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

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

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

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

No. 5, 2013

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

Contents
Regulatory matters
Safety of medicines
Signal
Feature
TABLE OF CONTENTS

**Regulatory Matters**

Acetaminophen ................................................................................................. 4
Caffeine for apnoea of prematurity ................................................................. 4
Calcitonin medicines ..................................................................................... 4
Codeine ...................................................................................................... 5
Diclofenac .................................................................................................. 6
Ergot derivatives ......................................................................................... 6
Filgrastim and pegfilgrastim ................................................................. 7
Flupirtine-containing medicines ...................................................................... 7
Intravenous iron-containing medicines .................................................... 8
Ketoconazole, oral ..................................................................................... 8
Mefloquine Hydrochloride .............................................................................. 9
Meprobamate ............................................................................................. 10
Metoclopramide .......................................................................................... 10
Ondansetron for intravenous use ................................................................. 11
Retigabine .................................................................................................. 11
Sunitinib malate .......................................................................................... 11

**Safety of medicines**

Nitrofurantoin ............................................................................................. 13
Panitumumab ............................................................................................. 13
Pazopanib hydrochloride .............................................................................. 13
Rituximab .................................................................................................. 14
Vemurafinib ............................................................................................. 14

**Signal**

Mirtazapine and Rhabdomyolysis ............................................................... 15
Roflumilast and Melaena ............................................................................. 18
Tapentadol and Delusion ............................................................................. 23
Acetaminophen

Association with risk of serious skin reactions

USA. The U.S. Food and Drug Administration (FDA) notified health-care professionals and patients that acetaminophen has been associated with a risk of rare but serious skin reactions. Acetaminophen is a common active ingredient to treat pain and reduce fever; it is included in many prescription and over-the-counter products. These skin reactions, known as Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), and acute generalized exanthematous pustulosis (AGEP), can be fatal. These reactions can occur with first-time use of acetaminophen or at any time while it is being taken. Other drugs used to treat fever and pain/body aches (e.g., non-steroidal anti-inflammatory drugs, or NSAIDs, such as ibuprofen and naproxen) also carry the risk of causing serious skin reactions, which is already described in the warnings section of their drug labels.

This new information resulted from the Agency’s review of the FDA Adverse Event Reporting System (FAERS) database and the medical literature to evaluate cases of serious skin reactions associated with acetaminophen. It is difficult to determine how frequently serious skin reactions occur with acetaminophen, due to the widespread use of the drug, differences in usage among individuals (e.g., occasional vs. long-term use), and the long period of time that the drug has been on the market; however it is likely that these events (i.e., SJS, TEN, and AGEP) occur rarely.

It is recommended that health-care professionals should be aware of this rare risk and consider acetaminophen, along with other drugs already known to have such an association, when assessing patients with potentially drug-induced skin reactions. Any patient who develops a skin rash or reaction while using acetaminophen or any other pain reliever/fever reducer should stop the drug and seek medical attention right away. Anyone who has experienced a serious skin reaction with acetaminophen should not take the drug again and should contact their health-care professional to discuss alternative pain relievers/fever reducers.

The US FDA will require that a warning be added to the labels of prescription drug products containing acetaminophen to address the risk of serious skin reactions. The US FDA will also request that manufacturers add a warning about serious skin reactions to the product labels of OTC acetaminophen drug products marketed under a new drug application and will encourage manufacturers of drug products marketed under the OTC monograph do the same.

References:

Caffeine for apnoea of prematurity

All products to be named and prescribed as caffeine citrate

UK. The MHRA announced that the name of caffeine products supplied by Viridian Pharma Limited is being changed to caffeine citrate in order to minimise potential risk to premature newborns when prescribing or dispensing. This change brings the Viridian products in line with the naming of other products available on the UK market (i.e., which are already named in the salt form as caffeine citrate). All product doses should be prescribed as caffeine citrate, taking into account the different strengths of the marketed products. Caffeine (citrate) is authorised for treatment of apnoea of premature newborns and may be given orally or intravenously.

There is no change to the formulation of these products. The new packaging of Viridian Pharma products displaying the new name may not be immediately available. However, all packaging (current and new) has dual labelling, which clearly states the strengths of both caffeine and caffeine citrate. Doses specified when prescribing should always be expressed as caffeine citrate because of a risk of confusion and potential for dosing errors (2 mg caffeine citrate is equivalent to 1 mg caffeine).

Health-care professionals are also advised that caffeine citrate is for use in neonatal intensive care units only, and treatment must be initiated under the supervision of a physician experienced in neonatal intensive care.

Reference:
Drug Safety Update, August 2013, Volume 7, Issue 1, A2

Calcitonin medicines

Important changes to the availability and conditions of use

Canada. Health Canada informed of important changes to the availability and recommended conditions of use of drugs containing calcitonin. Calcitonin is used as a nasal spray to treat osteoporosis in postmenopausal women and as an injection to treat Paget’s disease and hypercalcemia.
A safety review conducted by Health Canada concluded that there is a slightly increased risk of cancer associated with the prolonged use of calcitonin products. A review of the benefits and risks of the nasal spray products found that there was not enough evidence of benefit to continue using calcitonin nasal sprays in treating osteoporosis, given the increased risk of cancer.

As a result of these reviews, calcitonin nasal spray products will no longer be authorized for sale in Canada as of October 1, 2013.

Calcitonin injectable products will continue to be authorized for sale in Canada. The benefits of these products are considered to outweigh the risks when the product is used as directed in the Product Monograph (i.e., for Paget’s disease and hypercalcaemia). However, the labels for calcitonin injectable products are being updated to include a new warning about this risk, and to recommend that treatment with calcitonin solution for injection be limited to the shortest possible time, using the minimum effective dose. Treatment of symptomatic Paget’s disease with calcitonin medicine should be limited to patients who are unable to use other treatments. Patients who are taking a calcitonin medicine and who have questions should speak to their health care practitioner before making any change to their treatment. There are other medications authorized in Canada for the treatment of osteoporosis, Paget’s disease and hypercalcaemia. Patients should speak to their pharmacist regarding the safe disposal of calcitonin nasal spray products.

(See WHO Pharmaceuticals Newsletters No.4, 2012 for intranasal formulation for osteoporosis treatment to be withdrawn; new restriction to indication for injectable use in Paget’s disease in EU)

Reference:

Codeine

Restrictions on use of codeine for pain relief in children

Europe. The Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) endorsed by consensus a series of risk-minimisation measures to address safety concerns with codeine-containing medicines when used for the management of pain in children. Codeine is an opioid that is authorised as a painkiller in adults and children. The effect of codeine on pain is due to its conversion into morphine in the patient’s body.

This follows a review of these medicines by the European Medicines Agency’s Pharmacovigilance Risk Assessment Committee (PRAC), which investigated reports of serious and fatal respiratory depression in children after taking codeine for pain relief. Most of the cases occurred after surgical removal of the tonsils or adenoids for obstructive sleep apnoea (frequent interruption of breathing during sleep).

Some of the children who had suffered severe side effects had evidence of being ‘ultra-rapid metabolisers’ of codeine. In these patients, codeine is converted into morphine in the body at a faster rate than normal, resulting in high levels of morphine in the blood that can cause toxic effects such as respiratory depression.

The PRAC concluded that a number of risk-minimisation measures are necessary to ensure that only children for whom the benefits are greater than the risks are given the medicine for pain relief. The CMDh agreed with the PRAC’s conclusions and endorsed the following recommendations:

- Codeine-containing medicines should only be used to treat acute moderate pain in children above 12 years of age, and only if it cannot be relieved by other painkillers such as paracetamol or ibuprofen, because of the risk of respiratory depression associated with codeine use.

- Codeine should not be used at all in children (aged below 18 years) who undergo surgery for the removal of the tonsils or adenoids to treat obstructive sleep apnoea, as these patients are more susceptible to respiratory problems.

- The product information of these medicines should carry a warning that children with conditions associated with breathing problems should not use codeine.

The risk of side effects with codeine may also apply to adults. Codeine should therefore not be used in people of any age who are known to be ultra-rapid metabolisers nor in breastfeeding mothers (because codeine can pass to the baby through breast milk). The product information for codeine should also include general information for healthcare professionals, patients and carers on the risk of morphine side effects with codeine, and how to recognise their symptoms.

(See WHO Pharmaceuticals Newsletters No.4, 2013 for restricted use as analgesic in children and adolescents under 18 in the UK).

Reference:
Diclofenac

**New measures to minimise cardiovascular risks**

**Europe.** The CMDh endorsed by majority new safety advice for diclofenac-containing medicines that are given by means such as capsules, tablets, suppositories or injections, intended to have an effect on the whole body (known as a systemic effect). The new advice aims to minimise the risks of effects on the heart and circulation from these medicines.

This follows a recent review by PRAC, which found that the effects of systemic diclofenac on the heart and circulation are similar to those of selective COX-2 inhibitors, another group of painkillers. This applies particularly when diclofenac is used at a high dose and for long-term treatment. The PRAC therefore recommended that the same precautions already in place to minimise the risks of blood clots in the arteries with selective COX-2 inhibitors should be applied to diclofenac. The CMDh agreed with the PRAC conclusion that although the benefits of systemic diclofenac still outweigh the risks, those risks were similar to the risks with COX-2 inhibitors, and it endorsed the recommendation that similar precautions should be applied.

Diclofenac is a widely used medicine for relieving pain and inflammation, particularly in painful conditions such as arthritis. It belongs to a group of medicines called 'non-steroidal anti-inflammatory drugs' (NSAIDs).

Health-care professionals are informed that,

- Use of diclofenac is contraindicated in patients with established congestive heart failure (New York Heart Association class II-IV), ischaemic heart disease, peripheral arterial disease or cerebrovascular disease.
- Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus, smoking) should only be treated with diclofenac after careful consideration.
- As the cardiovascular risks of diclofenac may increase with dose and duration of exposure, the shortest duration possible and the lowest effective daily dose should be used. The patient's need for symptomatic relief and response to therapy should be re-evaluated periodically.
- In the light of the above, all patients receiving regular diclofenac therapy should be reviewed at the next scheduled appointment.

(See WHO Pharmaceuticals Newsletter No.4, 2013 for New contraindications and warnings after a Europe-wide review of cardiovascular safety in the UK, and No.6, 2012 for need for updated treatment advice for diclofenac in follow-on review in EU).

**Reference:**

**Ergot derivatives**

**New restrictions on use of medicines containing ergot derivatives**

**Europe.** The European Medicines Agency’s Committee for Medicinal Products for Human Use (CHMP) recommended restricting the use of medicines containing dihydroergocristine, dihydroergotamine, dihydroergotoxine, nicergoline or a combination of dihydroergocryptine with caffeine. These medicines should no longer be used for any of the following indications:

- symptomatic treatment of chronic pathological cognitive and neurosensorial impairment in the elderly (excluding Alzheimer’s disease and other dementia);
- ancillary treatment of intermittent claudication in symptomatic peripheral arterial occlusive disease (PAOD stage II);
- ancillary treatment of Raynaud’s syndrome;
- ancillary treatment of visual acuity decrease and visual field disturbances presumably of vascular origin;
- acute retinopathies of vascular origin;
- prophylaxis of migraine headache;
- orthostatic hypotension;
- symptomatic treatment of veno-lymphatic insufficiency.

This is based on a review of data showing an increased risk of fibrosis and ergotism with these medicines.

Fibrosis can be a serious, sometimes fatal disease, which is often difficult to diagnose because of delayed symptoms and may be irreversible. The CHMP noted that there is a plausible mechanism by which ergot derivatives could cause fibrosis and ergotism. Given that the evidence for these medicines’ benefits in these indications was very limited, the CHMP concluded that the benefits in the concerned indications did not outweigh the risk of fibrosis and ergotism.

Health-care professionals are also advised that patients currently taking these medicines for any of the above indications should have their treatment reviewed at a
routine (non-urgent) medical appointment.

Ergot derivatives that are only indicated for these conditions will have their marketing authorisations suspended across the European Union (EU). Some ergot derivatives are approved in some EU Member States for use in other therapeutic indications, including other circulatory disorders, treatment of dementia (including Alzheimer’s disease) and treatment of acute migraine. These indications were not included in the CHMP review. Therefore these products will remain authorised and may continue to be used in those indications.

(See WHO Pharmaceuticals Newsletters No.4, 2008 for new warning on fibrosis in EU).

Reference:

Filgrastim and pegfilgrastim

Risk of potentially life-threatening capillary leak syndrome

UK. The Medicines and Healthcare products Regulatory Agency (MHRA) announced that capillary leak syndrome (CLS) has been reported in recipients of filgrastim, including patients undergoing chemotherapy and a healthy donor undergoing peripheral blood progenitor-cell mobilisation; it has also been reported in recipients of pegfilgrastim undergoing chemotherapy. Episodes varied in severity and frequency. CLS is characterised by: hypotension and oedema; hypoalbuminaemia; and haemoconcentration, and may be fatal unless promptly diagnosed and managed.

Filgrastim (Neupogen®) and pegfilgrastim (Neulasta®) are recombinant granulocyte colony-stimulating factors (G-CSF) used to stimulate the proliferation and differentiation of granulocytes, especially polymorphonuclear, in various forms of neutropenia induced by chemotherapy. Filgrastim is also used to help release blood stem cells from the bone marrow of healthy donors.

The postmarketing adverse reaction reports provide good evidence of a temporal and causal association between filgrastim or pegfilgrastim treatment and CLS. However, the benefits of filgrastim and pegfilgrastim continue to outweigh the risks. Healthcare professionals should note the following to help manage and minimise the risk of CLS:

Health-care professionals are advised the following:
• Closely monitor all patients and healthy donors for CLS symptoms, which commonly have rapid onset. Symptoms include: generalised body swelling; puffiness (which may be associated with less-frequent urination); difficulty breathing; abdominal swelling; and tiredness
• Give standard symptomatic treatment immediately if symptoms occur
• Advise patients and healthy donors to contact their doctor immediately if they develop CLS symptoms
• Any suspected adverse reactions to filgrastim or pegfilgrastim should be reported on a Yellow Card

Reference:

Flupirtine-containing medicines

Restrictions in the use of oral flupirtine

Europe. The CMDh endorsed new recommendations to restrict the use of oral flupirtine medicines and suppositories. Flupirtine is a non-opoid analgesic that has been used to treat pain, such as pain associated with muscle tension, cancer pain, menstrual pain and pain following orthopaedic surgery or injuries. These medicines should now only be used for treating acute pain in adults who cannot use other painkillers, such as non-steroidal anti-inflammatory drugs (NSAIDs) and weak opioids, and treatment should not last longer than two weeks. In addition, patients’ liver function should be checked after each full week of treatment and treatment should be stopped if the patient has any signs of liver problems. Flupirtine must also not be used in patients with pre-existing liver disease or alcohol abuse problems or in patients taking other medicines known to cause liver problems.

In addition to oral medicines and suppositories, this review also covered injectable flupirtine medicines which were being given as a single injection for pain following surgery. The PRAC concluded that the benefits of injectable flupirtine continue to outweigh their risks when used in this way. Doctors using the injectable flupirtine should also follow relevant advice to minimise risk to patients.

With regard to the evidence of efficacy, the review highlighted a lack of sufficient data on the benefits of flupirtine in chronic pain. In particular, there was a lack of efficacy data on the use of flupirtine for longer than eight weeks.
Based on the findings of this review, health-care professionals were advised of the following updated recommendations:

- oral flupirtine medicines and suppositories should only be used to treat adults with acute pain and only if treatment with other painkillers (such as NSAIDs and weak opioids) is contraindicated;
- the duration of treatment with flupirtine should not exceed two weeks and patients' liver function should be checked after each full week of treatment;
- treatment must be stopped in any patient with abnormal liver function tests results or symptoms of liver disease;
- flupirtine must not be used in patients with pre-existing liver disease or alcohol abuse problems or in patients taking other medicines known to cause liver problems;
- healthcare professionals should review the treatment of patients taking flupirtine taking into account the recommendations above.

**Reference:**

### Intravenous iron-containing medicines

#### Risk of allergic reactions with intravenous iron-containing medicines

**Europe.** The CHMP completed its review of intravenous iron-containing medicines used to treat iron deficiency and anaemia associated with low iron levels and concluded that the benefits of these medicines are greater than their risks, provided that adequate measures are taken to minimise the risk of allergic reactions.

Intravenous iron medicines are used when iron supplements given by mouth cannot be used or do not work. All intravenous iron medicines have a small risk of causing allergic reactions which can be life-threatening if not treated promptly. The Committee therefore concluded that measures should be put in place to ensure the early detection and effective management of allergic reactions that may occur. Iron preparations should only be given in an environment where resuscitation facilities are available, so that patients who develop an allergic reaction can be treated immediately. In addition, the CHMP considered that the current practice of first giving the patient a small test dose is not a reliable way to predict how the patient will respond when the full dose is given. A test dose is therefore no longer recommended but instead caution is warranted with every dose of intravenous iron that is given, even if previous administrations have been well tolerated.

The CHMP also considered that, during pregnancy, allergic reactions are of particular concern as they can put both the mother and unborn child at risk. Intravenous iron medicines should therefore not be used during pregnancy unless clearly necessary. Treatment should be confined to the second or third trimester, provided the benefits of treatment clearly outweigh the risks to the unborn baby. The Committee also recommended further activities, including yearly reviews of allergic reaction reports and a study to confirm the safety of intravenous iron medicines.

**Reference:**

### Ketoconazole, oral

#### Potentially fatal liver injury, risk of drug interactions and adrenal gland problems

**USA (1).** The US FDA took several actions related to ketoconazole (Nizoral®) oral tablets, including limiting the drug’s use, warning that it can cause severe liver injuries, which may potentially result in liver transplantation or death and adrenal insufficiency by decreasing the body’s production of corticosteroids, and advised that it can lead to harmful drug interactions with other medications.

The US FDA approved label changes and added a new Medication Guide to address these safety issues including a strong recommendation against its use (contraindication) in patients with liver disease, and new recommendations for assessing and monitoring patients for liver toxicity. As a result, ketoconazole oral tablets should not be a first-line treatment for any fungal infection. Ketoconazole should be used for the treatment of certain fungal infections, known as endemic mycoses, only when alternative antifungal therapies are not available or tolerated.

It is also recommended that health-care professionals should assess the liver status of the patient before starting oral ketoconazole, and monitor serum ALT levels during treatment. Adrenal function should be monitored in patients with adrenal insufficiency or with borderline adrenal function and in patients under prolonged periods of stress (major surgery, intensive care, etc.).
They should review all concomitant medications for the potential for drug interactions with ketoconazole tablets.

According to the US FDA, the topical formulations of ketoconazole have not been associated with liver damage, adrenal problems, or drug interactions. These formulations include creams, shampoos, foams, and gels applied to the skin.

**Suspension of marketing authorisations for oral ketoconazole recommended**

**Europe (2).** The CHMP recommended that the marketing authorisations of oral ketoconazole-containing medicines should be suspended throughout EU. The CHMP concluded that the risk of liver injury is greater than the benefits in treating fungal infections.

Having assessed the available data on the risks with oral ketoconazole, the CHMP concluded that, although liver injury such as hepatitis is a known side effect of antifungal medicines, the incidence and the seriousness of liver injury with oral ketoconazole were higher than with other antifungals. The CHMP was concerned that reports of liver injury occurred early after starting treatment with recommended doses, and it was not possible to identify measures to adequately reduce this risk. The Committee also concluded that the clinical benefit of oral ketoconazole is uncertain as data on its effectiveness are limited and do not meet current standards, and alternative treatments are available.

Taking into account the increased rate of liver injury and the availability of alternative antifungal treatments, the CHMP concluded that the benefits did not outweigh the risks. Topical formulations of ketoconazole (such as creams, ointments and shampoos) can continue to be used as the amount of ketoconazole absorbed throughout the body is very low with these formulations.

It is recommended that patients currently taking oral ketoconazole for fungal infections should make a non-urgent appointment with their doctor to discuss suitable alternative treatments. Doctors should no longer prescribe oral ketoconazole and should review patients’ treatment options.

Ketoconazole is an antifungal medicine used to treat infections caused by dermatophytes and yeasts.

The European Medicines Agency is aware that ketoconazole is used off-label for treating patients with Cushing’s syndrome. In order to ensure that these patients will not be left without treatment, national competent authorities may make these medicines available under controlled conditions.

**References:**


**Mefloquine Hydrochloride**

**Risk of serious psychiatric and nerve side effects**

**USA.** The US FDA advised the public about strengthened and updated warnings regarding neurologic and psychiatric side effects associated with mefloquine hydrochloride. A boxed warning was added to the drug label. The US FDA revised the patient Medication Guide dispensed with each prescription and wallet card to include this information and the possibility that the neurologic side effects may persist or become permanent. The neurologic side effects can include dizziness, loss of balance, or ringing in the ears. The psychiatric side effects can include feeling anxious, mistrustful, depressed, or having hallucinations.

Neurologic side effects can occur at any time during drug use, and can last for months to years after the drug is stopped or can be permanent.

Mefloquine hydrochloride is indicated for the treatment of mild to moderate acute malaria caused by mefloquine-susceptible *P. falciparum* and *P. vivax*, and prevention of malaria infections by *P. falciparum* (including chloroquine-resistant *P. falciparum*) and *P. vivax*. It was previously marketed under the brand name Lariam®; however, the Lariam product is not currently marketed. Generic mefloquine products are available in the US.

The US FDA recommended that patients, caregivers, and health-care professionals should watch for these side effects. When using the drug to prevent malaria, if a patient develops neurologic or psychiatric symptoms, mefloquine should be stopped, and an alternate medicine should be used. If a patient develops neurologic or psychiatric symptoms while on mefloquine, the patient should contact the prescribing health care professional. The patient should not stop taking mefloquine before discussing symptoms with the health care professional.

**References:**

Meprobamate

Market Withdrawal of 282 MEP®
(Meprobamate-Containing Medicine)

Canada. PENDOPHARM, in collaboration with Health Canada, informed of the market withdrawal of 282 MEP®. Following the review of safety and efficacy information for 282 MEP® mostly focused on its meprobamate content, Health Canada has concluded, in the light of the risk of overdose/abuse/misuse, that the benefit-risk profile is no longer considered favourable.

282 MEP® is indicated for the relief of pain of various origins, accompanied by muscle spasm and anxiety. Each tablet contains as medicinal ingredients acetylsalicylic acid (350 mg), codeine phosphate (15 mg), meprobamate (200 mg), and caffeine (15 mg, equivalent to 30 mg caffeine citrate). As of July 30th, 2013, PENDOPHARM discontinued the sale of the drug.

Meprobamate has a narrow therapeutic index and may cause serious adverse events (including overdose, loss of consciousness, abuse, pharmacodependence and withdrawal symptoms), even under normal conditions of use. Since the approval of meprobamate, other medications (e.g., muscle relaxants, anxiolytics, antidepressants) have largely displaced the use of meprobamate in Canada and in other countries. Taking this new safety information and the available efficacy data into account, Health Canada concluded that the risks of 282 MEP® (meprobamate-containing medicine) outweigh the benefits under normal conditions of use. Following the discontinuation of 282 MEP®, no medications containing meprobamate will be available in Canada.

It is advised that health-care professionals should no longer prescribe 282 MEP® and are advised to transition their patients to alternative therapies before October 28th, 2013. Pharmacists are advised that dispensing should cease by October 28th, 2013. To ensure full inventory depletion, 282 MEP® should be removed from pharmacy inventory by October 28th, 2013.

(See WHO Pharmaceuticals Newsletters No.2, 2008 for benefit/risk profile adjudged no longer favourable in the UK).

Reference:

Metoclopramide

Recommends changes to reduce the risk of neurological side effects

Europe. The CHMP recommended changes to the use of metoclopramide-containing medicines in EU, including restricting the dose and duration of use of the medicine to minimise the known risks of potentially serious neurological side effects.

Metoclopramide-containing medicines have been authorised separately in individual Member States of the EU, with differing licensed indications such as nausea and vomiting of various causes (for example after treatment with anticancer chemotherapy or radiotherapy, after surgery, or associated with migraine) and gastrointestinal motility disorders (conditions in which the normal passage of food through the gut is delayed).

The review confirmed the well-known risks of neurological effects such as short-term extrapyramidal disorders, a group of involuntary movement disorders that may include muscle spasms (often involving the head and neck), and tardive dyskinesia. The risk of acute neurological effects is higher in children, although tardive dyskinesia is reported more often in the elderly, and the risk is increased at high doses or with long-term treatment. The evidence indicated that these risks outweighed the benefits of metoclopramide in conditions requiring long-term treatment. There have also been very rare cases of serious effects on the heart or circulation, particularly after injection.

The Committee recommended that metoclopramide should only be prescribed for short-term use (up to five days), that it should not be used in children below one year of age and that in children over one year of age, it should only be used as a second-choice treatment for the prevention of delayed nausea and vomiting after chemotherapy and for the treatment of post-operative nausea and vomiting. In adults, it may be used for the prevention and treatment of nausea and vomiting such as that associated with chemotherapy, radiotherapy, surgery and in the management of migraine. In addition, the maximum recommended doses in adults and children should be restricted, and higher strength formulations removed from the market.

(See WHO Pharmaceuticals Newsletters No.1, 2010 for risk for development of movement disorders including tardive dyskinesia in Australia and No.1, 2009 for warning against chronic use in the USA).

Reference:
**Ondansetron for intravenous use**

**Dose-dependent QT interval prolongation**

**UK.** The MHRA issued new guidance for intravenous use of ondansetron. Ondansetron (Zofran® and its generics) is indicated for the prevention and treatment of nausea and vomiting induced by cytotoxic chemotherapy and radiotherapy, and for the prevention and treatment of postoperative nausea and vomiting. Prolongation of QTc interval and cardiac arrhythmia, including Torsade de Pointes, are known risks with ondansetron.

The MHRA announced that the results of a study that showed ondansetron causes a dose-dependent prolongation of QTc, together with other data sources, have enabled greater understanding of the relation between dose and risk of QT prolongation. As a result, further specific guidance is available for intravenous ondansetron in relation to: repeat dosing in all adults; dosing for prevention of chemotherapy-induced nausea and vomiting (CINV) in patients aged 75 years or older; and dilution and administration for prevention of CINV for patients age 65 years or older.

New advice for health-care professionals are the followings,

Patients aged 75 years or older:
- A single dose of intravenous ondansetron for the prevention of CINV must not exceed 8 mg (infused over at least 15 minutes)

Adult patients younger than 75 years:
- A single dose of intravenous ondansetron for prevention of CINV must not exceed 16 mg (infused over at least 15 minutes)

Dilution administration in patients aged 65 years or older:
- All intravenous doses for prevention of CINV should be diluted in 50–100 mL saline or other compatible fluid and infused over at least 15 minutes

Repeat dosing in all adults (including elderly patients):
- Repeat intravenous doses of ondansetron should be given no less than 4 hours apart

(See WHO Pharmaceuticals Newsletters No.4 2012 for new dose restriction for intravenous use due to dose-dependent QT interval prolongation in UK and No.6 2012 in Canada and No.1, 2013 for product removal due to potential for serious cardiac risks in the USA).

**Reference:**

**Retigabine**

**Restricted to last-line use, and new monitoring requirements after reports of pigment changes in ocular tissue, skin, lips, or nails**

**UK.** The MHRA announced that retigabine (Trobalt®) should now only be used as an adjunctive treatment for drug-resistant partial onset seizures with or without secondary generalisation in patients age 18 years or older with epilepsy, where other appropriate drug combinations have proved inadequate or have not been tolerated. This restricted indication is due to reports of pigment changes.

Pigment changes (ie, discolouration) of ocular tissue—including the retina—have been reported in two long-term clinical studies of retigabine and a compassionate use programme. These studies also observed blue-grey discoloration of the nails, lips, or skin. These reports are considered to be very common (ie, occurring in ≥1/10 patients) after prolonged retigabine treatment.

Patients who are currently receiving retigabine treatment should be reviewed at a routine appointment.

Comprehensive ophthalmic examination should be done at the start of treatment and at least every 6 months thereafter during treatment. Treatment should only continue after a careful reassessment of the balance of benefits and risks if pigment changes are detected.

(See WHO Pharmaceuticals Newsletters No.4, 2013 for restriction on use recommended due to risk of retinal pigmentation in EU).

**Reference:**

**Sunitinib malate**

**Association with Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis**

**Canada.** Pfizer Canada Inc., in collaboration with Health Canada, informed that a statement was added to the Product Monograph about a potential association between the use of sunitinib malate (Sutent®) and severe cutaneous reactions suggestive of Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN). Early recognition is important in improving prognosis. Cases of TEN and SJS, including fatal cases, have been very rarely reported, mostly in the post-marketing setting, in patients who have used the drug.

WHO Pharmaceuticals Newsletter No. 5, 2013 • 11
It is advised that, if signs or symptoms of SJS or TEN are present, treatment should be discontinued. If the diagnosis of SJS or TEN is confirmed, treatment must not be restarted.

Sutent is indicated for the treatment of gastrointestinal stromal tumour (GIST) after failure of imatinib mesylate treatment due to resistance or intolerance. It is also indicated for the treatment of metastatic renal cell carcinoma (MRCC) of clear cell histology and for the treatment of patients with unresectable locally advanced or metastatic, well-differentiated pancreatic neuroendocrine tumours (pancreatic NET), whose disease is progressive.

**Reference:**
Advisories, Warnings and Recalls, Health Canada, 9 September 2013 ([www.hc-sc.gc.ca](http://www.hc-sc.gc.ca)).
Nitrofurantoin

Reminder on precautions for use, especially renal impairment in (elderly) patients

UK. The MHRA reminded that use of nitrofurantoin for urinary tract infections is contraindicated in patients with <60 mL/min creatinine clearance. Health-care professionals should be aware of a patient's current renal function when prescribing, especially for elderly patients.

Nitrofurantoin is an oral antibiotic used in the treatment of urinary tract infections. The antibacterial efficacy in this infection depends on the renal secretion of nitrofurantoin into the urinary tract. In patients with renal impairment, renal secretion of nitrofurantoin is reduced, which can result in treatment failure.

Nitrofurantoin is therefore contraindicated in those with <60 mL/min creatinine clearance.

It is also advised that the product information should be consulted in relation to established risks of nitrofurantoin, which include: pulmonary toxicity; hepatic toxicity; peripheral neuropathy; and contraindications in G6PD deficiency and acute porphyria and that guidance on the appropriate use of antibiotics and the prevalence of resistance (such as NICE guidance) should be considered when prescribing nitrofurantoin.

Reference:

Panitumumab

Importance of establishing wildtype RAS (KRAS and NRAS) status before treatment of metastatic colorectal cancer

UK. The MHRA announced that evidence of wildtype rat sarcoma viral oncogene (RAS) status (at exons 2, 3, and 4 of KRAS and NRAS) is required before initiating treatment with panitumumab (Vectibix®) alone or in combination with other chemotherapy in the treatment of metastatic colorectal cancer. Inferior progression-free survival and overall survival have been shown in patients with RAS mutations beyond KRAS exon 2 who received panitumumab combined with FOLFOX (oxaliplatin-containing) chemotherapy versus FOLFOX alone.

These findings are important and emphasise that panitumumab is contraindicated in combination with oxaliplatin-based chemotherapy in patients with mutant RAS (at exons 2, 3, or 4 of KRAS and NRAS), or in whom RAS status is unknown. It is also important that evidence of wildtype RAS status is established before initiation of treatment with panitumumab in all patients. Health-care professionals are also advised that RAS mutation status should be determined by an experienced laboratory using a validated test method.

Panitumumab is a treatment for adults with metastatic colorectal cancer. It is given alone or in combination with other chemotherapy.

Reference:

Pazopanib hydrochloride

Important change to frequency of serum liver test monitoring for hepatotoxicity

Canada. GlaxoSmithKline Inc., in consultation with Health Canada, informed that pazopanib hydrochloride (Votrient®) is associated with hepatotoxicity including hepatic failure and fatalities and the drug should not be used in patients who have baseline plasma bilirubin concentrations >1.5 X Upper Limit of Normal (ULN) with direct bilirubin >35% and ALT elevations of >2 X ULN, or who have moderate or severe hepatic impairment (Child Pugh B and C). These are not new recommendations, and remain unaltered from the previously approved Product Monograph.

It is also advised that physicians are asked to monitor serum liver tests before initiation of treatment, during treatment with pazopanib hydrochloride and interrupt, reduce or discontinue dosing as recommended in the Product Monograph. Testing of serum liver enzyme and bilirubin levels during treatment has increased in frequency to include monitoring during weeks 2, 4, 6, 8 and months 3 & 4, and as clinically indicated. Periodic monitoring should continue after Month 4.

Pazopanib hydrochloride is a tyrosine kinase inhibitor indicated for the treatment of patients with metastatic renal cell (clear cell) carcinoma as first-line systemic therapy or as second line systemic therapy after treatment with cytokines for metastatic disease. It is also indicated for the treatment of patients with selective subtypes of advanced soft tissue sarcoma who have received prior chemotherapy.
for metastatic disease, or who have progressed within 12 months after (neo) adjuvant therapy.

Concomitant use of pazopanib hydrochloride and simvastatin increases the risk of ALT elevations. Concomitant use of the drug and statins should be undertaken with caution and close monitoring.

**Reference:**

---

**Rituximab**

**Hepatitis B Virus (HBV) recurrence in patients and updates on screening and management**

Canada. Hoffmann-La Roche Limited (Roche), in consultation with Health Canada, informed that use of rituximab (Rituxan®) was shown to be associated with reactivation of hepatitis B virus in seropositive patients. It is advised that all patients be screened for hepatitis B virus (HBV) before initiation of treatment with the drug and rituximab is not to be used in patients with active hepatitis B viral disease. It is also advised that, prior to starting treatment in HBV seropositive patients, consultation with a liver disease expert is recommended to determine on-going monitoring of HBV reactivation and its management.

The use of rituximab has been associated with HBV reactivation in patients with positive HBV surface antigen (HBsAg+ve) and in those with negative HBV surface antigen plus positive anti-HB core antibody (HBsAg-ve/HBcAb+ve), particularly when administered in combination with steroids or chemotherapy.

Rituximab is an anti-CD20 monoclonal antibody indicated in the treatment of Non-Hodgkin’s Lymphoma (NHL), Chronic Lymphocytic Leukemia (CLL), Rheumatoid Arthritis (RA), Granulomatosis with Polyangiitis (GPA, also known as Wegener’s Granulomatosis) and Microscopic Polyangiitis (MPA).

**Reference:**

---

**Vemurafenib**

**Risks of malignancy progression and Drug Rash with Eosinophilia and Systemic Symptoms**

Canada. Hoffmann-La Roche Limited (Roche Canada), in collaboration with Health Canada, informed of important new safety information associated with vemurafenib (Zelboraf®) regarding the risk of malignancy progression as well as the risk of Drug Rash with Eosinophilia and Systemic Symptoms (DRESS Syndrome).

Vemurafenib is indicated as a monotherapy for the treatment of proto-oncogene serine/threonine-protein kinase B-Raf (BRAF) V600 mutation-positive unresectable or metastatic melanoma. A validated test is required to identify BRAF V600 mutation status.

1. **Progression of Malignancies Associated with Rat Sarcoma Viral Oncogene (RAS) Mutation**

Based on its mechanism of action, vemurafenib may cause progression of cancers associated with RAS mutations. A recent article reported a case of accelerated growth of a pre-existing neuroblastoma RAS (NRAS)-mutated chronic myelomonocytic leukemia in a 76-year-old patient shortly after he had initiated a treatment with vemurafenib. These findings suggest that ZELBORAF can cause paradoxical activation of extracellular signal-regulated kinase (ERK) signaling in the RAS-mutant leukemic cell population, which could lead to leukemic cell proliferation. Vemurafenib should be used with caution in patients with prior or concurrent cancers associated with RAS mutation.

2. **DRESS Syndrome**

Cases of DRESS syndrome were reported with the use of vemurafenib. The cases of DRESS syndrome were characterized by rash, eosinophilia, and systemic involvement (e.g. fever, lymphadenopathy, elevated transaminases and renal insufficiency). The typical time to onset was 7-25 days. Vemurafenib treatment should be permanently discontinued in patients who develop DRESS syndrome.

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

The signals in this Newsletter are based on information derived from Individual Case Safety Reports (ICSRs) available in the WHO Global ICSR database, VigiBase™. The database contains over 8 million reports of suspected adverse drug reactions, submitted by National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring. VigiBase is, on behalf of the WHO, maintained by the Uppsala Monitoring Centre (UMC) and periodic analysis of VigiBase data is performed in accordance with UMC’s current routine signal detection process.

More information regarding the ICSRs, their limitations and proper use, is provided in the UMC Caveat document available at the end of SIGNAL section (page 23). For information on the UMC Measures of Disproportionate Reporting please refer to WHO Pharmaceuticals Newsletter Issue No. 1, 2012.

UMC, a WHO Collaborating Centre, is an independent foundation and a centre for international service and scientific research within the field of pharmacovigilance. UMC’s vision is to improve worldwide patient safety and welfare by reducing the risks 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.

Mirtazapine and Rhabdomyolysis
Signal from UMC

Summary
The drug-adverse drug reaction (ADR) combination mirtazapine and rhabdomyolysis was identified as a potential signal in 2000. This follow-up shows that in February 2013, the WHO Global Individual Case Safety Report (ICSR) Database, VigiBase™, contained 47 ICSRs, but the ADR is not labelled in the UK Summary of Product Characteristics or US FDA Label. A literature search reveals that four of the cases found in VigiBase have been published and the information these provide together with the assessment of the other ICSRs suggest that the association of rhabdomyolysis with mirtazapine is a signal and should be investigated further.

Introduction
The drug-ADR combination mirtazapine and rhabdomyolysis was published in the Signal document in 2000 describing 15 Individual Case Safety Reports (ICSRs) from six countries with myositis, rhabdomyolysis and neuroleptic malignant syndrome in relation to either mirtazapine or mianserin.¹ Mirtazapine and rhabdomyolysis was again highlighted during a research project at the UMC and prompted further review.²

The mianserin analogue, mirtazapine, is a noradrenergic and specific serotonergic antidepressant (NaSSA) and is broadly classified as a centrally acting presynaptic α₂-adrenergic receptor antagonist. Structurally it can be classified as a tetracyclic antidepressant.³ Mirtazapine acts by enhancing the release of noradrenaline and by blocking central presynaptic adrenergic receptors. It is a potent antagonist at histamine (H₁) receptors which is responsible for the drug’s sedative properties.³

Mirtazapine is primarily used as an anti-depressant, but can also be prescribed to treat anxiety disorders such as Obsessive-Compulsive Disorder (OCD), panic disorder and post-traumatic stress. It has been investigated in the management of nausea and vomiting. Mirtazapine is generally well tolerated and has a faster onset of efficacy (one week) than other comparable antidepressants. As the cytochrome P450 isoenzyme CYP3A4 is involved in the metabolism of mirtazapine, caution is advised when mirtazapine is given with potent inhibitors of this isoenzyme. The concomitant use of mirtazapine with monoamine oxidase inhibitors (MAOIs) intended to treat psychiatric disorders is contraindicated as it may lead to serotonin syndrome.³

Mirtazapine is usually administered orally, but may also be given by intravenous infusion. The initial oral daily dose is 15-30 mg for the treatment of depression, but may be increased gradually according to response. The usual dose ranges between 15 and 45 mg once or twice daily.³,⁴

Common side effects of mirtazapine are increased appetite and weight, oedema, and drowsiness or sedation in the first weeks of treatment. Other less common or rare side effects of interest include paraesthesia, convulsions, tremor, myoclonus,
akathisia, arthralgia, myalgia, muscle rigidity, neuroleptic malignant syndrome and serotonin syndrome.\textsuperscript{3,5}

Rhabdomyolysis is the breakdown of muscle fibers that leads to the release of myoglobin into the bloodstream. Normally, myoglobin is loosely bound to plasma globulins and only small amounts reach the urine but when large amounts are released the binding capacity of the plasma protein is exceeded. Myoglobin is filtered out of the body via the kidneys and may cause obstruction in the tubules and renal dysfunction. Rhabdomyolysis is one of the leading causes of acute renal failure and although it may be fatal, it is usually relatively benign. Rhabdomyolysis may be caused by any condition that damages skeletal muscles, especially injury or strainful exercise, the toxic effect of drugs such as statins and/or fibrates, illegal drugs and/or alcohol abuse. Other risk factors include electrolyte abnormalities such as hypokalaemia and hypernatraemia, infections, electric shock and occlusion of blood supply to muscles. Management may include the infusion of bicarbonate-containing fluids (to enhance urinary secretion of myoglobin) or hemodialysis.\textsuperscript{6,7,8}

\textbf{Reports in VigiBase}

As of 24 April 2013, 61 ICSRs mentioning mirtazapine and rhabdomyolysis were found in the WHO Global ICSR Database, VigiBase\textsuperscript{\textregistered}, with an IC value of 0.81 and IC\textsubscript{925} of 0.43. This number was reduced to 47 reports after duplicates were removed. Gender was provided for all ICSRs with 31 concerning men and 16 women. Age was mentioned on 89\% (42/47) of the ICSRs ranging from four days to four years. The reported time to onset ranged from three days to seven months from starting mirtazapine.\textsuperscript{9}

Twelve countries, across three continents, had reported this suspected drug-ADR combination; Germany had 17 cases, United States and Switzerland six each, Spain five, Canada and United Kingdom three each, Australia two and Greece, Czech Republic, Denmark, France and the Netherlands had one case each. The first ICSR entered into VigiBase was from Spain in 1999 and the last was from Switzerland in 2012.

Mirtazapine was the sole suspected drug on 18 ICSRs. Co-suspected or interacting drugs of interest included lamotrigine, venlafaxine, risperidone, pregabalin, escitalopram, citalopram, olanzapine, quetiapine, pramipexole, atorvastatin and ziprasidone which are all known to cause rhabdomyolysis.\textsuperscript{9} Concomitant drugs were reported on 21 ICSRs.

Where dose was stated, it was generally ranging from 15 to 45 mg daily. Among the ICSRs there were six cases of suicide attempt. In two of these cases suicide attempt is not specifically stated, but in one case the dose taken was 1.7 g and this case was also found in literature where it was described as a suicide attempt.\textsuperscript{10} In the other case, the term overdose was reported (the patient had taken 840 mg) but it was unclear if it was intentional. There was also one case where an infant developed rhabdomyolysis following in utero exposure to mirtazapine and venlafaxine, when the mother attempted suicide by overdosing on these medicines.\textsuperscript{11}

Treatment dates were given on less than half of the ICSRs (21), ranging from four days to four years. The reported time to onset ranged from three days to seven months from starting mirtazapine.

\textbf{Literature and Labelling}

Rhabdomyolysis is not labelled in the UK Summary of Product Characteristics (SPC) or US FDA Label for mirtazapine, but it is, however, seen in association with the serious ADRs neuroleptic malignant syndrome and serotonin syndrome, both known for mirtazapine according to the US FDA Label information for Remeron.\textsuperscript{9} The UK SPC does not mention this association.

A literature search revealed four published cases, all of which had been reported to VigiBase. The first concerns a 74 year old man from the US with a history of major depressive disorder who was brought to the emergency department for odd behaviour. He had started taking mirtazapine four months earlier and had been using lisinopril for two years. Three months prior to the incident he had had a dose increase of mirtazapine from 30 to 45 mg per day and lisinopril from 10 to 30 mg per day. The man was diagnosed with rhabdomyolysis and both drugs were discontinued. Other possible confounders were ruled out and lisinopril was reinstated with a negative rechallenge. The authors found a causative relationship between mirtazapine and rhabdomyolysis.\textsuperscript{12}

The second case concerns an overdose where a 40 year old man from Australia had been admitted to the emergency department for attempted suicide. He had taken 1.8 g of mirtazapine together with two litres of alcohol and developed rhabdomyolysis. Although the dose is not exactly the same as that reported in VigiBase, it is believed to concern the same event. The author suggests that the rhabdomyolysis may have been caused by mirtazapine.\textsuperscript{10}

In the third case a 40 year old man from Germany taking risperidone (8 mg daily) and biperiden (2 mg daily) after having developed a syndrome consistent with schizophrenia, was given mirtazapine (45 mg daily) for treatment of a following episode of major depression. When treatment failed, the mirtazapine dose was increased to 60 mg daily and risperidone reduced to 3 mg daily whereafter the patient improved. Six weeks after starting this combination therapy, the patient was admitted to hospital and diagnosed with pulmonary embolism and rhabdomyolysis. Mirtazapine and risperidone were withdrawn and
replaced and after receiving medical therapy the patient recovered. The authors suggest the causal relationship to be likely for the psychotropic medications and the adverse events after having ruled out other confounders.\textsuperscript{13}

The final case describes a neonate being delivered by emergency caesarean section in the 36th week of pregnancy after the mother had attempted suicide. The mother had overdosed on mirtazapine and venlafaxine 11 hours prior to this incident. The newborn had to be resuscitated and experienced seizures and rhabdomyolysis. Blood samples showed extremely high concentrations of the two compounds. Both mother and child survived.\textsuperscript{11}

**Discussion**

Rhabdomyolysis is a serious ADR and may be due to a number of causes. In the cases assessed in this analysis there are several confounders, such as co-reported drugs known to cause rhabdomyolysis, alcohol intoxication and possible infection. Rhabdomyolysis may be secondary to muscle rigidity seen in patients with serotonin syndrome or neuroleptic malignant syndrome. Serotonin syndrome was listed in three cases and neuroleptic malignant syndrome was listed in one case. Other co-reported terms of interest included hypertonia, convulsions, involuntary muscle contractions and extrapyramidal disorders which all might, theoretically and if severe enough, have contributed to the rhabdomyolysis.

Data on causality assessment, co-morbidities and de-and re-challenge was extremely limited. In the 27 cases where information on causality assessment was given, 21 were graded as possible, three were not (yet) assessed, two were probable (one according to narrative information) and one was recorded as unknown. 17 reports provided information on co-morbidities, a few with possible confounders such as alcoholism and high cholesterol (statin use). De-challenge information was provided on 30 of the ICSRs; the drug was withdrawn in 26 cases and in eight of these it was mentioned that the reaction abated. Only one positive re-challenge was reported. Outcome was stated on 91\% (43/47) of the ICSRs. 31 patients had recovered or were recovering, two of these with sequelae, three had not recovered at the time of reporting, one patient died and in eight cases the outcome was unknown.

**Conclusion**

The reports found in VigiBase together with the added information from the cases described in literature suggest that there is a positive causal relationship between mirtazapine and rhabdomyolysis that should be investigated further.

**References**

Roflumilast and Melaena
Dr. Tamás Paál, Hungary

Summary
From November 2010 to January 2013, seven Individual Case Safety Reports (ICSRs) of melaena in association with roflumilast were entered into the WHO Global ICSR Database, VigiBase™, raising the possibility of a causal relationship. Although melaena in some of these cases could have been caused by the patients’ concomitant conditions (e.g. gastrointestinal neoplasm, duodenal ulcer, and proctitis) or their concurrent medication (e.g. anticoagulant drugs), a causal relationship cannot be ruled out. It is known that phosphodiesterase inhibitors, the group of drugs to which roflumilast belongs, may cause gastrointestinal disturbances (duodenal ulcer, colitis), and melaena is an easily diagnosable symptom of these adverse conditions.

Introduction
Roflumilast is a selective, long-acting inhibitor of the enzyme phosphodiesterase (PDE) type 4. PDE4 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. It is administered orally for the treatment of inflammatory conditions of the lung such as chronic obstructive pulmonary disease (COPD).¹

Melaena means black, tarry faeces, associated with gastrointestinal (GI) haemorrhage. It should be distinguished from haematochezia, which is passage of bright red blood originating from the lower GI tract. The black colour is caused by enzymatic oxidation of the iron in haemoglobin. Only blood that originates from a higher source (such as stomach or small intestine) or very slow bleeding from the lower GI source allow enough time for this enzymatic breakdown.²

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

<table>
<thead>
<tr>
<th>ICSR</th>
<th>Country</th>
<th>Reporter</th>
<th>Age/Gender</th>
<th>Roflumilast dosage</th>
<th>Other suspected (S) or concomitant (C) drugs</th>
<th>Reactions (WHO-ART preferred terms)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Germany</td>
<td>Physician</td>
<td>78/M</td>
<td>Oral, 500 µg/day, 4 days</td>
<td>Tiotropium, fluticasone/salmeterol (both C)</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Germany</td>
<td>Physician (clinical trial)</td>
<td>63/M</td>
<td>Oral, 500 µg/day, 4 days*</td>
<td>Cefixime, tiotropium, hydrochlorothiazide/ramipril, fenoterol/ipratropium, phenazone (all C)</td>
<td>Melaena, paroniria, nausea, depression, chole-cystitis, diverticula, constipation, proctitis</td>
</tr>
<tr>
<td>3</td>
<td>Germany</td>
<td>Physician (clinical trial)</td>
<td>71/M</td>
<td>Oral, 500 µg/day, 84 days, then 4 months</td>
<td>Fluticasone/salmeterol, budesonide/formoterol, tiotropium, salbutamol, ramipril, phenprocoumon, digitoxin, verapamil, valsartan, pravastatin, pantoprazole, insulin, metrazapine, furosemide, allopurinol (all C)</td>
<td>Melaena, chest pain, dyspnoea, diverticulosis colonic, GI neoplasm benign, anorexia, anaemia</td>
</tr>
<tr>
<td>4</td>
<td>Germany</td>
<td>Physician (clinical trial)</td>
<td>77/F</td>
<td>Oral, 500 µg/day, 77 days*</td>
<td>Azithromycin (C)</td>
<td>Melaena, nausea, abdominal pain, gastritis, GI haemorrhage, duodenal ulcer</td>
</tr>
<tr>
<td>5</td>
<td>USA</td>
<td>Not known</td>
<td>77/F</td>
<td>Oral, once daily, 2.5 months</td>
<td>Azithromycin (C)</td>
<td>Melaena, nausea, gastritis, duodenal ulcer, GI haemorrhage, abdominal pain</td>
</tr>
<tr>
<td>6</td>
<td>USA</td>
<td>Consumer/non health professional</td>
<td>80/M</td>
<td>Oral, 500 µg/day, 2 months</td>
<td>Tiotropium, famotidine, acetylsalicylic acid, calcium, rosvastatin, fluoxetine, cyanocobalamin, digoxin, metoprolol, warfarin, fluticasone, fish oil, magnesium (all C)</td>
<td>Bismuth (S)</td>
</tr>
<tr>
<td>7</td>
<td>Italy</td>
<td>Consumer/non health professional</td>
<td>-/M</td>
<td>Oral, 500 µg/day, 1 month</td>
<td>Risedronic acid, lercanidipine, fluticasone/salmeterol, ketotifen, tiotropium, deflazacort (all C)</td>
<td>Melaena, abdominal pain, back pain, gastritis</td>
</tr>
</tbody>
</table>

*Re-challenge with roflumilast positive
**Reports in VigiBase**

From November 2010 to January 2013, seven Individual Case Safety Reports (ICSRs) (IC 1.23, IC025 -0.03) in the WHO Global ICSR Database, VigiBase™, raised the possibility of a causal relationship between roflumilast administration and the adverse effect melaena. The ICSRs are summarised in Table 1.

Before starting any assessment, it should be noted that there are similarities between the ICSRs 4 and 5 (female, 77 years old, 68 kg, same reactions, same dates of treatment and onset of reaction) that suggest that they describe the same case, even if the ICSRs come from different countries. For this reason, only the ICSR 4 was used for further evaluation.

It should also be considered that there are three ICSRs (2, 3 and 4) related to patients involved in clinical trials with roflumilast. In these cases, the reporting physician(s) classified the melaena as not related to the drug. According to the reporters, these patients had other alternative plausible explanations for the development of the event, such as suspicion of an upper GI haemorrhage (even if not diagnosed), possibility of concurrent haemorrhoids and/or active duodenal ulcer as well as concomitant treatment with an anticoagulant (phenprocoumon).

**Literature and Labelling**

In an assessment of roflumilast made by The Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency, it was pointed out that increased gastric acid secretion and delayed gastric emptying were observed during safety pharmacology studies. These effects were possibly related to the class of PDE4 inhibitors. Indeed, such effects of PDE inhibitors have been known for over forty years. For instance, Harris et al. described stimulation of hydrochloric acid production by methylxanthines in the isolated frog gastric mucosa by inhibition of PDE that destroys cAMP. Scratcherd et al. found proof that methylxanthines can both initiate gastric secretion and potentiate histaminic-stimulated gastric secretion. Moreover, according to CHMP, morphological changes in the GI tract (erosion and ulceration) were seen in both rats and monkeys in higher doses. Such changes were not normally expected at therapeutic doses in humans, yet the approved European Summary of Product Characteristics contains, in addition to the adverse reactions gastritis (uncommon, i.e. >1/1,000 - <1/100) and constipation (rare, i.e. >1/10,000 - <1/1,000), haematochezia as a rare ADR.

Assessing the concomitant medication in the reports in Table 1, it is evident that all reported patients took either blood anticoagulants (discussed above) or another drug that might have caused blood in the stool. Tiotropium may cause constipation and intestinal obstruction, which may lead to hard and bloody stools. Similarly, known ADRs of azithromycin are bloody diarrhoea and constipation. Constipation may also lead to haemorrhoids (swollen veins in the rectum). However, blood in the stool formed this way can better be classified as haematochezia than melaena.

Returning to the potential GI class adverse effects of PDE4 inhibitors, a somewhat different explanation was offered recently. It was pointed out that for second-generation PDE4 inhibitors, including roflumilast, GI disturbances were the most prevalent adverse drug reactions (ADRs). They could be accounted for by the ubiquitous distribution of PDE4 isoforms across many tissues. The most worrying potential toxicity generic to such PDE4 inhibitors could be arteritis. In recent human clinical trials with some PDE4 inhibitors the main reason for drop-outs was an incidence of colitis, raising the possibility that it was secondary to arteritis. In clinical trials with cilomilast, another PDE4 inhibitor, GI adverse effects including melaena did occur and were monitored with colonoscopy. Although the findings did not establish a relationship between melaena and vasculitis, the FDA concluded, from the low number of cases, that there was insufficient evidence to rule it out in humans.

**Discussion**

It is worth starting the assessment with the three cases describing clinical trial patients, in which the reporting physicians classified the melaena as not related to roflumilast treatment. If the casual relationship between roflumilast administration and melaena could be completely ruled out in these three cases, the remaining three cases might not generate a signal.

According to the narrative in ICSR 2, the patient went to the outpatient clinic 19 days after the first dose of roflumilast because of bowel movement difficulties (constipation and delayed gastric emptying are accepted ADRs of roflumilast3). The patient had also experienced, among other symptoms, blood in stool with known haemorrhoids two days after the first dose of roflumilast. When roflumilast treatment was discontinued the symptoms stopped. When roflumilast was resumed intermittently, the symptoms re-appeared. According to the reporter, the concurrent haemorrhoids provided a more plausible alternative explanation for the occurrence of blood in the stool than roflumilast treatment. However, this conclusion requires closer scrutiny. The original reported term used by the investigator was "faecal occult blood (FOB) with known haemorrhoids". FOB means small amounts of blood, not visible to the eye, in the stool indicating that bleeding has occurred somewhere in the upper or lower GI tract.
case it might have been caused by the mild proctitis (inflammation of the rectum) that was also reported. The reporting physician pointed out that FOB might be a sign of the proctitis (i.e. haematochezia and not melaena); however, it would not explain why the patient, after discontinuation of the therapy "had recovered" and then, when roflumilast was later resumed, the symptoms re-appeared. Roflumilast is known to cause constipation and delayed gastric emptying (so possibly also has a more global effect on gut motility). Haemorrhoids are exacerbated by constipation, and the patient has a past history of haemorrhoids. However, there is no mention of haemorrhoids in the examination findings but a colonoscopy revealed proctitis. The patient reported blood in the stool only two days after the first dose of roflumilast, which may be too soon for the drug to have caused constipation. The proctitis appears to be a more plausible explanation for the visible blood in the stool, but it is not clear that the roflumilast caused the proctitis.

In ICSR 3 the patient, treated concomitantly with phenprocoumon, started roflumilast therapy on 23 February. On 17 May he was admitted to hospital and reported having had melaena for approximately four weeks. He also had a medical history of chronic gastritis. Roflumilast (and perhaps phenprocoumon) therapy was discontinued on 17 May. Gastroscopy did not reveal a source of haemorrhage in the upper GI tract. The patient was diagnosed with diverticulosis and a solitary polyp in the ascending colon. Phenprocoumon therapy was then reintroduced (there are no exact dates in the report, but it seems to have occurred earlier than the reintroduction of roflumilast). Roflumilast was resumed on 2 June but was discontinued on 17 October at the patient's request. According to the reporting physician, other plausible explanations, such as phenprocoumon therapy and undiagnosed GI haemorrhage, make a causal relationship between roflumilast treatment and melaena unlikely. However, roflumilast may have been responsible for the gastritis or have exacerbated it, which could have led to the mentioned GI haemorrhage (causing melaena). If this were the case, phenprocoumon may have made the symptoms worse.

The patient in ICSR 4 developed duodenal ulcers, erosive antral gastritis, upper gastrointestinal haemorrhage and tarry stool approximately two months after the first dose of roflumilast. Roflumilast was discontinued and the patient recovered. The symptoms then re-occurred upon re-challenge. The sender commented on the case that, in the absence of any pharmacological indication that roflumilast could favour the occurrence of the patient’s symptoms, the concurrent erosive antral gastritis provided a more plausible explanation. However, as described above, the literature states that PDE inhibitors are expected to increase gastric acid secretion (which may lead to other GI disturbances). Thus, there may be a plausible pharmacological explanation, and the causality chain, gastritis — duodenal ulcer — GI haemorrhage — melaena, is at least not impossible.

One could summarise the analysis of the three clinical trial reports by saying that there is no convincing evidence for the causal relationship between roflumilast treatment and melaena. However, if there is a pharmacologically plausible explanation for a causal relationship between a medicine and an event, the fact that other plausible explanations may also exist is not enough to rule out the possibility of an ADR completely.

Tiotropium may cause blood in faeces from the lower GI tract. Although the patient in ICSR 1 was treated with tiotropium, the reporter, a physician, was unlikely to have confused melaena with haematochezia. It is worth noting that the reporter in ICSR 7 was not a health care professional, and bleeding from the lower GI tract in this case might have been mistaken for melaena.

Because of the confounding concomitant medication (tiotropium, acetylsalicylic acid and warfarin), ICSR 6 provides no convincing evidence of a causal relationship.

If one assesses the issue in a narrower context, i.e. whether a causal relationship between roflumilast administration and melaena can be established solely on the basis of the reports, the result would be controversial. Four patients of the assessed six (ICSRs 2, 3, 4 and 6) suffered from illnesses (proctitis, GI neoplasm, duodenal ulcer) and/or were treated with anticoagulant drugs that could also account for the melaena.

On the other hand, if one assesses the possible relationship between a group of possibly interrelated GI adverse effects assuming that their single root cause can be the administration of roflumilast (or, in general, of PDE inhibitors) and their possible manifestations including melaena, the causality is plausible. It has been shown previously that GI adverse effects of PDE inhibitors have been suspected with various mechanisms for decades.4,5,10 These mechanisms, increased gastric acid production (described as "possibly related to the class of the compound" by the CHMP) and/or arteritis, may lead to manifestations of the various GI reactions reported (duodenal ulcer, gastritis, diverticulosis etc.); with consequent, melaena particularly in sensitive patients (for example when treated with anticoagulants). The fact that the GI manifestations have been reported as adverse effects and not as concomitant sicknesses in all cases, seem to support this explanation.

It is almost a philosophical question that, if the above analysis is true, what should be called "the"
adverse reaction; the increased gastric acid production and/or its possible sequel: the gastric ulcer, and/or its plausible consequence: the intestinal haemorrhage, and/or its symptom: the melaena?

One possible answer is that, since patients are now being encouraged to report their drug adverse effects; listing of those symptoms that may be easily self-diagnosed may be advocated.

Conclusion
Causal relationships between PDE inhibitors (including roflumilast) and various GI adverse reactions have previously been established. Although melaena is one of the rare but plausible sequelae of these GI conditions, which is not in itself a new adverse reaction but an easily recognisable symptom that is not yet labelled, the reports discussed here suggest that it is worth listing as a rare ADR of roflumilast.

References
Response from Forest Laboratories

COPD patients have been shown to have an increased incidence of gastroduodenal erosions and ulcers (Fukumura et al. 1992). Epidemiological studies show an increased risk of upper GI bleeding amongst COPD patients who are not exposed to roflumilast with an almost two-fold risk compared to controls [HR:1.93, 95% CI:1.73-2.17] (Huang et al. 2012). Although the primary etiology of these erosions/ulcers is the hypersecretion of gastric acid induced by hypoxemia or hypercapnia, additional risk factors include advanced age, male gender, smoking history, comorbidities of heart failure, chronic renal disease, hypertension, diabetes, and the use of ulcerogenic medications.

Roflumilast, a selective phosphodiesterase type 4 (PDE4) inhibitor indicated for severe COPD, was first approved in 2010 and is now marketed in 43 countries. Through 2012, exposure is estimated at 286,000 patient-years. A search of the roflumilast global safety database identified 5 cases of "melaena", 4 of which are medically-confirmed. Events occurred in patients aged 60-80 years with latencies between 4 days and 4 months with no clear pattern. Reports of these events present confounding factors that could account for the melaena, including co-morbid conditions (e.g.; duodenal ulcer, gastritis, proctitis, heart failure), a previous history of gastrointestinal bleeding, and/or co-suspect medications (e.g., anticoagulants, ASA, azithromycin).

Statistical signal detection efforts using the Empirica Signal tool, with data from VigiBase™ and AERS, did not identify a statistical signal (EB05 >2) for "melaena" or any of the preferred terms that comprise the GI haemorrhage SMQ.

Rates of upper GI AEs associated with haemorrhage, including "melaena", from the COPD clinical development program were infrequent and slightly lower in roflumilast than in placebo. 15/6,563 COPD subjects exposed to roflumilast (0.23%) reported terms indicative of upper GI haemorrhage compared to 18/5, 491 placebo-treated subjects (0.33%). "Melaena", specifically, was reported in 2 subjects in each arm with roflumilast (0.03%) and placebo (0.04%). Systematic hemoccult testing, conducted in five placebo-controlled studies with roflumilast, and follow-up gastrointestinal investigations (colonoscopy) to detect GI bleeding, revealed no difference from placebo.

Biologically, while first generation PDE4 inhibitors were reported to increase acid secretion due to gastric parietal cell stimulation, less activity is expected with later-generation inhibitors, including roflumilast, due to lower-affinity binding at the rolipram binding site in the gastric glands. Indeed, cilomilast revealed improved GI tolerability and, in phase 1 studies, had no effect on gastric pH in healthy subjects (Houghton et al. 2006). Subacute and chronic toxicity studies of roflumilast in mice, hamsters, and dogs revealed no histological changes in the glandular stomach or intestine suggestive of GI toxicity. GI changes were seen in rats and monkeys at doses 50- to 200- times above the clinical dose of 500 [ig/day. These data demonstrated that roflumilast, at therapeutic doses, is unlikely to significantly stimulate acid secretion or produce GI bleeding.

Conclusion

The available evidence does not suggest a causal relationship between the occurrence of melaena and the use of roflumilast. Upper GI haemorrhage is known to be increased in the COPD population. The cases of melaena identified (5 cases out of 286,000 patient-years of exposure) are confounded and occur at a rate which is anticipated in a COPD population. Additionally, evidence from pre-clinical and controlled clinical studies does not support an association. Nevertheless, the MAHs are committed to the close monitoring of AE reports of melaena through their routine pharmacovigilance processes.

References


Tapentadol and Delusion
Dr. Ian Boyd, Australia

Summary
Tapentadol is a centrally acting synthetic analgesic combining opioid and non-opioid (noradrenaline reuptake inhibition) activity in a single molecule. In the WHO Global Individual Case Safety Report (ICSR) Database, VigiBase™, there are currently (25 January 2013) 10 ICSRs of delusion in association with tapentadol. The ICSRs are from the United States and Germany. The association has an IC value of 3.05 with an IC025 value of 2.02. Tapentadol was the only drug suspected in six cases. The outcome was stated in seven ICSRs. The patients were reported as recovered or recovering in six cases and not recovered in one case.

The association of delusion with tapentadol appears to be a signal. The IC value is relatively high. Tapentadol was the only drug suspected in six of the 10 cases, the time to onset is particularly suggestive of a drug-induced effect and the observation of recovery after dechallenge in four of six cases in which recovery was documented is also supportive of the signal. In addition, the observation in the product information that other psychiatric reactions occurred commonly and uncommonly in clinical trials suggests that a mechanism for the development of another psychiatric reaction such as delusion may be possible. The fact that delusion has been reported in VigiBase at a similar level to some of these reactions is also suggestive of a signal.

Introduction
Tapentadol is a centrally acting synthetic analgesic combining opioid and non-opioid (noradrenaline reuptake inhibition) activity in a single molecule. It has 18 times less binding affinity than morphine to the human mu-opioid receptor but was only 2-3 times less potent in producing analgesia in animal models (on a dose per body weight basis). This low in vivo potency difference is consistent with its two mechanisms of action. Tapentadol has been shown to inhibit noradrenaline reuptake in the brains of rats resulting in increased noradrenaline concentrations. In preclinical models, the analgesic activity due to the mu-opioid receptor agonist activity of tapentadol can be antagonized by selective mu-opioid receptor antagonists (e.g., naloxone), whereas the noradrenaline reuptake inhibition is sensitive to noradrenaline modulators.1 Tapentadol is indicated for the management of moderate to severe chronic pain unresponsive to non-narcotic analgesia.1

Very common adverse reactions observed in clinical trials with tapentadol include gastrointestinal effects such as nausea and constipation and nervous system disorders such as dizziness, headache and somnolence. Common reactions include gastrointestinal effects such as vomiting, dry mouth and diarrhoea, nervous system disorders such as disturbance in attention, tremor and involuntary muscle contractions, psychiatric effects such as anxiety, depressed mood, sleep disorder, nervousness, restlessness, skin disorders such as pruritus and hyperhidrosis, fatigue, myalgia, vertigo, flushing and decreased appetite.1

Delusional disorder is an illness characterized by the presence of non-bizarre delusions in the absence of other mood or psychotic symptoms, according to the Diagnostic Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR).2,3 It defines delusions as false beliefs based on incorrect inference about external reality that persist despite the evidence to the contrary and these beliefs are not ordinarily accepted by other members of the person’s culture or subculture. Non-bizarre refers to the fact that this type of delusion is about situations that could occur in real life, such as being followed, being loved, having an infection, and being deceived by one's spouse. Delusional disorder is on a spectrum between more severe psychosis and overvalued ideas.2

The prevalence of delusional disorder in the United States is estimated in the DSM-IV-TR to be around 0.03%, which is considerably lower than the prevalence of schizophrenia (1%) and mood disorders (5%).2,3,4 Medications known to be associated with delusion include adrenocorticotropic hormones, anabolic steroids, corticosteroids, cimetidine, antibiotics (eg, cephalosporins, penicillin), disulfiram and anticholinergic agents.2

Reports in VigiBase
As of 25 January 2013 there are 10 Individual Case Safety Reports (ICSRs) of delusion in association with tapentadol in the WHO Global ICSR Database, VigiBase™ (Table 1). The association has an IC value of 3.05 with an IC025 value of 2.02. The ICSRs were submitted from the United States (nine cases) and Germany (one case). The patients ranged in age from nine to 88 years with a median of 57 years but only eight cases provided this information. The gender distribution was nine females and one male.

Tapentadol was the only drug suspected in six cases. Other suspected drugs included other drugs which might be expected to be used in a pain management situation including oxycodone (three cases), cyclobenzaprine (two cases), phenobarbital (one case) and benzodiazepines (three cases).
Concomitant (but not suspected) drugs were reported in five cases and also included drugs involved in a pain management setting such as oxycodone, morphine, NSAIDs and benzodiazepines. Tapentadol was reported to have been administered orally, as expected, in all 10 cases. The indication for use was included in seven ICSRs and included treatment for pain in each case.

Time to onset was reported with clarity in only one of the ICSRs and was two days after drug administration began. In six other cases, however, the reaction appeared to have occurred soon after the administration or an increase in the dose of tapentadol. In one of these cases, the patient experienced delusion soon after an overdose of 26 tablets. Three of the other cases reported the reaction in association with an increase in dose: in one case the dose was increased from 50 mg to 100 mg; in another case the dose was doubled from 100 mg to 200 mg; in the other case the dose was increased but the details were not provided. Another case appeared to describe the reaction soon after the first dose and a further case appeared to describe the reaction soon after the second dose.

The outcome was stated in seven ICSRs. The patients were reported as recovered or recovering in six cases and not recovered in one case. In four of the six cases, the patient recovered after dechallenge.

Other reactions were described in seven ICSRs. In six of those ICSRs, other neuropsychiatric effects were described including hallucination (three cases), anxiety and confusion (both two cases).

Table 1. Case overview of ICSRs in VigiBase™ of delusion in association with tapentadol

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/Gender</th>
<th>Other suspected (S) or concomitant (C) drugs</th>
<th>Reactions (WHO-ART preferred terms)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>61/F</td>
<td>Paracetamol, oxycodone hydrochloride, cyclobenzaprine (both S)</td>
<td>Delusion, therapeutic response increased</td>
<td>Not recovered</td>
</tr>
<tr>
<td>2</td>
<td>28/M</td>
<td>Morphine (C)</td>
<td>Delusion, hallucination</td>
<td>Recovered</td>
</tr>
<tr>
<td>3</td>
<td>80/F</td>
<td>Sitagliptin, simvastatin, metamizole, cilostazol, etoricoxib, lercanidipine, insulin aspart, insulin aspart protamine, metoprolol, levethroxyric acid, zopiclone, torasemide, acetylsalicylic acid (all C)</td>
<td>Delusion, hallucination, confusion, aggressive reaction</td>
<td>Recovering</td>
</tr>
<tr>
<td>4</td>
<td>80/F</td>
<td>None</td>
<td>Delusion</td>
<td>Unknown</td>
</tr>
<tr>
<td>5</td>
<td>-.F</td>
<td>Duloxetine (S)</td>
<td>Delusion, serotonin syndrome</td>
<td>Recovered</td>
</tr>
<tr>
<td>6</td>
<td>34/F</td>
<td>Alprazolam (C)</td>
<td>Delusion, amenorrhea, cardiac failure, depression, tremor, personality disorder, delusional, euphoria, crying abnormal, anxiety</td>
<td>Recovered</td>
</tr>
<tr>
<td>7</td>
<td>-.F</td>
<td>Phenytoin, all other therapeutic products (all C)</td>
<td>Delusion</td>
<td>Recovered</td>
</tr>
<tr>
<td>8</td>
<td>53/F</td>
<td>Amitriptyline, cyclobenzaprine, oxycodone, paracetamol, oxycodone hydrochloride, sulfentanil, formoterol fumarate, budenoside, tamoxifen, buspirone, lorazepam, phenobarbital (all C)</td>
<td>Delusion, confusion, anxiety, dizziness, dry mouth</td>
<td>Recovered</td>
</tr>
<tr>
<td>9</td>
<td>88/F</td>
<td>None</td>
<td>Delusion</td>
<td>Unknown</td>
</tr>
<tr>
<td>10</td>
<td>52/F</td>
<td>Alprazolam, ethanol, oxycodone (all S)</td>
<td>Delusion, hallucination, arthritis, myalgia, intentional overdose</td>
<td>Unknown</td>
</tr>
</tbody>
</table>
Literature and Labelling

The product literature does not refer to delusion. However, other psychiatric reactions such as anxiety, depressed mood, sleep disorder, nervousness and restlessness are described as common and disorientation, confusion, agitation, perception disturbances, abnormal dreams and euphoria are described as uncommon. There have been no reports in the literature of delusion in association with tapentadol.

Discussion and Conclusion

Case reports in VigiBase suggest that there is a signal for the association of tapentadol and delusion. Tapentadol was the only drug suspected in six of the 10 cases. Other suspected drugs included other drugs which might be expected to be used in a pain management situation including oxycodone, cyclobenzaprine, phenobarbital and benzodiazepines and it is possible that these drugs may have made a contribution to the adverse reaction observed.

Time to onset is suggestive of a signal. It was reported with clarity in only one of the ICSRs and was two days after drug administration began. In six other cases, however, the reaction appeared to have occurred soon after the administration or an increase in the dose of tapentadol, consistent with a drug-induced effect.

Dechallenge is also possibly suggestive of a signal. The outcome was stated in seven ICSRs. The patients were reported as recovered or recovering in six cases and not recovered in one case. In four of these cases, the patients recovered or were recovering after the drug was reported to have been withdrawn.

It is not surprising that neuropsychiatric effects may be associated with a drug such as tapentadol which combines both noradrenaline reuptake inhibition and mu-opioid receptor agonist activity. In addition, in the product information, psychiatric reactions such as anxiety, depressed mood, sleep disorder, nervousness and restlessness are described as common and disorientation, confusion, agitation, perception disturbances, abnormal dreams and euphoria are described as uncommon. The occurrence of delusion as an adverse reaction would not be inconsistent with these observations.

In VigiBase, many psychiatric reactions have been reported. These include hallucinations (which are perception disturbances) (110 cases), confusion (which includes disorientation) (100 cases), agitation (which includes restlessness) (60 cases), depression (51), anxiety (36), nervousness (22), sleep disorder (12), abnormal dreams (five) and euphoria (five). All of these terms are considered as common or uncommon in the product information and the presence of 10 ICSRs of delusion is consistent with the proposal that delusion is a signal.

References


Response from Grünenthal GmbH and Janssen Pharmaceuticals, Inc.

Delusional disorders as defined in DSM-IV-TR require the presence of at least one non bizarre delusion persisting for at least one month. It is also important to note that the diagnosis of delusion can only be made in the absence of other relevant psychiatric disorder, such as prominent auditory or visual hallucinations.

The signal of disproportionate reporting on tapentadol and delusion has been a topic of internal review during the routine signal detection activities. The integrated analysis included data from the clinical development program, spontaneous reports and literature review with the conclusion that the review of evidence did not support an association between tapentadol administration and delusion.

Clinical Experience
Perceptional disturbances, with its most prominent manifestation being hallucinations, have been identified as adverse drug reactions (ADRs) during the clinical development program of tapentadol. These are acknowledged class effects of mu-opioid agonist drugs in general. Further recognized neuropsychiatric ADRs include disorientation and confusion.

To date, only 0.02% of subjects treated with tapentadol experienced delusion during the clinical development program. All these events were non-serious, with mild or moderate intensity, and did not lead to a change of the safety profile of tapentadol.

Postmarketing Experience
Cases retrieved from the safety database with a cumulative search for the Preferred Term 'Delusion' were reviewed in detail. All cases were sparsely documented, especially regarding medical history and the diagnosis, as symptoms or circumstances describing the delusion were not mentioned.

More than a third of the cases reported hallucination concurrently. Furthermore the events of disorientation and confusion were reported, which confounded a clear medical assessment.

With exception for one case, all other cases were medically confirmed.

Overall, there were no cases with sufficient information providing phenomenological evidence regarding the diagnosis and lacking confounders.

Discussion
The review of post-marketing cases suggests that the distinction between hallucination and delusional disorder is often not made by the reporting health care professional and the terms are used interchangeably in some of the cases. According to the definition of delusional disorder provided in the DSM-VI-TR1 classification, a prominent hallucination would preclude the diagnosis of delusional disorder making the diagnosis of delusional disorder in these cases questionable, although most of the cases were medically confirmed.

The rest of the cases lacked information on the symptoms related to the diagnosis of delusional disorder, or there was missing information on important medical history or concomitant treatment. Bearing in mind the challenges of establishing an accurate psychiatric diagnosis, these cases do not provide sufficient information for a reasonable assessment.

Although tapentadol as a centrally acting drug already lists neuropsychiatric effects such as anxiety, disorientation, confusion and perception disturbances including hallucinations, delusional disorder is a distinct medical concept. As the diagnosis is clearly distinguished from other psychiatric disorders, particularly hallucinations it cannot automatically be regarded as an expected drug reaction.

Conclusion
The integrated analysis revealed insufficient evidence for an association between tapentadol and delusion. Therefore, currently delusion is not regarded as a valid safety signal. The topic will however be reviewed on a routine basis to monitor for a change in the level of evidence.

Reference
CAVEAT DOCUMENT

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

Uppsala Monitoring Centre (UMC) in its role as the WHO Collaborating Centre for International Drug Monitoring receives reports of suspected adverse reactions to medicinal products from National Centres in countries participating in the WHO pharmacovigilance network, the WHO Programme for International Drug Monitoring. Limited details about each suspected adverse reaction are received by the UMC. The information is stored in the WHO Global Individual Case Safety Report database, VigiBase. It is important to understand the limitations and qualifications that apply to this information and its use.

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

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

The volume of reports for a particular medicinal product may be influenced by the extent of use of the product, publicity, the nature of the reactions and other factors. No information is provided on the number of patients exposed to the product.

Some National Centres that contribute information to VigiBase make an assessment of the likelihood that a medicinal product caused the suspected reaction, while others do not.

Time from receipt of a report by a National Centre until submission to UMC varies from country to country. Information obtained from UMC may therefore differ from those obtained directly from National Centres.

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

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

Any publication, in whole or in part, of information obtained from UMC must include a statement:

(i) regarding the source of the information,
(ii) that the information comes from a variety of sources, and the likelihood that the suspected adverse reaction is drug-related is not the same in all cases,
(iii) that the information does not represent the opinion of the World Health Organization.

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