WHO PHARMACEUTICALS NEWSLETTER

World Health Organization

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

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

Safety and Vigilance,

EMP-HIS,
World Health Organization,
1211 Geneva 27, Switzerland,
E-mail address: pals@who.int

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

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

No. 1, 2014

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

This issue includes recommendations from the working groups of the thirty-sixth annual meeting of national pharmacovigilance centres that was held in Rome last year.

Contents

Printed by the WHO Document Production Services, Geneva, Switzerland

TABLE OF CONTENTS

Regulatory Matters

Safety of medicines

Signal

Feature

Acetaminophen (Paracetamol INN)

Recommendation to discontinue prescribing and dispensing acetaminophen prescription combination drug products with more than 325 mg

USA. The U.S. Food and Drug Administration (FDA) recommended that health-care professionals discontinue prescribing and dispensing prescription combination drug products that contain more than 325 milligrams (mg) of acetaminophen per tablet, capsule or other dosage unit. There are no available data to show that taking more than 325 mg of acetaminophen per dosage unit provides additional benefit that outweighs the added risks for liver injury. Further, limiting the amount of acetaminophen per dosage unit will reduce the risk of severe liver injury from inadvertent acetaminophen overdose, which can lead to liver failure, liver transplant, and death.

Cases of severe liver injury with acetaminophen have occurred in patients who:

- took more than the prescribed dose of an acetaminophen-containing product in a 24-hour period;
- took more than one acetaminophen-containing product at the same time; or
- drank alcohol while taking acetaminophen products.

The US FDA also recommended that when a pharmacist receives a prescription for a combination product with more than 325 mg of acetaminophen per dosage unit that they contact the prescriber to discuss a product with a lower dose of acetaminophen. A two tablet or two capsule dose may still be prescribed, if appropriate. In that case, the total dose of acetaminophen would be 650 mg (the amount in two 325 mg dosage units). When making individual dosing determinations, health-care providers should always consider the amounts of both the acetaminophen and the opioid components in the prescription combination drug product.

In January 2011, the US FDA asked manufacturers of prescription combination drug products containing acetaminophen to limit the amount of acetaminophen to no more than 325 mg in each tablet or capsule by January 14, 2014. The US FDA requested this action to protect consumers from the risk of severe liver damage which can result from taking too much acetaminophen. This category of prescription drugs combines acetaminophen with another ingredient intended to treat pain (most often an opioid), and these products are commonly prescribed to consumers for pain, such as pain from acute injuries, post-operative pain, or pain following dental procedures. Acetaminophen is also widely used as an over-the-counter (OTC) pain and fever medication, and is often combined with other ingredients, such as cough and cold ingredients. The US FDA will address OTC acetaminophen products in another regulatory action. It is also notified that many consumers are often unaware that many products (both prescription and OTC) contain acetaminophen, making it easy to accidentally take too much.

(See WHO Pharmaceuticals Newsletter No.1, 2011 for the maximum amount limited to 325 mg per dosage unit and a boxed Warning will highlight the potential for severe liver failure in the USA).

References:

FDA Drug Safety Communication, US FDA 14 January 2014 (www.fda.gov).

Acipimox

Only to be used as additional or alternative treatment to reduce high triglyceride levels

Europe. The Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) confirmed by majority that medicines containing acipimox (Olbetam® and generics) should have their marketing authorisations amended to ensure that they are used across the European Union (EU) only as an additional or alternative treatment in Fredrickson type IIb or type IV hyperlipoproteinaemia. These are conditions involving hypertriglyceridaemia with or without increased cholesterol. Acipimox-containing medicines should be used when changes in lifestyle, including diet and exercise, and treatment with other medicines are not adequate.

Health-care professionals are informed that, based on the available data, the indications for acipimox should be restricted to alternative or adjunct treatment in patients who have not responded adequately to other treatments such as statin or fibrate treatment. Patients receiving acipimox should have their treatment reviewed at their next regular appointment. The main role of acipimox is to prevent the non-cardiovascular complications of hypertriglyceridaemia and acipimox should not be used for the prevention of cardiovascular disease in the absence of convincing LDL-C or outcome data.

Prescribers are warned of the potential increased risk of myopathy when acipimox is

used in combination with a statin.

Reference:
Press release, EMA, 22 November 2013 (*www.ema.europa.eu*).

Capecitabine

Risk of severe skin reactions

Canada (1). Hoffmann-La Roche Limited (Roche), in consultation with Health Canada, informed health-care professionals that very rare cases of severe cutaneous reactions such as Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN), in some cases with fatal outcome, have been reported during treatment with capecitabine (Xeloda®). It is advised that the drug should be immediately discontinued if signs and symptoms of SJS or TEN are present.

UK (2). The Medicines and Healthcare products Regulatory Agency (MHRA) announced that severe skin reactions such as SJS and TEN were reported during treatment with capecitabine. Some cases were fatal. The MHRA advised health-care professionals that capecitabine should be discontinued if a serious skin reaction occurs, and the reaction should be treated promptly.

Capecitabine is a first-line, adjuvant, or combination treatment for colon cancer, and for metastatic colorectal cancer, gastric cancer, or breast cancer.

Skin reactions associated with the use of capecitabine include palmar-plantar erythrodysaesthesia (hand-foot syndrome) and dermatitis, which occur very commonly (ie, >10% of patients). Rash, alopecia, erythema, and dry skin are common reactions. Furthermore, pruritus, localised exfoliation, skin hyperpigmentation, photosensitivity reactions, and radiation recall syndromes (severe skin reactions that can occur when chemotherapy agents are administered after radiotherapy) have also been seen with capecitabine.

Reference:
(1) Advisories, Warnings and Recalls, Health Canada, 3 December 2013 (*www.hc-sc.gc.ca*).
(2) Drug Safety Update, January 2013, Volume 7, issue 6, A4 MHRA, (*www.mhra.gov.uk*).

Clobazam

Risk of serious skin reactions

USA. The US FDA warned that clobazam (Onfi®) can cause rare but serious skin reactions Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) that can result in permanent harm and death. These skin reactions can occur at any time during clobazam treatment. However, the likelihood of skin reactions is greater during the first 8 weeks of treatment or when the drug is stopped and then re-started. All cases of SJS and TEN in the US FDA case series have resulted in hospitalization, one case resulted in blindness, and one case resulted in death. The clobazam drug label has been revised to add information about the risk for serious skin reactions to the Warnings and Precautions section and to the Medication Guide.

Clobazam is a benzodiazepine medication used in combination with other medicines to treat seizures associated with a severe form of epilepsy called Lennox-Gastaut Syndrome.

It is recommended that patients should be closely monitored for signs or symptoms of SJS/TEN, especially during the first 8 weeks of treatment or when re-introducing therapy. Health-care professionals should discontinue use and consider an alternate therapy at the first sign of rash, unless it is clearly not drug-related.

Patients are also recommended to seek immediate medical treatment if they develop a rash, blistering or peeling of the skin, sores in the mouth, or hives. Patients should not stop taking clobazam without first talking to their health-care professionals.

References:
FDA Drug Safety Communication, US FDA 3 December 2013 (*www.fda.gov*).

Duloxetine

Serotonin syndrome

Australia. The Therapeutic Goods Administration (TGA) reminded health-care professionals that, while serotonin syndrome most commonly occurs when serotonergic drugs are used in combination, it can be caused by a single drug. The TGA received 21 reports of serotonin syndrome in which duloxetine (Cymbalta® and generics) is the sole suspected drug.

Duloxetine is a serotonin and noradrenaline reuptake inhibitor indicated for the treatment of major depressive disorder, generalised anxiety disorder and diabetic peripheral neuropathic pain.

Serotonin syndrome is a known risk associated with duloxetine therapy and is listed as a precaution in the Product Information (PI).

Serotonin syndrome is characterised by:
- altered mental state, e.g. confusion and agitation
- autonomic dysfunction, e.g. tachycardia and sweating
- neuromuscular excitation, e.g. hyperreflexia, tremor.

Duloxetine should be used with caution with other serotonergic drugs, and concomitant treatment with monoamine oxidase inhibitors (MAOIs), including moclobemide, is contraindicated. Duloxetine should not be used within 14 days of discontinuing treatment with an MAOI, and at least five days should be allowed after stopping duloxetine before starting an MAOI. Similarly, as duloxetine is metabolised by both CYP1A2 and CYP2D6, it should not be used in combination with potent inhibitors of CYP1A2 (such as fluvoxamine). Treatment with duloxetine should be discontinued if signs or symptoms of serotonin syndrome are identified. Duloxetine should also not be used in patients with hepatic impairment, and use of a lower dose is recommended in patients with end-stage renal disease (creatinine clearance <30 mL/min).

Reference:
Medicines Safety Update Vol 4, No. 6, December 2013 (www.tga.gov.au).

Finasteride and dutasteride

Risk of high-grade prostate cancer

Australia. The TGA added new warnings regarding the risk of high-grade prostate cancer to the Product Information (PI) documents for the 5-alpha reductase inhibitors (5ARIs) finasteride and dutasteride. 5ARIs are a class of drug primarily used to treat symptomatic benign prostatic hyperplasia (BPH) in men. The two 5ARIs registered in Australia are finasteride (Proscar® and Propecia®) and dutasteride (Avodart® and Duodart® [in combination with tamsulosin]). Propecia is only indicated for the treatment of male pattern hair loss.

The TGA has reviewed a US Food and Drug Administration (FDA) assessment of two large trials that evaluated the use of finasteride or dutasteride daily versus placebo for the reduction in risk of prostate cancer. Both trials showed an increased incidence of high-grade prostate cancer. The TGA has since worked with the sponsors of finasteride and dutasteride to update the Australian PI documents to include a new precaution regarding the risk of patients developing high-grade prostate cancer.

The TGA informed health-care professionals that 5ARIs are not approved for the treatment of prostate cancer and no clinical benefit has yet been demonstrated in patients with prostate cancer treated with 5ARIs and recommended that, before making a decision to prescribe a 5ARI, the known risks should be weighed against the benefits of 5ARI therapy and discussed with the patient.

(See WHO Pharmaceuticals Newsletter No. 4, 2011 for increased risk of prostate cancer in the USA and No. 6, 2009 for finasteride's potential risk of male breast cancer in the UK).

Reference:
Medicines Safety Update Vol 4, No. 6, December 2013 (www.tga.gov.au).

Methylphenidate

Risk of long-lasting erections

USA. The US FDA warned that methylphenidate products (Concerta®, Daytrana®, Focalin®/Focalin® XR, Metadate™ CD/Metadate™ ER, Methylin®/Methylin® ER, Quillivant XR™, Ritalin®/Ritalin® LA/Ritalin-SR®) may in rare instances cause prolonged and sometimes painful erections known as priapism. Based on a recent review of methylphenidate products, the US FDA updated drug labels and patient Medication Guides to include information about the rare but serious risk of priapism. If not treated right away, priapism can lead to permanent damage to the penis.

Methylphenidate products are central nervous system (CNS) stimulants used to treat attention deficit hyperactivity disorder (ADHD).

Priapism can occur in males of any age and happens when blood in the penis becomes trapped, leading to an abnormally long-lasting and sometimes painful erection. According to the US FDA, another ADHD drug, atomoxetine (Strattera®), has also been associated with priapism in children, teens, and adults. Priapism appears to be more common in patients taking atomoxetine than in those taking methylphenidate products; however, because of limitations in available information, the US FDA does not know how often priapism occurs in patients taking either type of product.

It is recommended that health-care professionals should talk to male patients and their caregivers to make sure they know the signs and symptoms of priapism and stress the need for immediate medical treatment should it occur. Younger males, especially those who have not yet reached puberty, may not recognize the problem or may be embarrassed to tell anyone if it occurs. It is also recommended to encourage their patients to read the Medication Guide they receive with every filled prescription.

References:
FDA Drug Safety Communication, US FDA 17 December 2013 (*www.fda.gov*).

Ofatumumab

Screen for hepatitis B virus before treatment

UK (1). The MHRA advised that all patients should be screened for hepatitis B virus infection before starting treatment with ofatumumab (Arzerra®). Patients with active infection with this virus should not be treated with ofatumumab. Those with positive hepatitis B serology should be referred to a specialist in liver disease for consultation about monitoring and initiation of antiviral treatment. If reactivation of hepatitis B virus occurs, ofatumumab and any concomitant chemotherapy should be interrupted immediately, and appropriate treatment instituted

Ofatumumab is indicated for the treatment of chronic lymphocytic leukaemia in patients who are refractory to fludarabine and alemtuzumab. Ofatumumab is a monocolonal antibody that acts against CD20.

Canada (2). GSK, in consultation with Health Canada, informed health-care professionals of important new updates to the recommendations for screening, monitoring and management of Hepatitis B reactivation in patients treated with ofatumumab (ARZERRA™).

Ofatumumab is an anti-CD20 antibody that is authorized in Canada under a Notice of Compliance with conditions, for the treatment of patients with chronic lymphocytic leukemia (CLL) refractory to fludarabine and alemtuzumab.

Health-care professionals are advised that the use of anti-CD20 antibody therapies such as ofatumumab were shown to be associated with Hepatitis B virus reactivation in seropositive patients. Patients who have active Hepatitis B virus (HBV) infection should not be treated with the drug. All patients should be screened for HBV infection before starting treatment with the drug. In seropositive patients, consultation with a physician having expertise in liver disease is recommended. Patients should be monitored for clinical and laboratory signs of hepatitis or HBV reactivation during therapy and for several months after completion of treatment.

(See WHO Pharmaceuticals Newsletter No.6, 2013 for new boxed warning, recommendations to decrease risk of hepatitis B reactivation in the USA).

Reference:

(1) Drug Safety Update, January 2013, Volume 7, issue 6, A2 MHRA, (www.mhra.gov.uk).
(2) Advisories, Warnings and Recalls, Health Canada, 27 January 2013 (www.hc-sc.gc.ca).

Prasugrel

Association with increased risk of bleeding in patients treated in hospital for certain types of heart attacks

Canada (1). Eli Lilly Canada Inc. in collaboration with Health Canada informed health-care professionals of important safety information about prasugrel hydrochloride (Effint®), an antiplatelet agent indicated for the prevention of atherothrombotic events in patients with acute coronary syndromes. This information concerns the indication related to UA (unstable angina) or NSTEMI (non-ST-segment elevation myocardial infarction).

In UA/NSTEMI patients, when coronary angiography is performed within 48 hours after admission, the loading dose of prasugrel hydrochloride should generally be given at the time of percutaneous coronary intervention (PCI) in order to minimize the risk of bleeding.

It is also advised that UA/NSTEMI patients should generally be administered a 60 mg loading dose of prasugrel hydrochloride at the time of PCI, followed by a 10 mg maintenance dose.

UK (2). The MHRA advised health-care professionals that:

- Prasugrel is approved as a single 60 mg loading dose (followed by a maintenance dose recommended for up to 1 year); this remains unchanged
- Patients with unstable angina or NSTEMI, who undergo coronary angiography within 48 hours of admission, should be given a loading dose of 60 mg at the time of PCI only, to minimise bleeding risk
- Remember that a reduced maintenance dose of 5 mg once daily should be used (recommended for up to 1 year) if patients are age 75 years or older, or if their bodyweight is less than 60 kg

Prasugrel is a member of the thienopyridine class of medicines, and it inhibits platelet activation and aggregation. Prasugrel is indicated, in combination with aspirin, for the prevention of atherothrombotic events in patients with acute coronary syndrome undergoing primary or delayed percutaneous coronary intervention (PCI).

Reference:

(1) Advisories, Warnings and Recalls, Health Canada, 17 January 2013 (www.hc-sc.gc.ca).
(2) Drug Safety Update, January 2013, Volume 7, issue 6, A1 MHRA, (www.mhra.gov.uk).

Recombinant interferon-beta

Thrombotic microangiopathy

UK. The MHRA is investigating a cluster of reports of thrombotic microangiopathy with recombinant interferon-beta, which is used in the treatment of multiple sclerosis. Thrombotic microangiopathy is a very rare but serious condition characterised by occlusive microvascular thrombosis and secondary haemolysis, and it is a hallmark of haemolytic uraemic syndrome and thrombotic thrombocytopenic purpura. The MHRA received a total of 10 reports in the UK of thrombotic microangiopathy, haemolytic uraemic syndrome and/or thrombotic thrombocytopenic purpura.

Health-care professionals are advised to be vigilant for symptoms and signs that may be an early indication of this complication in patients receiving recombinant interferon-beta.

Reference:
Drug Safety Update, December 2013, Volume 7, issue 5, S3 MHRA, (*www.mhra.gov.uk*).

Regadenoson and adenosine

Rare but serious risk of heart attack and death

USA. The US FDA warned health-care professionals of the rare but serious risk of heart attack and death with use of regadenoson (Lexiscan®) and adenosine (Adenoscan®). These drugs are approved for use during cardiac nuclear stress tests in patients who cannot exercise adequately. These drugs help identify coronary artery disease. They do this by dilating the arteries of the heart and increasing blood flow to help identify blocks or obstructions in the heart's arteries. Regadenoson and adenosine cause blood to flow preferentially to the healthier, unblocked or unobstructed arteries, which can reduce blood flow in the obstructed artery. In some cases, this reduced blood flow can lead to a heart attack, which can be fatal.

The Warnings & Precautions section of the regadenoson and adenosine labels previously contained information about the possible risk of heart attack and death with use of these drugs. However, recent reports of serious adverse events in the US FDA Adverse Event Reporting System (FAERS) database and the medical literature prompted approval changes to the drug labels to include updated recommendations for use.

It is recommended to screen all nuclear stress test candidates for their suitability to receive regadenoson or adenosine. Avoid using these drugs in patients with signs or symptoms of unstable angina or cardiovascular instability, as these patients may be at greater risk for serious cardiovascular adverse reactions. Cardiac resuscitation equipment and trained staff should be available before administering regadenoson or adenosine.

The US FDA approved changes to the drug labels to reflect these serious events and updated recommendations for use of these agents.

References:
FDA Drug Safety Communication, US FDA 20 November 2013 (*www.fda.gov*).

Rituximab

Screening for hepatitis B virus before treatment

UK. The MHRA recommended to screen for hepatitis B virus in all patients (not only those at risk of this infection) before starting treatment for all indications. A patient with positive serology for hepatitis B virus should be referred to a specialist in liver disease before starting treatment with rituximab. During treatment, these patients should be monitored and managed to prevent reactivation of the virus. Health-care professionals are also advised that patients with active hepatitis B disease should not be treated with rituximab.

Rituximab (MabThera®) is a treatment for adults with non-Hodgkin's lymphoma; chronic lymphocytic leukaemia; rheumatoid arthritis; or granulomatosis with polyangiitis and microscopic polyangiitis.

A recent review of all available data has shown that rituximab has been associated with reactivation of hepatitis B virus when used in the indications of cancer and rheumatoid arthritis.

(See WHO Pharmaceuticals Newsletter No.5, 2013 for HBV recurrence in patients and updates on screening and management in Canada and No.6, 2013 for new boxed warning, recommendations to decrease risk of HBV reactivation in the USA)

Reference:
Drug Safety Update, December 2013, Volume 7, issue 5, A1 MHRA, (*www.mhra.gov.uk*).

Rosiglitazone

Removal of some prescribing and dispensing restrictions

USA. The US FDA determined that recent data for rosiglitazone-containing drugs (Avandia®, Avandamet®, Avandaryl® and generics) do not show an increased risk of heart attack compared to the standard type 2 diabetes

medicines metformin and sulfonylurea. As a result, the US FDA is requiring removal of the prescribing and dispensing restrictions for rosiglitazone medicines that were put in place in 2010. This decision is based on the US FDA review of data from a large, long-term clinical trial and is supported by a comprehensive, outside, expert re-evaluation of the data conducted by the Duke Clinical Research Institute (DCRI). Rosiglitazone is a treatment option that can improve blood sugar control in some patients with type 2 diabetes.

Previously, the US FDA required a Risk Evaluation and Mitigation Strategy (REMS), called the Rosiglitazone REMS program which restricted the use of rosiglitazone medicines to help ensure that their benefits outweighed the risks.

Now, in light of the new re-evaluation of the Rosiglitazone Evaluated for Cardiovascular Outcomes and Regulation of Glycemia in Diabetes (RECORD) trial, FDAs concern is substantially reduced and the rosiglitazone REMS program requirements will be modified. FDA is also requiring revisions to the rosiglitazone prescribing information and the patient Medication Guide to include this new information.

Health-care professionals, pharmacies, and patients will no longer be required to enroll in the rosiglitazone REMS program to be able to prescribe, dispense, or receive rosiglitazone medicines.

(See WHO Pharmaceuticals Newsletter No.6, 2011 for risk of cardiovascular events in the USA, No. 3, 2011 for new restrictions in the USA and reports in WHO global ICSR database in the USA and No. 2, 2011 for suspension of marketing authorizations in New Zealand, No. 6, 2010 for new restrictions due to the risk of cardiovascular events in Canada and No. 5, 2010 for suspension of marketing authorizations in Europe).

References:
FDA Drug Safety Communication, US FDA 25 November 2013 (*www.fda.gov*).

Sodium Phosphate Over-the-Counter Products

Possible harm from exceeding recommended dose

USA. The US FDA warned that using more than one dose in 24 hours of over-the-counter (OTC) sodium phosphate drugs (Fleet®, store brands and generics) to treat constipation can cause rare but serious harm to the kidneys and heart, and even death.

The US FDA has become aware of reports of severe dehydration and changes in the levels of serum electrolytes from taking more than the recommended dose of OTC sodium phosphate products, resulting in serious adverse effects on organs, such as the kidneys and heart, and in some cases resulting in death. These serum electrolytes include calcium, sodium, and phosphate. According to the reports, most cases of serious harm occurred with a single dose of sodium phosphate that was larger than recommended or with more than one dose in a day.

The US FDA recommended that consumers and health-care professionals should always read the Drug Facts label for OTC sodium phosphate drugs and use these products as recommended on the label, and not exceed the labeled dose. Caregivers should not give the oral products to children 5 years and younger without first discussing with a health care professional. Health care professionals should use caution when recommending an oral dose of these products for children 5 years and younger. The rectal form of these products should never be given to children younger than 2 years.

References:
FDA Drug Safety Communication, US FDA 8 January 2014 (*www.fda.gov*).

Strontium ranelate

Recommendation to suspend

Europe. The European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) recommended that strontium ranelate (Protelos® and Osseor®) should no longer be used to treat osteoporosis.

Strontium ranelate is authorised in the EU to treat severe osteoporosis in women who have been through menopause and who are at high risk of fracture in the spine and the hip. It is also used to treat severe osteoporosis in men who are at increased risk of fracture.

The PRAC noted that for every 1,000 patient-years there were 4 more cases of serious heart problems (including heart attacks) and 4 more cases of blood clots or blockages of blood vessels with Protelos/Osseor than with placebo (a dummy treatment). In addition, Protelos/Osseor is associated with a number of other risks, such as serious skin reactions, disturbances in consciousness, seizures (fits), liver inflammation and reduced number of blood cells.

With regard to its benefits, Protelos/Osseor has been shown to have a modest effect in osteoporosis, preventing about 5 non-spinal fractures, 15 new spinal fractures and 0.4 hip fractures for every 1,000 patient-years.

The PRAC weighed the benefits of the medicine against the known risks and concluded that the balance was no longer favourable and recommended strontium ranelate be suspended until there are new data showing a favourable balance in a defined patient group.

(See WHO Pharmaceuticals Newsletter No. 3, 2013 for risk of serious cardiac disorders in UK and No. 4, 2013 for recommendation to restrict the use and further review started in EU).

Reference:
Press release, EMA, 10 January 2013 (*www.ema.europa.eu*).

Temozolomide

Risk of hepatic injury, including fatal hepatic failure

UK. The MHRA announced that hepatic injury, including hepatic failure with fatal outcome, was reported in patients treated with temozolomide (Temodal® and generics).

The MHRA advised that baseline liver function tests (LFTs) should be done before starting temozolomide treatment. If these tests are abnormal, physicians should consider the balance of benefits and risks when deciding whether to start treatment. Patients on a 42-day treatment cycle should have LFTs repeated midway through this cycle. All patients should have LFTs checked after every treatment cycle. If a patient develops significantly abnormal LFTs, the benefits of continuing treatment should be carefully considered versus the risk of potentially severe liver injury. It is noted that liver toxicity may occur several weeks or more after initiation of treatment or after the last treatment with temozolomide

Temozolomide is an alkylating agent indicated for the treatment of newly diagnosed glioblastoma multiforme in adults in combination with radiotherapy, and for treatment of malignant glioma showing recurrence or progression after standard therapy in children and adults.

Reference:
Drug Safety Update, January 2013, Volume 7, issue 6, A3 MHRA, (*www.mhra.gov.uk*).

Lenalidomide

Risk of hepatotoxicity

Canada. Celgene Inc., in collaboration with Health Canada, informed health-care professionals that in multiple myeloma patients treated with lenalidomide (Revlimid®) in combination with dexamethasone, the following severe cases of liver injuries were reported: acute hepatic failure, toxic hepatitis, cytolytic hepatitis, cholestatic hepatitis, and mixed cytolytic/cholestatic hepatitis, and that some of these cases had a fatal outcome. The mechanism of severe drug-induced hepatotoxicity in lenalidomide exposed patients is unknown. Pre-existing viral liver disease, elevated baseline liver enzymes, and concomitant medications may be risk factors. It is advised that liver enzymes should be monitored periodically. Lenalidomide should be stopped if an elevation of liver enzymes is observed. After return to baseline values, treatment at a lower dose may be considered.

Lenalidomide is an antineoplastic and immunomodulatory agent indicated for the treatment of patients with transfusion-dependent anemia due to Low- or Intermediate-1-risk myelodysplastic syndromes (MDS) associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities (approval is based on red blood cell transfusion independence response rates). Lenalidomide is also indicated in combination with dexamethasone for the treatment of multiple myeloma (MM) in patients who have received at least one prior therapy.

(See WHO Pharmaceuticals Newsletter NO.2 2013 for risk of serious hepatic adverse drug reactions in the UK).

Reference:
Advisories, Warnings and Recalls, Health Canada, 27 December 2013 (*www.hc-sc.gc.ca*).

Zolpidem tartrate

New dosage recommendations to minimize risk of next-day impairment in both women and men

Canada. Meda Valeant Pharma Canada Inc., in consultation with Health Canada, informed health-care professionals of new dosage recommendations to minimize risk of next-day impairment in both women and men. The recommended initial dose of zolpidem tartrate (Sublinox™) was revised to 5 mg for women and either 5 or 10 mg for men, taken only once per night immediately before bedtime with at least 7-8 hours remaining before the planned time of awakening. The total dose of the drug should not exceed 10 mg once daily immediately before bedtime. The lowest effective dose for the patient should be used. In some patients, the higher morning blood levels following use of the 10 mg dose increase the risk of next day impairment of driving and other activities that require full alertness. The recommended initial doses for women and men are different because of lower rate of clearance and

higher blood levels of zolpidem in women compared to men.

Zolpidem tartrate is indicated for the short-term treatment and symptomatic relief of insomnia characterized by difficulty in falling asleep, frequent nocturnal awakenings and/or early morning awakenings.

Health-care professionals are also reminded that in geriatric patients (≥65 years of age) clearance rate of zolpidem is lower in both men and women when compared to young adults. The recommended dose of the drug in geriatric patients is 5 mg regardless of gender.

Additionally, health-care professionals should advise patients (men and women) who use zolpidem tartrate about the risk of next-day impairment for activities that require complete mental alertness, including driving. In particular, the following points should be mentioned:

- That this risk is increased if dosing instructions are not carefully followed;
- Not to drive a car or engage in hazardous activities requiring complete alertness until they know how the drug affects them the next day;
- Tell patients that if they took zolpidem tartrate as instructed and do not feel drowsy in the morning, they still have to wait for at least 8 hours after dosing before driving or engaging in other activities requiring full mental alertness;

(See WHO Pharmaceuticals Newsletter No. 1 and No.4, 2013 for lower recommended doses in the USA).

Reference:

Advisories, Warnings and Recalls, Health Canada, 3 January 2013 (*www.hc-sc.*

Clopidogrel

Risk of acquired haemophilia

UK. The MHRA announced that reports of acquired haemophilia were received in association with clopidogrel. This very rare but serious condition may be missed due to the established risk of bleeding associated with clopidogrel treatment.

Clopidogrel is a thienopyridine, inhibiting platelet activation and aggregation. It is indicated for prevention of:

- atherothrombotic events in patients with acute coronary syndrome, ischaemic stroke, or established peripheral arterial disease
- atherothrombotic and thromboembolic events in patients with atrial fibrillation and at least one other risk factor, who are unsuitable for treatment with vitamin K antagonists

Acquired haemophilia is a very rare condition that affects between one and four men or women per million people per year; it generally occurs in the elderly. About half of cases are idiopathic and half associated with illness (eg, rheumatoid arthritis, cancer). Occasionally, cases of acquired haemophilia may occur in association with drug treatment. Morbidity and mortality associated with acquired haemophilia are high. The condition tends to cause bleeding into the skin and soft tissues; by contrast with severe congenital haemophilia, bleeding into the joints is unusual.

A total of 11 cases of acquired haemophilia A and one case of acquired haemophilia B have been received worldwide by the licence (marketing authorisation) holder in association with clopidogrel, four of which were published case reports. This number of reports should be considered in the context of the very high use of clopidogrel (more than 153 million patients worldwide).

The case reports described patients aged between 65 years and 81 years, with no previous history of abnormal haemostasis. In six cases, it was reported that symptoms of acquired haemophilia resolved after stopping clopidogrel and corrective treatment (including steroids). Although no cases had a fatal outcome, two were considered life-threatening. Although these events are very rare, it is important to be aware of the possibility that a patient may develop acquired haemophilia, as distinct from the risk of bleeding associated with clopidogrel.

Health-care professionals are advised the following:

- Health-care professionals should be aware of the risk of acquired haemophilia in association with clopidogrel
- Prompt diagnosis is required to minimise the time the patient is at risk of bleeding and to avoid major bleeding
- Acquired haemophilia should be considered in the event of isolated prolonged activated partial thromboplastin time (aPTT)
- Patients with confirmed acquired haemophilia should be managed by specialists, and clopidogrel should be discontinued. Invasive procedures should be avoided

Reference:

Drug Safety Update, December 2013, Volume 7, issue 5, A2 MHRA, (*www.mhra.gov.uk*).

Minocycline

Possibility of benign intracranial hypertension

Australia. The TGA reminded health-care professionals to consider the possibility of benign intracranial hypertension in patients being treated with minocycline if signs and symptoms consistent with that diagnosis are identified. Health-care professionals should advise patients being treated with minocycline of the signs of benign intracranial hypertension and consider recommending that they read the Consumer Medicine Information.

Minocycline belongs to the tetracycline group of antibiotics and is used to treat acne that is resistant to other antibiotics, as well as various other infections.

While rare, benign intracranial hypertension, also known as pseudotumour cerebri, is a known adverse event associated with tetracyclines, and minocycline treatment in particular. Benign intracranial hypertension involves a persistent rise in cerebrospinal fluid pressure and is characterised by headache, nausea, vomiting and vision disturbances, including papilloedema with occasional sixth-nerve palsy.

To reduce the risk of benign intracranial hypertension, concomitant treatment with tetracyclines and vitamin A or retinoids, such as isotretinoin, is contraindicated.

Reference:

Medicines Safety Update Vol 4, No. 6, December 2013 (www.tga.gov.au).

Pioglitazone

Review found a favourable long-term risk-benefit balance

Australia. The TGA announced that a recently completed review of pioglitazone (Actos® and generics) found that the drug has a favourable long-term risk-benefit balance. However, TGA recommended

health professionals to weigh the known risks against the benefits of pioglitazone therapy and discuss these with patients. Pioglitazone is a thiazolidinedione (TZD) oral antidiabetic drug.

The TGA's review was prompted by the identification of an increased risk of bladder cancer with long-term use of pioglitazone. In light of ongoing safety concerns with rosiglitazone, another drug in the same class, the TGA conducted a full risk-benefit review of pioglitazone.

(See WHO Pharmaceuticals Newsletter No.6, 2011 for an increased risk of bladder cancer for Australia, No. 5, 2010 for ongoing safety review on potential increased risk of bladder cancer in the USA, No. 4, 2011 for the suspension in France and risk-characterization study in EU and reports in WHO global ICSR database and No.3, 2012 for potential association with bladder cancer in Canada).

Reference:
Medicines Safety Update Vol 4, No. 6, December 2013 (www.tga.gov.au).

Ponatinib

Risk of vascular occlusive events

UK. The MHRA announced that a review of the latest data was conducted after new information suggested that vascular occlusive events occur at a higher cumulative incidence than initially observed at the time of licensing.

The cumulative incidence of arterial and venous thrombotic events has increased with longer-term follow-up of patients in ongoing phase I and II clinical trials. Furthermore, preliminary data from a recently discontinued phase III comparison of ponatinib with imatinib have shown a higher number of vascular occlusive events in the ponatinib group. These events include: cardiovascular; cerebrovascular; and peripheral vascular adverse events, and venous thrombotic events.

These events occurred in patients with or without cardiovascular risk factors, including those age 50 years or younger. Vascular occlusive adverse events were more frequent with increasing age and in patients with a history of myocardial infarction, stroke, hypertension, diabetes, or hyperlipidaemia.

Ponatinib (Iclusig®) is a treatment for adults with chronic myeloid leukaemia or Philadelphia-chromosome-positive acute lymphoblastic leukaemia. The medicine's authorised use is restricted to patients who have limited alternative treatment options with tyrosine kinase inhibitors.

Health-care professionals are advised that

- Ponatinib should not be used in patients with a history of myocardial infarction or stroke, unless the potential benefit of treatment outweighs the potential risk.
- Cardiovascular status of patients should be assessed, and cardiovascular risk factors should be actively managed before starting treatment with ponatinib. Cardiovascular status should continue to be monitored and optimised during treatment.
- Hypertension should be medically controlled during ponatinib treatment, interruption of which should be considered if hypertension is not controlled
- Patients should be monitored for evidence of vascular occlusion or thromboembolism, and treatment should be interrupted immediately if this occurs

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

Reference:
Drug Safety Update, December 2013, Volume 7, issue 5, S1 MHRA, (www.mhra.gov.uk).

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

The signals in this Newsletter are based on information derived from Individual Case Safety Reports (ICSRs) available in the WHO Global ICSR database, VigiBase™. The database contains over 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 35).

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

Emtricitabine/Efavirenz/Tenofovir Disoproxil Fumarate and Phosphatase Alkaline Increased

Prof. Alfonso Carvajal, Spain

Summary

In the WHO Global Individual Case Safety Report (ICSR) Database, VigiBase™, there is currently (as of 5 May 2013) seven ICSRs of increased alkaline phosphatase (ALP) in association with the fixed-dose combination of emtricitabine, efavirenz and tenofovir disoproxil fumarate. There is one duplicate, which leaves a total of six ICSRs. The reports come from five different countries; Canada, Netherlands, United States, United Kingdom and Switzerland. The ICSRs were reported by a physician in five of the cases and by a pharmacist in one case. The association has an IC value of 1.58 with an IC_{025} value of 0.32.

Data from spontaneous reporting are sparse and incomplete, however, the fact that an increased ALP occurred after long treatment durations coincidental with this reaction's known latency — and along with other reactions such as hepatic injuries for which ALP is a well-known indicator, points to a causal relationship. In addition, in observational studies with different designs, a clear association between treatment with the fixed-dose combination of the three antiretroviral drugs emtricitabine, efavirenz and tenofovir disoproxil fumarate and an increased ALP has been found. Since the reaction is a useful indicator, the information on increased ALP should be included in the Summary of Product Characteristics for this medication.

Introduction

Alkaline phosphatase (ALP) is a group of enzymes responsible for removing the phosphate groups, dephosphorylation, from different types of molecules including nucleotides, proteins, and alkaloids. ALP is found in high concentrations in liver, bone, kidney, intestine, and placenta. In adults, circulating ALP is predominantly of hepatic and bone origin. The normal range for this group of enzymes is between 44 and 147 international units per litre (IU/L).[1] Reference intervals are age- and sex-related and include 95% of the population i.e. 2.5% of the normal population have a value above the upper reference limit. Minor increases in serum ALP levels are therefore more likely to be analytical, physiological, or statistical anomalies rather than an indication of disease. High ALP levels usually mean that either the liver has been damaged or that a condition causing increased bone cell activity is present. If other liver parameters such as bilirubin and transaminases are abnormal, high ALP-levels usually have a hepatic cause. Abnormal measurements of calcium and phosphorus indicate that the ALP-level has a bone origin. Evidence-based data is lacking in the differential diagnosis and outcome of an isolated increased serum ALP level, that is, a raised serum ALP level in the presence of normal serum levels of bilirubin, transaminases, and calcium.[2]

The fixed-dose combination contains three widely used antiretroviral drugs: efavirenz (600 mg), a

non-nucleoside reverse transcriptase inhibitor, and emtricitabine (200 mg) and tenofovir disoproxil fumarate (245 mg), two nucleoside reverse transcriptase inhibitors. All three active substances act by blocking the activity of reverse transcriptase, an enzyme produced by human immunodeficiency virus (HIV). The drug is indicated to delay damage to the immune system and thus the development of infections and diseases associated with the acquired immunodeficiency syndrome (AIDS). The drug does not cure HIV or AIDS. The most severe but rare reactions that have been associated with this combination are osteomalacia, a condition manifested as bone pain and infrequently contributing to fractures, hepatitis and renal failure. Hypophosphataemia (an electrolyte disturbance in the blood) may occur as a consequence of proximal renal tubulopathy.[3,4]

Reports in VigiBase

As of 5 May 2013, seven Individual Case Safety Reports (ICSRs) of increased ALP in association with the fixed-dose combination of emtricitabine, efavirenz and tenofovir disoproxil fumarate, marketed with the brandname Atripla in some countries, were identified in the WHO Global ICSR Database, VigiBase™ (Table 1). All reported patients did take Atripla as an antiretro-viral drug. There is one duplicate, case one and two (Table 1), which leaves a total of six cases. The gender distribution was three females and three males. The age range was from 38 to 55 years old. The indication was reported as HIV infection in five cases and not stated in one case report. Five cases were reported by a physician and one by a pharmacist. The ICSRs were submitted from Canada (two cases), United States, United Kingdom, Netherlands and Switzerland, one case each.

In all ICSRs the patients developed other severe reactions such as: hepatic injury (four patients) and renal injury (one patient). One died due to development of hepatic failure. In a male patient, the only reported reactions were hypophosphataemia, vitamin D deficiency and increased ALP after one year of treatment. In all cases the reaction appeared after two to 36 months of treatment, and in at least one case it reverted after the medication was stopped. The fixed-drug combination of emtricitabine, efavirenz and tenofovir disoproxil fumarate was the only suspected medication in all cases. The association had an IC value of 1.58 with an IC_{025} value of 0.32 meaning that the reaction occurs more frequently than statistically expected.

Literature and Labelling

Though clear statements about hepatic reactions and bone mineral density loss are made in the Summary of Product Characteristics (SPC) of the fixed-dose combination of emtricitabine, efavirenz and tenofovir disoproxil fumarate, there is no explicit mention of increased ALP.[5] Several epidemiological studies have found a relationship between the drug combination and this ADR. In a follow-up study comprising patients initiating (n=657), reinitiating (n=361) and discontinuing (n=73) combined antiretroviral therapy, tenofivir disoproxil fumarate was associated with a significant increase of ALP.[6] There was no correlation with glomerular filtration rates, changes in serum alanine aminotransferase or active hepatitis C. According to the authors, this suggests that the increase in ALP is due to the bone isoenzyme and indicates that stimulated bone turnover is due to loss of bone mineral density. Similarly, in an open-label study (n=385), all markers of bone density loss were significantly greater in the tenofovir disoproxil fumarate-emtricitabine treatment group than in the abacavir-lamivudine group at week 24. Finally, a cross-sectional study (n=1077) found that efavirenz and tenofovir were associated with ALP increased.[7,8]

Table 1. Case overview of reports in VigiBase™ of phosphatase alkaline increased in association with the fixed-dose combination of emtricitabine, efavirenz and tenofovir disoproxil fumarate

Case	Age/Sex	Other suspected (S) or concomitant (C) drugs	Other reactions (WHO-ART)	Outcome
1*	47/ F	Cefuroxime (C)	Hypovolaemia, Gamma-GT increased, prothrombin decreased, international normalised ratio increased, bilirubin increased, increased aspartate aminotransferase (AST), increased alanine aminotransferase (ALT), hepatic enzymes increased, urine discolouration, jaundice, fatigue, vomiting, nausea, GI haemorrhage, hepatic failure	Unknown
2*	47/ F	Cefuroxime (C)	Hypovolaemia, Gamma-GT increased, prothrombin decreased, international normalised ratio increased, bilirubin increased, AST increased, ALT increased, hepatic enzymes increased, urine discolouration, jaundice, fatigue, vomiting, nausea, GI haemorrhage, hepatic failure	Unknown
3	40/ M	Paracetamol (C)	Cholangitis, bilirubin increased, red blood cell abnormality, AST increased, ALT increased, hepatitis	Unknown
4	55/ F		Resistance metabolic, liver injury, hepatomegaly, hepatic steatosis, hepatic cirrhosis, aspartate aminotransferase increased, alanine aminotransferase increased	Unknown
5	-/ M		Hypophosphataemia, vitamin D deficiency	Unknown
6	38/ F	Terbutaline, colecalciferol (both C)	Renal function abnormal	Not recovered
7	51/M	-	Liver function tests abnormal nos, Gamma-glutamyltransferase increased, ALT increased, drug-alcohol interaction	Recovered

**Case 1 and 2, duplicate of each other*

Discussion and Conclusion

The reaction of interest, increased ALP, appeared in all ICSRs after a prolonged period of exposure to the fixed-drug combination of emtricitabine, efavirenz and tenofovir disoproxil fumarate. This is in agreement with what is known of this particular reaction's latency. In one case, the reaction reverted after cessation of the drug. Conversely, previous conditions such as kaposi sarcoma or other concomitant reactions including liver injury which appeared in these patients might somehow explain this particular reaction.

The association as estimated by the IC values is statistically significant, IC=1.58; IC_{025}=0.32, meaning that the association is occurring more frequently than statistically expected. On the other hand, increased ALP is not a proper condition but a non-specific indicator of different conditions, mainly liver injury or bone mineral loss. These conditions are known to occur in the course of long treatments with these medications and in fact they did occur in the cases assessed. There is clear evidence in the literature that this reaction is associated with this fixed-dose combination, in particular with tenofovir disoproxil fumarate.

Therefore, it is very likely that the fixed-dose combination of emtricitabine, efavirenz and tenofovir disoproxil fumarate has increased ALP levels in those patients after several months of treatment. Since the reaction is a useful indicator, information about ALP increased should be included in the SPC of this medication.

References

1. ALP - blood test. Medline Plus. URL: http://www.nlm.nih.gov/medlineplus/ency/article/003470.htm. Accessed 7 July 2013.

2. Shipman KE, Holt AD, Gama R. Interpreting an isolated raised serum alkaline phosphatase level in an asymptomatic patient. BMJ 2013;346:f976.

3. FDA approval of Atripla, 3-drug fixed dose combination antiretroviral. URL: http://www.fda.gov/ForConsumers/ByAudience/ForPatientAdvocates/HIVandAIDSActivities/ucm124444.htm. Accessed 7 July 2013.

4. European Medicines Agency Summary for the Public (Atripla). URL: http://www.ema.europa.eu/ema/index.jsp?curl=p

ages/medicines/human/medicines/000797/human_med_000657.jsp&murl=menus/medicines/medicines.jsp&mid=WC0b01ac058001d125. Accessed 7 July 2013.

5. European Medicines Agency Summary of Product Characteristics. URL: http://www.ema.europa.eu/ema/.Accessed 7 July 2013.

6. Fux C, Rauch A, Simcock M, Fux CA, Rauch A, Simcock M, Bucher HC, Hirschel B, Opravil M, et al. Tenofovir use is associated with an increase in serum alkaline phosphatase in the Swiss HIV Cohort Study. Antivir Ther 2008; 13(8):1077-82.

7. Stellbrink HJ, Orkin C, Arribas JR, Compston J, Gerstoft J, Van Wijngaerden E, et al. Comparison of changes in bone density and turnover with abacavir-lamivudine versus tenofovir-emtricitabine in HIV-infected adults: 48-week results from the ASSERT study. Clin Infect Dis. 2010 Oct; 51(8):963-72.

8. Welz T, Childs K, Ibrahim F, Poulton M, Taylor CB, Moniz CF, et al. Efavirenz is associated with severe vitamin D deficiency and increased alkaline phosphatase. AIDS 2010 Jul 31; 24(12):1923-8.

Response from Bristol-Myers Squibb & Gilead Sciences Limited for Atripla

On 16 August 2013 the World Health Organization (WHO) Uppsala Monitoring Centre (UMC) notified

the Marketing Authorization Holder (MAH) for Atripla (Bristol-Myers Squibb and Gilead Sciences Limited) of a potential safety signal for the product (increased alkaline phosphatase [ALP]) and invited the MAH to comment on the signal.

Gilead is the holder of the global safety database for Atripla and is responsible for the production of aggregate reports and ongoing pharmacovigilance and risk management activities, in collaboration with BMS and Merck (with whom Gilead have entered into an "Access Territory Distribution Agreement" for countries outside the European Economic Area (EEA), Canada and United States of America). Safety information received by the MAH is carefully evaluated on an ongoing basis for any new safety signals and prescribing information is updated as soon as new adverse reactions are identified.

The UMC identified 7 individual case safety reports (ICSRs) of increased ALP in association with Atripla in the WHO Global database, Vigibase. One of these cases was a duplicate. In 4 of the ICSRs identified by the UMC, the increased ALP was associated with elevations of other liver function tests, with severe hepatic events (hepatic failure, drug-induced hepatitis, cholangitis, and/or hepatic cirrhosis) reported in 3 of the 4 cases. Concurrent alcohol use (described as a drug-alcohol interaction) was reported in the fourth case. These concurrent events suggest that the elevations of ALP in these cases are hepatic in origin. In 1 ICSR the reported events of hypophosphataemia and vitamin D deficiency suggest that the elevated ALP may originate from the bone. Concurrent bone or hepatic events were not reported in the final ICSR (a report of abnormal renal function). However concurrent medications included cholecalciferol, suggesting the patient may have been deficient in vitamin D. Of note, 4 of these 6 cases were already on the Gilead safety database.

The literature articles referenced in the WHO report, involving elevated ALP in patients on Atripla therapy or efavirenz with a Truvada backbone, were reviewed closely. Each of the referenced articles discussed more specific etiologies and diagnoses for the subjects' elevated ALP levels. Fux *et al* correlated the elevation in ALP levels in the cohort study specifically to the bone isoenzyme. The authors concluded that the elevated ALP resulted from increased bone turnover secondary to hypophosphatemia and proximal renal tubulopathy.

Stellbrink *et al* similarly describes elevated serum ALP in setting of increased bone turnover and decreased bone mineral density. They noted that limitations in their study included a failure to monitor phosphate and vitamin D levels. Welz *et al* described elevated ALP associated with Vitamin D deficiency. In subjects with elevated ALP in the setting of normal AST levels, bone turnover was likely.

The Atripla EU SmPC already includes a detailed description of hepatic and bone effects and appropriate monitoring information and there has been extensive patient exposure to Atripla to date (over 1.4 million patient-years of treatment cumulative to 30 June 2013). In addition, given the small number of cases (n=14) of increased ALP reported in the Gilead Drug Safety database (which were either reported with concurrent bone [n=1] or hepatic events [n=5], or were poorly documented [n=8]), the specific etiologies and diagnoses for the subjects' elevated ALP levels in the literature articles referenced, as well as the limited utility of elevated ALP levels alone without other clinical data to make a specific diagnosis, the MAH does not consider an update to the EU SmPC is warranted.

Ibuprofen and Erectile Dysfunction

Prof. Alfonso Carvajal, Spain

Summary

In the WHO Global Individual Case Safety Report (ICSR) Database, VigiBase™ there are currently (7 June 2013) 37 ICSRs of erectile dysfunction in association with ibuprofen. The reports are from Australia, Canada, Denmark, Germany, Netherlands, Spain, United States and the United Kingdom. The association has an IC value of -2.12 with an IC_{025} value of -2.62. Ibuprofen was the only drug suspected in all but five cases. The outcome was stated in 22 of the 37 ICSRs.

The patients were reported as recovered in 15 cases, not recovered in seven cases and the outcome was unknown in 14 ICSRs. The drug had been stopped in 11 of the recovered cases, four of the not recovered cases and in one case in the group with an unknown outcome.

The association between ibuprofen and erectile dysfunction is assessed with data coming from spontaneous reporting. The data is sparse (37 ICSRs) and has a negative IC value, however, 11 patients recovered after stopping the drug and there is a case with positive re-challenge. There is some data from the literature, two observational studies that point to an association; in addition, data from preclinical experiments give a biologically plausible explanation. It is possible that erectile dysfunction is an underreported reaction. The association cannot be ruled out and the signal should be followed up.

Introduction

The drug-ADR combination of ibuprofen and erectile dysfunction was highlighted during testing of a new quantitative method for detecting potential signals at the UMC in 2012.[1]

Ibuprofen is an orally administered (2RS)-1[4-(2-methyl propyl) phenyl] propionic acid and the first member of the propionic acid derivatives group, introduced as early as in 1969. The drug belongs to the Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) family and acts as a non-selective inhibitor of cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2). Cyclooxygenases are involved in the synthesis of prostaglandins. Ibuprofen is normally used as an analgesic, anti-inflammatory and antipyretic agent. It is supplied in different formulations such as liquid, suppositories and tablets with a potency of 60 to 800 mg. The usual oral dose for adults is 400 to 800 mg three times a day.[2] The most common adverse reactions include gastrointestinal disorders such as peptic ulcers, intestinal perforation or gastrointestinal bleeding. Other adverse events reported less commonly include blood and lymphatic system disorders, for example leucopenia, thrombocytopenia, neutropenia and haemolytic anaemia.[3]

Erectile dysfunction is defined as the inability to achieve or maintain an erection adequate for sexual satisfaction.[4] The underlying reason may have multiple causes and can be classified as; psychogenic, neurologic, endocrinologic, vasculogenic or organic. This condition is a common problem in middle-aged and elderly men. According to the USA National Institutes of Health, approximately five percent of 40-year-old men and between 15 and 25% of 65-year-old men experience erectile dysfunction on a long-term basis.4 Erectile dysfunction may appear in conditions like depression, and in those affecting blood vessels (hypertension) or nerves (diabetes). It also may appear related to drugs such as antihypertensive agents, antidepressants, antipsychotics and statins.[5]

Reports in VigiBase

As of 7 June 2013 there are 37 Individual Case Safety Reports (ICSRs) of erectile dysfunction in association with ibuprofen in the WHO Global ICSR Database, VigiBase™ (Table 1). The association has an IC value of -2.12 with an IC025 value of -2.62 meaning that the combination occurs less frequently than statistically expected. The ICSRs were submitted from United Kingdom (13 cases), United States (12 cases), Australia (four cases), Germany (two cases), Denmark (two cases), Netherlands (two cases) and both Spain and Canada one case each. The patients ranged in age from 26 to 76 years. In nine of the 27 ICSRs with age reported, the patients were older than 60 years.

Ibuprofen was the only suspected drug in 32 cases. Concomitant drugs were reported in 12 cases. In eight of these cases, concomitant conditions including diabetes and neuropathy and/or concomitant substances including beta-blockers, tramadol, cimetidine and ethanol that could cause erectile dysfunction were reported. The indication for use was stated in eight ICSRs.

One of the cases describes a positive re-challenge. This 67-year-old, with no concomitant reported drugs and with a daily dose of 1200 mg for arthritis, experienced a decreased libido and erectile dysfunction. The reaction disappeared after the drug was not taken for three-four days and reoccurred when the drug was restarted.

Table 1. Case overview of ICSRs in VigiBase™ of erectile dysfunction in association with Ibuprofen

Case	Age/Sex	Other suspected (S) or concomitant (C) drugs	Reactions (MedDRA preferred terms)	Outcome
1	43/M	None	Erectile dysfunction	Not recovered
2	42/ M	None	Erectile dysfunction, libido decreased	Recovered
3	63/ M	Sodium aurothiomalate (C)	Erectile dysfunction	Recovered
4	52/ M	None	Dyspepsia, erectile dysfunction	Recovered
5	-/M	None	Erectile dysfunction	Unknown
6	63/ M	None	Confusional state, insomnia, hypertonia, erectile dysfunction	Unknown
7	-/M	None	Erectile dysfunction	Unknown
8	-/M	None	Erectile dysfunction	Unknown
9	-/M	Ethanol (C)	Erectile dysfunction	Unknown
10	65/ M	Levothyroxine (C)	Epididymitis, erectile dysfunction, hair texture abnormal	Recovered
11	52/ M	None	Erectile dysfunction	Recovered
12	76/M	Nifedipine (C)	Erectile dysfunction	Recovered
13	-/M	None	Erectile dysfunction	Recovered
14	70/M	Acetylsalicylic acid/codeine phosphate, cimetidine, acebutolol, sodium bicarbonate/aluminium hydroxide gel, dried/alginic acid/ magnesium trisilicate (all C)	Erectile dysfunction	Recovered
15	-/M	Cimetidine (C)	Erectile dysfunction, libido decreased	Unknown
16	39/ M	None	Erectile dysfunction	Not recovered
17	40/ M	None	Erectile dysfunction	Unknown
18	26/M	Paracetamol (S)	Erectile dysfunction	Unknown
19	44/M	None	Erectile dysfunction	Unknown
20	50/M	Dextropropoxyphene, levomepromazine, ranitidine, phenoxybenzamine (all C)	Constipation, erectile dysfunction	Unknown
21	63/ M	None	Erectile dysfunction	Not recovered
22	40/M	None	Erectile dysfunction	Recovered
23	44/M	None	Erectile dysfunction	Recovered
24	65/M	None	Erectile dysfunction	Recovered
25	55/M	None	Erectile dysfunction	Not recovered
26	58/M	None	Erectile dysfunction	Not recovered
27	-/M	None	Erectile dysfunction	Unknown
28	35/M	Piroxicam, lorazepam, tramadol, acexamate zinc (all S)	Erectile dysfunction	Recovered
29	72/ M	Amlodopine, famotidine (both S)	Erectile dysfunction	Unknown
30	61/M	None	Erectile dysfunction	Not recovered
31	47/M	None	Erectile dysfunction	Not recovered
32	33/M	None	Erectile dysfunction	Recovered
33	53/M	None	Erectile dysfunction, arrhythmia	Recovered
34	-/M	Antihypertensives, atorvastatin, pregabalin, sildenafil (all S), vitamins nos (C)	Visual acuity reduced, vision blurred, shoulder operation, pain in extremity, neuropathy peripheral, nasal congestion, myalgia, herpes zoster, feeling drunk, feeling abnormal, euphoric mood, erectile dysfunction, dyspnoea, drug tolerance, drug ineffective, diabetes mellitus, coordination abnormal, blood cholesterol increased, balance disorder	Unknown
35	67/ M	None	Erectile dysfunction, libido decreased	Recovered
36	-/M	Clonidine, hydrochlorothiazide, atenolol, potassium (all C)	Stress, somnolence, impaired work ability, impaired driving ability, erectile dysfunction, dizziness, disturbance in attention, diarrhoea, asthenia, abdominal pain upper	Unknown
37	-/M	None	Erectile dysfunction	Unknown

Time to onset was reported in 18 cases and ranged from one day to several months. The patients recovered in 15 ICSRs and the outcome was unknown in 14 cases. The drug was reported to have been stopped in 11 cases out of the 15 where the patients recovered.

Other reactions were described in 10 ICSRs, including libido decreased, which was described in three ICSRs.

Labelling and Literature

The product literature does not refer to this particular association. Two observational studies have found that regular NSAID use is associated with erectile dysfunction beyond what would be expected due to age and co-morbidity.[6,7]

Discussion

ICSRs in VigiBase and overall information coming from spontaneous reporting for this ADR are of poor quality. Only a small proportion of the total reports for ibuprofen refer to erectile dysfunction. The IC value for this association was -2.12 with an IC_{025} -2.62 meaning that the combination is occurring less frequently than statistically expected in the database; but this in no way means that there is no causal association. Confounders included age (some of the patients were older than 60 years), medical conditions which may lead to this ADR, concomitant drugs and alcohol. However, in one case, a 67-year-old man with no concomitant drugs reported had a positive de- and re-challenge.

Two observational studies have found an association between regular exposure to NSAIDs and erectile dysfunction compared to in what would be expected due to age, disease or co-morbidity. This risk was estimated to range between 1.4 and two times higher.

Ibuprofen, like other NSAIDs, has the ability to inhibit cyclooxygenase which in turn reduces the prostaglandin synthesis. Prostaglandins are hormone-like substances involved in different processes including penis erection. Some of these substances have been used to treat erectile dysfunction. In theory, the inhibition of prostaglandin synthesis could account for erectile dysfunction.

In preclinical rat studies, single-dose administration of indomethacin significantly reduced erectile responses to electrical stimulation at all frequencies tested in a dose-response method. Longer treatment with indomethacin completely abolished erectile responses at low frequencies and significantly reduced intracavernosal pressure at high frequencies, while diclofenac reduced erectile responses only at low frequencies.[8] On the other hand, continued use of ibuprofen increases blood pressure and raises the incidence of hypertension.[9] Hypertension in turn is a well-known risk factor for erectile dysfunction. All in all, it also has to be taken into account that erectile dysfunction could be an underreported reaction.

Conclusion

Although the information coming from spontaneous reporting is barely sufficient to support a possible signal, evidence from epidemiological studies point to a possible causal association between ibuprofen and erectile dysfunction; in addition, there is a biologically plausible explanation. There is the possibility that in certain patients and with certain dosages ibuprofen may be able to induce erectile dysfunction. The association cannot be ruled out and should be followed up.

References

1. Caster O, Norén GN, Madigan D, Bate A. Large-scale regression-based pattern discovery: the example of screening the WHO global drug safety database. Stat Anal Data Min. 2010;3(4):197-208.

2. Aslam N, Bushra R. An overview of clinical pharmacology of ibuprofen. Oman Medical Journal 2010, Volume 25, Issue 3, July 2010.

3. Electronic Medicines Compendium UK, Summary Product Characteristics for Brufen. URL: http://www.medicines.org.uk/emc/medicine/10849/SPC/Brufen+400+mg+Tablets/#UNDESIRABLE_EFFECTS. Accessed 11 June, 2013.

4. Brown University, health education. URL: http://brown.edu/Student_Services/Health_Services/Health_Education/mens_health/erectile_dysfunction.php. Accessed 11 June, 2013.

5. Korenman SG. Epidemiology of erectile dysfunction. Endocrine 2004;23:87-91.

6. Shiri R, Koskimäki J, Häkkinen J, Tammela TL, Auvinen A, Hakama M. Effect of nonsteroidal anti-inflammatory drug use on the incidence of erectile dysfunction. J Urol. 2006;175:1812-5.

7. Gleason JM, Slezak JM, Jung H, Reynolds K, Van den Eeden SK, Haque R, et al. Regular nonsteroidal anti-inflammatory drug use and erectile dysfunction. J Urol. 2011;185:1388-93.

8. Senbel AM. Functional inhibition of erectile process in rats by indomethacin. World J Urol. 2011;29:523-7.

9. Morrison A, Ramey DR, van Adelsberg J, Watson DJ. Systematic review of trials of the effect of continued use of oral non-selective NSAIDs on blood pressure and

hypertension. Curr Med Res Opin. 2007;23:2395-404.

Parathyroid Hormone and Myocardial Ischaemia

Dr. Ian Boyd, Australia

Summary

Parathyroid hormone (PTH) is the most important endocrine regulator of calcium and phosphorus concentration in extracellular fluid. This hormone is secreted from cells of the parathyroid glands and finds its major target cells in bone and kidney. Physiological actions of PTH include stimulation of bone formation by direct effects on bone forming cells (osteoblasts). This indirectly increases the intestinal absorption of calcium and the tubular reabsorption of calcium and excretion of phosphate by the kidney. The hormone is indicated for the treatment of osteoporosis in postmenopausal women at high risk of fractures.

In the WHO Global Individual Case Safety Report (ICSR) Database, VigiBase™ there are currently (2 July 2013) four ICSRs of angina pectoris, five ICSRs of myocardial infarction and one ICSR of myocardial ischaemia in association with PTH. The reports are from Germany, Denmark, Ireland, Mexico and Spain. The association with angina has an IC value of 1.95 with an IC_{025} value of 0.25; The IC value is negative for myocardial infarction and myocardial ischaemia. PTH was the only drug suspected in all 10 cases. The outcome was stated in six ICSRs. The patients were reported as recovered in four cases and the outcome was fatal in two cases.

Case reports in VigiBase suggest that there is a signal for the association of parathyroid hormone and reactions suggesting myocardial ischaemia including angina pectoris and myocardial infarction. There were only a small number of concomitant drugs reported and few other reactions were reported in addition to the cardiac reactions. Time to onset is not particularly suggestive of a signal but if the mechanism of the effect is related to serum levels of PTH, then the long time to onset may be explained by the time required for PTH levels to reach a particular level. Dechallenge is suggestive of a signal and in three cases recovery was reported after withdrawal of the drug.

The product information does not mention myocardial ischaemia, angina pectoris or myocardial infarction but it is known that there are PTH receptors in the heart and it has been reported that there may be a role for PTH in the development of Coronary Heart Disease so a mechanism for the development of myocardial ischaemia is possible.

Introduction

Parathyroid hormone (PTH) is the most important endocrine regulator of calcium and phosphorus concentration in extracellular fluid. This hormone is secreted from cells of the parathyroid glands and finds its major target cells in bone and kidney.[1] Physiological actions of PTH include stimulation of bone formation by direct effects on bone forming cells (osteoblasts) indirectly increasing the intestinal absorption of calcium and the tubular reabsorption of calcium and excretion of phosphate by the kidney. The therapeutic product is recombinant human PTH which is identical to the full-length native 84-amino acid polypeptide. It is indicated for the treatment of osteoporosis in postmenopausal women at high risk of fractures. A significant reduction in the incidence of vertebral, but not hip fractures has been demonstrated.[2]

Very common adverse effects reported in clinical trials included hypercalcaemia and/or hypercalciuria which reflect the known pharmacodynamic actions of PTH in the gastrointestinal tract, the kidney, and the bone. The only other very commonly reported ADR was nausea. Also reported commonly in clinical trials were nervous system disorders such as headache and dizziness, gastrointestinal disorders such as vomiting, diarrhoea, constipation and dyspepsia, musculoskeletal and connective tissue disorders such as muscle cramp, pain in extremity, and back pain, general disorders such as injection site erythema, fatigue and asthenia, and cardiac disorders such as palpitation.[2]

Myocardial ischaemia is an inadequate coronary blood supply resulting in oxygen deprivation of the myocardium.3 Angina pectoris is a symptom of myocardial ischaemia. It is characterized by attacks of precordial retrosternal pain or tightness, sometimes radiating into the back and often into the neck and the left shoulder and arm, and often precipitated by effort or excitement. It is frequently experienced in myocardial ischaemia, occurring when myocardial oxygen demand exceeds supply. It can be precipitated by increased oxygen demand (exercise) as well as by reduced supply (coronary vasoconstriction). It is associated with disturbed myocardial function.[3]

Angina symptoms can be caused or aggravated by drugs, including vasodilating agents, which in the presence of coronary artery obstruction may lead to more marked dilatation of healthy vessels and thereby reduce blood flow in the diseased areas, thus leading to a so-called 'steal phenomenon'.

Sometimes for the differential diagnosis, chest pain of non-cardiac origin must be excluded. Myocardial infarction is myocardial necrosis resulting from inadequate blood supply. It represents in most cases the most severe stage of ischaemic heart disease resulting from coronary atherosclerosis. It may, however, also occur as a consequence of embolization or severe spasm of a coronary artery.[3]

Reports in VigiBase

As of 2 July 2013 there are four Individual Case Safety Reports (ICSRs) of angina pectoris, five ICSRs of myocardial infarction and one ICSR of myocardial ischaemia in association with PTH in the WHO Global ICSR Database, VigiBase™ (Table 1). The association with angina pectoris has an IC value of 1.95 with an IC025 value of 0.25. The IC value is negative for myocardial infarction and myocardial ischaemia. The reports were submitted from Germany (five cases), Ireland (two), Denmark, Mexico and Spain (one case each). The patients ranged in age from 66 to 81 years with a median of 75 years in the seven cases which provided the information and all 10 patients were female, as expected from the indication of the drug.

PTH was the only drug suspected in all 10 cases. Concomitant drugs were reported in four of the 10 cases and included calcium/calciferol combinations in three cases. PTH was reported to have been administered subcutaneously in all seven cases which provided this information. The indication for use was stated in eight reports and was, as expected, for treatment of osteoporosis. Time to onset was reported in eight of the reports and ranged from 10 days to one year (median five months).

The outcome was stated in six reports. Four of these patients were reported as recovered and the outcome was fatal in the other two reports. In the four cases with recovery, PTH was withdrawn in three cases and continued in the other case. In the two fatal cases, the drug was withdrawn in one case and the fate of the drug was unknown in the other case. The drug was withdrawn in two of the cases where the outcome was unknown, continued in one of the cases where the outcome was unknown and in the fourth case, both the outcome and the fate of the drug were unknown.

There were few other reactions reported. In two cases where myocardial infarction was reported, hypercalcaemia was also reported. In one of these cases, diarrhoea and heart disorder were also reported.

Literature and Labelling

The product literature does not refer to angina pectoris, myocardial ischaemia or myocardial infarction. The only cardiac disorder that was reported in clinical trials was palpitations, noticeable changes in the heartbeat. There are also no reports in the literature which link angina, myocardial ischaemia or myocardial infarction with PTH. It has been noted that PTH raises the plasma calcium level by causing release of calcium from the bones, increases the absorption of calcium from the small intestine, and reduces the renal excretion of calcium. In addition to these classical PTH target organs, it appears that PTH may have effects on other tissues as well. Accordingly, PTH receptors have been demonstrated in the heart, and in vitro, PTH induces hypertrophy of cardiomyocytes.[4]

It has also been found that a rise in serum levels of PTH was common and related to the severity of disease and mortality in a mixed emergency department population which consisted of a broad spectrum of 140 acutely ill patients suffering from common diseases such as stroke, acute abdominal disorders, obstructive lung diseases, heart failure, acute myocardial infarction, angina pectoris, trauma and infectious diseases.[5] It is also known that primary hyperparathyroidism (PHPT) is associated with hypertension, coronary atherosclerosis and other cardiovascular diseases. In a population-based cross-sectional study, the Tromso Study involving 27159 subjects aged 25-79 years, when stratified for age, the rate of coronary heart disease (CHD) was found to be higher in the subjects with serum PTH > 6.8 picomole/liter (pmol/L) than in those with normal or low serum PTH levels. The authors concluded that serum PTH predicts CHD in subjects with calcium levels within the reference range.[6] This may indicate a role for PTH in the development of CHD.

Discussion and Conclusion

Case reports in VigiBase suggest that there is a possible signal for the association of parathyroid hormone and angina pectoris, myocardial ischaemia or myocardial infarction. PTH was the only drug suspected in all 10 cases. There were only a small number of concomitant drugs reported and few other reactions were reported.

Time to onset is not particularly suggestive of a signal in that, apart from three cases in which the onset was four days, 11 days and 10 weeks, onset was many months with a median time to onset of five months which seems long for a drug-induced effect.

If, however, the mechanism of the effect is related to serum levels of PTH, then the long time to onset may be explained by the time required for PTH levels to reach a particular level.

Dechallenge is suggestive of a signal. There were four cases with recovery and in three of those cases, the drug was withdrawn. In the other case with recovery, the drug was continued. In the two

cases where the outcome was fatal, the drug was withdrawn in one case and the fate of the drug was unknown in the other. For an acute event such as myocardial infarction, however, recovery after drug withdrawal is not as meaningful as it is for an ongoing reaction such as angina.

The product information does not mention myocardial ischaemia but it is known that there are PTH receptors in the heart and it has been reported that there may be a role for PTH in the development of CHD so a mechanism for the development of myocardial ischaemia is possible. There may, of course be other explanations for the reactions reported in this case series. Most of the patients were elderly. In some of the cases, there are possible alternative explanations such as chronic obstructive pulmonary disease in Case 5, stress in Case 6 and a history of transient ischaemic attacks, ischaemic cardiomyopathy and pulmonary fibrosis in Case 9. All cases, however, had PTH as the only suspected drug and the cases in VigiBase suggest that the association of myocardial infarction with PTH should be further reviewed.

References

1. Bowen RA, Austgen L, Rouge M. Pathophysiology of the endocrine system: parathyroid hormone. URL: http://www.vivo.colostate.edu/hbooks/pathphys/endocrine/thyroid/pth.html?. Accessed: 8 July 2013.

2. European Medicines Agency Summary of Product Characteristics for Parathyroid hormone (Preotact) URL: http://www.ema.europa.eu/ema. Accessed: 8 July 2013.

3. The Council for International Organizations of Medical Sciences (CIOMS). Reporting Adverse Drug Reactions: Definitions of Terms and Criteria for their Use. CIOMS, Geneva, 1999. URL: http://www.cioms.ch/publications/reporting_adverse_drug.pdf. Accessed: 8 July 2013.

4. Saleh FN, Schirmer H, Sundsfjord J, Jorde R. Parathyroid hormone and left ventricular hypertrophy. Eur Heart J. 2003 Nov;24(22):2054-60.

5. Carlstedt F, Lind L, Wide L, Lindahl B, Hanni A, Rastad J, et.al. Serum levels of parathyroid hormone are related to the mortality and severity of illness in patients in the emergency department. Eur J Clin Invest. 1997 Dec;27(12):977-81.

6. Kamycheva E, Sundsfjord J, Jorde R. Serum parathyroid hormone levels predict coronary heart disease: the Troms0 Study. Eur J Prevent Cardiol. 2004;11:69-74.

Response from Takeda Pharma

Background Information

The Signal team at the Uppsala Monitoring Centre (the UMC) has identified that case reports in VigiBase™ suggest that there is a possible signal for the association of parathyroid hormone and angina pectoris, myocardial ischaemia or myocardial infarction.

Namely, as of 02 July 2013 there are four Individual Case Safety Reports (ICSRs) of angina pectoris, five ICSRs of myocardial infarction and one ICSR of myocardial ischaemia in statistical association with PTH in VigiBase. The association with angina pectoris has an IC value of 1.95 with an IC025 value of 0.25. However, the IC value is negative for myocardial infarction and myocardial ischaemia, indicating no relationship between the administration of PTH and such cardiac ischemic related events in this database.

The indication for use of Preotact® (rhPTH[1-84]) is osteoporosis in postmenopausal woman at high risk of fractures. Thus, the population of concern is female, mainly elderly patients. Presented here is a summary of clinical trial data, post-marketing surveillance reporting, and epidemiological evidence not showing any evidence of this potential signal and supporting the cardiovascular safety of Preotact in patients with osteoporosis.

Osteoporosis Clinical Trial Data

In the recombinant human parathyroid hormone (rhPTH[1-84]) summary of clinical safety, pooled data from the Phase 2 and 3 placebocontrolled studies in subjects with osteoporosis were presented.

Most of the subjects (n = 2530 of the 3121) in the pooled analysis came from Study ALX1-11-93001 (TOP), which was 18 months in duration. Study CL1-11-008 (CAP) contributed 374 subjects and was of 6 months duration and the Phase 2 dose ranging study (ALX1-11-821) contributed 217 subjects and was of 12 months duration. Given that the studies in this analysis were randomized, prospective, placebo-controlled and of relatively long duration (up to 18 months), it represents the best information to date regarding any potential effect of rhPTH(1-84) on cardiovascular safety in patients with osteoporosis. All doses in placebocontrolled studies were 100 ug daily except for the Phase 2 dose-ranging trial where doses of 50, 75, and 100 ug were administered.

Table 1 Incidence of Cardiac Disorder Treatment-emergent Serious Adverse Events – Placebo Controlled Studies in Osteoporosis

System Organ Class Preferred Term	Placebo Controlled Studies in Osteoporosis	
	Placebo (N = 1425)	rhPTH(1-84) (N = 1696)
	n (%)	n (%)
Any TESAE	95 (6.7)	90 (5.3)
Cardiac disorders	15 (1.1)	11 (0.6)
Angina pectoris	4 (0.3)	2 (0.1)
Atrial fibrillation	5 (0.4)	0
Myocardial infarction	1 (0.1)	1 (0.1)
Coronary artery disease	3 (0.2)	2 (0.1)
Supraventricular tachycardia	1 (0.1)	2 (0.1)
Atrioventricular block second degree	0	1 (0.1)
Ventricular extrasystoles	0	1 (0.1)
Angina unstable	2 (0.1)	0
Atrioventricular block complete	0	1 (0.1)
Cardiac arrest	0	1 (0.1)
Cardiac failure congestive	1 (0.1)	0
Coronary artery occlusion	0	1 (0.1)
Tachycardia	1 (0.1)	0
Bradycardia	1 (0.1)	0

N = total number of subjects in the treatment group; n = number of subjects in category noted;

TESAE = treatment-emergent serious adverse event

A summary of the incidence of on-treatment, treatment-emergent serious adverse events (TESAEs) of cardiac disorders by treatment group for the placebo-controlled dataset is presented in Table 1 below Overall, the frequency of subjects with any TESAE was slightly lower in the rhPTH(184) group. The incidence of cardiac ischaemic-related TESAEs of angina pectoris, unstable angina, myocardial infarction, coronary artery disease and coronary artery occlusion in the rhPTH(1-84)-treated subjects was comparable to or lower than that in placebo subjects.

Table 2 shows the incidence of cardiac ischaemic-related on-treatment, treatment-emergent adverse events (TEAEs) (serious and non-serious) in the placebo-controlled dataset in osteoporosis. Again, the incidence of such cardiac ischemic adverse events in rhPTH(1-84)-treated subjects was comparable to or lower than that for placebo subjects.

Table 2 Incidence of Selected Cardiac Disorder Treatment-emergent Adverse Events - Placebo Controlled Studies in Osteoporosis

System Organ Class Preferred Term	*Placebo* (N=1425) n (%)	*rhPTH(1-84)* (N=1696) n (%)
Cardiac disorders	102 (7.2)	128 (7.5)
Angina Pectoris	27 (1.9)	30 (1.8)
Coronary artery disease	6 (0.4)	4 (0.2)
Myocardial ischaemia	3 (0.2)	4 (0.2)
Myocardial infarction	3 (0.2)	1 (0.1)
Angina unstable	2 (0.1)	1 (0.1)
Coronary artery occlusion	0	2 (0.1)
N = total number of subjects in the treatment group; n = number of subjects in category noted		

Post-marketing Data

As of 24 April 2013, rhPTH(1-84) (Preotact®) has

been marketed in 15 countries for the treatment of osteoporosis at a labeled dose of 100 ug/day. Based on the number of units of Preotact sold, the patient exposure is estimated to be approximately 61,091 patient years of treatment. As reported in the Periodic Safety Update Reports (PSURs), the reported serious cardiovascular-related cases (Table 1) were not unexpected considering the advanced age and prevalence of cardiovascular disease in the patient population treated with Preotact. Moreover, as reported most of the subjects had prior history or risk factors for the adverse event in question or were taking concomitant medications which could cause or contribute to the event.

Epidemiological Studies in Cardiovascular Disease Incidence

A comparison with the expected incidence of coronary ischaemic events in the EU and US does not show an increase in the number of observed cases of angina pectoris, myocardial ischemia, or myocardial infarction in the VigiBase.

Summary and Discussion

Based on a thorough medical evaluation of the available data, including a pooled analysis of randomized, prospective placebo-controlled trials, there is currently no evidence for a direct causal relationship between angina pectoris, myocardial infarction, myocardial ischaemia nor any cardiac adverse event and PTH(1-84) treatment in patients with osteoporosis.

Two of the three cardiac ischemic events noted in the VigiBase for Preotact, myocardial ischemia and myocardial infarction, had negative IC values indicating no association.

Epidemiologic data indicate that the number of cardiac ischemic related events noted in VigiBase for Preotact are within or lower than expected based on published cardiac event rates.

Given the aforementioned lines of evidence, no signal for cardiac ischemic-related adverse effects of Preotact in osteoporosis patients can be discerned at the present time. Accordingly, no changes to the reference safety information for Preotact is at present considered necessary.

Roflumilast and Pancreatitis

Signal from Uppsala Monitoring Centre

Summary

In the WHO Global Individual Case Safety Report (ICSR) Database, VigiBase™, there are nine ICSRs of pancreatitis in association with roflumilast. There was one suspected duplicate which leaves a total number of eight ICSRs. In all eight cases, roflumilast was the only suspected drug and in the five cases where an outcome was reported the patient had recovered or was recovering. Acute pancreatitis is labelled in the US FDA drug safety information, based on clinical trial data but not mentioned in the EMA SPC. Drug induced pancreatitis is rare: 1.4% of the cases of pancreatitis have been considered drug related, and it might be difficult to diagnose due to predisposing factors such as alcohol consumption and biliary disorder, comorbidities or unknown risk factors, but the eight cases in this assessment strengthen the signal.

Introduction

Roflumilast is a phosphodiesterase type-4 inhibitor used in the treatment of inflammatory conditions of the lungs. It was approved in the European Union (EU) in June 2010 for severe chronic obstructive pulmonary disease (COPD) associated with chronic bronchitis as an add-on to bronchodilator therapy and in the United States (US) in March 2011 for reducing COPD exacerbations. The recommended daily dose is 500 microgram (mcg) daily taken orally.[1]

Pancreatitis, inflammation of the pancreas, is usually caused by gallstones or alcohol abuse, but may also be caused by drugs such as corticosteroids, diuretics, ACE inhibitors, tetracyclines, sulphonamides and statins. The incidence of drug induced pancreatitis has been estimated as 1.2-1.4%.[2,3] Other risk factors include trauma, mumps or measles, autoimmune disease, old age, smoking and obesity. The inflammation can affect surrounding organs such as the bowel, spleen, lungs and stomach and lead to multiorgan failure. The condition can either be acute with a sudden onset or chronic with symptoms ranging over a spectrum of mild to severe. Severe cases can be life threatening and require intensive care.[4,5] The potential mechanisms of drug induced pancreatitis include pancreatic duct constriction, cytotoxic and metabolic effects, and hypersensitivity reactions.[6]

Reports in VigiBase

As of July 2013 there were nine Individual Case Safety

Reports (ICSRs) in the WHO Global ICSR Database, VigiBase™ relating to roflumilast and pancreatitis with an IC of 1.03 and IC025 of -0.06. An overview of the ICSRs is presented in Table 1. There was one suspected duplicate which leaves eight reports from four countries; United States of America (four cases), Spain (two cases), Germany and United Kingdom (one case each). The ICSRs concern four women and four men and where age was provided (on six ICSRs) it ranged from 58 to 92 years with a median of 75 years.

COPD was the given indication on six ICSRs and on two ICSRs the indication was not stated. Only two ICSRs had a clearly reported dosage which was given as 500 mcg daily in both cases. Roflumilast was the only suspected drug on all the ICSRs and where time to onset was reported (in four cases) it ranged from 10 days to two months. In two other cases it was not specified when the reaction occurred but the patients only took the drug for one and five days respectively before it was discontinued.

Although one might expect polypharmacy for these patients, other drugs were only reported in four cases. Co-reported drugs of interest included amlodipine, azithromycin, dexlansoprazole, furosemide, lisinopril, methylprednisolone, prednisolone, theophyllin and simvastatin, all of which may cause pancreatitis, but were only listed as concomitant by the reporter. No therapy dates were given for any of these drugs. Two patients were on medicinal treatment for diabetes mellitus. Only one of the reports gives any information on recreational habits: recent alcohol consumption is denied in this case without further information.

In five cases, roflumilast was withdrawn and the patient recovered/was recovering at the time of reporting. There was one positive rechallenge in a case where the drug was reintroduced but again withdrawn after one day as the patient experienced abdominal pain. One report had a fatal outcome, but the cause of death was not stated.

Table 1. Case overview of ICSRs in VigiBase™ of roflumilast and pancreatitis

Case	Age/Sex	Other suspected (S) or concomitant (C) drugs	Outcome of the pancreatitis
1	- /M	-	Unknown
2	- /F	-	Unknown
3*	58/F	-	Unknown
4*	58/F	-	Unknown
5**	92/M	Cetirizine, budesonide, formoterol, tiotropium bromide, insulin, phenytoin, fluticasone propionate/salmeterol xinafoate, amlodipine, simvastatin, docusate, theophylline, tamsulosin, dexlansoprazole, montelukast, salbutamol (all C)	Unknown
6	82/M	Allopurinol, acetylsalicylic acid, lisinopril, sotalol (all C)	Recovering
7	87/F	Simvastatin, omeprazole, methylprednisolone, metformin, ipratropium, gliclazide, furosemide, fluticasone propionate/ salmeterol xinafoate, azithromycin and amlodipine (all C)	Recovered
8***	61/M	-	Recovered
9	69/F	Ipratropium, furosemide, diazepam, citalopram, carbocisteine, calcium carbonate, azithromycin, formoterol, theophylline, cyclizine, salbutamol, beclometasone, prednisolone, omeprazole and mirtazapine (all C)	Recovering

** Suspected duplicates of each other*

*** Patient died*

**** After restarting the drug, the patient again suffered from abdominalpain and recovered when the drug was withdrawn.*

Literature and Labelling

Acute pancreatitis is labelled in the US FDA Product Label for roflumilast and refers to clinical trial data from eight clinical studies; four one-year placebo controlled trials, two six-months placebo controlled trials and two six-months drug add-on trials. 8630 COPD patients were enrolled; 1232 patients received a dosage of 500 mcg daily for one year and 3136 patients were given the same dosage for six months. 4192 patients received placebo. The most common adverse effects were nausea, diarrhoea, weight loss and headache.[7] A letter in The Lancet, comparing FDA's review of the clinical trial data for roflumilast with the publications from the same clinical trials, highlights that severe adverse events reported in the clinical trial data were not mentioned in the publications, among them acute pancreatitis.8,9 There is no mention of pancreatitis in the EMA Summary of Product Characteristics (SPC).[10]

Discussion and Conclusion

Several of the eight cases presented in this assessment have reported confounders that may have caused or contributed to the pancreatitis, and the general lack of data on the ICSRs also makes the assessment difficult. Patients suffering from COPD often take a combination of medicines in order to reduce and relieve their symptoms but other drugs were only reported in half of the cases. There were no treatment dates for any of the co-reported drugs, but none of them were suspected by the reporter to have caused the reaction. Only one of the reports gives any information on recreational habits: recent alcohol consumption is denied in this case without further information. Time to onset varied from days up to approximately two months and there may be a possibility that introduction of this drug could have caused the pancreatitis regardless of any previous confounders.

Five out of eight patients recovered/were recovering when the drug was withdrawn and there was one positive rechallenge. Cases of acute pancreatitis were also seen during clinical trials and can be found in the US FDA Product Label.

Drug induced pancreatitis is rare, however despite possible confounders and unreported predisposing factors the cases presented in this assessment together with the results from the clinical trials support a possible causal association between roflumilast and pancreatitis. This reaction should be investigated further for inclusion in the product information in all countries.

References

1. New Drugs Online Report for roflumilast. URL: http://www.ukmi.nhs.uk/applications/ndo/record_view_open. asp?newDrugID=3320. Accessed: 28 July 2013.

2. Sekimoto M, Takada T, Kawarada Y, Hirata K, Mayumi T, Yoshida M, et al. JPN guidelines for the management of acute pancreatitis: epidemiology, etiology, natural history, and outcome predictors in acute pancreatitis. J Hepatobiliary Pancreat Surg. 2006;13(1):10-24.

3. Lankisch PG, Droge M, Gottesleben F. Drug induced acute pancreatitis: incidence and severity. Gut. 1995;37(4):565-67.

4. Taber's online. URL: http://www.tabers.com/tabersonline/view/Tabers-Dictionary/744381/all/pancreatitis?q=pancreatitis. Accessed: July 2013.

5. NHS choices, Acute pancreatitis. http://www.nhs.uk/ Conditions/Pancreatitis. Accessed: July 2013.

6. Underwood TW, Frye CB. Drug-induced pancreatitis. Clin Pharm. 1993;12(6):440-48.

7. US FDA Label for roflumilast (Daliresp) URL:http://www.accessdata.fda.gov/drugsatfda_docs/ label/2011/022522s000lbl.pdf. Accessed: 28 July 2013.

8. Gupta S. Side-effects of roflumilast. The Lancet, 2012;379(9817):710-11. URL: http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(12)60304-3/fulltext. Accessed: 28 July 2013.

9. Center for drug evaluation and research, medical reviews. URL:http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/022522Orig1s000MedR.pdf. Accessed: 28 July 2013.

10. European Medicines Agency: Roflumilast Summary of Product Characteristics (SPC). URL: http://www.ema. europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/002398/WC500103078. pdf. Accessed 28 July 2013.

Response from Takeda and Forest Laboratories

The reported annual incidence of acute pancreatitis ranges from 4.9 to 35 per 100,000 population.[1] Drugs are a rare cause of acute pancreatitis, with an estimated incidence of 0.1-2% of all cases.[2] Alcohol consumption and gallstones are the most common causes of acute pancreatitis in many parts of the world[3], though multiple other causes exist, many of which are found amongst the profile of severe COPD patients, for whom roflumilast is indicated, including obesity, hyperlipidemia, old age, the use of steroids, gastrointestinal, cardiovascular, and anti-diabetic medications, and smoking, which has been shown to be an independent risk factor for pancreatitis.[4-10] Additionally, 10% to 25% of cases of acute pancreatitis are idiopathic.[11]

Roflumilast, a selective phophodiesterase type 4 inhibitor, was first approved in 2010 and is now marketed in more than 50 countries worldwide, with an estimated patient exposure of 365,000 patient-years since first launch.

Non-clinical toxicity studies in rodent and non-rodent species failed to demonstrate pancreatic effects after administration of roflumilast, although in the 4-week rat toxicity study with direct administration of roflumilast N-oxide (RNO) at the highest dose of 3.6 mg/kg/day, inflammatory changes were seen in abdominal organs, including the pancreas. These effects occurred at a free drug exposure ratio of RNO (active principle) more than 20x above human exposure at 500 ug

In the extensive clinical development program (during which more than 24,000 subjects were enrolled in 114 clinical studies, of whom more than 14,000 were exposed to roflumilast at a variety of dose levels), a total of 17 pancreatitis cases (including AEs of "pancreatitis", "pancreatitis acute", and "pancreatitis chronic") were reported. These 17 cases demonstrated a balanced distribution between treatment arms (9 in roflumilast-treated and 8 in non-roflumilast-treated patients). Alternative reasons for pancreatitis in roflumilast-treated patients were provided in most cases (e.g. dietary causes, pre-existing conditions, concomitant medications with known potential to cause pancreatitis). In some cases, the temporal association was not suggestive of a causal relationship with roflumilast. All cases of pancreatitis with roflumilast treatment were considered unrelated or unlikely related to study medication by the sponsor and the investigators with one exception, a case of exacerbation of pre-existing chronic pancreatitis was assessed as likely related by the investigator, however assessed as unlikely related by the sponsor.

Takeda and Forest Laboratories concluded that there was no causal association with roflumilast and that no signal of pancreatitis had been identified. Per the clinical assessment report to the European Medicines Agency (EMA) for Day 150 during the centralized EU marketing authorization procedure in 2010, the Assessor concluded: "The analysis of reports of pancreatitis is reassuring in that there is no excess in the active treatment arms. There is no need for a change to the SPC."

For Periodic Safety Update Report (PSUR) #4 (reporting period 6-Jan-2012 to 05-Jul-2012), the Pharmacovigilance Risk Assessment Committee (PRAC) of the EMA requested a cumulative review of all spontaneously reported pancreatitis cases occurring with roflumilast treatment (10 cases). Based on this cumulative review, Takeda and Forest Laboratories concluded that the data did not provide evidence for a causal association with roflumilast. The PRAC agreed with this conclusion and the decision to close this signal, with the recommendation that Takeda should monitor cases of pancreatitis on an ongoing basis. Since PSUR #4, 4 additional cases of pancreatitis have been received, all of which have been evaluated and have not changed the current safety profile of roflumilast.

A search of the roflumilast global safety database identified in total 14 spontaneous post-marketing cases of pancreatitis, including the 8 cases identified from the Uppsala Monitoring Centre (UMC). Takeda and Forest Laboratories have closely tracked all reports of pancreatitis and reviewed each case individually and cumulatively. The majority of cases reporting pancreatitis presented with confounding factors that could potentially account for the event, including co-morbid conditions (e.g., smoking, obesity, old age, hyperlipidemia), the use of concomitant medications known to cause drug-induced pancreatitis (e.g., amlodipine, azithromycin, dexlansoprazole, furosemide, lisinopril, methyl-prednisolone, prednisolone, theophyllin, simvastatin) and an implausible time to onset. Often cases lacked sufficient information to allow for a substantive medical assessment.

In addition, statistical signal detection efforts conducted by Forest using the Empirica Signal tool, with data from VigiBase™ and AERS, did not identify a statistical signal (EB05>2) for "pancreatitis" nor any of the preferred terms that comprise the acute pancreatitis SMQ [narrow]. The Bayesian Confidence Propagation Neural Network used by the UMC detected an IC of 1.03 and an IC_{025} (the lower limit of a 95% credibility interval for the IC) of -0.06. If the lower limit of the IC value is negative, the likelihood of a positive quantitative association between the drug and the adverse reaction is low. It should furthermore be noted that the IC scores obtained were based on 9 cases of pancreatitis, 1 of which was suspected to be a duplicate case.

Conclusion

The available evidence does not suggest a causal relationship between the occurrence of pancreatitis and the use of roflumilast. Post-marketing cases of pancreatitis (14 cases out of 365,000 patient years) were either confounded by known risk factors, implausible latencies or were missing sufficient information for a substantive medical assessment. Furthermore, statistical signal detection efforts have failed to identify a statistical signal for pancreatitis. Finally, evidence from pre-clinical and controlled clinical studies does not support an association.

Based on this investigation, and in agreement with the EMA's assessment of pancreatitis following PSUR#4, the core safety profile of roflumilast is deemed unchanged and the current EMA SPC is considered appropriate. No safety variation will be initiated to establish "pancreatitis" as a globally labeled Adverse Drug Reaction at this time.

Takeda and Forest Laboratories are committed to the close monitoring of pancreatitis through their pharmacovigilance processes on an ongoing basis.

References

1. Vege SS, Yadav D, Chari ST. Pancreatitis. In: GI Epidemiology, 1st ed, Talley NJ, Locke GR, Saito YA (Eds), Blackwell Publishing, Malden, MA 2007.

2. Balani AR, Grendell JH. Drug-induced pancreatitis: incidence, management and prevention. Drug Safety

2008, 3(10):823-837.

3. Guo-Jun W, Chun-Fang G, Dong W, Cun W, Si-Qin D. Acute pancreatitis: Etiology and common pathogenesis. World J Gastroenterol. 2009 March 28; 15(12): 1427¬1430.

4. Fortson MR, Freedman SN, Webster PD 3rd. Clinical assessment of hyperlipidemic pancreatitis. Am J Gastroenterol. 1995;90(12):2134.

5. Noel RA, Braun DK, Patterson RE, Bloomgren GL. Increased Risk of Acute Pancreatitis and Biliary Disease Observed in Patients With Type 2 Diabetes A retrospective cohort study. Diabetes Care 2009 vol. 32 no.5 834-838.

6. Badalov N, Baradarian R, Iswara K, Li J, Steinberg W Tenner S. Drug-induced acute pancreatitis: an evidence-based review. Clin Gastroenterol Hepatol. 2007;5(6):648.

7. Lindkvist B, Appelros S, Manjer J, Berglund G, Borgstrom A. A prospective cohort study of smoking in acute pancreatitis. Pancreatology. 2008;8(1):63.

8. Tolstrup JS, Kristiansen L, Becker U, Gronbaek M. Smoking and risk of acute and chronic pancreatitis among women and men: a population-based cohort study. Arch Intern Med. 2009;169(6):603.

9. Yadav D, Hawes RH, Brand RE, Anderson MA, Money ME, Banks PA, Bishop MD, Baillie J, Sherman

S, DiSario J, Burton FR, Gardner TB, Amann ST, Gelrud A, Lawrence C, Elinoff B, Greer JB, O'Connell M, Barmada MM, Slivka A, Whitcomb DC, North American Pancreatic Study Group. Alcohol consumption, cigarette smoking, and the risk of recurrent acute and chronic pancreatitis. Arch Intern Med. 2009;169(11):1035.

10. Sadr-Azodi O, Andrén-SandbergÂ, Orsini N, Wolk A. Cigarette smoking, smoking cessation and acute pancreatitis: a prospective population-based study. Gut. 2012 Feb;61(2):262-7. Epub 2011 Aug 11.

11. Banks PA. Epidemiology, natural history, and predictors of disease outcome in acute and chronic pancreatitis. Gastrointest Endosc. 2002 Dec;56(6 Suppl):S226-30.

Vemurafenib and Granulocytopenia

Dr. Geraldine Hill, UMC and Dr. Ron Meyboom, The Netherlands

Summary

Routine screening of the WHO Global Individual Case Safety Report (ICSR) Database, VigiBase™, identified granulocytopenia as a potential signal associated with vemurafenib. The related terms leucopenia and agranulocytosis were also examined.

As of 29 March 2013, 35 ICSRs of granulocytopenia and/or the related terms leucopenia and agranulocytosis in connection with vemurafenib treatment had been reported to VigiBase. The IC values (IC_{025}) for these combinations were: 1.02 (0.30) for granulocytopenia, 0.72 (-0.05) for leucopenia and 0.50 (-0.76) for agranulocytosis.

In 29 cases, vemurafenib was the only suspected drug and in 14 cases the patient was reported as recovered or recovering after ceasing the medication. The time to onset, where provided, is consistent across most of the cases (occurring during the second to fifth week of treatment) suggesting a common mechanism. Vemurafenib target a mutated B-Raf protein in one of the intracellular mitogen activated protein kinase pathways which is present in over half of all melanomas. This same MAPK pathway is also involved in haematopoiesis, and it is possible that vemurafenib may interfere with haematopoietic cell differentiation in susceptible patients. The case reports in VigiBase support a signal of granulocytopenia associated with vemurafenib.

Introduction

Vemurafenib is a first-in-class serine-threonine protein kinase inhibitor, which inhibits the kinase activity of mutated B-Raf protein. The Ras-Raf-MEK-ERK mitogen activated protein kinase (MAPK) cascade is an important cytoplasmic signalling pathway involved in the regulation of normal somatic cell proliferation. Mutations in the genes encoding components of this pathway have been associated with a number of human cancers.[1] An activating mutation in the BRAF gene, which encodes the serine-threonine protein kinase B-Raf, has been found to be present in 40-60 percent of melanomas, most commonly the BRAF V600E mutation.[2]

Vemurafenib received FDA approval in August 2011 for use in the treatment of metastatic or unresectable melanomas that carry the BRAF V600E mutation; vemurafenib is available as 240 mg oral tablets; the recommended dose is 960 mg twice daily.[3]

Granulocytopenia is defined as a reduced number of blood granulocytes, which include neutrophils, basophils and eosinophils, but the term is often used synonymously with *neutropenia*, in which only the neutrophil count is reduced. A normal absolute neutrophil count (ANC) is 2.0 — $7.0x10^9$/L. Neutropenia is graded from 1 to 4, according to the level of the ANC: grade 1 neutropenia has an ANC >1.5 — $<2.0x10^9$/L; grade 4 neutropenia implies an ANC $<0.5x10^9$/L and at this life-threatening level the term *agranulocytosis* is also used. The risk of serious bacterial or fungal infection increases with the degree and duration of neutropenia. Neutropenia blunts the inflammatory response to infection and patients with neutropenia may present with fever as the only sign of infection; such patients are said to have *febrile neutropenia*, which should be treated as a medical emergency.[4]

There are many possible causes of acquired neutropenia but they generally fall into three categories: infection, drug induced or immune-mediated. Some drug-induced neutropenias may in fact be immune-mediated (e.g cephalosporins, penicillins, sulfonamides and phenothiazines), while others have direct toxic effects on haematopoietic progenitor cells (e.g. chloramphenicol).[5] Agranulocytosis is attributable to drugs in more than 70 percent of cases, most commonly antithyroid drugs, clozapine, ticlopidine, sulfasalazine, dipyrone, trimethoprim/ sulfamethoxazole, carbamazepine and rituximab.[6]

Reports in VigiBase

Routine screening of the WHO Global Individual Case Safety Report (ICSR) Database, VigiBase™, identified granulocytopenia as a potential signal associated with vemurafenib. The related terms leucopenia and agranulocytosis were also examined. The IC values (IC025) for these combinations were 1.02 (0.30) for granulocytopenia, 0.72 (-0.05) for leucopenia and 0.50 (-0.76) for agranulocytosis.

After excluding two probable duplicates, a total of 33 ICSRs (as of 29 March 2013) containing the terms granulocytopenia (19), leucopenia (15) and agranulocytosis (6), in which vemurafenib was indicated as the suspected drug, were reviewed. Additional information was requested from the national pharmacovigilance centres for selected cases.

Twenty-four ICSRs contained the terms granulocytopenia and/or agranulocytosis. An additional nine ICSRs contained only the term leucopenia and, because the term leucopenia could be used in the context of lymphopenia, we looked

for further evidence suggestive of granulocytopenia in these cases. Three ICSRs co-reported infection (urinary tract infection, pneumonia and infection not further specified) and one case reported an extremely low white cell count, such that granulocytopenia was implied; the white cell count was not provided for the remaining five ICSRs. In three of the nine cases, leucopenia was associated with thrombocytopenia.

All of the ICSRs containing the WHO-ART term granulocytopenia had originally been reported as neutropenia (18) or neutrophil count abnormal (1). For the six ICSRs containing the WHO-ART term agranulocytosis, the original reported terms included: febrile neutropenia (4), netropenic sepsis (1) and agranulocytosis (1).

The ICSRs came from five countries: United States (22), United Kingdom (6), Austria (3), Switzerland (1) and Germany (1). Seven of the cases from the United States were found to have occurred in other countries and were recorded as 'foreign source': the country was identified in four of these reports (Australia, France, Israel and Poland), bringing the total number of countries identified to nine. At least 12 of the reports originated from clinical trials. Age was reported in 14 ICSRs and ranged from 27 to 81 years; there were more females (19) than males (14).

The dose was reported for 20 cases: the total daily dose ranged from 960 mg to 7680 mg. Two-thirds of the ICSRs reported a dose of 960 mg twice daily. Time to onset was available for 16 ICSRs and ranged from 9 to 84 days; onset occurred during the second to fifth week after treatment initiation in over 75 percent of the reports. Positive dechallenge could be identified in 14 ICSRs; re-exposure at a lower dose occurred in three cases but the outcome was not reported.

Vemurafenib was the only reported medicine in 19 of the ICSRs and was the only suspected drug in a further 10 ICSRs. In four ICSRs other suspected drugs were reported, including fotemustine[7], clobazam, levetiracetam, fluconazole[8] and metamizole[9], all of which are known to be associated with leucopenia, neutropenia and/or agranulocytosis. Nine of the ICSRs in which vemurafenib was the only suspected drug included at least one concomitant medicine that has been associated with leucopenia, neutropenia and/or agranulocytosis (according to the UK SPC[10]). Dates of administration for the concomitant medicines were provided in only four of these cases; three of the cases included concomitant medicines with start dates that suggested the drug could also be implicated in the granulocytopenia.

Literature and Labelling

Haematopoietic side-effects have not been reported with vemurafenib in either the US FDA product label or the UK SPC.[3,11] Neutropenia was not reported in phase 1 or 2 clinical trials of vemurafenib, but two cases of neutropenia were observed among 336 patients in the vemurafenib arm of the phase 3 clinical trial of vemurafenib vs. dacarbazine.[12,14]

Discussion

Vemurafenib is not known to be haematotoxic. VigiBase contains 33 ICSRs with the term granulocytopenia (which includes the term neutropenia) or the related terms leucopenia or agranulocytosis (severe granulocytopenia) in association with vemurafenib. Vemurafenib was the only suspected drug in 29 cases. Dates were often missing for concomitant medications, nine cases involved the use of concomitant drugs that have been associated either rarely or very rarely with leucopenia, neutropenia and/or agranulocytosis.

Sudden profound granulocytopenia, as was noted in several of the reported cases, is suggestive of a drug reaction. Pharmacokinetic information for vemurafenib indicates that steady-state concentration is achieved in 15-22 days.[3] The relatively consistent time to onset, from the second to fifth week in the majority of cases in which this information was reported, suggests that a common mechanism may be involved and that it appears to occur as blood concentrations approach steady-state. Additionally, 14 ICSRs reported a positive dechallenge; in three of these cases, vemurafenib was reintroduced at a lower dose with no subsequent report of granulocytopenia, suggesting that such a mechanism may be dose-dependent.

Vemurafenib acts in the Ras-Raf-MEK-ERK MAPK pathway; this same pathway is involved in haematopoiesis, where it plays an important role in regulating myeloid, erythroid and megakaryocyte differentiation.[15,16] It is therefore plausible that vemurafenib may have an effect on haematopoiesis. Neutropenia has been reported with other protein kinase inhibitors. The product label for sorafenib, a multi-kinase inhibitor with potent activity against B-Raf, lists neutropenia as a common adverse effect but the drug also inhibits other kinases that are known to be involved in haematopoiesis.[17,18] Vemurafenib is a potent and selective inhibitor of mutated B-Raf but it has also been shown to activate wild-type B-Raf (which is thought to account for the relatively common development of squamous cell carcinomas in patients treated with vemurafenib) and other intracellular signalling kinases.[19,20,21] It is possible that vemurafenib may inhibit kinases that are involved in haematopoiesis resulting in granulocytopenia.

Conclusion

The reports in VigiBase support a causal relationship between vemurafenib and granulocytopenia. Evidence for a signal includes: the relatively consistent time to onset, the high proportion of cases with a positive dechallenge and the consistency of reports from several countries. In addition, the hypothesized mechanism of action strengthens the signal and this possible association merits further investigation.

References

1. Davies H, Bignell GR, Cox C, Stephens P, Edkins S, Clegg S, et al. Mutations of the BRAF gene in human cancer. Nature 2002;417(6892):949-54.

2. Roberts PJ, Der CJ. Targeting the Raf-MEK-ERK mitogen-activated protein kinase cascade for the treatment of cancer. Oncogene 2007;26(22):3291-310.

3. US Food and Drug Administration. Zelboraf Label (July 2013). URL: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/202429s002s003lbl.pdf. Accessed 29 July 2013.

4. Crawford J, Dale DC, Lyman GH. Chemotherapy-induced neutropenia: risks, consequences, and new directions for its management. Cancer 2004;100(2):228-37.

5. Godwin JE. Neutropenia. Medscape Reference. URL:http://emedicine.medscape.com/article/204821-overview. Accessed 2 August 2013.

6. Andersohn F, Konzen C, Garbe E. Systematic review: agranulocytosis induced by nonchemotherapy drugs. Annals of internal medicine 2007;146(9):657-65.

7. Medsafe New Zealand. Muphoran label. URL: http://www.medsafe.govt.nz/profs/datasheet/m/Muphoraninj. pdf. Accessed 30 August 2013.

8. US Food and Drug Administration. URL: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed 28 August 2013.

9. SwissMedic. Product Information Metamizole. URL: http://wwwswissmedicinfo.ch/. Accessed 30 August 2013.

10. Electronic Medicines Compendium UK. URL: http:// www.medicines.org.uk/emc/. Accessed 10 July 2013.

11. Electronic Medicines Compendium UK. Zelboraf 240 mg film-coated tablets. URL: http://www.medicines.org.uk/emc/medicine/26056/SPC/Zelboraf+240+mg+Film-coated+Tablets/ Accessed 29 July 2013.

12. Chapman PB, Hauschild A, Robert C, Haanen JB, Ascierto P, Larkin J, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. The New England journal of medicine 2011;364(26):2507-16.

13. Flaherty KT, Puzanov I, Kim KB, Ribas A, McArthur GA, Sosman JA, et al. Inhibition of mutated, activated BRAF in metastatic melanoma. The New England journal of medicine 2010;363(9):809-19.

14. Sosman JA, Kim KB, Schuchter L, Gonzalez R, Pavlick AC, Weber JS, et al. Survival in BRAF V600-mutant advanced melanoma treated with vemurafenib. The New England journal of medicine 2012;366(8):707-14.

15. Chung E, Kondo M. Role of Ras/Raf/MEK/ERK signaling in physiological hematopoiesis and leukemia development. Immunologic research 2011;49(1-3):248-68.

16. Geest CR, Coffer PJ. MAPK signaling pathways in the regulation of hematopoiesis. Journal of Leukocyte Biology 2009;86(2):237-50.

17. Toffalini F, Demoulin JB. New insights into the mechanisms of hematopoietic cell transformation by activated receptor tyrosine kinases. Blood 2010;116(14):2429-37.

18. US Food and Drug Administration. Nexavar Label (June 2013). URL: http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021923s014lbl.pdf. Accessed 14 August 2013.

19. Su F, Viros A, Milagre C, Trunzer K, Bollag G, Spleiss O, et al. RAS mutations in cutaneous squamous-cell carcinomas in patients treated with BRAF inhibitors. The New England journal of medicine 2012;366(3):207-15.

20. Poulikakos PI, Zhang C, Bollag G, Shokat KM, Rosen N. RAF inhibitors transactivate RAF dimers and ERK signalling in cells with wild-type BRAF. Nature 2010;464(7287):427-30.

21. Bollag G, Hirth P, Tsai J, Zhang J, Ibrahim PN, Cho H, et al. Clinical efficacy of a RAF inhibitor needs broad target blockade in BRAF-mutant melanoma. Nature 2010;467(7315):596-9.

Response from Roche

Roche would like to thank the WHO for the opportunity to review and comment on the "Vemurafenib and Granulocytopenia" draft document. Roche, through its routine signal detection activities, has recently identified neutropenia as a potential signal and it is currently being assessed. A comprehensive review of the safety data on this adverse event is being done.

In the WHO report, based on the verbatim terms reported in the 33 ICSRs in the WHO VigiBase, it appears that the event of concern is neutropenia rather than the WHO-ART coded terms of granulocytopenia and/or agranulocytosis; no cases of low basophil or eosinophil count have been reported. Further, it would appear based on these spontaneous reports that only insufficient data is available for most of these 33 cases, preventing us from reaching a definitive conclusion regarding causality with vemurafenib. It should be noted that the reporters' designation of drug-suspect versus attribution to concomitant medication is not always clearly defined. It has been recognized that newly marketed pharmaceutical products are often reported spontaneously as being suspect for an adverse event even in the presence of obvious confounding factors including co-medications. A related issue is that the concomitant medications may not be initially reported in a spontaneous report of a newly marketed product and may become known only after follow-up queries requesting additional information have been received. Thus, based on what is presented in the WHO report there still remain a number of open questions on possible confounders in many of these cases. Thus, this possible signal needs further medical evaluation of each of the individual cases.

Furthermore, it is Roche's opinion based on the data presented in the WHO report that at this time there are a few challenges in establishing a causal relationship between Zelboraf and the safety signal under discussion:

- There does not appear to be

convincing evidence to support a consistent time to onset for most of the 33 cases

- We do not have sufficient information regarding the overall severity and patient outcomes for this laboratory adverse event
- Insufficient data is available at this time regarding cases with a true "positive dechallenge"
- The proposed MOA is hypothetical

In determining causality, each of these cases needs to be thoroughly reviewed and assessed individually as well as in aggregate. Therefore, Roche suggests that the conclusion of the WHO report should indicate the limitations in the data presented, as proposed in the following sentence: "*This signal is still uncertain and preliminary in nature at this time but currently under further investigation by the manufacturer; the assessment may change over time one way or another as more information becomes available*"

As Roche's assessment has not yet been completed on this laboratory abnormality of neutropenia, Roche cannot further comment on this potential signal for the moment, but following completion of our assessment, we will communicate and formally share our findings with you, the regulatory authorities, and other appropriate recipients.

The UMC Measures of Disproportionate Reporting
A brief guide to their interpretation

The Information Component (IC)

The Information Component (IC), originally introduced through the BCPNN (Bayesian Confidence Propagation Neural Network), is a measure of the disproportionally between the observed and the expected reporting of a drug-ADR pair. A positive IC value indicates that a particular drug-ADR pair is reported more often than expected, based on all the reports in the database. Similarly, a negative IC value means that the drug-ADR pair is reported less frequently than expected. The higher the value of the IC, the more the combination stands out from the background. The IC value is solely calculated from:

- the total number of reports in the database (N_{tot})
- the total number of reports on the ADR term (N_{adr})
- the number of reports on the drug (N_{drug}), and
- the total number of reports on the specific drug- ADR pair (N_{comb}).

New reports may cause the IC to either increase or decrease. When the IC is calculated from large numbers, a new report is less likely to cause a major fluctuation in the IC value. The IC_{025} value is the lower limit of a 95% credibility interval for the IC. The credibility interval provides information about the stability of a particular IC value: the narrower the interval, the higher the stability. The IC does not imply causality of a potential adverse reaction caused by a drug. The IC shows the quantitative dependency between the ADR and the drug, based on the reporting to the WHO Global ICSR database. If the IC value increases over time and the IC025 value is positive, this is suggestive of a connection between the drug and the adverse reaction. However as alternative explanations for the positive IC need to be considered, clinical assessment remains essential in the identification of a signal.

Omega (Ω)

Omega (Ω) is, just as the IC, a measure of disproportionate reporting, however not for a drug-ADR pair but for a drug-drug-ADR triplet. The purpose of Ω is to detect potential signals of drug-drug interactions. For Ω, the expected reporting on a drug-drug-ADR triplet is based on a model where both drugs add to the baseline risk of the ADR, independently of each other. A positive Ω indicates that the two drugs, when used together, increase the risk of the ADR more than the sum of the risks attributable to each drug separately.

Ω is calculated based on the following information:

- the relative reporting rate of the ADR for reports listing neither of the drugs (f_{00})
- the relative reporting rate of the ADR for reports listing drug 1 but not drug 2 (f_{10})
- the relative reporting rate of the ADR for reports listing drug 2 but not drug 1 (f_{01}), and
- the relative reporting rate of the ADR for reports listing both drugs (f_{11}).

As the IC, Ω may fluctuate over time as new reports enter the database. Also like the IC, each Ω comes with a 95% credibility interval, whose lower limit is denoted Ω_{025}. Ω does not imply causality of a potential drug-drug interaction. It is a quantitative measure of the deviation in reporting on the drug-drug-ADR triplet relative to a baseline model where the drugs are assumed to independently add to the baseline risk of the ADR. If Ω increases over time and Ω_{025} is positive, this is suggestive of a drug-drug interaction, based on the reporting to the WHO Global ICSR database. However, as alternative explanations for the positive Ω need to be considered, clinical assessment of the case series is essential in the identification of an interaction signal.

References:

Bate A, Lindquist M, Edwards IR, Olsson S, Orre R, Lansner A, De Freitas RM. A Bayesian neural network method for adverse drug reaction signal generation. *European Journal of Clinical Pharmacology* 1998; 54:315-321.

Norén GN, Hopstadius J and Bate A. Shrinkage observed-to-expected ratios for robust and transparent large-scale pattern discovery. *Statistical Methods in Medical Research* 2011; 22(1) 57–69.

Norén GN, Sundberg R, Bate A, Edwards IR. A statistical methodology for drug-drug interaction surveillance. *Statistics in Medicine* 2008; DOI: 10.1002/sim.3247.

WHO Collaborating Centre
for International Drug Monitoring
Box 1051, SE-751 40 Uppsala, Sweden

Tel: +46-18-65 60 60 Fax:
+46-18-65 60 88 E-mail:
info@who-umc.org

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.

2011

Recommendations from the Thirty-sixth Annual Meeting of National Pharmacovigilance Centres

The Annual meeting of Representatives of National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring was held in Rome, Italy, 26-28 September 2013. At the meeting eight working groups discussed various issues in pharmacovigilance (PV). A summary of these discussions is provided.

1. Ensure government commitment to Pharmacovigilance (PV)

All countries agreed that there needs to be more support from the government to PV. The importance of support to, and recognition for PV from the highest relevant authority was discussed. The barriers to gain support were identified and the strategies to overcome such barriers were considered. The following recommendations were made:

National PV centres to:

1. Initiate policies, fundraising dialogue and advocate
2. Develop good qualitative and quantitative metrics
3. Involve patients to educate and promote PV (via media, parliament or other means)
4. Build networks of interested parties
5. Develop media and public communication strategies

WHO Collaborating Centres to:

1. Adopt a proactive approach
2. Provide a better assistance by sharing, updating, adapting and translating technical documents

WHO to:

1. Provide comprehensive and relevant recommendations
2. Liaise with governments and collaborate with partner programmes (HIV, TB, Vaccines)
3. Promote PV as an essential part of public health programmes

It was suggested that studies which measure the performance of PV be published to demonstrate the successes in and economic impact of preventing adverse drug reactions (ADRs).

2. National Pharmacovigilance Centre (NPVC) experiences with different systems for ICSR data management

The number of reports submitted is rapidly increasing in all countries; these reports are often related to patient reporting and an increased number of PV activities. Objectives of this working group were to: discuss and review the different systems countries are using for managing data from individual case safety reports (ICSRs); to review NPVCs' experience with WHO ICSR data management system *VigiFlow;* and to discuss funding for the development of such a system. The following recommendations and conclusions were made.

1. Systems should be adapted to the country's PV specificities (report numbers, report types, available resources, internet and software capability, centralised vs decentralised PV systems)
2. Electronic reporting should be encouraged as it is needed to reduce work of NCs
3. The choice of the software is related to the number of reports
4. WHO should make a revision of the 1996 booklet '*Safety Monitoring of Medicinal Products: how to set up a pharmacovigilance centre'*.

3. PV of herbal medicines

The objectives were to review *the 2008 Herbal Working Group Recommendations* and to discuss key issues on the PV of herbal medicines (regulation, legislative loopholes, guidelines for safety monitoring, constraints with reporting herbal ADRs and training courses). The following recommendations were made.

National Pharmacovigilance Centres (NPVCs) to:

1. Collect data about herbal medicine practice
2. Organize training for herbal medicines practitioners and providers
3. Collect reports of ADRs with herbal medicines and send them to the Uppsala Monitoring Centre (UMC)

WHO Collaborating Centres to:

1. Communicate to NPVCs to engage in and develop PV of herbal medicines
2. Provide training and financial support for PV of herbal medicines
3. Assist WHO in developing and promoting this area of work

WHO to:

1. Promote and build capacity in NPVCs
2. Provide a platform for the exchange of experiences
3. Create an international committee of experts
4. Provide grants for local initiatives
5. Develop recommendations for data collection

It was suggested that PV of herbal medicines be increased by inviting people with most impact to the NPVC meetings, and to also increase collaboration with herbal practices. Additional considerations are to establish regional centres for herbal medicines which can liaise with NPVCs; encourage practitioners to report; and ensure all new herbal medications are entered in the WHO Herbals Dictionary.

4. Promote safety monitoring of medicines in children

Despite all the general agreement on the subject, monitoring of medicines in children remains inadequate worldwide. The working group reviewed the methodologies and ongoing efforts on safety monitoring of medicines in children. The following recommendations were made.

Member states and NPVCs to:

1. Enable and stimulate reporting of ADRs in children
2. Enable and promote reporting of off-label use and information sharing by protecting reporters' identity
3. Collect and use data from poison control centres and drug information centres
4. Provide more information to prescribers and patients on ADR monitoring in children

WHO Collaborating Centres and WHO to:

1. Provide PV training for paediatricians and family doctors
2. Gather and share information on off-label use with NPVCs
3. Collect and provide information on outcome with off-label drug use for policy decisions.

5. PV Centres to support the work of product quality surveillance systems

The objectives were to understand, define and evaluate the national strategies and role of NPVCs in detecting poor quality products. The following recommendations were made.

NPVCs to:

1. Proactively investigate and manage quality-related adverse events
2. Cooperate with Regulatory authorities to avoid duplication of efforts
3. Accept reports on quality defects even if no ADR has occurred
4. Maintain traceability of product batches in ADR reporting systems
5. Adopt relevant tools and technology for the detection of quality related ADRs on site
6. Refer to global ADR resources (*VigiBase, Vigimed*) when investigating local cases

Healthcare Professionals to:

1. Report the absence of therapeutic efficacy
2. Report absence of expected ADRs since this may also indicate lack of active pharmaceutical ingredient in the product
3. Report suspected quality defects and contribute to the prevention of ADRs
4. Learn how to respond to and collaborate in the investigation of reports of quality-related ADRs.

WHO to:

1. Collate and share the related experiences from countries in this area of work
2. Draft a guideline on how to deal with reports related to quality defects at NPVCs.

Recommendations for the Patient to report on reactions (especially on OTCs); and for the Pharmaceutical manufacturers to maintain tight control of their customer service, PV and quality control units were also mentioned.

6. How can we use mass media to promote PV

Most NPVCs are aware of the importance and influence of media and have a public relations office. It was discussed that the media should be used more to introduce PV to the public and highlight patient safety. The importance of linking media, advocacy and government was mentioned. To establish a positive relationship with media a direct, regular and good communication between the press and PV should be established. The following recommendations were made.

National Centres to:

1. Make PV activities and PV data more transparent
2. Provide in-house training on how to communicate with the media
3. Establish regular workshops, conferences and updates for journalists
4. Adopt a proactive approach (PV campaigns)

WHO Collaborating Centres (CCs) to:

1. Promote the use of platforms such as *Vigimed* for sharing experiences between NPVCs.
2. Establish a toolkit to promote adequate communication with media (e.g. materials for in-house training)

WHO to:

1. Establish an "International PV day" as part of the better communication principles
2. Develop guidance for better media communication for NPVC

7. How can sentinel sites and their networks support PV

The objectives of the working group were: to debate the use and value of sentinel sites for PV; identify situations when it could be useful; provide examples of sentinel sites around the world; and discuss whether disease-specific sentinel sites could be used for PV. The following recommendations were made to WHO.

1. Create an inventory of sentinel sites in collaboration with each country, and document their experiences
2. Develop or review guidelines on the use of sentinel sites for PV
3. Identify priorities for setting up or contracting sentinel sites
4. Foster international collaboration for establishment and interaction between sentinel sites in different countries
5. Set up protocols based on previous examples to enable collaboration and data integration
6. Examine how these sentinel sites would be set up and sustained.

8. Integrating PV in curricula

The objective of this working group was to: highlight the importance of PV in curricula; discuss the broad content of PV; discuss ways to integrate it in curricula; and highlight the ongoing activities. It was discussed that PV should be integrated into the curriculum to: educate healthcare providers who will in turn provide quality PV reports; PV knowledge can reduce cost to society by avoiding preventable side effects; it will enhance patient safety; and it will support recruitment of well-trained PV workers. The level and content of PV education should be adapted to the situation, the country, and different professional groups. The 3 most important target groups identified were: medical, pharmacy and nursing students. PV education should be introduced early, and integrated into clinical diagnosis training or as part of existing subjects such as pharmacology. There should be practical sessions where students would be trained to fill in ADR forms. The NPVC staff, regulators and industry representatives should be invited as lecturers, and WHO PV toolkits or online courses could help as teaching aids.

Announcement:

The next annual course in ATC/DDD Methodology will be held in Oslo 5-6 June 2014.

Please note that the deadline for registration is 20 May 2014.

For more information check our website (http://www.whocc.no/courses/).