions are recommended to mitigate the risk of QT prolongation in elderly patients (>65years of age).

The dosing restrictions for geriatrics are summarized below:

- In patients **≥75** years of age, the initial IV dose must not exceed **8mg**.

• In patients years of age, the initial IV dose must no exceed **16mg**.
• Subsequent IV doses must not exceed 8mg and may even be given 4 and 8 hours after the initial dose.
• All IV doses must be diluted in 50-100mL of saline or other compatible fluid.
• All IV doses must be infused over no less than 15 minutes.

There are no changes to the recommended oral dosing.

These recommendations follow a previous risk communication, which detailed that ondansetron caused dose-dependent prolongation of the QT interval, which can lead to the Torsade de Points, a potentially life-threatening heart arrhythmia. Caution must be used if administering the ondansetron to patients with risk factors for QT interval prolongation or cardiac arrhythmias and electrolyte imbalances should be corrected prior to ondansetron administration.

Reference: Health Canada, Important Safety Information. June 12, 2014. (www.canada.gc.ca)

Renin-Angiotensin system (RAS) acting agents

Restricted use, especially in diabetic nephropathy

Europe. The EMA's Committee for Medicinal Products for Human Use (CHMP) has endorsed restrictions on combining different classes of medicines that act on the renin-angiotensin system (RAS), a hormone system that controls blood pressure and the volume of fluids in the body.

These medicines (called RAS-acting agents) belong to three main classes: angiotensin-receptor blockers (ARBs, sometimes known as sartans), angiotensin-converting enzyme inhibitors (ACE-inhibitors) and direct renin inhibitors such as aliskiren. Combination of medicines from any two of these classes is not recommended and, in particular, patients with diabetes-related kidney problems (diabetic nephropathy) should not be given an ARB with an ACE-inhibitor.

Where combination of these medicines (dual blockade) is considered absolutely necessary, it must be carried out under specialist supervision with close monitoring of kidney function, fluid and salt balance and blood pressure. This would include the licensed use of the ARBs candesartan or valsartan as add-on therapy to ACE-inhibitors in patients with heart failure who require such a combination. The combination of aliskiren with an ARB or ACE-inhibitor is strictly contraindicated in those with kidney impairment or diabetes.

The CHMP opinion confirms recommendations made by the Agency's Pharmacovigilance Risk Assessment Committee (PRAC) in April 2014, following assessment of evidence from several large studies in patients with various pre-existing heart and circulatory disorders, or with type 2 diabetes. These studies found that combination of an ARB with an ACE-inhibitor was associated with an increased risk of hyperkalaemia (increased potassium in the blood), kidney damage or low blood pressure compared with using either medicine alone.

Reference: Press Release, EMA, 23 May 2014. (www.ema.europa.eu)

Serotonin Antagonists

Risk of seretonin syndrome

Canada. Health Canada has completed a safety review of the serotonin blocking drugs (serotonin antagonists): palonosetron, dolasetron, granisetron and ondansetron. These drugs are used for treating nausea and vomiting due to cancer therapy. This review identified a potential risk of serotonin syndrome occurring when serotonin accumulates to high levels in the body.

Health Canada has requested that manufacturers incorporate the risk of serotonin syndrome into the Warnings and Precautions section and the Consumer Information section of the Canadian Product Monograph for these drugs.

A 2012 signal in the World Health Organization (WHO) Pharmaceuticals Newsletter prompted the review. The publication indicated that ondansetron used together with other drugs that affect serotonin levels (serotonergic drugs) may contribute to the development of serotonin syndrome in susceptible patients.

Serotonin syndrome occurs when serotonin, a chemical normally found in the body, accumulates to high levels. This usually happens with combinations of certain drugs that affect serotonin levels, but may also occur with a single drug.

It is very important to diagnose serotonin syndrome early as it can be fatal if not treated. Symptoms of serotonin syndrome may include any combination of confusion, agitation, restlessness, muscle twitching or stiffness, fever, increased sweating and heart rate, blood pressure fluctuations, pupil

dilatation, nausea and/or vomiting, loss of consciousness and coma. Neuroleptic malignant syndrome is a life-threatening condition with changes in the nervous, muscular and cardiovascular system. Neuroleptic malignant syndrome is associated with the use of antipsychotics and dopamine enhancing drug and it presents with clinical features similar to serotonin syndrome. Dopamine is another chemical normally found in the body. The way neuroleptic malignant syndrome occurs in the body is different to how serotonin syndrome occurs in the body. However, these two syndromes raise a diagnostic problem to the healthcare professional. As the treating healthcare professional could misdiagnose serotonin syndrome, it is important that patients who experience any of these symptoms talk to a healthcare professional immediately.

Health Canada received two Canadian reports of serotonin syndrome with serotonin blocking drugs used to treat nausea and vomiting. One report described an incident of serotonin syndrome in a 30-year-old man taking ondansetron and other medications. The other report described an incident of serotonin syndrome and neuroleptic malignant syndrome in a 12-year-old boy taking granisetron and olanzapine. Both patients recovered

The Health Canada review noted that when used as indicated, serotonin blocking drugs used to treat nausea and vomiting alone are unlikely to cause serotonin syndrome. However, when these drugs are used in combination with other drugs that affect serotonin levels, the way they work together in the body could explain how serotonin syndrome can occur.

The Canadian Product Monographs for ALOXI®, KYTRIL®, and ZOFRAN® now contain this new safety information. ANZEMET® has recently been discontinued by the manufacturer in Canada. Manufacturers of generic versions of these drugs will also update their Product Monographs. On May 14, 2014 Health Canada also issued an Information Update to the public communicating the risk of serotonin syndrome with serotonin blocking drugs used to treat nausea and vomiting.

Reference: Advisories, Warnings and Recalls, Health Canada, May 14, 2014. (www.hc-sc.gc.ca)

Strontium ranelate

Cardiovascular and Skin Reactions reported

Saudi Arabia. The Saudi Food and Drug Authority (SFDA) advised health-care providers that strontium ranelate (Protelos®), which is indicated in treating severe osteoporosis in postmenopausal women, is no longer available in the Saudi market due to serious cardiovascular and skin adverse drug events.

This decision was based on a comprehensive review of the available evidence to assess the benefit/risk balance of using strontium ranelate in patients suffering from osteoporosis. This review involved a number of clinical trials, observational studies and post-marketing surveillance data for the product.

The evaluated data indicated that there is an increased risk of heart problems (such as myocardial infarction) among strontium ranelate users. Furthermore there were confirmed cases of serious skin and hypersensitivity reactions such as drug rash with eosinophilia and systemic symptoms (DRESS).

The aforementioned issue was discussed in the Saudi Pharmacovigilance Advisory Committee meeting and it was concluded that based on the available evidence, the risks associated with using strontium ranelate for osteoporosis outweigh potential benefits and the proposed risk minimization measures may not be sufficient to protect the patients. Therefore, the SFDA decided to revoke the marketing authorization of strontium ranelate from the local market due to aforementioned risks and the availability of safer alternatives.

Reference: Communication from National Pharmacovigilance and Drug Safety Centre, SFDA, 01 June 14 (www.sfda.gov.sa/npc)

Testosterone products

Risk of venous blood clots

USA. The US Food and Drug Administration (FDA) notified health professionals and their medical care organizations that it is requiring the manufacturers of all approved testosterone products to include a warning in the drug labelling about the risk of blood clots in the veins, also known as venous thromboembolism (VTE), including deep vein thrombosis (DVT) and pulmonary embolism (PE).

The risk of venous blood clots as a possible consequence of polycythaemia is already included in the labelling of testosterone products. Because there have been post market reports of venous blood clots unrelated to polycythaemia, FDA is requiring a change to drug labelling of all testosterone products to provide a more general warning regarding venous

blood clots, to ensure this risk is described consistently in the labelling of all approved testosterone products.
This new warning, a class labelling change, is not related to an ongoing FDA evaluation of the possible risk of stroke, heart attack, and death in patients taking testosterone products. FDA is currently evaluating the potential risk of these cardiovascular events, which are related to blood clots in the arteries.

Reference: FDA Safety Communications, US FDA, 20 June 2014 (www.fda.gov).

Chlorhexidine solution

Risk of chemical burn injury to skin in premature infants

Europe. The MHRA has warned health-care professionals about the risk of chemical burn injury to skin in premature infants.

Chlorhexidine is an antiseptic frequently used for skin disinfection before catheterisation of premature infants.

Advice for health-care professionals are:

- When using alcohol-based or water-based chlorhexidine solutions on preterm infants, bear in mind the risk of severe chemical injuries.
- Use the minimum amount of chlorhexidine solution required and do not allow the solution to pool. Remove any excess solution and any soaked materials, drapes, or gowns from the skin.
- Monitor patients frequently to detect and manage cutaneous side effects at an early stage.

The MHRA received 14 reports of serious side effects in premature infants who were treated with chlorhexidine solution before central venous catheterisation (umbilical catheterisation or long line insertion). Another 14 cases were identified in the medical literature. The side effects included erythema and chemical burns with and without skin loss. Four of these had a fatal outcome, although severe complications of prematurity might have contributed to two of the fatal cases. The chemical injuries occurred in infants of less than 32 weeks gestation and within the first few days of life when alcohol based chlorhexidine solutions (0.5% or 2% in 70% alcohol) or 2% aqueous chlorhexidine solutions were used.

This issue will be reviewed at a European level. The MHRA will publish the outcomes of the review and any regulatory changes.

***Reference*:** MHRA, Drug Safety Update, volume 7, issue 11, June 2014: S4. (www.mhra.gov.uk)

Ferumoxytol

New Restrictions

Canada. Health Canada has endorsed important safety information on ferumoxytol due to serious hypersensitivity reactions. The Product Monograph has been revised to reflect new usage restrictions in patients treated with ferumoxytol.

Ferumoxytol is an intravenous iron product authorized for the treatment of iron deficiency anaemia in adult patients with chronic kidney disease (CKD).

Ferumoxytol is now contraindicated in patients with any allergy to other parenteral iron products or in patients with multiple (two or more) drug allergies.

Health-care professionals are also reminded that:

- Serious hypersensitivity reactions including life threatening and fatal anaphylaxis /anaphylactoid reactions have occurred in patients receiving intravenous iron products including ferumoxytol.
- Ferumoxytol should only be administered when personnel and therapies are immediately available for the treatment of anaphylaxis and other hypersensitivity reactions.
- Patients should be closely monitored for signs and symptoms of hypersensitivity, including clinically significant hypotension, during and for at least 30 minutes after each administration of ferumoxytol.
- Before each administration patients should be informed of the risk of hypersensitivity. Patients should also be informed of the relevant symptoms and asked to seek urgent medical attention if a reaction occurs.

Reference: Health Canada, Important Safety Information. July 11, 2014. (www.canada.gc.ca)

Intravenous dantrolene

Risk of skin and injection site reactions

UK. The Medicines and Health-care products Regulatory Agency (MHRA) announced that there is an increased risk of skin and injection reactions due to undissolved crystals in the product. Intravenous dantrolene (Dantrium intravenous) is indicated for the treatment of malignant hyperthermia, a rare and potentially fatal condition induced by inhalational anaesthetics and depolarising neuromuscular blockers. Dantrium intravenous is the only product licensed in the EU for this indication.

Dantrolene is associated with injection site reactions including redness, rash, swelling, localized pain, thrombophlebitis, and tissue necrosis. This risk may be increased by the crystals, from affected vials.

Although using filter needles should reduce this risk, users are advised to be vigilant for the development of injection site reactions.

Reference: *Drug Safety Update. July 2014.* (www.mhra.gov.uk)

Ivabradine

Emerging clinical trial evidence of increased cardiovascular risk

Europe. The MHRA has recommended health-care professionals to carefully monitor for bradycardia in patients given ivabradine.

Ivabradine (Procorolan) is used to treat symptoms of long-term stable angina in adults with coronary heart disease who have a normal heart rhythm. Ivabradine is also used in patients with long-term heart failure who have a normal heart rhythm but whose heart rate is at least 75 beats per minute (bpm).

The EMA is reviewing how the data from the SIGNIFY study impact the balance of benefits and risks of ivabradine. While the review is ongoing, health-care professionals are advised as follows:

Posology and Monitoring

- The starting dose of ivabradine is 5mg twice daily. The maintenance dose should not exceed 7.5mg twice daily.
- Carefully monitor patients for bradycardia or its symptoms (e.g. Dizziness, fatigue, hypotension).
- Down-titrate the dose if resting heart rate decreases persistently below 50 bpm or if the patient experiences symptoms of bradycardia. The dose can be down-titrated to 2.5mg daily if necessary.
- Stop ivabradine treatment if the resting heart rate remains below 50bpm or symptoms of bradycardia persist.
- Only increase the dose to 7.5mg twice daily after 3 to 4 weeks of treatment and if the 5mg dose is well tolerated but insufficient. Carefully monitor the effect of a dose increase on the heart rate.

Other considerations

- Avoid concomitant use of ivabradine with heart rate-reducing calcium channel blockers such as verapamil or diltiazem.
- Review the treatment of patients currently using ivabradine where appropriate.

Reference: MHRA, Drug Safety Update, volume 7, issue 11, June 2014: S1. (www.mhra.gov.uk)

Meningococcal B Vaccine

Associated with fever in children

Australia. The TGA has been undertaking enhanced monitoring of the recently launched meningococcal B vaccine, Bexsero (Bexsero ®). This is following reports of fever associated with vaccination with Meningococcal B Vaccine.

Bexsero® is the first vaccine in Australia intended to prevent invasive meningococcal disease caused by strains of *Neisseria meningitidis* serogroup B (meningococcal B).

Meningococcal B Vaccine is indicated for immunization of patients aged two months and older. For infants aged under six months, three primary doses of Meningococcal B Vaccine, plus a booster at 12 months of age, are recommended. Fewer doses are required for older age groups.

The highest incidence of group B disease occurs in children aged under five years, particularly infants aged under 12 months. A lower, secondary peak in incidence has been observed in late adolescence and early adulthood.

As with many other vaccines, patients may experience a rise in temperature following vaccination with Bexsero®.

During pre-market evaluation of Bexsero®, the TGA identified that use of the vaccine commonly induced fever in infants and children, including high fever, which is a risk factor for inducing a seizure.

When fever occurred, it generally followed a predictable pattern starting within six hours after vaccination. In the majority of cases, the fever had ceased by the next day.

Reference: *Medicine Safety Update.* June 2014. (www.tga.gov.au)

Meso-2, 3-dimercaptosuccinic acid

Potential health risks

USA. The US Food and Drug Administration (FDA) is warning consumers not to purchase or to use meso-2, 3-dimercaptosuccinic acid (Captomer ®) marketed as a dietary supplement for heavy metal toxicity and heavy metal chelation therapy. The products list DMSA (meso-2, 3-dimercaptosuccinic acid), as an active ingredient, which is contained in an FDA-approved prescription product indicated for the treatment of lead poisoning in children. FDA advises consumers to avoid all products offered over-the-counter (OTC) for chelation or detoxification. There are no FDA-approved OTC chelation products.

Procedures involving chelation agents carry significant risks and should be performed only under medical supervision.

Thorne Research, the company responsible for the distribution of Captomer® has received several adverse event reports associated with these products and has agreed to voluntarily

recall the products. For recall information, contact Thorne Research.

FDA-approved chelating agents are available by prescription only and are approved for use in specific indications such as lead poisoning and iron overload.

Consumers are advised not to purchase or use Captomer or Captomer-250 and avoid all products offered over-the-counter (OTC) for chelation or detoxification.

References: FDA Safety Communications, US FDA, 13 June 2014 (www.fda.gov).

Ofatumumab

Reminder of risk of serious and fatal infusion reactions

Europe. The MHRA has reminded health-care professionals about the risk using ofatumumab and to always give premedication and monitor patients carefully.

Ofatumumab (Arzerra) is indicated for the treatment of patients with chronic lymphocytic leukemia refractory to fludarabine and alemtuzumab.

Serious fatal infusion reactions have occurred with ofatumumab and other anti-CD20 monoclonal antibodies. Health-care professionals are reminded to always give premedication before each ofatumumab infusion. If a severe reaction occurs, ofatumumab infusion should be interrupted and the reaction treated. Patients with a history of decreased pulmonary function are at high risk of pulmonary complications from severe reactions.

***References*:** MHRA, Drug Safety Update, volume 8, issue 1, August 2014: A2. (www.mhra.gov.uk)

Fentanyl "patches"

Reminder of potential life-threatening harm from accidental exposure, particularly in children

Europe. The MHRA has reminded the need of safe handling of Transdermal fentanyl patches.

Accidental exposure can occur if a patch is swallowed or transferred to another individual. Children are at risk as they may touch, suck, chew, or swallow a patch that has not been disposed of properly. Also, children have a lower threshold for fentanyl overdose than adults. Two of the three Yellow Card reports received by the MHRA have concerned children.

Health-care professionals are reminded to provide clear information to patients and caregivers regarding risk of accidental exposure and the need for its appropriate disposal.

References: MHRA, Drug Safety Update volume 7 issue 12, July 2014:S1. (www.mhra.gov.uk)

Vaccines

Complex regional pain syndrome

Australia. The TGA has reported cases of complex regional pain syndrome following vaccination.

Health professionals are advised to be mindful of the potential for this adverse event when administering vaccinations and are encouraged to report any suspected cases.

Complex regional pain syndrome (CRPS) is characterized by continuing pain that is disproportionate to any potential inciting event, when accompanied by sensory, motor, vasomotor and sweating/oedema signs and symptoms.[1]

There are two forms of CRPS, type 1 (CRPS-I) and type 2 (CRPS-II). CRPS-I is more common and describes a situation in which the patient does not have demonstrable nerve injury. CRPS-II tends to be more serious and describes a situation in which the patient has confirmed nerve injury.

While the cause of CRPS is unknown, it has been diagnosed after trauma, infection, surgery, cervical radiculopathy and myocardial infarction, as well as following vaccination.

The TGA has received five adverse event reports following vaccinations that are consistent with CRPS. Three of those cases involved a human papillomavirus vaccine. Of the other two reports, one involved an influenza vaccine and the other related to diphtheriatetanus-acellular pertussis vaccination. Some other reports that listed CRPS as an adverse event did not meet the diagnostic criteria.

As part of a recent review of CRPS following vaccination, the TGA referred the issue to its Advisory Committee on the Safety of Vaccines for consideration.

The Committee noted that cases of CRPS were hard to capture, as there was a large variation in causes, but advised that CRPS following vaccination would have been triggered by the pain caused by the process of immunization, rather than the contents of the vaccine itself.

Analysis of three cases of CRPS involving human papillomavirus vaccine in Australia, found that:

- Intramuscular immunization is sufficient painful stimulus to trigger the development of CRPS-I, and that it is the process of a needle

penetrating the skin that is the trigger, rather than a particular vaccine antigen or adjuvant being causally related.

• The Advisory Committee on the Safety of Vaccines deemed CRPS following vaccination was under-reported in Australia.

• Following consideration of Australian and international data, the TGA review has concluded that CRPS following vaccination with any vaccine is a very rare event. However, there may be under-diagnosis and/or under-reporting of this adverse event in Australia.

References: *Medicine Safety Update.* June 2014. *(www.tga.gov.au)*

Voriconazole

Reminder of risk of liver toxicity, phototoxicity, and squamous cell carcinoma

Europe. The Medicines and Health-care products Regulatory Agency (MHRA) advised health-care professionals to test liver function before starting treatment with voriconazole (Vfend) and at least weekly during the first month of treatment. Patients should be advised to avoid sunlight exposure while taking voriconazole. New tools to help monitor and manage these risks are being distributed.

Voriconazole is an antifungal medicine indicated for certain worsening, possibly life-threatening fungal infections in adults and children over 2 years. Voriconazole is known to be associated with a risk of liver toxicity, phototoxicity, and squamous cell carcinoma of the skin.

The advice below applies to both adults and children taking voriconazole.

Liver toxicity

• Test liver function before starting treatment with voriconazole (specifically, aspartate transaminase [AST] and alanine transaminase [ALT] levels).

• Continue testing liver function at least weekly for the first month of treatment and monthly thereafter if there are no changes in the first month of treatment.

• Stop voriconazole if AST or ALT levels become markedly elevated, unless you consider the benefits of voriconazole treatment to outweigh the risk of liver toxicity in that individual.

Phototoxicity and squamous cell carcinoma

• Tell patients to avoid sunlight exposure while taking voriconazole. Advise patients to wear protective clothing and use sunscreen with a high sun protection factor if in sunlight.

• Refer patients with phototoxic reactions to a dermatologist and consider stopping voriconazole treatment.

• If voriconazole is continued despite a phototoxic reaction, check the skin frequently and thoroughly to detect and manage pre-cancerous lesions as early as possible.

• Stop voriconazole if pre-cancerous skin lesions or squamous cell carcinoma are identified. Note that patients may develop squamous cell carcinoma without a prior phototoxic reaction.

***References*:** MHRA, Drug Safety Update, volume 7, issue 10, May 2014:A2. (www.mhra.gov.uk)

Zolpidem

Reminder of risk of impaired driving ability the next day

Europe. The MHRA has advised health-care professionals about the risk of impaired driving ability the next day when taking zolpidem. Zolpidem is used to treat insomnia. To reduce this risk patients are advised:

- To take 10mg of zolpidem at bedtime and not to take it again in the same night
- Not to drive, operate machinery, or work at heights until at least 8 hours after taking zolpidem
- Not to take zolpidem with alcohol, illicit drugs, or other central nervous system suppressants
- Not to drive, operate machinery or work at heights if they are still drowsy after taking zolpidem.

People with liver impairment and the elderly should take no more than 5 mg of zolpidem a night.

***References*:** MHRA, Drug Safety Update, volume 7, issue 10, May 2014. (www.mhra.gov.uk)

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

The signals in this Newsletter are based on information derived from Individual Case Safety Reports (ICSRs) available in the WHO Global ICSR Database, VigiBase®. The database contains over 7 million reports of suspected adverse drug reactions, submitted by National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring. VigiBase is, on behalf of the WHO, maintained by the Uppsala Monitoring Centre (UMC) and periodic analysis of VigiBase data is performed in accordance with UMC's current routine signal detection process.

More information regarding the ICSRs, their limitations and proper use, is provided in the UMC Caveat document available at the end of SIGNAL (on page 37). 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.

Agomelatine and Hypotension

Signal from Uppsala Monitoring Centre

Summary

Agomelatine is a MT1 and MT2 melatonin receptor agonist prescribed for the treatment of major depressive episodes. Melatonin and to some extent melatoninergic drugs have shown cardiovascular effects in animal models and human studies, probably due to their chronobiotic and sympatholytic effects. Of the 20 reports in the WHO Global Individual Case Safety Report (ICSR) Database, VigiBase®, on hypotension under agomelatine from eight different countries, twelve were eligible for assessment. They revealed a consistent pattern of time to onset and recovery on dechallenge with a positive rechallenge in one case. The vast majority of these ICSRs (10 out of 12) reported no co-suspect medication. A possible mechanism of action, together with suggestive and consistent ICSRs, points at a signal.

Introduction

Agomelatine is a MT1 and MT2 melatonin receptor agonist and a serotonin (5-HT2c) antagonist. It is approved in Europe (2009), Australia and Latin American countries for the treatment of depression in patients over 18 years in a dosage of 25-50 mg orally once daily. It is not recommended in patients under 18 years since safety and efficacy have not been established in this age group. Agomelatine has a positive effect on the resynchronisation of circadian rhythms in animal models of circadian rhythm disruption and has shown efficacy in placebo controlled trials. The results from seven clinical trials involving SSRIs as comparators were less convincing with non-inferiority being shown in four and superiority in two trials.[1] No improvement was observed in very elderly patients (>75 years).

The safety profile of agomelatine requires regular monitoring of liver function in all patients treated. Agomelatine is metabolised mainly by cytochrome P450 1A2 (CYP1A2) (90%) and by CYP2C9/19 (10%). Caution must therefore be exercised when inhibitors of these two isoenzymes are prescribed concomitantly.[1]

Agomelatine is not approved for marketing in the USA.

Hypotension is a physiologic state characterized by abnormally low blood pressure. As normal blood pressure varies with age, there is no absolute threshold to define hypotension. In a younger adult hypotension might be defined as systolic pressure <90 mmHg and diastolic pressure <60 mmHg. As blood pressure is influenced by different factors such as cardiac output, vascular resistance and venous return and pressure, any change in one of these variables can lead to fluctuations in blood pressure.

Statistically disproportional reporting has been observed in the WHO Global Individual Case

Table 1. Overview of reports in VigiBase® of hypotension in association with Agomelatine

Case	Age/Sex	Other suspected (S) or concomitant (C) drugs	Reported reactions (MedDRA)	Dechallenge/ Rechallenge	Outcome
1	30/M	None	Blood pressure decreased, weakness, fainting, sleepiness	Positive/NA	Recovered
2	52/F	Prothipendyl (S)	Hypotension, syncope, somnolence	Agomelatine continued, prothipendyl discontinued	Recovered
3	44/F	None	Blood pressure drop arterial, vertigo subjective, vomiting, sleep disturbed, paraesthesia of limbs, flash hot	Positive/NA	Recovered
4	62/M	Diuretics (C)	Hypotension, dizziness, fall, weakness, gait instability	Agomelatine continued, concomitant diuretics reduced	Recovered
5	59/F	Simvastatin, pantoprazole, doxepin, lamotrigine (all C)	Blood pressure decreased, weakness, syncope, TIA, blindness transient	Positive/NA	Recovered
6	81/F	Mirtazapine, olanzapine (both S) Zolpidem, simvastatin, levothyroxine, ramipril, acetylsalicylic acid, lorazepam (all C)	Hypotension, fainting, memory loss transient, drug interaction	Positive/unknown	Recovered
7	84/M	None	Hypotension, fall, hyponatraemia, gait abnormal	Agomelatine continued	Unknown
8	50/F	Omeprazole, theophylline, budesonide (all C)	Orthostatic hypotension, lightheadedness, hallucination visual, visual field defect	Positive/positive	Recovered
9	44/F	None	Blood pressure decreased, syncope, muscular weakness, infection, light sensitivity to eye	Positive/unknown	Recovered
10	22/F	None	Orthostatic hypotension, syncope	Positive/unknown	Recovered
11	65/F	Trazodone, ramipril, quetiapine, warfarin (all C)	Hypotension, depression, adaptation abnormal	Agomelatine dose reduced	Unknown
12	28/M	None	Hypotension, dizziness, weakness	Positive/unknown	Recovered
13	41/F	Pipamperone, zoplicone, paracetamol (all C)	Blood pressure decreased, syncope, allergic reaction, itching, hyperhidrosis	Positive/unknown	Recovered
14	43/F	Diazepam, promethazine (both C)	Hypotension orthostatic, convulsions grand mal, syncope, hypokalaemia, muscle soreness	Agomelatine continued	Recovered
15	83/M	Tizanidine, delorazepam (both S)	Hypotension, bradycardia, bradykinesia, bradyphrenia, sopor, dryness oral, deliberate overdose	Positive/unknown	Recovered
16	52/F	Duloxetine, desvenlafaxine, baclofen, antidepressants NOS (all S)	Hypotension, suicide attempt, multiple drug overdose, bradycardia, therapeutic aspiration	Unknown	Unknown
17	41/F	None	Blood pressure low, dizziness, vomiting, intentional overdose	Agomelatine continued at normal dose	Recovered
18	18/M	Risperidone, mirtazapine (both S)	Hypotension, suicide attempt, intentional overdose, tachycardia, somnolence, decreased activity	Unknown	Unknown
19	51/F	Trolnitrate, etofylline, pentoxifylline (all S)	Hypotension, vomiting, attempted suicide, multiple drug overdose intentional, restlessness	Unknown	Recovered
20	25/F	Bisoprolol, venlafaxine (both S)	Hypotension, suicide attempt, multiple drug overdose intentional, double vision, mydriasis	Agomelatine continued at normal dose	Recovered

Safety Report (ICSR) Database, VigiBase® for syncope under agomelatine treatment. An assessment of these reports revealed that in most cases the reported ADR term syncope did not meet the case definition criteria. These ICSRs however hinted at a possible association between agomelatine and hypotension and it was decided to investigate this combination despite negative IC values (hypotension IC -0.4, IC025 -1.16 and hypotension postural IC 0.66, IC025 -1.08).

Reports in VigiBase

Twenty-one ICSRs concerning hypotension/orthostatic hypotension were retrieved from VigiBase as per 8 January 2014 including one duplicate. The ICSRs originate from eight countries (Argentina, Australia, Czech Republic, Germany, Spain, United Kingdom, Italy and Netherlands) and concern 14 women and six men aged between 18 and 84 years (median 50 years). One ICSR describes hypotension in the context of an allergic reaction and six ICSRs describe intentional overdose/suicide attempts. A further report must be looked at with caution as convulsion grand mal is co-reported and the sequence of the events is not clear: convulsions were excluded in the beginning, then reported retrospectively based on myalgia. These eight reports were excluded which leaves 12 reports for analysis (eight women, four men, age 22-84 years). The table lists all 20 reports for completeness (Table 1).

Agomelatine was the only suspected drug in ten out of twelve ICSRs. Eight out of twelve report a positive dechallenge and one of them a positive rechallenge. In one case the agomelatine dose was reported as reduced but unfortunately the outcome was unknown. Another report lists prothipendyl as a co-suspect drug. This drug was discontinued while maintaining agomelatine and the patient recovered. In another case the concomitant diuretic therapy was reduced while maintaining agomelatine at the same dose and this patient recovered as well.

Time to onset was reported in nine cases (one to five days in six cases, eight days after dose increase in one report, 39 days and 1 year 3 months in two other reports) and remains unknown in three cases. In one case, orthostatic hypotension and other symptoms lasted for twelve hours after each agomelatine intake.

Blood pressure readings were provided for four patients regularly treated (90/60 mmHg; 74/40 mmHg; 100/75 mmHg; 110/70 mmHg) and for three patients with an intentional overdose (70/40 mmHg; 70/(not available) mmHg; 106/45 mmHg).

The ICSRs do not provide any information on the time of the day when the reported hypotensive episodes occurred.

Literature and Labelling

Hypotension/orthostatic hypotension is not listed in the European SPC for agomelatine. According to the same text, agomelatine had neutral effect on heart rate and blood pressure in clinical trials.

The effect of melatonin and melatoninergic drugs on the cardiovascular system has been investigated in animal models and human studies, but the published data concerning melatoninergic drugs is unfortunately rather scarce compared to data from studies performed with melatonin itself.

Campos et al studied the effect of exogenous melatonin in normotensive rats: a continuous infusion of melatonin induced a significant decrease in blood pressure as well as a reduction in heart rate, hinting at a blunting of the baroreceptor reflex through the area postrema. Ablation of the area postrema, on the other hand, abolished the melatonin effects.

Melatonin and piromelatine showed an antihypertensive effect when administered to hypertensive rats3 and slow-release melatonin significantly decreased nocturnal blood pressure in normo- and hypertensive middle aged women.[4]

Melatoninergic drugs were developed in the first place to compensate for the short half life of melatonin and to achieve higher receptor affinity. Conclusions derived from studies with melatonin might not be unrestrictedly applicable to all melatonin receptor agonists. In a review of the cardiovascular effects of melatonin receptor agonists Paulis et al postulate different possible mechanisms that could work towards a reduction in blood pressure: activation of MT1 and MT2 receptors is regarded as having chronobiotic as well as sympatholytic effects.

Discussion and Conclusion

The combination agomelatine — hypotension does not stand out statistically in VigiBase. However, the published literature on melatonin (and to a significantly lesser extent on melatoninergic drugs) supports a possible, multifactorial involvement of these compounds in the regulation of arterial pressure.

The analysed ICSRs point at a positive causal relationship based on a consistent time to onset (the two outliers with longer times to onset might be explained by a concurrent reported infection that might have triggered the hypotensive episode in one case and an extensive comedication with missing therapy dates in the other), the high number of positive dechallenges reported and the patient experiencing a positive rechallenge.

In conclusion, we consider hypotension under agomelatine a signal that should be taken into consideration when prescribing this medication.

Note! This article has been edited for clarification about case five in Table 1 not having a positive rechallenge reported according to the response from Servier.

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Response from Servier

Regarding the signal "hypotension", all sources were considered and are presented thereafter:

Pharmacological Data

During agomelatine safety pharmacology studies, haemodynamic parameters have been investigated in animals:
In rats, agomelatine (up to 12.5mg/kg i.p.) did not modify mean systolic arterial blood pressure up to 2h following administration (112+4 mmHg and 118+8 mmHg for vehicle and agomelatine-treated rats respectively at 30min).
In monkeys, up to the cumulative dose of agomelatine of 32mg/kg i.v., mean systemic arterial blood pressure and mean arterial blood flow remained unchanged. Resistance in each vascular bed was unaltered. No safety concerns emerge from these animal studies.
Agomelatine is acting through melatonergic and 5-HT2C antagonist properties. As concern, additional pharmacological data showed that in animals (1,2,3) and/or humans (4) with hypertension, melatonin or 5HT2c/5HT2B antagonists could induce an antihypertensive effect, however no significant effect on blood pressure was observed under normal conditions (5).
The analysis was performed in patients included in the agomelatine development program. This overall safety set included 14377 patients: 8693 on agomelatine, 1886 on placebo (and 3798 on comparators). The incidence of emergent hypotension was similar in the agomelatine and placebo groups, 0.40% and 0.58% respectively.

Post-Marketing data

From Market Authorisation (19-FEB-2009) up to 19-FEB-2014 (PSUR 7 data-lock point), 66 cases were reported: 38 Hypotension, 16 Orthostatic hypotension, 11 Blood pressure decreased and 1 Blood pressure ambulatory decreased i.e. a reported incidence of 5.4 / 100 000 patient-years. Out of these 66 cases, 9 occurred in a context of drug overdose with agomelatine. These 9 cases represent 4.3% of the 207 cases of agomelatine overdose received since MA. Eight cases occurred in a context of multiple drug overdose, with at least one concomitant drug known to induce hypotension (venlafaxine, desvenlafaxine, bisoprolol, duloxetine, hydroxyzine, chlorpromazine, verapamil, pentoxifylline, ziprasidone, risperidone, mirtazapine), amongst which one occurred in association with alcohol poisoning.

Clinical Trial Data

One case occurred after a single intake of 700mg of agomelatine: the patient presented with dizziness, hypotension and vomiting leading to hospitalisation. Agomelatine was maintained at therapeutic dosage and hypotension did not reoccur. The amount of agomelatine varied from 200mg to 3500mg in these cases. Of note, the aglomelatine SmPC refers to an ingestion of 2450mg with out subsequent cardiovascular abnormalities.
Amongst the 57 remaining cases:
One case occurred after a single overdose of ivabradine for which hypotension is a listed event "sensation" of hypotension was reported in 5 cases in 25 cases of reported hypotension, no BP value was provided. In the 26 cases with BP values, hypotension was considered as non-severe (BP > 100/60 mmHg) in 11 cases. while in the remaining

15 severe cases, dizziness (5), fatigue (5), syncope (4), presyncope (2) and fall (2), were associated with hypotension and one patient did not experience symptoms. Analysis of the 51 cases of reported hypotension (25 cases without BP value and 26 cases with BP value) is displayed thereafter (Table).

Out of the 17 cases without alternative causes (absence of relevant medical history, context or concomitant drugs likely to induce hypotension): 4 cases were poorly documented, no BP value was provided in 9 cases and BP was greater or equal to 100/60 mmHg in 4 cases. Overall, the role of agomelatine in these 51 cases was assessed as doubtful. In conclusion, the analysis of post-marketing data showed: A moderate incidence of events: 5.4/100 000 PY, No cases with a "likely" or "possible" causality assessment. In most cases (34 cases - 67%), confounding factors such as relevant medical history and/or relevant context and/or concomitant treatment(s) known to induce these kinds of events were present.

Thus the review of post-marketing did not raise new safety concerns. In summary, although melatonin or 5HT2C/ 5HT2B antagonists could induce an antihypertensive effect in animals and/or humans with hypertension, no safety concern regarding "hypotension" was raised with agomelatine from nonclinical data, clinical data or postmarketing surveillance. Thus the signal "Hypotension" was refuted and closed. This event will remain under close monitoring.

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	Gender: - Female: 32 - Male: 18 - Unknown: 1 Median age: 58 years
Occurrence after the 1st intake of the drug	• within 2 weeks: 27 • between 2 weeks and 1 month: 4 • between 1 month and 3 months: 6 • over 3 months: 4 • unknown: 10
Dechallenge / Rechallenge	Positive dechallenge: 25/51 No positive rechallenge* Recovered under treatment: 8/51
Alternative explanation *34/51*	Relevant medical history 19/51: Treated hypertension (11) Orthostatic hypotension/Hypotension (3) Cardiac failure (2) Anorexia (2) Alcohol abuse (1) Vasomotor disorder (1) Sick sinus syndrome (1) Relevant context (13/51): Infection (4) Vomiting/Diarrhoea (1) Hypernatremia (2) Seizure (1) Alcohol poisoning (1) Physical effort (1) Allergic reaction (1) Uncontrolled BP (1) Abrupt switch of benzodiazepine treatments (1) Concomitant drugs (22/51): Antihypertensive drugs including ß-blockers, anti-arrhythmic, SNRI, SSRI.

#5 and #8 from the WHO table were not considered as cases with challenge by the MAH

Dronedarone and Polyneuropathy

Signal from Uppsala Monitoring Centre

Summary

Dronedarone is a benzofurane antiarrhythmic drug indicated for the second line treatment of atrial fibrillation after successful conversion to sinus rhythm. Risk minimizing action was taken by regulatory authorities in 2011, due to serious cardiovascular adverse events as well as hepato- and pulmonary toxicity. Dronedarone is structurally closely related to amiodarone, a drug commonly associated with neuropathy.

Polyneuropathy in association with dronedarone has been disproportionately reported in the WHO Global Individual Case Safety Report (ICSR) Database, VigiBase™ with an IC value of 2.2 and an IC025 of 0.95. Eight ICSRs have been retrieved and assessed. Even though some reports lack information on treatment dates and others are confounded by concomitant medication with neurotoxic potential, overall they point towards a possible causal relationship. This is further supported by the statistical disproportional reporting rate in VigiBase as well as a plausible potential mechanism of action.

Introduction

Dronedarone is an anti-arrhythmic medicine, prescribed for maintaining sinus rhythm after successful cardioversion in patients with paroxysmal or persistent atrial fibrillation. Regulatory authorities restricted the indication for treatment in September 2011 due to an increased risk of liver failure and lung toxicity as well as of serious cardiovascular events.

The clinical Phase 3b trial PALLAS had been suspended due to an increase in cardiovascular events with dronedarone (significant increase in major cardiovascular events defined as a composite of stroke, myocardial infarction, systemic embolism, and cardiovascular death) compared to the placebo group. Dronedarone should only be prescribed after alternative treatment options have been considered. Neither the European Medicines Agency Summary of Product Characteristics (EMA SPC) nor the US FDA label list polyneuropathy. Only taste disturbances are mentioned from the System Organ Class Nervous System Disorders.[1,2]

The exact mechanism of action of dronedarone hydrochloride, a non-iodinated amiodarone analogue, is unknown. Dronedarone exerts antiarrhythmic effects similar to all four Vaughan-Williams4 classes; however, the relationship to the clinical effect is unknown. Like amiodarone, dronedarone inhibits the calcium, sodium, and potassium channels and is an alpha- and beta-adrenergic receptor antagonist. Unlike amiodarone, dronedarone has minimal to no inhibitory effect on the alpha- and beta-thyroid receptors. Peripheral neuropathy has been reported to occur in up to 10% of patients taking amiodarone.

Axonal, demyelinating and mixed type neuropathy have been reported with no apparent correlation to daily or total dose or treatment duration. Histologically, lysosomal inclusions in peripheral nerve tissues have been documented and seem to be a characteristic finding. Compared to amiodarone, dronedarone is non-iodinated and in order to reduce the neurotoxic potential a methylsulfonamide group was added to reduce lipophilicity.

Peripheral neuropathy is characterized by sensory loss, muscle weakness and atrophy as well as decreased deep tendon reflexes. It can affect one single nerve (mononeuropathy) or many nerves at the same time (polyneuropathy). Polyneuropathy can be caused by nutritional deficiencies and metabolic disorders, and occurs with diseases such as diabetes mellitus, porphyria, sarcoidosis and in uraemia. It can present as paraneoplastic syndrome as seen with multiple myeloma. Polyneuropathy can be of autoimmune origin, as in Guillain-Barre syndrome. It is commonly associated with alcohol abuse and can be drug induced (sulphonamides, oncologic drugs such as vinca alcaloides and heavy metal complexes as well as antiretrovirals).

Reports in VigiBase

Eight Individual Case Safety Reports (ICSRs) were retrieved from the WHO Global ICSR Database, VigiBaseTM. One is a duplicate, which leaves seven ICSRs for assessment. One ICSR is from Sweden, the other six were reported from Germany. The reports concern six men and one woman, aged between 71 and 92 years (median 80 years, age was not stated in two reports).

As treatment and onset dates are missing in many reports, a time to onset can be calculated only for case 1 (five weeks), case 2 (seven months) and case 7 (2.5 years). In four out of seven ICSRs the dechallenge was positive. Cases 1 and 4 lack this information and in case 7 the medication was continued and the outcome reported as not recovered. No rechallenge was reported.

In two out of seven ICSRs no concomitant therapy associated with neuropathy or paraesthesia was

reported. Five patients were concomitantly treated with at least one drug that has been associated with paresthesia and two of these patients also with statins, which are known to very rarely cause neuropathy. However, no therapy dates are given for any concomitant medication and none was taken into consideration as co-suspected by the reporter.

One patient was reported to have a pre-existing diabetic neuropathy that worsened after administration of dronedarone and went back to baseline after discontinuation (case 6). Case 7 reports that the patient had been treated with oxaliplatin, 5FU and folinic acid two years previously and had experienced paraesthesia after every administration. The extensive neurological examinations performed were not conclusive and it is possible that the adverse drug reactions (ADRs) reported in 2012 were still related to the previous chemotherapy.

IC 2.2 and IC0 25 0.95 indicate a disproportional reporting of this association in VigiBase.

Literature and Labelling

Neither the US FDA label nor the EU SPC for dronedarone lists neuropathy or polyneuropathy.[1,2]

Only a few case reports on neuropathy under dronedarone treatment have been published so far. The German arzneitelegramm published a case report of polyneuropathy and visual disturbance in 2012; a 50-year-old man developed polyneuropathy with stocking-like loss of sensibility in the left foot as well as visual problems after taking dronedarone for just under one year. The patient had not yet recovered one year after discontinuing the medication.

At the 2011 International Conference of the American Thoracic Society, Di Trapani and Freeman presented a case of dronedarone induced neurotoxicity involving the central nervous system; a 75-year-old woman developed encephalopathy, tremor, myoclonic jerking and incoordination under dronedarone. A most extensive diagnostic work up yielded no explanation. The symptoms improved after discontinuation of dronedarone.

Tab1. Characteristics of ICSRs in VigiBase™ on dronedarone and polyneuropathy

Case	Age/Sex	Concomitant drugs	Reported ADRs (WHO-ART)	Dechallenge	Outcome
1	76/ M	Furosemide, warfarin, metoprolol	Polyneuropathy	Unknown	Unknown
2	82/ M	Furosemide, perindopril, phenprocoumon	Polyneuropathy, neuropathy peripheral, muscle atrophy, gout, infection bacterial, immune responsiveness decreased	Positive	Recoverin g
3	-/M	Pravastatin, lercanipidine, metoprolol, phenprocoumon	Polyneuropathy, hypoaesthesia, visual disturbance	Positive	Recovere d with sequelae
4	92/ M	None reported	Polyneuropathy, gait disturbance	Unknown	Recoverin g
5	-/F	Dabigatran, metoprolol, bisoprolol	Polyneuropathy, paraesthesia, formication, Creatinine clearance decreased	Positive	Recovere d
6	80/ M	Phenprocoumon	Polyneuropathy, gait disturbance, fibrillation atrial	Positive	Recoverin g
7	71/ M	Torasemide, simvastatin, ramipril, clopido-grel, pantoprazole, certoparin, phenprocoumon, fluvastatin, isosorbide dinitrate, hydrochlorothiazide, ezetimibe, metoprolol	Polyneuropathy, paralysis, hypoaesthesia, gait disturbance, coordination abnormal, asthenia	Drug continued	Not recovered

A further case report published in 2013 in the International Journal of Cardiology, concerns a 74-year-old man who developed optic neuropathy under dronedarone. While the pain subsided after discontinuation of dronedarone, the visual loss is is still persisting.

Discussion and Conclusion

The spontaneous reports in VigiBase point overall towards a causal association between dronedarone and polyneuropathy despite confounders such as previous neurotoxic treatment in one case and co-medication with statins in two cases. The four reported dechallenges led to recovery and in the only case where drug continuation was reported, the patient did not recover from polyneuropathy. Dates for start of treatment and onset of polyneuropathy are incompletely reported. Dronedarone is, however, the only drug suspected by the reporters to have caused the ADR.

Dronedarone is structurally closely related to amiodarone, a drug for which neuropathy is a well-documented adverse reaction. While the addition of a methylsulfonamide group might have significantly reduced the neurotoxic potential of the drug as the results of the DIONYSOS study seem to indicate,[2] it cannot be safely assumed that this structural change has completely eliminated neurotoxicity and a class effect seems therefore possible.

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Response from Sanofi

Dronedarone is similar to amiodarone in its molecular structure with an important difference consisting in the presence of methylsulfonamide group to reduce solubility in fats (lipophilicity) and thus reduce neurotoxic effects. Amiodarone may induce peripheral sensorimotor neuropathy and/or myopathy (uncommon, i.e. reported as >0.1% and <1%); both these conditions may be severe although recovery usually occurs within several months after amiodarone withdrawal, but may sometimes be incomplete. Visual impairment has been documented as well, which in some cases has progressed to permanent blindness. Vision disorders have been reported in 4-9% of patients on amiodarone . Most publications on optic neuropathy are case reports. Theoretically, dronedarone might share the latter class effect, therefore since its launch on the market, close surveillance of neuropathy ADRs 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 as a potential pharmacological class effect encouraging regular data review by the MAH. From periodic analyses of the cases reporting neuropathy (NOS) ADRs, the MAH has not confirmed an evidence of a causal link between dronedarone and neurologic disorders including neuropathy NOS or optic neuropathy. In the Assessment Report to the most 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 4 solicited cases including: polyneuropathy (n=2), neuropathy peripheral (n=1), peripheral sensory neuropathy (n=1) ; 21 unsolicited cases including: polyneuropathy (n=8), peripheral neuropathy (n = 6), neuritis Peripheral (n = 1), neuropathy (n = 1), neuromyopathy (n = 1), axonal neuropathy (n = 1), acute polyneuropathy (n = 1), neuritis (n = 1), peripheral sensory neuropathy (n = 1) and 4 consumer cases including: neuropathy peripheral (n=3) and polyneuropathy (n=1) . Among 29 case reports, 14 cases were serious. The reports concern 16 men and 12 women (gender was unspecified in 1 case), aged between 50 and 92 years (median 75 years, age was not stated in 7 reports). The onset dates were reported in 13 reports, from 1 day to 2.3 years with median of 42 days. In 6 out of 9 case reports, the dechallenge was positive. No rechallenge was reported. The analysis of the 29 showed:

- In 1 case, incompatible chronology was reported as the event was reported 4 months after stopping dronedarone
- In 3 cases, dronedarone was continued and the patients recovered
- In 2 cases, alternative explanations were provided (mild Guillain-Barré syndrome in 1 case and previous chemotherapy with FU and cisplatin in the other case)
- In 8 cases, possible confounding factors were reported such as, underlying diabetes mellitus in 1 case , cervical spondylosis in 1 case , concomitant use of statin or mirtazapine in 3 cases, and in 3 cases, previous episode with amiodarone and recurrence under dronedarone)
- In 15 cases, the case documentation elements were not sufficient in order to allow drawing a clear conclusion:
  - Missing neurological investigation results to rule out alternative explanations in 6 cases
  - Missing medical history, past and concomitant drugs or action taken on dronedarone in 7 cases
  - No objective diagnostic conclusion in 2 cases

From launch of dronedarone to 31 October 2013, the MAH has also collected the cases related to optic neuropathy (NOS) worldwide 3 solicited cases including: optic ischaemic neuropathy (n=1), visual impairment (n=2) and 39 unsolicited cases including: visual impairment (n=25), visual field defect (n=1), visual acuity reduced (n=2), scotoma (n=2), papilloedema (n=6), optic neuropathy (n=1), optic neuritis (n=3), optic nerve injury (n=1), optic ischaemic neuropathy (n=1), hemianopia (n=1), demyelination (n=1), colour vision tests abnormal (n=1), blindness unilateral (n=2), blindness (n=1), Basedow's disease (n=1) and and maurosis fugax (n=1).

Overall, in all cases, alternative explanation or confounding factors were provided. In 2 cases, the causal role of dronedarone appeared possible as described below:

- One case of optic neuritis was reported in 60-year-old male patient, 3 weeks after starting dronedarone. Dronedarone was withdrawn and the patient was recovering. The case is missing details on neurological examination at the time of reaction onset, information on potential previous use of amiodarone and differential diagnosis to rule out systemic disease, viral, and mainly ischaemic origin (the most frequent cause in elderly) was not available.

- One case of optic nerve atrophy and papilloedema reported in a 74-year-old male patient (previous amiodarone use was denied). Dronedarone was discontinued and at 1-year follow-up the patient was not recovered based on ophthalmological exams (NOS). For proper medical assessment this case is missing information on neurological and ophthalmological investigation results at baseline, furthermore, poor blood flow causing ischemic optic neuropathy may have contributed for the development of optic atrophy. To be noted that optic nerve atrophy may be secondary to prolonged papilloedema.

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

Worldwide use of dronedarone yielding low number of cases is to be noted. Due to these confounding factors combined with lack of relevant information further discussion of the data was not possible.

Available clinical MAH data are not supportive of dronedarone-induced neuropathy (NOS).

In placebo-controlled clinical trial program in the pooled population, the incidence of patients with peripheral neuropathies were analyzed using the SMQ 'Peripheral neuropathy' was (<0.1%) in both the dronedarone 400 mg BID and the placebo groups: Vision disorders were reported in 1.3% of patients in dronedarone 400 mg BID and 1.1% of patients in placebo groups.
In the DIONYSOS study, no peripheral neuropathy was reported. No differences between dronedarone 400mg BID and placebo concerning vision disorders.

Based on available up-to-date information the MAH concludes that there is insufficient evidence to support a causal association between dronedarone and neuropathy(NOS) including optic neuropathy.

Finasteride and Convulsions

Signal from Uppsala Monitoring Centre

Summary

Finasteride is used for the treatment of benign prostatic hyperplasia (BPH), male androgenic baldness and female hirsutism, and has been studied in the prevention of prostatic carcinoma. It acts as a competitive inhibitor of the 5a-reductase enzyme family, which is responsible for converting testosterone to dihydrotestosterone (DHT), a hormone that is present in higher concentrations in the conditions for which it is used. The WHO Global Individual Case Safety Report (ICSR) Database, VigiBase®, contains 34 ICSRs with the WHO-ART terms 'convulsions' and 'convulsions grand mal' in association with finasteride. Inhibition of the production of endogenous neurosteroids, which modulate the GABAA receptor and reduce neuronal excitability, provides a plausible explanation for a causal association between finasteride and convulsions/ convulsions grand mal. The association is also coherent with the current biological understanding of epilepsy and with experimental animal data, and is consistent with the drug's pharmacokinetic profile.

Introduction

Finasteride is a 5a-reductase inhibitor that received approval from the FDA in 1992. It is marketed by Merck Sharp & Dohme as Proscar (5 mg) and Propecia (1 mg), and is also available under several generic names. The higher dose regimen is intended for the treatment of benign prostatic hyperplasia (BPH) and hirsutism, while the lower dose regimen is intended for the management of androgenic alopecia. Each of these conditions is associated with elevated levels of the potent testosterone metabolite dihydrotestosterone (DHT). 5a-reductase is the enzyme responsible for converting testosterone to DHT; finasteride acts by inhibiting this enzyme, particulary the a-R2 and a-R3 isoforms. Finasteride was also found to reduce the incidence of low grade prostate cancer but concerns about a possible increased incidence of high grade prostate cancer among patients on finasteride has precluded its role in preventive therapy; a recent follow-up of a placebo-controlled study of finasteride for the

prevention of prostate cancer showed no significant between-group difference in the rates of overall survival or survival after the diagnosis of prostate cancer.

An epileptic seizure is defined as a transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain.

Seizures can be generalized and concerning activity in both hemispheres; or partial, concerning a localized group of neurons. Partial seizures can further be defined as complex if consciousness is altered during an episode and simple if they do not affect memory and awareness. Seizures that can be attributed to an agent or underlying condition are considered symptomatic; seizures for which no underlying factor can be identified are considered unprovoked and attributable to epilepsy. Symptomatic seizures can be induced by a multitude of factors including: stroke, head injury, anoxia, hypoglycaemia, infections, fever, menstruation, drugs and non-adherence to antiepileptic drugs. The incidence of acute symptomatic seizures is 29-39 per 100 000 per year, while the incidence of single unprovoked seizures is 23-61 per 100,000 person-years.[4] The incidence of drug-induced seizures is difficult to determine.[5] Although numerous drugs can induce a convulsive state or lower the seizure threshold, the most common classes of drug are central acting agents, anti-diabetics, sympathomimetics and anti-asthmatics.

The term 'convulsions' in WHO-ART covers all seizure types, including absence seizures, partial seizures (simple and complex), tonic seizures, convulsions and epilepsy. The term 'convulsions grand mal' includes terms such as tonic-clonic convulsions, epilepsy grand mal and status epilepticus. Due to differences in coding, 10 ICSRs that were originally reported as 'convulsions' has been mapped to 'convulsions grand mal', these cases are marked with an asterisk in Table 1.

Reports in VigiBase

As of 3 December 2013, the WHO Global Individual Case Safety Report (ICSR) Database, VigiBase®, contained 28 ICSRs of 'convulsions' and another 24 ICSRs of 'convulsions grand mal' in association with finasteride. After the removal of duplicates, 15 distinct ICSRs were identified for the preferred term 'convulsions' and 19 ICSRs for 'convulsions grand mal', yielding a total of 34 cases. The ICSRs for both combinations had been submitted to VigiBase from five countries: US (25), UK (4), Canada (2), Germany (2) and Italy (1). All patients but one were male and age, where reported, ranged from 19 to 84 years (median age 49 years). Finasteride was considered the only suspected drug in 30 cases; in one case the drug was reported as interacting, and in 15 cases it was the only reported drug. Co-suspected drugs were reported in four ICSRs (case 1, 9, 22 and 23) and are listed along with concomitant drugs in Table 1. Concomitant drugs for which the UK SPC and the FDA label list 'convulsions' or 'seizures' are included in three cases (case 11, 12 and 24), all of which are indicated for epilepsy. The dose of 5 mg was reported 14 times, 1 mg was reported 16 times, in one instance the reported dose was 0.5 mg to 1 mg, while in three cases the dose was not reported. Time to onset was reported in 17 of the 34 cases and ranged from six days to two years (median time to onset two months). Epilepsy had previously been diagnosed in six of 34 patients (case 1, 4, 5, 12, 13 and 24), seizure disorder in one (case 34, also non compliant to valproate), and two patients were reported to never have had a history of seizures (case 22 and 26). Two patients (case 3 — alcoholic, and 21), were found to have high levels of alcohol when the event occurred, and one patient accidentally took two doses of finasteride instead of one (case 29). Two patients (case 22 and 23) suffered from small vessel or white matter ischemia, and in two further cases (case 18 and 27) the reporter attributed the reaction to benzodiazepine withdrawal or stroke. Finally, in three cases (case 2, 8 and 17) the EEG was regular despite the onset of seizures.

There were eight positive dechallenges, two of which were followed by positive rechallenge and one by negative rechallenge. One patient had a negative dechallenge. In eight cases the drug was withdrawn: the outcome was reported as unknown in five cases and recovered in three. Another three patients chose not to change their dosage or interrupt treatment: the outcome was unknown in one case, recovered in another and not recovered in the remaining case. Finally, dechallenge or rechallenge actions were not reported in 14 cases: eleven of these cases had

unknown outcomes, two recovered and one did not.

Literature and Labelling

As of February 2014, there are two literature cases involving finasteride and seizures. One of the case reports (which was also reported to VigiBase and appears as case 15 in Table 1 below) concerns a woman from Italy who developed focal seizures at the age of 43 years. Two years later the seizures intensified and carbamazepine 800 mg per day was initiated. The seizures were kept under control for one year, until one night she experienced a convulsive seizure and, despite therapeutic levels of carbamazepine, her seizures relapsed with a frequency of eight to 10 seizures per year. Lamotrigine (300 mg) was added to her treatment regimen but the seizures were not controlled. The patient had a history of mild hirsutism for which she was treated with finasteride from age 45 years. Following discontinuation of finasteride at age 50 years, the lamotrigine dose was gradually reduced and withdrawn, and the carbamazepine dose was reduced to 600 mg without further seizures.[8]

The second case describes a 34-year-old obese, woman with hirsutism who suffered from intractable complex partial and generalized seizures, managed with 400 mg carbamazepine per day. She was treated with progesterone and her general seizure profile improved for two years. However, seizure frequency and severity increased after the introduction of finasteride, even though carbamazepine levels were within therapeutic range. The patient's condition returned to baseline levels after finasteride was withdrawn.

There is no mention in the UK SPC or FDA label that finasteride could either induce seizures or lower seizure threshold.

Discussion and Conclusion

The original case report narratives describe patients who either had a history or predisposition to seizures (case 1, 4, 6, and 13), who had epilepsy that was well controlled on anti-epileptic therapy (case 5) or who had a regular pattern of seizures (case 12 and 24) but deve-loped convulsions after taking finasteride. Additionally, patients who were adherent to anti-epileptic therapy (case 7, 27 and 33) developed more seizures after their first within a few months of starting finasteride. One patient reported to have had his first seizure after one year of treatment with finasteride, but the seizures occurred at shorter intervals thereafter and resolved upon discontinuation of the medicine (case 30). One case (case 25) had a negative dechallenge: the patient continued to take finasteride despite the onset of three separate seizure episodes and did not recover after dis-continuing the drug. Finally, case 3 involves an alcoholic patient who had one hypoglycaemic seizure and recovered after glucose infusion.

The enzyme 5a-reductase is involved in the production of the endogenous neurosteroids 5a-THDOC (from deoxycorticosterone) ,allopregnanolone (from progesterone) and androstanediol (from testosterone). Recent studies on mice have shown that these endogenous neurosteroids may reduce seizure susceptibility by enhancing the inhibitory effects of GABA on GABAA receptors.

Hence, neurosteroids act as allosteric modulators of GABAA, similar to barbiturates or benzodiazepines.[16] Inhibition of 5a-reductase by finasteride, with consequent reduction in the production of endogenous neurosteroids, may increase the potential for seizure activity. Permanently lowering the seizure threshold in rats and subsequently administering finasteride in dose ranges compatible with humans, resulted in the development of seizures.[15] Relatively long times to seizure onset have been explained by the time it takes for existing neurosteroids to be broken down.[17]

The convulsogenic potential of finasteride has yet to be demonstrated in humans, but the impact of finasteride on neurosteroid formation may interfere with the regulation of seizures in susceptible individuals. Finasteride crosses the blood-brain barrier so it has the potential to reduce neurosteroid synthesis in the brain, through inhibition of 5a-reductase: in patients who exhibit seizure susceptibility, this might be enough to further lower seizure threshold and trigger convulsions. Additionally, progesterone acts as an anticonvulsant, while testosterone has pro-convulsant properties. An excess of testosterone brought about by finasteride treatment (through inhibition of the enzyme that converts it to 5a-DHT) results in a higher concentration of 17P-estradiol, a potent pro-convulsant hormone.[18] Despite the presence of alternative explanations in many of the reported

cases, including predisposition to seizures and non-adherence to anticonvulsant medications, the plausible mechanism described above strengthens the signal that finasteride may cause increased seizure activity, particularly in susceptible patients with a history of seizures.

Table 1. Case overview of reports in VigiBase® of convulsions and convulsion grand mal in association with finasteride.

Case	Age/Sex	Other suspected (S) or concomitant (C) drugs	Finasteride daily dose	Reactions (WHO-ART preferred terms)	Time to onset	Dechallenge/ Rechallenge	Outcome
1	56/M	Phenytoin (S), gemfibrozil (C)	5 mg	Convulsions, drug level decreased	26 days	Drug withdrawn	Unknown
2	72/M	-	5 mg	Convulsions, confusion, syncope	6 days	Positive dechalleng e	Recovered
3	79/M	Lisinopril, digoxin, propranolol, furosemide, docusate (all C)	5 mg	Convulsions, hypoglycaemia, hepatocellular damage		Positive dechallenge / Negative rechallenge	Recovered
4	57/M	Terbinafine, terbutaline, beclometasone (all C)	5 mg	Convulsions	264 days	-	Recovered
5	-/M	Phenytoin (C)	-	Convulsions, drug interaction	-	-	Unknown
6	75/M	Carbamazepine, diltiazem (both C)	5 mg	Convulsions	24 days	-	Unknown
7	31/M	-	1 mg	Convulsions	2 months	Drug withdrawn	Unknown
8	61/M	Minoxidil (C)	-	Convulsions	-	-	Unknown
9	-/M	Paracetamol/ pseudoephedrine (S)	1 mg	Convulsions, drug interaction	-	-	Unknown
10	-/M	-	1 mg	Convulsions, depression, malaise, weight decrease	-	-	Unknown
11	48/M	Tetracycline, gabapentin, carisoprodol, phenytoin, warfarin, naproxen, folic acid, nizatidine, lamotrigine (all C)	5 mg	Convulsions, faeces discoloured	9 days		Not Recovered
12	31/M	Carbamazepine, levetiracetam (both C)	1 mg	Convulsions	14 days	Positive dechalleng e	Recovered
13	-/M	-	1 mg	Convulsions	6 months	-	Unknown
14	24/M		1 mg	Convulsions, weight decrease, neurologic disorder NOS, muscle contractions involuntary, muscle atrophy, malaise, diarrhoea, hair discolouration, depression, bone disorder		Positive dechallenge / Positive rechallenge	Recovered
15	45/F	Carbamazepine, lamotrigine (both C)	5 mg	Convulsions, condition aggravated	-	Positive dechalleng e	Recovered
16	49/M	Terfenadine (C)	5 mg	Convulsions grand mal, withdrawal syndrome	170 days	Drug withdrawn	Recovered

17	79/M	Atenolol, bendroflumethiazide, glyceryl trinitrate (all C)	5 mg	Convulsions grand mal, erythema multiforme	27 days	Drug withdrawn	Recovered
18	73/M	Oxazepam (C)	5 mg	Convulsions grand mal	2 months	-	Unknown
19	19/M	-	1 mg	Convulsions grand mal	-	-	Unknown
20	50/M	-	-	Convulsions grand mal	-	-	Recovered
21	22/M	-	1 mg	Convulsion grand mal	-	-	Unknown
22	79/M	Simvastatin (S), diltiazem (C), labetalol (C), tamsulosin (c), terazosin (C)	5 mg	Convulsions grand mal, aggressive reaction, AV block complete, bronchospasm, cellulitis, purpura		Drug withdrawn	Unknown
23	67/M	Acetylsalicylic acid, atorvastatin, ergocalciferol/ ascorbic acid/folic acid/ thiamine hydrochloride/ retinol/riboflavin/nicotinic acid (all C), tamsulosin (S)	5 mg	Convulsions grand mal, bite, cardiomegaly, cerebral ischaemia, confusion, stupor, EEG abnormal, ECG abnormal specific	~2 years	Dose not changed	Recovered
24	25/M	Topiramate, lorazepam, lamotrigine (all C)	1 mg	Convulsions grand mal	10 days	Positive dechallenge	Recovered
25	47/M	-	1 mg	Convulsions grand mal*	-	Negative dechallenge	Not recovered
26	-/M	-	1 mg	Convulsions grand mal*	-	Dose not changed	Unknown
27	84/M	Quetiapine, doxazosin, celecoxib, allopurinol, hydrochlorothiazide/ triamterene, memantine, prednisone, sulfasalazine, ranitidine, acetylsalicylic acid, ascorbic acid (all C)	5 mg	Convulsions grand mal*, cerebral ischaemia, death		Dose not changed	Not recovered

28	22/M	-	1 mg	Convulsions grand mal*	-	Drug withdrawn	Unknown
29	80/M	Acetylsalicylic acid, levothyroxine (both C)	5 mg	Convulsions grand mal*, medication error, arrhythmia, hypotension	~4 months	Drug withdrawn	Unknown
30	39/M	Nebivolol (C)	1 mg	Convulsions grand mal*, muscle contractions involuntary, heart disorder	1 year	Positive dechallenge/ Positive rechallenge	Recovered
31	23/M		0.5-1 mg	Convulsions grand mal*, agitation, impotence, anxiety, psychosis, resistance, neurologic disorder NOS, follicle stimulating hormone decreased	~7 months	Drug withdrawn	Recovered
32	53/M		1 mg	Convulsions grand mal*, impotence, cognitive disorders, neurologic disorder NOS			Unknown
33	22/M	-	1 mg	Convulsions grand mal*	4 months	Positive dechallenge	Recovered
34	23/M	Valproic acid, phenytoin, carbamazepine, felbamate, lamotrigine (all C)	1 mg	Convulsions grand mal*, sexual function abnormal, libido decreased, depression, anxiety, migraine, back pain, hepatocellular damage (all together over 50 terms reported)			Unknown

**The term was originally coded as convulsions*

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Roflumilast and Pneumonia

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Summary

From November 2011 to September 2013, 31 Individual Case Safety Reports (ICSRs) of pneumonia in association with roflumilast had been submitted to the WHO Global ICSR Database, VigiBase™, raising the possibility of a causal relationship. After elimination of probable duplicates 25 ICSRs remained. Since roflumilast is used to treat chronic obstructive pulmonary disease (COPD) and patients with COPD are susceptible to pneumonia, it is difficult to make a strong case for a causal association. A plausible pharmacological model indicating a possible relationship between the use of roflumilast as a PDE4 inhibitor and the increased susceptibility towards infectious agents could however be derived. Based on the information in VigiBase and the identified mechanism, one cannot rule out a possible link between roflumilast treatment and pneumonia.

Introduction

Roflumilast is a selective, long-acting inhibitor of the enzyme phosphodiesterase type 4 (PDE4), which is an important regulator of cyclic adenosine monophosphate (cAMP) involved in inflammatory processes. Inhibition of PDE4 reduces the breakdown of cAMP, which in turn down-regulates the inflammatory process. Roflumilast is administered orally for the treatment of inflammatory conditions of the lung such as chronic obstructive pulmonary disease (COPD).

COPD refers to a group of diseases that block airflow and make breathing difficult. Emphysema and chronic bronchitis are its most common conditions. Chronic bronchitis is an inflammation of the lining of the bronchial tubes. Emphysema occurs when the alveoli at the end of the smallest air passages in the lungs are gradually destroyed.

Pneumonia is an infection that inflames the air sacks in the lungs. The air sacks may fill with phlegm or pus, causing cough with phlegm or pus, fever, chill and difficulty in breathing. A variety of organisms, including bacteria, viruses and fungi can cause pneumonia.

Reports in VigiBase

From November 2011 to September 2013, 31 Individual Case Safety Reports (ICSRs) in the WHO Global ICSRs Database, VigiBase™ raised the possibility of a causal relationship between roflumilast administration and the adverse effect pneumonia. After identification and elimination of duplicates and removal of two other reports where pneumonia had occurred before roflumilast treatment started, 25 ICSRs (IC 1.28, IC025 0.66) remained. These are summarized in Table 1.

The ICSRs come from five countries: USA (13), Canada (12), Spain (five), Finland and Spain (one case each). They concern 15 men and 10 women. Patient age is reported as ranging from 52 to 81 years, but unknown in eight cases. There are four fatal cases and six that were recovering or had recovered at the time of reporting. The outcome is unknown in the rest of the cases. Time to onset is possible to calculate in nine of the reports, differing from one day to nine months with a median value of 24 days. Concomitant drugs are reported in 16 of the ICSRs, see Table 1.

It should be noted that there are seven ICSRs (1, 2, 3, 5, 6, 18 and 19) that were evaluated also by the physicians of the marketing authorisation holder for roflumilast. In these cases the reporting physicians classified pneumonia as not related to the drug. According to the reporters, these patients had other plausible explanations for the development of the event, such as the underlying COPD, the patients' age, heart conditions, and the history of smoking as well as the use of inhaled corticosteroids. These are all risk factors for the development of pneumonia. Moreover, it was emphasized by the reporters that there is no pharmacological indication that roflumilast can favour the occurrence of pneumonia.

Literature and Labelling

Respiratory tract infections, with the exception of pneumonia, are described as rare adverse reactions in the European Summary of Product Characteristics of roflumilast.[4] Due to lack of relevant experience, it is not advised to administer roflumilast to patients with severe immune deficiencies or acute/latent infectious diseases. The assessment report made by the European Medicines Agency Committee on Human Medicinal Products[5] points out that pneumonia was not more common in the roflumilast than in the placebo group (5,491 versus 5,766 patients in the safety pool of all clinical trials).[6] When only the pivotal studies: 1,546 versus 1,547 patients were evaluated, the incidence of pneumonia was a little higher in the treatment arm 42 versus 31 patients In the roflumilast adverse event pool reported to the Food and Drug Administration between 2004 and 2012 only 1.01% of all the adverse events was pneumonia.

Literature reviews on the adverse effect profile of roflumilast (e.g.8-10) do not mention pneumonia or describe its occurrence as differing significantly from that in the placebo group.

Discussion

Analysing the data in Table 1 it appears that in 16 of the 25 cases (ICSRs 1-6, 8, 13-14 and 16-22) the patients also received inhaled corticosteroids. This group of drugs is well known to increase the risk of pneumonia in COPD patients.[6,11] Thus, the anti-inflammatory therapy with inhaled corticosteroids may provide a plausible explanation for pneumonia in these cases. In the other nine cases (ICSRs 7, 9-12, 15, 23-25) no concomitant medication was reported. However, these reports were quite incomplete in general; moreover, the lack of adequate medication in the serious condition described by ICSR 10 is hardly possible. These ICSRs seem to be less useful in determining causality.

In addition, the marketing authorisation holder's reporting physicians correctly pointed out that elderly COPD patient are more susceptible for pneumonia. The clinical course of COPD is punctuated by exa-cerbations, periods of deterioration characterised by worsening dyspnoea and increases in cough, sputum volume, and sputum purulence usually associated with respiratory tract infection,[1] the more so as many COPD patients are chronically colonised with bacteria, among others Streptococcus pneumoniae, and these are also dyspnoea and increases in cough, sputum volume, and sputum purulence usually associated with respiratory tract infection,[1] the

Table 1. Characteristics of ICSRs in VigiBase™ indicating pneumoniaduring treatment with roflumilast

Case	Age/ gender	Dosage	Time to onset	Other suspected (S) or concomitant (C) drugs	Other reported reactions (WHO-ART)	Outcome
1	75/M	500 [jg/day 3 days	3 days	Teophylline, prednisolone, insulin, pantoprazole, ramiprl, torasemide, xipamide, formoterol /budesonide, prednisone (all C)	Acute renal failure, sepsis, hyperkalaemia, arr-hytmia, respiratory failure, acidosis respiratory	Died
2	52/M	-		Fenoterol/ipratropium, budesonide, tiotropium, indacaterol (all C)	Feeling unwell, dyspnoea aggravated, anxiety attack, tremor, mental disorder	Recovered
3	81/F	-	52 days	Oxycodone/naloxone, salbutamol, pantoprazole, metoclopramide, insulin, calcium, acetylsalicylic acid, prednisolone, ranelic acid, tiotropium (all C)	Systemic inflammatory response syndrome	Died
4	-/F	500 jg/day	-	Fluticasone/salmeterol, tiotropium (all C)	-	Not known
5	66/M	-	9 months	Bisoprolol, warfarin, carbimazole, lisinopril, prednisolone, tiotropium, formoterol/budesonide (all C)	Feeling unwell	Died
6	66/F	-	-	Salbutamol, formoterol, tiotropium,, agomelatine, prednisolone, acetylsalicylic acid, levothyroxine, ramipril, verapamil (all C)	Bronchitis	Not known
7	-/F	-	-	-	Nausea, vomiting	Not known
8	-/F	500 jjg/day, 4 days	24 days	Nystatin, alendronic acid, escitalopram, fluconazole, triazolam, theophylline, fluticasone/salmeterol, esomeprazole, naproxen, prednisone, phenazopyridine, diltiazem, alprazolam, ipratropium/ salbutamol, tiotropium, oxygen, ergocalciferol, omeprazole (all C)	Diarrhoea, decreased appetite, tremor, acute renal failure, headache, nausea, dizziness, fall	Died
9	59/M	500 jjg/day	-	-	-	Not known
10	77/F	250 jg/day, 3 days	-	-	Back pain, diarrhoea, agitation, malaise, respiratory distress, laboured breathing, mood swings, general body pain	Not known
11	57/F	500 jjg/day, 6 months	-	-	Bronchitis	Not known
12	65/M	500 jg/day	-	-	-	Not known
13	58/F	500 jg/day	-	Fluticasone/salmeterol, prednisone, tiotropium (all C)	Dyspnoea, condition aggravated, coughing	Not known
14	71/M	500 jg/day	-	Salbutamol, beclometasone, tiotropium, fluticasone/salmeterol (all C)	Breathing difficult	Not known
15	-/M	-	-	-	-	Not known

16	81/M	500 jg/day, 5 months		Levofloxacin (S), simvastatin (S), mometasone (C), acetylsalicylic acid (C), formoterol (C), tiotropium (C), multivitamin (C), allopurionol (C), tocopherol (C), ergocalciferol (C), salbutamol (C), ascorbic acid (C)	Ageusia, asthenia, dysgeusia, bronchitis, weight decreased, oedema peripherial, sepsis, fall, eructation, atrial fibrillation, muscular weakness, compression fracture, swelling face, frequent bowel movements, dry mouth, GI reflux, decreased appetite, nausea, tremor	
17	-/F	500 jg/day	1 day	Fluticasone, biotin/minerals/vitamins, tiotropium, famotidine, multivitamin, amlodipine, pantoprazole (all C)	Weight decreased, insomnia, rash pruritic, appetite decreased	Recovering
18	75/M	500 jg/48 hours, 5 days; 500 jg/24 hours, 27 days	19 days	Fluticasone, albuterol (=salbutamol), salbutamol, tiotropium (all C)	Diarrhoea	Recovered
19	75/F	68 days	21 days	Fenoterol/ipratropium, amoxicillin/clavunalate-K, cefuroxime, paracetamol, moxifloxacin, budesonide, erdosteine, tiotropium, fluticasonr/salmeterol, salbutamol, levothyroxine, calcium (all C)	Herpes simplex	Recovered
20	77/M			Budesonide, albuterol (=salbutamol), ranitidine, cortisone, ubidecarenone, lactobacillus, cetirizine, tocopherol, formoterol, clopidogrel, montelukast-Na, acetylcysteine, clotrimazole, alendronic acid, tiotropium, diltiazem, terazosin, sertraline, fluticasone calcium, atorvastatin, finasteride (all C)	Oedema peripheral, condition aggravated, dyspnoea, diastolic dysfunction, congestive cardiac failure, atrial fibrillation, hyponatraemia	Not known
21	72/F	500 jg/day	40 days	Ergocalciferol, simvastatin, formoterol/budenoside, calcium, tiotropium, omeprazole, metoprolol, iron, salbutamol (all C)	Unexpected therapeutic response	Recovered
22	62/M	500 jg/day	42 days	Leflunomide, metoprolol, amitriptyline, alprazolam, montelukast, tamsulosin/dutasterde, omeprazole, fentanyl, duloxetine (all C)	Acute psychosis, bronchitis	Recovered
23	62/M	1/day	-	-	Pancreas infection	Not known
24	64/M	500 jg/day	-	-	COPD exacerbations, condition aggravated, disease recurrent	Not known
25	70/M	1/day	-	-	-	Not known

more so as many COPD patients are chronically colonised with bacteria, among others Streptococcus pneumoniae, and these are also the most commonly isolated bacterial pathogens during acute exacerbations.

Taking all the above mentioned factors into consideration, no assumption of a causal relationship between roflumilast and pneumonia seems to be justified.

However, analysing the reports from another angle, in the ICSRs commented by the above physicians the repeatedly used argument was the lack of any pharma-cological indication that roflumilast could favour the occurrence of infections leading to pneumonia. This statement might be challenged.

Roflumilast is a (selective) PDE4 inhibitor. PDE is a generic term that describes a large 'superfamily' of enzymes that catalyse the breakdown of cyclic adenosine-3',5'-monophosphate (cAMP) and/or cyclic guanosine-3'-5'-monophosphate (cGMP) to their respective inactive nucleotide 5'-monophosphates.[1,12,13,14] PDE4 acts by regulating the degradation of cAMP and thus plays an important role in a wide spectrum of processes in almost all tissues, including activation of monocytes and macrophages. Examining the role of cAMP/cGMP in immunological mechanisms combating infections, one finds that they are ubiquitously expressed in cells of the immune system. Elevation in intracellular cAMP suppresses innate immune functions of phagocytes, predominantly through the modulation of three key effector functions of these cells: generation of anti-inflammatory mediators, phagocytosis, and intracellular killing of ingested pathogens. cAMP also suppresses the microbiocidal capacity of leukocytes toward bacteria, viruses and fungi.[15] Moreover, some research suggests that several pathogenic microorganisms have evolved mechanisms to exploit host cell cAMP signalling as a virulence factor. Some pathogens can increase the intracellular cAMP production of host cells directly or indirectly.[15] For example, in experimental conditions a persistent increase in cAMP levels in spleen macrophages during infection caused by virulent Salmonella strains has been demonstrated. Low-virulent Salmonella strains failed to cause the elevation of cAMP levels in spleen macrophages.[16] In such terms it can be understood that elevated cAMP/ cGMP levels at cell and tissue level decrease the capability of combating infections but are counterbalanced by the ubiquitous expression of PDE4. However, the latter is likely to be compromised in patients under treatment with PDE4 inhibitors.

Thus, contrasted with the above cited report statements, there may be a plausible pharmacological indication that roflumilast favours the occurrence of infections, including pneumonia.

Conclusion

One method of ADR signal assessment is to analyse reports and establish a signal only on the basis of ICSRs where neither the concomitant medication nor the sickness itself can offer an explanation for the ADR (even if no underlying pharmacological explanation is found). As a rule, this is the method that marketing authorisation holders use for ICSR handling (eg17) and it should be emphasized that it is accepted.

If an ADR may have more than one root cause, and the first exists in most of the cases, only this one would be recognized by the above described method. All others would be rejected because of the existence of other plausible explanations. (In our example: as COPD itself is a predisposing factor for pneumonia, and moreover, most of the patients receive inhaled corticosteroids concomitantly, it follows that even if a new drug for COPD increases the susceptibility to infections inclu-ding pneumonia, this effect would nevertheless always be classified as "presumably not related".)

However, there is another possibility for ADR signal analysis. Applying this, if there is a suspected ADR indicated by a series of ICSRs, the pharmacological-toxicological properties of the suspected drug should be reanalysed. If a plausible explanation is found for the ADR, and at least not contradicted by the information in the ICSRs, one may not rule out the possibility of causality. WHO after all defines an ADR signal as only a "possible" and by no means a "proven" causality.

The latter model permits identification of the suspect drug as an additional factor to those already known, that may lead to manifestation of an ADR. Taking into account that ADRs, like sicknesses, perhaps have multi-causal determination (with more than one predisposing or risk factor), its use may facilitate earlier establishment of the true safety profiles of drugs.

On the basis of the latter model, including a clear pharmacological model for PDE4 inhibition, the increased propensity for infections that can be derived from literature findings, and also taking into account the frequent reporting, a causal relationship between roflumilast treatment and increased susceptibility to respiratory infections including pneumonia may not be ruled out.

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Response from Takeda and Forest Laboratories

As a first-in-class product, roflumilast, a selective phosphodiesterase 4 (PDE4) inhibitor, has been approved for use in patients with severe COPD, specifically those with chronic bronchitis and a history of exacerbations.

Regarding the published Uppsala Monitoring Centre (UMC) review of Pneumonia in patients utilizing roflumilast, Takeda and Forest Laboratories concur with the UMC reviewer's conclusion that, based on the assessment of clinical and post-marketing data, "no assumption of a causal relationship between roflumilast and pneumonia seems to be justified". This conclusion is supported by the following key elements:

- data from roflumilast's extensive clinical development program which did not show a disproportio-nate reporting between roflumilast and placebo for pneumonia or other events indicative of infection (e.g. nasopharyngitis, upper respiratory tract infection, bronchitis, and influenza)
- a lack of evidence from literature reviews describing roflumilastvs adverse event profile
- the confounding of many ICSR reports, wherein multiple patients concomitantly received inhaled corticosteroids, had underlying medical history or there was insufficient information in postmarketing

reports to allow an appropriate causal determination

- an increased susceptibility to pneumonia and other respiratory infections in patients with COPD, particularly those with severe COPD who have a history of exacerbations

In addition to these points, data from repeat-dose toxicological studies on roflumilast do not indicate an increased risk for infection. Both roflumilast and roflumilast N-oxide did not result in any adverse effects on lymphohematopoietic organs in mice, rats, hamsters, dogs or monkeys even at repeated doses up to 52 weeks in toxicological studies. Further, there was no evidence of immunotoxic effects of roflumilast or roflumilast N-oxide as indicated by the absence of drug-related increases in infections and skin wounds or the occurrence of lymphohematopoietic malignancies. These conclusions are further supported by lack of immunosuppressive effects of roflumilast in a rat kidney transplant model (reference to roflumilast NDA The UMC reviewer, however, has postulated that increases in cAMP associated with PDE4 inhibition would impair host responses to bacterial infections.

Pharmacology studies investigating the risk of infections in roflumilast-treated animals have not been conducted. However, several lines of evidence suggest that roflumilast, at therapeutic levels, does not impair normal host response to bacterial infection. Accumulation of cAMP associated with roflumilast occurs in multiple cell types and in spatially distinct intracellular compartments; however, the effects are typically moderate (Hatzelmann A et al 2010), contrary to the higher levels of cAMP required to show an experimental effect on the immune response. It is also important to consider that, while PDE4 is the predominant PDE isoenzyme present in leukocytes, other PDE isoenzymes are also present (Torphy et al 1998). For example, expression of PDE4 predominates in monocytes and neutrophils, while monocyte-derived macrophages and human alveolar macrophages show a differential pattern, with PDE3 and PDE1 dominating. Accordingly, macrophage functions are only partly affected by PDE4 inhibition (Gantner F et al 1997). PDE4 is also expressed in bronchial epithelial cells, and several studies have shown that roflumilast increases ciliary beat frequency and reduces goblet cell hyperplasia and mucus production (Hatzelmann A et al 2010). Moreover, preliminary findings suggest that roflumilast may help rehydrate the airways of COPD patients (Tarran et al, ATS 2013 poster), thus suggesting a potential to improve mucociliary clearance of the lungs.

The mechanism by which cAMP inhibits the antimicrobial activity of leukocytes is not well understood but inhibition of reactive oxygen species (ROS) and phagosomal acidification have been considered (Serezani CH et al 2008). In this context, it has been reported that, in cystic fibrosis transmembrane conductance regulator (CFTR)-deficient alveolar macrophages, acidification of the phagosome is impaired, resulting in enhanced survival of bacterial loads (Di A et al 2006). Roflumilast has been shown to activate CFTR (Lambert JA et al 2013) and, by this mechanism, might promote phagosomal acidification. Regarding ROS formation, it has been shown that roflumilast N-oxide inhibits Formyl-Methionyl-Leucyl-Phenylalanine (fMLP)-induced release of ROS in human neutrophils by approximately 20% at 2 nM (Hatzelmann A et al 2001), supporting the assumption that, at therapeutically-relevant concentrations, the inhibition of ROS formation is incomplete, with minor effects on ROS-related host defence functions expected. Additionally, roflumilast N-oxide inhibits Respiratory Syncytial Virus infection of human bronchial epithelial cell cultures (Mata el al 2013) and has also been shown to increase surfactant protein A and D in human alveolar epithelial type II cells, which has been considered to contribute to improved alveolar host defence (Hohne et al 2012).

Finally, the use of ß-agonists is mainstay in COPD therapy and their bronchodilatory activity is clearly associated with cAMP accumulation in airway smooth muscle cells. Although it has been reported that the clearance of non-typeable H. influenzae from the lungs was impaired in salmeterol or salbutamol-treated mice (Maris et al 2006), a clinical study showed that salmeterol reduced the number of exacerbations in COPD patients (Calverley et al 2007), thus suggesting that ß-agonists may not impair antimicrobial responses in these patients.

Conclusion

Taken together, all of the available evidence from the pre-clinical studies and clinical use of roflumilast does not suggest a causal association between the occurrence of pneumonia, or other respiratory infections, and the use of roflumilast in the population of severe COPD patients. In vitro and in vivo studies at therapeutic levels of roflumilast suggest that accumulation of cAMP does not impair normal host response to bacterial infection.

Takeda and Forest Laboratories are committed to the close monitoring of relevant lung diseases and lower respiratory tract infections through their Pharmacovigilance processes on an ongoing basis.

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CAVEAT DOCUMENT

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

Uppsala Monitoring Centre (UMQ 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