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WHO Pharmaceuticals NEWSLETTER

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

The aim of the Newsletter is to disseminate information on the safety and efficacy of pharmaceutical products, based on communications received from our network of "drug information officers" and other sources such as specialized bulletins and journals, as well as partners in WHO.

The information is produced in the form of résumés in English, full texts of which may be obtained on request from:

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

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Safety of medicines

Signal

Amoxicillin containing products

Risk of erythroderma (dermatitis exfoliative) and meningitis aseptic

Japan. The Ministry of Health Labour and Welfare (MHLW) and the Pharmaceutical and Medical Devices Agency (PMDA) announced that revision of the package insert for amoxicillin containing products was necessary.

Amoxicillin is an antibiotic and used for the treatment of a number of bacterial infections.

The MHLW/PMDA informed that cases of erythroderma (dermatitis exfoliative) have been reported in patients treated with amoxicillin hydrate in Japan and in other countries, and the company core datasheet (CCDS) has been revised to include information on erythroderma (dermatitis exfoliative). The MHLW/PMDA also informed that cases of aseptic meningitis have been reported in patients treated with amoxicillin hydrate in some countries, and the CCDS has been revised to include information on this event.

Based on expert advice and available evidence, the MHLW/PMDA have recommended the following changes to the package insert.

- Erythroderma (dermatitis exfoliative) should be added in the toxic epidermal necrolysis, oculomucocutaneous syndrome, erythema multiforme, and acute generalised exanthematous pustulosis subsection in the "Clinically significant adverse reactions" section.
- Aseptic meningitis should be added in the "Clinically significant adverse reactions" section.

Reference:
Revisions of precaution, MHLW/PMDA, 9 January 2015 (*http://www.pmda.go.jp/english/*)

Cabazitaxel acetonate

Serious bone marrow depression

Japan. The MHLW and the PMDA have recommended revision of the package insert for cabazitaxel acetonate (Jevtana®).

Cabazitaxel acetonate is indicated for prostate cancer.

Based on expert opinion and available evidence, the MHLW/PMDA concluded that information on bone marrow depression in the "Important precautions" section should be revised as follows:
Serious bone marrow depression may frequently occur. Caution should be exercised for the following points (a higher incidence of bone marrow depression such as neutropenia and febrile neutropenia has been reported especially in patients whose body surface area is small or in elderly patients):

- When cabazitaxel acetonate is administered, proper use of granulocyte-colony stimulating factor (G-CSF) should be considered by referring to the current guidelines or recommendations. Primary prophylaxis with G-CSF product should be considered especially in patients with risk factors for febrile neutropenia. (ex. ≥65 years, poor performance status, medical history of febrile neutropenia, potent pretreatment history such as extended radiation exposure, and bone marrow tumour cell infiltration)
- Patients should be carefully monitored by frequent laboratory tests (ex. blood tests) after administration of cabazitaxel acetonate. If any abnormalities are observed, appropriate measures such as drug suspension, dose reduction, and/or discontinuation of administration should be taken. (See Precautions of dosage and administration section)
- Careful attention should be paid especially to infection. Signs and symptoms such as decreased neutrophil counts, increased levels of C-reactive protein, and pyrexia should be monitored. If infection occurred or was aggravated, appropriate measures such as administration of antibiotics should be taken immediately. If neutropenia occurred, the current guidelines or recommendations should be referred for proper use of antibiotics.

Reference:
Revisions of precaution, MHLW/PMDA, 22 December 2014 (*http://www.pmda.go.jp/english/*)

Combined hormonal contraceptives

Difference in risk of thromboembolism between products and the importance of individual risk factors

Egypt. Egyptian Pharmaceutical Vigilance Center (EPVC) has informed about the differences in risk of thromboembolism between products and the importance of individual risk factors with combined hormonal contraceptives (CHCs).

EPVC has recommended:

- When prescribing CHCs, careful consideration should be given to the individual

woman's current risk factors, particularly those for venous thromboembolism (VTE), and the difference in risk of VTE between products.
- A woman who has been using her combined contraceptive without any problems does not need to stop using it.
- The importance of an individual woman's risk factors should be emphasised and the risk factors need to be regularly reassessed.
- Signs and symptoms of VTE and arterial thromboembolism (ATE) should be described to women when a CHC is prescribed.
- The possibility of a CHC associated thromboembolism should be considered when a woman presents with the symptoms.

Reference:
Newsletter, Egyptian Pharmaceutical Vigilance Center (EPVC), Volume 5, Issue 12, December 2014

(See WHO Pharmaceuticals Newsletters No.2, 2014 and No.6, 2013 for related information on combined hormonal contraceptives)

Dimethyl fumarate

Case of progressive multifocal leukoencephalopathy reported

USA. The US Food and Drug Administration (FDA) warns that a patient with multiple sclerosis (MS) who was being treated with dimethyl fumarate (Tecfidera®) developed a rare and serious brain infection called progressive multifocal leukoencephalopathy (PML), and later died. The patient was not taking any other drugs that affect the immune system or drugs that are thought to be associated with PML. As a result, information describing this case of PML is being added to the drug label for dimethyl fumarate.

Dimethyl fumarate is a drug used to treat relapsing forms of MS, a brain and spinal cord disease in which patients experience multiple episodes of weakness, numbness, and other nervous system signs and symptoms that partially or completely resolve over weeks or months. Patients may develop persistent symptoms and disability over time.

PML is a rare and serious brain infection caused by the John Cunningham (JC) virus. The JC virus is a common virus that is harmless in most people but can cause PML in some patients who have weakened immune systems.

The US FDA has recommended that health-care professionals should:
- Tell patients taking dimethyl fumarate to contact health-care professionals if they develop any symptoms that may be suggestive of PML. Symptoms of PML are diverse, progress over days to weeks, and include the following: progressive weakness on one side of the body or clumsiness of limbs; disturbance of vision; and changes in thinking, memory and orientation, leading to confusion and personality changes. The progression of deficits can lead to severe disability or death.
- Stop dimethyl fumarate immediately at the first sign or symptom suggestive of PML and perform an appropriate diagnostic evaluation.
- Monitor lymphocyte counts in dimethyl fumarate-treated patients according to approved labelling.

Reference:
Drug Safety Communication, US FDA, 25 November 2014 (*www.fda.gov*)

Epoetin alfa

Increased risk of pure red cell aplasia with subcutaneous administration

Australia. The Therapeutic Goods Administration (TGA) announced that product information for epoetin alfa has been updated to provide further information regarding an increased risk of pure red cell aplasia with subcutaneous administration, particularly in patients who have chronic renal disease.

Epoetin alfa (Eprex®) is a recombinant product that stimulates erythropoiesis and reduces the need for blood transfusions.

It has been identified that there is an increased risk of pure red cell aplasia with subcutaneous use of epoetin alfa, particularly in patients with chronic renal disease.

The Product Information (PI) had previously stated that pure red cell aplasia was identified post-market as a potential rare adverse event, which could occur after months to years of treatment. However, there was no mention of an association between the development of pure red cell aplasia and either chronic renal disease or the route of administration.

The PI has been updated to advise health professionals that most cases of pure red cell aplasia associated with epoetin alfa occurred in patients with chronic renal failure receiving subcutaneous administration. The subcutaneous route should only be used when intravenous access is not readily available.

Information for health professionals:

- When administering epoetin alfa to patients with chronic renal disease, the intravenous route is preferable.
- Where intravenous access is not readily available, epoetin alfa can still be administered subcutaneously, but you should be mindful of the increased risk of pure red cell aplasia in these situations.
- If pure red cell aplasia is diagnosed, epoetin alfa must be immediately discontinued and testing for erythropoietin antibodies should be considered. If erythropoietin antibodies are detected, patients should not be switched to another erythropoiesis-stimulating agent.

Reference:
Medicines Safety Update Vol 5, No. 6, December 2014, TGA (*www.tga.gov.au*)

Freeze-dried live attenuated mumps virus vaccine

Risk of Acute pancreatitis

Japan. The MHLW and the PMDA announced revisions to the package insert for freeze-dried live attenuated mumps virus vaccine.

Freeze-dried live attenuated mumps virus is used for prevention of mumps.

The MHLW/PMDA informed that cases of acute pancreatitis have been reported in persons injected with freeze-dried live attenuated mumps virus vaccine in Japan.

Based on investigation results and other available evidence, the MHLW/PMDA concluded that Precautions should be revised in the package insert and that the following texts should be added in the "Clinically significant adverse reactions" subsection of the Adverse reactions section.

Acute pancreatitis:
Acute pancreatitis may occur. Patients should be carefully monitored. If any abnormalities such as abdominal pain, pyrexia, nausea, vomiting, and increased serum amylase are observed, appropriate measures should be taken.

Reference:
Revisions of precaution, MHLW/PMDA, 9 January 2015 (*http://www.pmda.go.jp/english/*)

Galantamine hydrobromide

Acute generalised exanthematous pustulosis

Japan. The MHLW and the PMDA announced revisions to the package insert for galantamine hydrobromide (Reminyl®).

Galantamine hydrobromide is indicated for suppression for progress of dementia symptoms in mild to moderate dementia in Alzheimer's type.

The MHLW/PMDA informed that cases of acute generalised exanthematous pustulosis have been reported in patients treated with galantamine hydrobromide in some countries, and the company core data sheet has been updated. Based on investigation results and other available evidence, the MHLW/PMDA recommended adding Acute generalised exanthematous pustulosis in the "Clinically significant adverse reactions" section of the package insert.

The MHLW/PMDA concluded that the following text should be added:

Acute generalised exanthematous pustulosis:
Acute generalised exanthematous pustulosis may occur. Patients should be carefully monitored. If any abnormalities such as pyrexia, erythema, and many small pustules are observed, administration of this drug should be discontinued and appropriate measures should be taken.

Reference:
Revisions of precaution, MHLW/PMDA, 20 November 2014 (*http://www.pmda.go.jp/english/*)

Hydroxychloroquine or chloroquine

Risk of hypoglycaemia

Singapore. The Health Sciences Authority (HSA) has informed health-care professionals about the risk of hypoglycaemia associated with the use of hydroxychloroquine or chloroquine.

Hydroxychloroquine and chloroquine are anti-malarial drugs used for the suppression and treatment of malaria. Hydroxychloroquine is also indicated for the treatment of rheumatoid arthritis, juvenile chronic arthritis, discoid and systemic lupus erythematosus and dermatological conditions caused or aggravated by sunlight.

Hydroxychloroquine is known to potentiate the hypoglycaemic effects of anti-diabetic agents. However, it has been reported in the literature that the risk of hypoglycaemia with hydroxychloroquine was also observed in patients who were not on concomitant hypoglycaemic agents. Two such case reports are highlighted below in patients who were prescribed hydroxychloroquine for the treatment of rheumatic diseases.

One overseas case report described a 62-year-old male patient with rheumatoid arthritis who was on sulphasalazine, methotrexate, prednisolone and leflunomide. Two months after hydroxychloroquine 200mg daily was added to his therapy, he developed hypoglycaemia (blood glucose level 10mg/dL or 0.56mmol/L) leading to unconsciousness. This patient was assessed to have developed hypoglycaemia secondary to hydroxychloroquine therapy after all predisposing conditions (e.g., insulinoma, ethanol intake, oral anti-diabetics, exogenous insulin usage) were ruled out. A second case report involved an 80-year-old female who reportedly had four events of hypoglycaemia leading to abrupt syncope and loss of consciousness. These events had all occurred within the four-month window period during which she was taking hydroxychloroquine 400mg daily. Her concomitant medications did not include any oral anti-diabetics or insulin. Upon discontinuation of hydroxychloroquine, no recurrence of the hypoglycaemia was reported in the 24-month follow-up period.

There was also a published overseas case report of hypoglycaemia associated with the use of chloroquine. In the report, the patient's blood glucose level repeatedly fell below 36mg/dL (or 2mmol/L) despite repeated infusions with dextrose. While the dose and indication for chloroquine use was unknown, a post-mortem toxicological examination found levels of chloroquine to be within the range associated with death from chloroquine poisoning (57.2mg of chloroquine per 100g liver tissue). The authors postulated that the hypoglycaemia was associated with chloroquine poisoning.

In October 2013, following the European Medicines Agency's (EMA's) review of information available in EudraVigilance and the literature, it was recommended that the product labelling for hydroxychloroquine and chloroquine should be strengthened on the risk of hypoglycaemia associated with their use. More recently, in July 2014, Health Canada has also concluded from its assessment that there is sufficient evidence to support a causal association between hydroxychloroquine use and the onset of hypoglycaemia, including serious cases involving a loss of consciousness and hospitalisation.

HSA is working with the companies to strengthen existing warnings in the local package inserts for hydroxychloroquine- or chloroquine-containing products regarding the additional information on the risk of hypoglycaemia.

Reference:
Product Safety Alerts, HSA, 26 December 2014 (*http://www.hsa.gov.sg/*)

Hydroxyethyl starch intravenous infusions

Contraindications and warnings

UK. The Medicines and Healthcare products Regulatory Agency (MHRA) has informed that hydroxyethyl starch (HES) use is subject to new contraindications, warnings, and monitoring.

HES products are synthetic colloid solutions used for plasma volume expansion. Large randomised clinical trials have reported an increased risk of kidney dysfunction and mortality over 90 days of follow-up in patients who received HES compared with crystalloids. Because of the risks highlighted by these trials, a review of the benefits and risks of HES was started by European regulators in November 2012.

After considering all the available evidence, the EMA concluded that HES should be contraindicated in critically ill patients or patients with sepsis or burns. However, HES can be used in patients with acute blood loss, where treatment with crystalloids alone is not sufficient. As well as new contraindications, HES use will be subject to updated warnings in the information leaflets supplied with HES products.

There is a lack of robust long term safety data in patients undergoing surgical procedures and in patients with trauma. The European Union (EU) decision requires licence holders to conduct further studies.

Reference:
Drug Safety Update, MHRA, Volume 8, issue 5, A3, December 2014 (*www.mhra.gov.uk*)

Canada. Health Canada published that a safety review was initiated to evaluate the currently available information regarding the possible increased risk of kidney injury and death associated with HES solutions when compared to alternative treatments. This review was prompted by the publication of three study results with HES solutions.

The data from the 3 published studies showed an increased risk of kidney injury or death requiring kidney replacement therapy in patients receiving HES solutions in comparison to alternative treatments. These studies involved critically ill patients, including patients with a severe blood infection called sepsis. These findings

were supported by 3 additional published analyses that took into consideration a large volume of related literature on this subject (meta-analyses).

Health Canada has received 28 reports of adverse reactions suspected of being associated with HES solutions. In general, the reports lacked important details regarding the health of the patient at the time the HES solution was given, as well as the amount of HES that was administered. Among the 28 reports, there was one case of kidney failure and one case of death involving a blood clotting disorder.

Health Canada has completed its review of the available safety information and has found that there is an increased risk of kidney injury and death in critically ill patients, including patients with a severe blood infection (sepsis), who are treated with HES solutions.

Health Canada has:

- communicated on the increased risk of kidney injury and death associated with currently marketed HES solutions to both patients and health-care professionals on June 24, 2013 and July 18, 2013, respectively.
- worked with the manufacturer of HES solutions to update the prescribing information of these products to indicate that they should no longer be used in patients with sepsis. The prescribing information has also been updated to include warnings on the increased risk of kidney injury requiring kidney replacement therapy and death in critically ill adult patients, and recommendations to
  - avoid use in patients with pre-existing kidney problems,
  - discontinue the product at the first sign of kidney injury and
  - monitor kidney function.

Reference:
Advisories, Warnings and Recalls, Health Canada, 3 December 2014 (*www.hc-sc.gc.ca*)

(See WHO Pharmaceuticals Newsletter No.4, 2013 for Suspension of licences in UK and new boxed warning in the US)

Interferon beta products

Risk of thrombotic microangiopathy and nephrotic syndrome

Singapore. The HSA has updated health-care professionals on overseas cases of thrombotic microangiopathy (TMA) and nephrotic syndrome that have been reported with the use of interferon beta products.

Interferon beta products are approved for the treatment of relapsing multiple sclerosis (for both 22mcg/0.5mL and 44mcg/0.5mL strengths) and treatment of patients with a single demyelinating event with an active inflammatory process, who are determined to be at high risk of developing relapsing multiple sclerosis (for 44mcg/0.5mL strength only). Interferon beta (Betaferon®) is also approved for the above two indications, as well as for the treatment of secondary progressive multiple sclerosis with active disease.

Both TMA and nephrotic syndrome may develop several weeks to several years after starting treatment with interferon beta.

The Pharmacovigilance Risk Assessment Committee (PRAC) of the EMA conducted a review on the risk of TMA and nephrotic syndrome associated with the use of interferon beta products in September and May 2013, respectively. In February 2014, PRAC concluded that a causal association between interferon beta products and TMA and nephrotic syndrome could not be ruled out. Consequently, their product labels were updated and a Dear Health-care Professional Letter was issued to communicate these safety issues to health-care professionals in the EU.

HSA has not received any local adverse reaction reports of TMA and nephrotic syndrome associated with the use of interferon beta products. However, the local package inserts of Rebif® and Betaferon® have been strengthened to include warnings on the risk of these safety concerns.

Health-care professionals are advised to monitor and consider the possibility of TMA and nephrotic syndrome in patients treated with interferon beta products, if signs and symptoms consistent with these diagnoses are identified.

Reference:
Product Safety Alerts, HSA, 26 December 2014. (*http://www.hsa.gov.sg/*)

Egypt. EPVC has warned about the risk of TMA and nephrotic syndrome with beta interferons.

EPVC has recommended the following:

- To remain vigilant for the development of these conditions and manage them promptly if they occur.
- Clinical features of TMA include thrombocytopenia, new onset hypertension, fever, central nervous system symptoms (e.g. confusion and paresis) and impaired renal function. If clinical features of TMA are observed, test blood platelet levels, serum lactate dehydrogenase levels and renal function.

Also test for red blood cell fragments on a blood film.
- If TMA is diagnosed, prompt treatment (considering plasma exchange) is required and immediate discontinuation of interferon beta is recommended.
- Monitor renal function periodically and be vigilant for early signs or symptoms of nephrotic syndrome such as oedema, proteinuria and impaired renal function especially in patients at high risk of renal disease. If nephrotic syndrome occurs, treat promptly and consider stopping treatment with interferon beta.

Reference:
Newsletter, Egyptian Pharmaceutical Vigilance Center (EPVC), Volume 5, Issue 12, December 2014

(See WHO Pharmaceuticals Newsletters No.1 and 6, 2014 for related information from the UK)

Ivabradine

Risk of cardiovascular events

Europe. The EMA has made recommendations aimed at reducing the risk of heart problems, including heart attack and bradycardia (excessively low heart rate), in patients taking ivabradine (Corlentor®/Procoralan®) for angina.

When used for angina, ivabradine should only be started if the patient's resting heart rate is at least 70 beats per minute (bpm). Because ivabradine has not been shown to provide benefits such as reducing the risk of heart attack or death, death due to heart problems, the medicine should only be used to alleviate symptoms of angina. Doctors should consider stopping treatment if there is no improvement in angina symptoms after 3 months, or if the improvement is only limited.

Other recommendations are that doctors must not prescribe ivabradine together with the medicines verapamil or diltiazem that reduce the heart rate, and that they should monitor their patients for atrial fibrillation. If atrial fibrillation develops during treatment, the balance of benefits and risks of continued ivabradine treatment should be carefully reconsidered.

Because of a small but significant increase of the combined risk of cardiovascular death, myocardial infarction and heart failure seen in patients with symptomatic angina, recommendations have been issued to reduce this risk.

Reference:
Press release, EMA, 21 November 2014 (*www.ema.europa.eu*)

Levetiracetam

Risk of Rhabdomyolysis

Japan. The MHLW and the PMDA announced revision to the package insert for levetiracetam (E Keppra®).

Levetiracetam is indicated as concomitant therapy with other antiepileptic drugs for partial seizures (including secondary generalized seizure) in patients who fail to show a satisfactory response to other antiepileptic drugs.

The MHLW/PMDA informed that cases of rhabdomyolysis have been reported in patients treated with levetiracetam in Japan. Based on result from the investigation and other available evidence, the MHLW/PMDA recommended the following addition to the "Clinically significant adverse reactions" section of the package insert.

Rhabdomyolysis: Rhabdomyolysis may occur. Patients should be carefully monitored. If signs or symptoms including myalgia, feeling of weakness, increased creatine kinase (creatine phosphokinase), increased blood myoglobin, and increased urine myoglobin are observed, administration of this drug should be discontinued and appropriate measures should be taken

Reference:
Revisions of precaution, MHLW/PMDA, 9 January 2015 (*http://www.pmda.go.jp/english/*)

Metoclopramide

Abnormal involuntary movements (Extrapyramidal symptoms) in children

Canada. Health Canada has informed health-care professionals of important new safety information regarding the risk of extrapyramidal symptoms in children taking the daily recommended dose of metoclopramide (0.5 mg/kg per day).

Metoclopramide is approved in Canada for the treatment of delayed gastric emptying and small bowel intubation.

Health Canada completed a safety review on neurological adverse events in children receiving metoclopramide within the daily recommended dosage of 0.5 mg/kg. The review concluded that a benefit-risk balance was negative in children under one year of age due to safety concerns. Furthermore, it showed that metoclopramide should not be used in children older than one year of age unless the anticipated benefits clearly outweigh potential risks.

The Canadian Product Monographs for

metoclopramide drugs were revised recently to include the new contraindication and restrictions on the use of metoclopramide in children.

Information for health professionals:

- Extrapyramidal symptoms may occur in children receiving the daily recommended dose of metoclopramide that should not exceed 0.5 mg/kg.
- Metoclopramide is now contraindicated in children less than one year of age as they appear to be at greater risk of extrapyramidal symptoms.
- Metoclopramide should not be used in children older than one year unless the anticipated benefits clearly outweigh potential risks.

Reference:
Advisories, Warnings and Recalls, Health Canada, 5 January 2015 (*www.hc-sc.gc.ca*)

(See WHO Pharmaceuticals Newsletter No.5, 2013 for regulatory actions taken to reduce the risk of neurological side effects in Europe)

Simeprevir sodium

Increase in blood bilirubin levels

Japan. The MHLW and the PMDA warned that a revision of the package insert of simeprevir (Sovriad®) to include fatal cases associated with remarkably increased blood bilirubin should be implemented urgently.

Simeprevir sodium is used for the treatment of chronic hepatitis C as a combination therapy with peginterferon and ribavirin.

A total of 8 cases of significantly increased blood bilirubin have been reported in patients treated with the combination therapy including simeprevir (including 7 cases in which causality could not be ruled out). Of the 8 cases, 3 fatalities have been reported and causality could not be ruled out in all 3 cases.

A total of 15 cases of serious hepatic dysfunction-associated events have been reported in patients treated with the combination therapy including simeprevir (including 12 cases in which causality could not be ruled out). Of the 15 cases, 3 fatalities have been reported and causality could not be ruled out in all 3 cases (the 3 fatalities are identical with the aforementioned 3 cases of remarkably increased blood bilirubin levels in the previous paragraph).

Based on available evidence, the MHLW/PMDA concluded that the marketing authorization holder, in collaboration with the MHLW/PMDA, should fully inform health-care professionals and patients of fatal cases associated with significantly increased blood bilirubin and appropriate safety measures to avoid serious outcomes.

Health-care professionals are advised to pay attention to following:

- Blood bilirubin tests should be performed regularly during the treatment courses with this drug.
- If any abnormalities are observed including persistent increase in blood bilirubin levels, administration of this drug should be discontinued and appropriate measures should be taken.
- Blood bilirubin levels may be increased even after discontinuation of this drug. Therefore the patients' condition should be carefully observed.
- Patients should be advised to see their doctor immediately when yellow colouring of ocular and/or skin, brown urine, and/or general malaise, etc. are observed after the treatment courses.

Reference:
Revisions of precaution, MHLW/PMDA, 19 November 2014 (*http://www.pmda.go.jp/english/*)

Risk of leukopenia and neutropenia

Japan. The MHLW and the PMDA have recommended the revision to the package insert for simeprevir sodium (Sovriad®).

Simeprevir sodium is indicated for improvement of viraemia in any of the following patients with serogroup 1 (genotype I [1a] or II [1b]) chronic hepatitis C virus infection:

- Treatment-naïve patients with high blood HCV RNA load.
- Patients who have failed to respond to, or have relapsed after therapy including interferon.

The MHLW/PMDA informed that cases of adverse events suggestive of leukopenia and/or neutropenia have been reported in patients treated with combination therapy of simeprevir sodium, peginterferon and ribavirin in Japan.

Based on investigation result and available evidence, the MHLW/PMDA concluded that the Precautions section should be revised in the package insert and the following texts should be added in the "Clinically significant adverse reactions" subsection of the Adverse reactions section.

Leukopenia, neutropenia: Leukopenia and/or neutropenia may occur. Patients should be carefully monitored through periodic blood tests, etc. If the abnormality is severe, discontinuation of simeprevir should be considered and appropriate measures should be taken.

Reference:
Revisions of precaution, MHLW/PMDA, 9 January 2015 (*http://www.pmda.go.jp/english/*)

Sodium-glucose co-transporter 2 inhibitors (ipragliflozin, dapagliflozin, tofogliflozin, luseogliflozin, canagliflozin and empagliflozin)

Risk of dehydration

Japan. The MHLW and the PMDA have recommended the revision to the package insert for sodium-glucose co-transporter 2 inhibitor containing products.

Sodium-glucose co-transporter 2 inhibitor containing products (ipragliflozin L-proline, dapagliflozin propylene glycolate hydrate, tofogliflozin hydrate, luseogliflozin hydrate, canagliflozin hydrate and empagliflozin) are indicated for type 2 diabetes mellitus.

The MHLW/PMDA informed that cases of pyelonephritis have been reported in patients treated with tofogliflozin hydrate in Japan. Based on investigation result and other available evidence, the MHLW/PMDA have recommended that the following text should be added in the "Clinically significant adverse reactions" subsection of the Adverse reactions section.

Dehydration:
Dehydration may occur. Patients should be advised on appropriate water intake and carefully monitored. If symptoms including thirst, polyuria, pollakiuria (frequent urination), and decreased blood pressure are observed and dehydration is suspected, appropriate measures such as drug suspension and fluid replacement should be taken. Careful attention should be exercised because cases of dehydration followed by thromboembolism including cerebral infarction and other diseases have been reported.

Reference:
Revisions of precaution, MHLW/PMDA, 9 January 2015 (*http://www.pmda.go.jp/english/*)

Tofogliflozin hydrate

Risk of Pyelonephritis

Japan. The MHLW and the PMDA have recommended the revision to the package insert for tofogliflozin hydrate (Apleway® and Deberza®).

Tofogliflozin hydrate is indicated for type 2 diabetes mellitus.

The MHLW/PMDA informed that cases of pyelonephritis have been reported in patients treated with tofogliflozin hydrate in Japan. Based on the investigation result and the available evidence, the MHLW/PMDA concluded that the following text should be added in the "Clinically significant adverse reactions" subsection of the Adverse reactions section.

Pyelonephritis:
Pyelonephritis may occur. Patients should be carefully monitored. If any abnormalities are observed, appropriate measures such as discontinuation of administration should be taken.

Reference:
Revisions of precaution, MHLW/PMDA, 9 January 2015 (*http://www.pmda.go.jp/english/*)

Topiramate

Visual field defects

Australia. The TGA has informed that the sponsor of topiramate has issued a Dear Health-care Professional letter advising that a precaution for visual field defects has been added to the Product Information (PI).

Topiramate is a sulfamate substituted monosaccharide. It is indicated in adults and children aged two years and over:

- as monotherapy in patients with newly diagnosed epilepsy
- for conversion to monotherapy in patients with epilepsy
- as add-on therapy in partial onset seizures (with or without secondary generalised seizures), primary generalised tonic-clonic seizures or drop attacks associated with Lennox-Gastaut syndrome.

Topiramate is also indicated for the prophylaxis of migraine headache in adults.

A precaution regarding visual field defects has been added to the PI for topiramate.

Visual field defects have been reported in patients being treated with topiramate independent of elevated intraocular pressure.

In clinical trials, most of these adverse events were reversible after topiramate was discontinued. However, some cases were not. In a large proportion of postmarket reports, reversibility was unknown. In cases where an outcome was reported, most were reversible.

The TGA recommends that health-care professionals should advise patients and caregivers of this issue and educate them regarding the signs and symptoms of visual field defects. Patients should

be instructed to seek immediate medical attention if any problems are suspected.

Reference:
Medicines Safety Update, TGA, Vol. 5, No. 6, December 2014, (www.tga.gov.au)

(See WHO Pharmaceuticals Newsletter No.5, 2014 for Visual field defects reported in New Zealand)

Ustekinumab

Serious skin disorders (Exfoliative dermatitis and erythrodermic psoriasis)

Canada. Health Canada has recommended changes to the package insert to include the risk of exfoliative dermatitis and erythrodermic psoriasis with ustekinumab.

Ustekinumab is a drug used to treat adults with moderate to severe psoriasis (a persistent inflammatory skin condition) and psoriatic arthritis, a variation of psoriasis that is associated with inflammation of the joints. Ustekinumab is given as an injection under the skin.

Internationally, 20 cases of exfoliative dermatitis and erythrodermic psoriasis have been reported in association with the use of ustekinumab. In 12 of the 20 cases, the reaction occurred shortly after the individual started the medication and in 4 of these, the affected patient had a similar reaction when given the medication again. However, it is difficult to determine to what extent ustekinumab contributed to the exfoliative dermatitis and erythrodermic psoriasis or if the patient's underlying psoriasis could also have contributed.

Additional information was recently obtained from a larger patient population in the EU which consisted of 46 additional cases. In 15 of these cases, ustekinumab was considered to have a role in the development of exfoliative dermatitis and erythrodermic psoriasis.

The new data from the larger population in Europe as well as foreign regulatory actions have prompted Health Canada to consider changes to the product information and to inform health-care professionals and the public about the risk of exfoliative dermatitis and erythrodermic psoriasis with ustekinumab. A risk communication has been issued to inform health-care professionals and patients about this risk and the changes to the Canadian prescribing information.

Reference:
Advisories, Warnings and Recalls, Health Canada, 24 November 2014 (www.hc-sc.gc.ca)

Ziprasidone

Rare but potentially fatal skin reactions

USA. The US FDA is warning that the antipsychotic drug ziprasidone (Geodon® and its generics) is associated with a rare but serious skin reaction that can progress to affect other parts of the body. A new warning has been added to the ziprasidone drug label to describe the serious condition known as Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).

DRESS may start as a rash that can spread to all parts of the body. It can include fever, swollen lymph nodes, and inflammation of organs such as the liver, kidney, lungs, heart, or pancreas. DRESS also causes a higher-than-normal number of a particular type of white blood cell called eosinophils in the blood. DRESS can lead to death.

Ziprasidone is an atypical antipsychotic drug used to treat schizophrenia and bipolar I disorder.

The US FDA reviewed information from six patients in whom the signs and symptoms of DRESS appeared between 11 and 30 days after ziprasidone treatment was started. Based on this information, the US FDA required the manufacturer of ziprasidone to add a new warning for DRESS to the "Warnings and Precautions" section of the drug labels for the capsule, oral suspension, and injection formulations.

The US FDA has recommended that health-care professionals should immediately stop treatment with ziprasidone if DRESS is suspected.

Reference:
FDA Drug Safety Communication, US FDA, 12 December 2014 (www.fda.gov)

Agomelatine

Risk of serious hepatic adverse reactions

Ireland. The Health Product Regulatory Authority (HPRA) has informed that hepatic adverse reactions have continued to be reported in the post marketing setting. An EU level review has concluded that the benefit risk balance for agomelatine remains positive. However there is a need to reiterate the importance of liver monitoring, which is the cornerstone for the safe use of this product.

Agomelatine is a melatonergic agonist (MT1 and MT2 receptors) and 5-HT2C antagonist, indicated in the treatment of major depressive episodes in adults.

In December 2012 and December 2013, the HPRA highlighted the risk of hepatotoxicity and emphasised the importance of liver function monitoring. The EMA's PRAC recently concluded its regular benefit-risk assessment (known as a periodic safety update report or PSUR) of agomelatine.

As part of this assessment, the PRAC considered cumulative data on severe hepatic adverse effects associated with agomelatine and recommended further reinforcement of measures to minimise the risk of hepatotoxicity. The majority of these abnormalities occurred during the first months of treatment. The pattern of liver damage appears mainly hepatocellular. Extra vigilance is advised for patients with risk factors for hepatic injury. The balance of benefits and risks should be carefully considered before initiating treatment in a patient with risk factors for hepatic injury e.g. obesity/overweight, substantial alcohol intake, non-alcoholic fatty liver disease, diabetes, and in patients receiving concomitant medicinal products associated with hepatic injury.

Caution should be exercised when agomelatine is administered to patients with pretreatment elevated transaminases. Efficacy has not been demonstrated in patients' ≥75 years and use of agomelatine is not recommended for patients in this age group. Prescribers are reminded that agomelatine is contraindicated in patients with hepatic impairment i.e. cirrhosis or active liver disease and in patients with transaminases exceeding 3 times the upper limit of normal.

Elevations of transaminases (>3 times the upper limit of the normal range) occur more frequently in patients treated with 50mg compared to 25mg. For some patients treated in clinical practice, hepatic reactions occurred following an increase in the dose.

Advice to Health-care Professionals:

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

Reference:
Drug Safety Newsletter, HPRA, December 2014

(See WHO Pharmaceuticals Newsletter No.6, 2014 for Risk of liver toxicity in Europe and No.6, 2012 for Risk of dose-related hepatotoxicity and liver failure in the UK)

Bromocriptine

Risk of cardiovascular, neurological and psychiatric adverse effects

Singapore. The HSA reminded health-care professionals about the risk of cardiovascular, neurological and psychiatric adverse effects that are known to be associated with the use of bromocriptine. These rare but potentially serious or fatal adverse effects were highlighted by the EMA's PRAC in its recently completed safety review, which advised against the routine use of bromocriptine-containing medicines for the prevention or suppression of lactation, as well as for relieving symptoms of pain or swelling of the breasts postpartum.

Bromocriptine is a dopamine agonist that has been authorised across Europe for use in the prevention and suppression of lactation postpartum. However, locally, it is not licensed for such use and is not recommended for the routine prevention or suppression of puerperal breast engorgement.

In Singapore, bromocriptine (Parlodel®) has been registered since May 1988 for the treatment of Parkinson's disease, prolactinomas, acromegaly, hyperprolactinaemia in men, as well as menstrual cycle

disorders and female infertility. There are also several generic brands of bromocriptine registered locally.

To date, HSA has received two non-serious adverse reaction reports associated with the use of bromocriptine for the suppression of lactation (off-label use). The adverse reactions reported included rash, facial oedema and peripheral oedema.

HSA highlighted to health-care professionals that bromocriptine-containing products are not licensed locally for the prevention and suppression of lactation postpartum. Bromocriptine-containing products are also not recommended for use in the routine prevention or suppression of puerperal breast engorgement since such symptoms can usually be treated with simple analgesics and managed by non-pharmacological interventions such as firm breast support or ice application.

There are existing warnings regarding cardiovascular, neurological and psychiatric concerns in the local package inserts of bromocriptine-containing products, including the need for periodic blood pressure monitoring. Health-care professionals are advised to take into consideration these labelled warnings when prescribing bromocriptine to patients. They should also be aware of the above safety review by PRAC and its recommendations on the use of bromocriptine for suppression of lactation as authorised in Europe.

Reference:
Product Safety Alerts, HSA, 26 December 2014. (*http://www.hsa.gov.sg/*)

(See WHO Pharmaceuticals Newsletter No.5, 2014 for Restriction on Europen use in preventing or stopping lactation)

Hydrogen peroxide

Risk of gas embolism

UK. The MHRA has informed that there have been life threatening and fatal cases of gas embolism with use of hydrogen peroxide during surgery and reminded health-care professionals that hydrogen peroxide must not be used during surgery.

Hydrogen peroxide is indicated at concentrations of up to 6% for disinfection of minor cuts, wounds and skin ulcers. It is also indicated at a concentration of 1.5% as a mouthwash or gargle.

The MHRA has reminded health-care professionals that the use of hydrogen peroxide in closed body cavities and deep or large wounds is contraindicated. Hydrogen peroxide breaks down rapidly to water and oxygen on contact with tissues. If this reaction occurs in an enclosed space, the large amount of oxygen produced can cause gas embolism.

In May 2014 the MHRA received a report of gas embolism linked to the use of hydrogen peroxide in surgery. The MHRA is also aware of several case reports that have been published from around the world of life threatening or fatal gas embolism with use of hydrogen peroxide in surgery, of which five were from the UK. Most of the global reports describe cardiorespiratory collapse occurring within seconds to minutes of instillation of hydrogen peroxide as wound irrigation or when used to soak swabs for wound packing. This was sometimes accompanied by features associated with excess gas generation such as surgical emphysema, pneumocephalus, aspiration of gas from central venous lines, or the presence of gas bubbles on transoesophageal echocardiography. Non-fatal events were sometimes associated with permanent neurological damage such as neuro-vegetative state and hypoxic encephalopathy.

Advice for health-care professionals:

- Do not use hydrogen peroxide during surgery.
- It is contraindicated for use in closed body cavities or on deep or large wounds due to the risk of gas embolism.

Reference:
Drug Safety Update, MHRA, Volume 8, issue 5, A4, December 2014 (*www.mhra.gov.uk*)

Ipilimumab

Posterior Reversible Encephalopathy Syndrome (PRES)

Canada. Health Canada informed that a safety review was conducted to evaluate the currently available information regarding the possible risk of posterior reversible encephalopathy syndrome (PRES), a serious condition which affects the brain, with the use of ipilimumab (Yervoy®), an anti-cancer agent. The review was prompted by a published case report of PRES during ipilimumab therapy in the scientific publication.

Ipilimumab is a prescription medicine used to treat melanoma (a kind of skin cancer) that has spread or cannot be removed by surgery. It is administered into a vein (intravenous infusion) for the treatment of melanoma in adults.

PRES is characterized by seizures, mental status changes, visual disturbances, severe headache, nausea, vomiting, and/or difficulties in communicating. This condition usually starts rapidly. It is reversible if identified and

treated appropriately. However, if undetected, PRES may lead to permanent neurologic damage or death.

No Canadian cases of PRES had been reported in association with ipilimumab at the time of this review. A 2012 publication identified a possible case of PRES in the medical literature. It occurred in a 58 year-old woman treated with ipilimumab for melanoma. The patient also had renal failure and hypertension.

At the time of this review, the WHO Database (VigiBase®) contained a single case of PRES following ipilimumab exposure in a 50 year-old man. The potential risk of PRES with the use of ipilimumab is also being investigated by other regulators.

PRES is a disorder that is not yet fully understood. In addition, there is no clear explanation of how ipilimumab may cause PRES. Given that this product is new to the Canadian market, there is limited information concerning this possible risk. It has been determined that information is too limited to accurately assess the risk of PRES with the use of ipilimumab.

Therefore, Health Canada has asked the manufacturer of ipilimumab to perform continued surveillance of this adverse event with Periodic Safety Update Reports (or PSURs), which provide an update of the worldwide safety experience of a health product. Health Canada will also continue its ongoing monitoring of adverse reaction information involving ipilimumab to identify and assess potential harms.

Reference:

Advisories, Warnings and Recalls, Health Canada, 1 December 2014 (*www.hc-sc.gc.ca*)

Isotretinoin

Possible risk of psychiatric disorders

UK. The MHRA has reminded health-care professionals to monitor all patients for signs of depression and refer for appropriate treatment if necessary following a review of the latest evidence of an association between isotretinoin and psychiatric disorders

Isotretinoin (Roaccutane® and Rizuderm®) is licensed for the treatment of severe acne resistant to systemic antibacterials and topical therapy.

There have been reports of psychiatric disorders in patients taking isotretinoin (eg, depression, anxiety, and very rarely suicidal ideation and suicide).

The MHRA reviewed all available evidence from published literature and individual case reports. Due to conflicting study results and the limitations in the data it was not possible to identify a clear increase in risk of psychiatric disorders in people who take isotretinoin compared to those that do not. In addition there was no clear biological mechanism by which isotretinoin would cause psychiatric disorders. Acne itself is associated with some psychiatric disorders. Also, the age at which many patients take isotretinoin is also the age at which some psychiatric disorders are commonly diagnosed.

Although the review was inconclusive, the MHRA considered the evidence sufficient to support the current warnings in the summary of product characteristics. The patient information leaflet already advises patients to discuss any history of mental illness with their doctor before taking isotretinoin. It also tells patients to contact their doctor straight away if they experience any of the psychiatric disorders listed. The MHRA is updating the leaflet to advise patients to ask family and friends to help watch out for symptoms of psychiatric disorders.

Advice for health-care professionals:

- Isotretinoin should only be prescribed by or under the supervision of a consultant dermatologist with expertise in the use of systemic retinoids for the treatment of severe acne and a full understanding of the risks of isotretinoin therapy and monitoring requirements.
- Patients should be warned and their family that isotretinoin might cause psychiatric disorders such as depression, anxiety, and in rare cases suicidal thoughts, they should be warned to watch out for symptoms.
- When prescribing isotretinoin to patients with a history of depression, health-care professionals should carefully consider the balance of benefits of treatment against the possible risk of psychiatric disorders.
- Health-care professionals should monitor all patients for signs of depression and refer them for appropriate treatment if necessary. Stopping isotretinoin may not be enough to alleviate symptoms and further psychiatric or psychological evaluation may be necessary.

Reference:

Drug Safety Update, December 2014, Volume 8, issue 5, A2, MHRA, (*www.mhra.gov.uk*)

Nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and acetaminophen

Risks during pregnancy

USA. Severe and persistent pain that is not effectively treated during pregnancy can result in depression, anxiety, and high blood pressure in the mother. Medicines including nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, and acetaminophen can help treat severe and persistent pain. However, it is important to carefully weigh the benefits and risks of using prescription and OTC pain medicines during pregnancy.

The US FDA is aware of and understands the concerns arising from recent reports questioning the safety of prescription and over-the-counter (OTC) pain medicines when used during pregnancy. As a result, the US FDA evaluated research studies published in the medical literature and determined they are too limited to make any recommendations based on these studies at this time. Because of this uncertainty, the use of pain medicines during pregnancy should be carefully considered.

The US FDA recommended that health-care professionals should talk with each patient about the benefits and risks of analgesic use during pregnancy, which may differ among patients and by treatment indication. Health-care professionals are advised to follow the existing recommendations in current drug labels regarding the use of analgesics during pregnancy.

Reference:
FDA Drug Safety Communication, US FDA, 9 January 2015 (*www.fda.gov*)

Valproate-containing medicines

Further restriction of the valproate use in women and girls

Ireland. The HPRA has recommended that valproate should not be prescribed to female children, female adolescents, women of childbearing potential or pregnant women unless other treatments are ineffective or not tolerated. There are already detailed warnings contained in product information for patients and prescribers on the potential for birth defects and developmental disorders in children born to women taking valproate during pregnancy, which will now be strengthened further.

Prescribers should carefully weigh the benefits of valproate treatment against the risks when prescribing valproate for the first time, at routine treatment reviews, when a female child reaches puberty and when a woman plans a pregnancy or becomes pregnant.

Valproate treatment must be started and supervised by a doctor experienced in managing epilepsy or bipolar disorder.

All female patients should be informed of and understand:

- the risks associated with valproate during pregnancy;
- the need to use effective contraception;
- the need for regular review and treatment;
- the need to rapidly consult if a woman is planning a pregnancy or becomes pregnant.

Reference:
Drug Safety Newsletter, HPRA, December 2014

(See WHO Pharmaceuticals Newsletters No.5, 2014, No.6, 2013 and No. 3, 2013 for related information)

Vascular endothelial growth factor receptor inhibitors

Thrombotic microangiopathy

Canada. Health Canada has announced that a safety review was initiated to evaluate the possible risk of blood clots in small vessels, called thrombotic microangiopathy (TMA) associated with the use of vascular endothelial growth factor (VEGF) receptor inhibitors. This review was prompted by information submitted by one of the manufacturers of this class of drugs.

VEGF receptor inhibitors are used for treating various types of cancer. The type of cancer treated varies with each specific VEGF receptor inhibitor used. VEGF receptor inhibitors work by slowing down the growth and spread of cancer cells by cutting off the blood supply that keeps cancer cells growing.

The VEGF receptor inhibitors included in this review are: sunitinib (Sutent®); sorafenib (Nexavar®); pazopanib (Votrient®); vandetanib (Caprelsa®); axitinib (Inlyta®); and regorafenib (Stivarga®).

TMA, or blood clots in small vessels, refers to a group of disorders that involve the occurrence of blood clots in small blood vessels which can damage organs. Signs and symptoms of these disorders may include increased bruising, bleeding, fewer numbers of platelets and red blood cells, high blood pressure, and extreme weakness. Other organs and body systems that can be affected include the kidneys

and the nervous system. Information on the risk of TMA is included in the prescribing information of certain VEGF inhibitors, specifically sunitinib and pazopanib.

The review assessed the available evidence concerning VEGF receptor inhibitors and the risk of TMA and whether the risk of TMA is associated with all VEGF receptor inhibitors. At the time of this review, Health Canada had not received any reports of TMA suspected of being associated with any of the VEGF receptor inhibitors considered.

Eleven cases of TMA involving sunitinib were published in the scientific literature. In some of these cases, TMA resolved or improved when treatment with sunitinib was stopped. At the time of the review, no cases of TMA were published for the other VEGF receptor inhibitors (sorafenib, vandetanib, axitinib, regorafenib and pazopanib).

Health Canada therefore concluded that at this time there is insufficient evidence for updating the prescribing information for all VEGF receptor inhibitors.

Health Canada will continue to monitor adverse reaction information involving VEGF receptor inhibitors to identify and assess potential harms.

Reference:

Safety Review, Health Canada, 14 January 2015 (*www.hc-sc.gc.ca*)

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

The signals in this Newsletter are based on information derived from Individual Case Safety Reports (ICSRs) available in the WHO Global ICSR database, VigiBase®. The database contains over 10 million reports of suspected adverse drug reactions, submitted by National Pharmacovigilance Centres participating in the WHO Programme for International Drug Monitoring. VigiBase® is, on behalf of the WHO, maintained by the Uppsala Monitoring Centre (UMC) and periodic analysis of VigiBase® data is performed in accordance with UMC's current routine signal detection process.
More information regarding the ICSRs, their limitations and proper use, is provided in the UMC Caveat document available at the end of SIGNAL (page 34). For information on the UMC Measures of Disproportionate Reporting please refer to WHO Pharmaceuticals Newsletter Issue No. 1, 2012.

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

Hexetidine and Severe hypersensitivity reactions

Dr Pia-Caduff-Janosa, Uppsala Monitoring Centre

Summary

Hexetidine is a topical antiseptic used in the treatment of bacterial, fungal and yeast infections of the oral (and vaginal) mucosa, first approved for marketing in the 1960s in Europe, and currently holding a marketing authorization in Europe and Australia (export authorization only) but not in the USA. The different products are available over the counter and contain azorubin (E122), a known allergen to which individuals with a history of salicylate intolerance are especially sensitive. Disproportional reporting on mouth oedema under hexetidine was noticed in the WHO Global ICSR Database, VigiBase® and a broader analysis of reports referring to hypersensitivity reactions was performed. We analysed 27 reports on allergic reactions and conclude that the hexetidine containing products on the market have a substantial potential of inducing also life-threatening allergic reactions of the immediate type, and that healthcare professionals and patients need to be aware of this.

Introduction

Hexetidine is a local broad spectrum antimicrobial active against gram positive and negative bacteria, as well as yeasts and fungi, and it is indicated for the treatment of minor mouth infections and pre- and post-dental surgery. The product is available over the counter and is also used for simple mouth hygiene without a specific infection. The recommended dosage is 15 ml 2-3 times daily as mouth rinse and/or gargling solution.[1] Hexetidine containing vaginal suppositories for vaginal antisepsis are also available on the market.

Hexetidine is not as widely used as chlorhexidine, an antiseptic well known to induce severe allergic reactions and no cross-sensitivity between the two substances has been documented: hexetidine has been recommended as a therapeutic alternative for patients sensitized to chlorhexidine.

Commercial hexetidine solutions contain azorubin (E122), known as a potential allergen. Salicylate intolerance is considered a risk factor for allergic reactions to azorubin. While E122 is banned in the USA, it is allowed in Europe as a food colorant and as an additive to medicinal products which must be listed in the product information leaflet.

A disproportionate reporting on mouth oedema under hexetidine therapy has been noticed in the WHO Global ICSR Database, VigiBase® and as the retrieved reports listed additional, more severe allergic symptoms, the search was widened to include all reports pointing to a potential allergic reaction.

Hypersensitivity (or allergic/anaphylactic) reactions are caused by interactions between immunologically active antigens and humoral antibodies or sensitized lymphocytes causing a wide range of minor to life-threatening symptoms. Life-threatening reactions that compromise respiratory and circulatory functions are described as anaphylaxis. The Gell and Coombs classification describes Type I (immediate type) reactions as IgE mediated with release of potent vasoactive and inflammatory mediators that cause vasodilation, increased capillary permeability, spasms of smooth muscles and inflammatory tissues reactions within hours.[1] Anaphylactoid reactions are not IgE mediated but present the same clinical picture.[2]

Reports in VigiBase®

We searched VigiBase® for reports on the preferred terms mouth oedema (IC 3.76, IC_{025} 2.91), allergic reaction (IC 1.74, IC_{025} 0.57), anaphylactic reaction (IC 1.19, IC_{025} -1.40), and anaphylactic shock (IC 0.92, IC_{025} -1.67) in July 2014 and retrieved 27 reports for analysis. One of the reports, from a consumer, mentioned that the partner had also experienced the same symptoms but this second patient was excluded from the analysis because no more information was available.

All reports concern the preparation for topical oral use, none referred to the vaginal suppositories. The reports have been submitted by 10 different countries: Germany (12 reports), UK and Switzerland (three each), France and Ireland (two each). Norway, the Philippines, Denmark, Italy and the Russian Federation contributed one report each.

Gender (19 women and eight men), was available for all reports. The patients' age was stated in 22 reports, ranging from 24 to 74 years (median 43 years), and was evenly distributed among age groups. The indication for use was stated only in 10 reports (angina 1, gingivitis 2, throat pain 3, oral hygiene 1, gum bleeding 2 and acute laryngitis 1). In a further report we can conclude from the narrative that the medication was used in the post-operative setting.

Hexetidine was the only reported medication in 18 reports and the only suspected medication in a further six. Three reports listed co-suspected medications such as amoxicillin (1), paracetamol, helicidine and other cold remedies (1), ibuprofen, benzocaine, paracetamol, dextromethorphan, and doxylamine (1) - all known to elicit allergic reactions - as well as ephedrine (1). Concomitant but not suspected medications were reported in six reports.

A single, local reaction (lip swelling) is reported only twice; the vast majority (26) of ICSRs list angioedema (face, larynx and throat), respiratory and/or circulatory symptoms in addition to allergic reaction and mouth oedema. Dyspnoea is co-reported in 11 cases, swelling of the glottic region in 12 cases.

The time to onset was reported in all but six reports and was listed as 0-1 day in 18 cases, 3 days, 7 days and 30 days (1 report each). This pattern is compatible with allergic reactions of the immediate type.

One patient experienced a positive de- and rechallenge. Dechallenge was positive in 14 reports, negative in one and not applicable in two cases in which the patients died. In three cases a dechallenge occurred but no information on outcome is reported and six further reports do not state whether the medication was discontinued or not.

The outcome was reported as recovered in 16 cases, fatal in two, not recovered in one case and unknown in the remaining eight cases.

Of the two reports with fatal outcome one describes a woman who died of unexplained reasons while under therapy with hexetidine. She had a medical history of surgery in the pharyngeal region as well as of aspirin allergy. The second report refers to a man who experienced anaphylactic shock, respiratory failure and circulatory arrest while taking not only hexetidine but also several other drugs that could not be excluded as causative agents.

Literature and Labelling

Literature on hexetidine is scarce and refers mostly to efficacy comparisons with other agents. One report of contact dermatitis has been published in 1982 but no other case reports on hypersensitivity reactions could be found.[4]

The marketing authorizations for hexetidine containing products go back to the 1960s and the available summaries of product characteristics (SPCs) vary in their information content on adverse reactions, warnings and precautions. The UK SPC mentions hypersensitivity and angioedema, the Irish SPC mentions allergic reactions to azorubin (E122) under precautions but lists only mild irritations of the buccal mucosa in the adverse reaction section.[5] The Swiss SPC mentions allergic reactions especially in patients with salicylate intolerance, but none lists anaphylactic reactions.[6]

Discussion and Conclusion

The available information on hexetidine and E122, the significant number of reports listing hexetidine as only or only suspected drug, the range, severity and consistent pattern of adverse reactions reported, the plausible time to onset and positive dechallenge (and rechallenge in one case) support the causal association between hexetidine preparations and severe hypersensitivity reactions. Three reports list co-administered medications also known to elicit allergic reactions; these might also have contributed to the reactions reported.

Given the available information from VigiBase®, it is not possible to determine if the reactions were elicited by hexetidine itself or E122. Individuals with a history of salicylate intolerance seem to be at a higher risk of developing an allergic reaction to products containing azorubin. The information currently available to prescribers and patients does not list severe, potentially life-threatening hypersensitivity reactions adequately.

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Linagliptin and Cardiac failure

Dr Raquel Herrera Comoglio, Argentina

Summary

Linagliptin is a reversible, selective inhibitor of the enzyme dipeptidyl peptidase-4 (DPP4), which is responsible for the metabolic inactivation of the incretin glucagon-like peptide 1 (GLP-1), thus extending the GLP-1 half-life. GLP-1 acts on glucose control by stimulating glucose-dependent insulin secretion and suppressing glucagon release. Linagliptin was approved in 2011 for patients with type 2 diabetes mellitus as monotherapy or in combination with other antidiabetic agents in the United States of America (US), the European Union, in Australia and in other countries.

Heart failure can be caused by structural or functional abnormalities of the heart. Up to 6 May 2014, 15 ISCRs associating cardiac failure with linagliptin had been received in the WHO Global ICSR Database, VigiBase®. All but two of these ISCRs were reported as serious, and there was one death reported. Linagliptin was reported as the only suspected drug in 13 cases. Age, reported in nine cases, ranged from 60 to 88 years. Five patients were 83 years and older.

Dipeptidyl peptidase-4 inhibitors (DPP4i) are expected to have beneficial effects on cardiac outcomes, mainly through the prolonged effect of GLP-1. However, two large trials assessing the impact of saxagliptin and alogliptin on cardiovascular death, non-fatal myocardial infarction and non-fatal stroke failed to show any beneficial effect of these drugs on the composite of major cardiovascular outcomes. In addition, concerns arose about the effect of saxagliptin and alogliptin on cardiac failure. A meta-analysis suggested that cardiac failure could be a DPP4i class effect; if it is a class effect, its mechanisms are unknown.

In spite of their inherent limitations, spontaneous reports from VigiBase® add observational data in support of the association cardiac failure - linagliptin/ (DPP4i) as a drug-related effect in some patients with risk factors (e.g. old age), underlying concomitant conditions or pre-existing cardiac failure and/or other concomitant medication. The pair linagliptin-cardiac failure should be considered as a signal, and deserves further investigation.

Introduction

Linagliptin is a synthetic, reversible inhibitor of dipeptidyl peptidase-4 (DPP4). Acting through inhibition of DPP4, linagliptin inhibits the proteolytic degradation of the incretin hormones glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP), resulting in increased glucose dependent insulin secretion. Linagliptin is indicated in the treatment of type 2 diabetes mellitus (T2DM) to improve glycaemic control in adults, as monotherapy or as combination therapy with metformin, or sulphonylurea and metformin, or in combination with insulin with or without metformin.[1-3]

Cardiac failure, or heart failure (HF), is a pathophysiologically complex clinical syndrome, not fully understood, which results from an impaired function of the heart as a pump supporting physiological circulation. Symptoms are dyspnoea, exercise intolerance, and sodium and water retention, often manifested as oedema. Cardiac failure can be caused by any abnormality of the structure, mechanical function or electrical activity of the heart, or as a secondary dysfunction of other organs and tissues, e.g. kidneys, liver or muscles; other systemic processes, as neurohumoral activation, are also involved.[4,5]

Receptors of GLP-1 (GLP-1R) are expressed in pancreas and extrapancreatic tissues (lung, kidney, central, enteric and peripheral nervous systems, lymphocytes, blood vessels, and heart). GLP-1 exerts direct actions on the cardiovascular system, the heart, vessels and kidney, mainly via GLP-1R. In preclinical studies, incretin-based agents control body weight, improve glycaemic control with a low risk of hypoglycaemia, decrease blood pressure, inhibit the secretion of intestinal chylomicrons, and reduce inflammation.[6]

GIP and GLP-1 are rapidly inactivated by DPP4, 1-3, 6-8 a transmembrane protein that removes N-terminal dipeptides from various substrate hormones, chemokines, neuropeptides, growth factors and incretins. Other cardioactive peptides cleaved by DPP4, are brain natriuretic peptide (BNP) and neuropeptide Y. BNP is a cardiac neurohormone with natriuretic and vasodilatory actions, secreted into the plasma from the ventricles in response to ventricular volume expansion and pressure overload.[6-8] BNP has been established as a diagnostic and prognostic marker of left ventricular (LV) systolic and diastolic dysfunction.[9] BNP plasma levels have been shown to be significantly higher in patients with decompensated chronic HF.[10]

Reports in VigiBase®

Fifteen ICSRs were retrieved from the WHO Global ICSR Database, VigiBase®, up to 6 May 2014 (Table 1). All but one (a case from literature) were spontaneous reports. All but two cases were serious (one case doesn't state serious- ness, another one was reported as not serious), and there was one death reported. The patients were 11 women (73%) and three men (20%), while the literature case doesn't report the patient's sex. Age was reported in nine cases (60%), being all patients 60 years or older; age ranged from 83 to 88 years in four out of nine patients (44%). Another patient's age (case 11) was estimated to 85-90 years.

Relevant medical history was reported in six cases (cases 8, 9, 10, 11, 12 and 13). In case 8, concomitant diseases included renal artery stenosis, renal insufficiency, renal disease (shrinked kidneys), renal anaemia, renal osteodystrophy, hyperuricaemia, dyslipidaemia, hypertension, and chronic obstructive pulmonary diseases (COPD). In case 9, relevant medical history mentions cardiovascular disease (CVD) (percutaneous coronary intervention, angina pectoris and myocardial ischaemia), hypertension, hyperlipidaemia, chronic renal failure and diabetes mellitus. Of note, both patients had low weight (43 kg and 40 kg). Case 10 reports hypertension pulmonale, cor pulmonale and lung fibrosis. Case 11 reports unspecified heart disease, case 12 mentions hypertension and atrial fibrillation and case 13 renal insufficiency and hypertension.

Reports come from Europe (six cases), the US (three), Canada (two), Australia (two) and Japan (one). ICSRs were sent by physicians (ten cases), manufacturers (two), pharmacist (one) consumers/non health professionals (one case) and other health professionals (one case). The completeness score of the ICSRs was low (0.17-0.27) in 31%, medium (0.33-0.53) in 44% and high (0.75-0.95) in 25% of the reports. One report mentions a recently published article about the effect of saxagliptin on cardiac outcomes.

Seven reports provide time to onset, which varied from 6 days (two reports) to 295 days.

In all cases but two, linagliptin is the only suspected drug. In the case from literature, metformin 2 g/day (part of the investigational product) was also suspected. In case 9, cilostazol was started nine days before the adverse event and was also mentioned as a suspected drug.

Co-administered medication was reported in nine cases, although it was not specified in one case. Three cases included calcium-channel blockers (amlodipine in two cases and nifedipine in one). T2DM medication was reported in six cases, metformin was the only antidiabetic drug concomitantly administrated in four (in the case from a clinical trial it was reported as a suspected drug), there was one case with metformin and pioglitazone, and another with insulin.

Dechallenge action was reported in nine cases (60%): linagliptin was reported as withdrawn in eight of these, and in one linagliptin dose was reported as not changed, the patient recovered with sequelae.

The fatal case (case 8) refers to a 66 year-old woman with renal insufficiency (renal artery stenosis, renal anaemia, renal dystrophia), hyperuricemia, dyslipemia, hypertension and COPD, who presented with acute dyspnoea and cardiac decompensation 16 days after having started therapy with linagliptin. The patient died 15 days later, and linagliptin was considered "implied".

The first spontaneous reporting (case 1) referred to a woman presenting with cardiac failure 44 days after having started her treatment with linagliptin 5 mg. All the other adverse events (urinary infection, pulmonary infection) occurred at least 11 days after the HF onset, and were probably related to complications derived from hospitalization. Linagliptin was withdrawn after the patient had recovered from her cardiac failure, and hypothetically, after hospitalization.

In the case reported by a manufacturer (case 2), a female patient was also treated with pioglitazone, amlodipine, metformin and irbesartan. Case 9 refers to a Japanese 87 year-old woman, weight 40 kg, treated with several drugs including nifedipine for hypertension, hyperlipidaemia, chronic renal failure and myocardial ischaemia. The patient presented with congestive HF and aggravated renal failure six days after having started linagliptin 5 mg/day and nine days after start of cilostazol treatment with 200 mg/day. In case 10, a 67 year-old woman with a history of scleroderma, lung fibrosis and pulmonary hypertension presented with atrial fibrillation and cardiac failure after approximately six months in treatment with linagliptin. The reporter, a physician, mentions an article of Scirica et al., published the previous month.[11]

In case 12, an 88 year-old woman who had started linagliptin 45 days earlier, went to a hospital for routine pacemaker battery replacement, and cardiac insufficiency was detected; the patient lost 13 kg with appropriate therapy (this indicates the amount of fluid retention), and her ejection fraction was 45%.

Case 13 reports that an 83 year-old man with renal insufficiency and hypertension presented with cardiac failure. Linagliptin was withdrawn, but there is no information about the outcome. Concomitant poly-medication is mentioned but details are not provided.

The case from literature (case 14) was extracted from a 52 weeks multifactorial design study, and reports two drug related serious adverse events (SAEs) in the same patient on day 295 after starting the study treatment (2.5 mg linagliptin + 1000 mg metformin). The patient experienced cardiogenic shock and supraventricular tachycardia within one hour of administration of medication. The patient required hospitalisation and study medication was discontinued; the patient recovered.[12]

Literature and Labelling

The EMA Summary of Product Characteristics for linagliptin, the Australian Public Assessment report and the product label for linagliptin (US FDA) do not mention heart/cardiac failure as an event associated with or described for linagliptin therapy.[1-3]

In a published clinical trial report, cardiac failure is mentioned as having occurred in a patient after 295 days of linagliptin 5 mg/metformin 2 g treatment.[12] This case has been retrieved in VigiBase® and already mentioned in the "Reports in VigiBase®" section.

A meta-analysis, published in February 2013, found that treatment with DPP4i reduces the risk of cardiovascular events (particularly myocardial infarction) and all-cause mortality in patients with type 2 diabetes. Although HF was a pre-specified component of major cardiovascular events (MACE), meta-analysis's results don't mention HF.[13] A trial in older patients does not mention cardiac failure among adverse events.[14] Results posted on Clinicaltrials.gov mention only rhythm abnormalities and coronary artery diseases as serious cardiac adverse events.[15]

A meta-analysis of 50 DPP4-inhibitors trials, enrolling 55,141 participants, found a statistically significant trend towards increased risk of HF outcomes with no increase in risk with regards to all-cause mortality, cardiovascular mortality, acute coronary syndrome (ACS) or stroke. Most of the HF cases were retrieved from results of SAVOR-TIMI-53 (saxagliptin, 66.2% of the data of HF), EXAMINE (alogliptin, 21.3%) and the VIVIDD trial (vildagliptin, 6.9%), the latter enrolled only patients with left ventricular fraction <40%. Seven clinical trials for linagliptin with 5,260 participants were included in the analysis.[16]

A meta-analysis of clinical trials with vildagliptin, sitagliptin, saxagliptin, alogliptin, linagliptin, and dutogliptin found that the overall risk of acute HF was higher in patients treated with DPP4i in comparison with those treated with placebo/active comparators, and suggested that DPP4i could be associated with an increased risk of HF.[17]

A recently published analysis of pooled data of 22 placebo-controlled trials found a negative relationship, with an incidence of HF adverse

events (AEs) for linagliptin- and placebo-treated patients of 0.2% (n = 11) for linagliptin and 0.3% (n = 7) for placebo.[18]

Discussion and Conclusion

Ageing, dyslipidaemia, hypertension, renal insufficiency and diabetes are risk factors for developing cardiac failure. As stated, all patients with a reported age were 60 years or older: four ISCRs refer to patients 83 year-old and older, and for the other five the patient's age was between 60 to 71 years. Another patient's age was estimated to 85-90 years.

Co-morbidities predisposing to HF (dyslipidaemia, hypertension, prior cardiac disease, renal insufficiency) are mentioned in six cases.

Concomitant medication was reported in nine cases (although not specified in one case). Linagliptin was the only suspected drug in thirteen ISCRs, in two cases another drug was reported as suspected (cilostazol and metformin, respectively). In three cases (cases 7, 8, and 9), cholesterol lowering agents, i.e. statins or ezetimibe or both, are reported among concomitant medication. Three patients (3, 8 and 9) were under diuretic treatment (furosemide/amiloride, hydrochlorotiazide and furosemide respectively). Two patients (7 and 9) were treated with angiotensin converting enzyme inhibitors (quinapril and enalapril), two other patients with angiotensin receptors antagonists (2 and 9, irbesartan and losartan respectively). Three patients were treated with calcium channel blockers and two patients with doxazocin (α-blocker).

Calcium channel blockers can lead to worsening HF and have been associated with an increased risk of cardiovascular events, especially the non vasoselective ones.[5] In three cases, patients were also treated with calcium channel blockers, two with amlodipine and one patient with nifedipine. Time to onset was reported in two out of these three cases (6 days and 16 days).

In case 8 (fatal outcome), a 66 year-old woman presented with HF 16 days after having started linagliptin. She was also treated with amlodipine 10 mg, quinapril 5 mg, bisoprolol 5 mg, gliquidone 30 mg, and simvastatin 20 mg. Recent studies have found that amlodipine does not exert favourable effects on the clinical course of patients with HF;[19,20] other not significant interactions for HF seem unlikely, such as simvastatin with amlodipine (amlodipine increases the systemic exposure of simvastatin, this patient being on amlodipine low-dose).

In case 9 (an 87 year-old woman treated with nifedipine and other cardiovascular therapies), cilostazol and linagliptin 5 mg had been added respectively nine days and five days before the HF onset. Cilostazol is a reversible phosphodiesterase III inhibitor with anti-platelet, vasodilatory and antithrombotic properties, metabolized by CYP3A4 and CYP2C19. Cilostazol is formally contraindicated in patients with pre-existing HF. Nifedipine is metabolized by CYP2C19 (interaction described in product information).

For the patient treated with pioglitazone/ metformin (case 2), no time to onset was reported. Pioglitazone is a thiazolidinedione, which selectively ligands the nuclear transcription factor peroxisome proliferator-activated receptor-γ (PPAR-γ). Thiazolidinediones improve glycaemic control by increasing insulin sensitivity. Fluid retention, that can cause or exacerbate HF in some patients, is a known effect of PPAR-γ, and pioglitazone can cause or exacerbate congestive HF in some patients.[21]

In eight cases, linagliptin was withdrawn. Except for the fatal case and one with unknown outcome, dechallenge was positive. No cases with rechallenge were reported. In case 3, the dose was not changed and the patient recovered with hospitalization.

Time to onset (reported in seven cases) was <6 months in six patients (44 days, 6 days, 147 days, 16 days, 6 days and 164 days respectively). In a large study with saxagliptin, the risk for HF hospitalization associated with the use of saxagliptin was highest in the first six months and declined thereafter.

DDP4 inhibitors have been expected to have beneficial effects on cardiac outcomes, both due to GLP-1 actions and to other peptide hormones with direct cardiorenal effects. Preclinical data and mechanistic studies suggested a possible additional non-glycaemic beneficial action on blood vessels and the heart, via both GLP-1 dependent and GLP-1-independent effects.[22] It has been suggested that DPP4 inhibitors reduce the risk for the multiple co-morbidities associated with obesity/T2DM including hypertension, cardiovascular and kidney disease.[23]

Table 1. Characteristics of reports in VigiBase® for linagliptin and cardiac failure

Case	Age/ Sex	Time to onset	Duration of treatment	Other suspected (S) or concomitant (C) drugs	Reported adverse reactions/ adverse events	Dechallenge action	Outcome
1	-/F	44days	68days	-	Urinary tract infection, pulmonary congestion, hypotension, pain, nausea, pleural fibrosis, hypoxia, cardiac congestive failure	Drug withdrawn	Recovered (before drug withdrawal)
2*	-/F	-	-	Pioglitazone, metformin, amlodipine, irbesartan (all C)	Cardiac failure	-	Unknown
3	84/M	6days	-	Metformin, clarithromycin, doxazocin, fluticasone, lactulose, senna, latanoprost, furosemide/amiloride, clopidogrel(allC)	Oedema, respiratory rate increased, wheezes, orthopnoea, condition aggravated, congestive heart failure	Dosenot changed	Recovered with sequelae
4	71/F	-	-	-	Heart failure	-	-
5	-/F	147days	147days	-	Anaemia, congestive heart failure, hypertension pulmonary	Drug withdrawn	Recovered with sequelae
6	60/F	-	-	-	Congestive heart failure	-	-
7*	69/F	-	-	-	Dyspnoea, swelling, cardiac failure	-	-
8**	66/F	16days	16days	Amlodipine, quinapril , colecalciferol, sodium ascorbate/ferrous sulfate, calcium acetate, calcium carbonate, sodium bicarbonate, cloxazolam, acetylsalicylic acid, bisoprolol, gliquidone, simvastatin(allC)	Vomiting, renal failure acute, acute dyspnoea, myocardial decompensation, general physical health deterioration	Drug withdrawn	Death
9	87/F	6days	6days	Cilostazol (S) Zopiclone doxazocin, haloperidol, ezetimibe, famotidine, nifedipine, hydrochlorotiazide/losartan potassium, acetylsalicylic acid (allC)	Renal failure aggravated, cardiac failure congestive	Drug withdrawn	Recovered
10	67/F	164days	176days	Estradiol, terbutaline, formoterol fumarate/ budesonide, prednisolone, insulin aspart, insulin glargine, acetylsalicylic acid, magnesium oxide, simvastatin, ezetimibe, enalapril, potassium, furosemide, sildenafil, cyclophosmamide (all C)	Disease progression, oedema, cardiac arrest, atrial fibrillation, myocardial decompensation	Drug withdrawn	Recovered
11	***/F	-	-	Metformin (C)	Myocardial decompensation	Drug withdrawn	Recovered
12	88/F	-	45days	Metformin (C)	Oedema, cardiac failure	-	Recovered
13	83/M	-	-	Polymedication (not further specified)	Cardiac failure	Drug withdrawn	Unknown
14	-/-	295days	295days	Metformin (S)	Supraventricular tachycardia, cardiogenic shock	Drug withdrawn	Recovered
15	-/M	-	-	-	Asthenia, hyperglycaemia, tremor, nocturnal dyspnoea, abdominal discomfort	Unknown	Unknown

causality reported as possible, ** causality reported as 'implied', * estimated age: 85-90 years*

However, a recently published meta-analysis suggested that HF is a class effect of DPP4i.[17] Two large trials specifically designed to assess composite cardiovascular outcomes contributed largely to this conclusion. A large trial found a higher statistically significant risk of hospitalization due to HF in the saxagliptin group than in the placebo group. Patients had T2DM and established cardiovascular disease or multiple cardiovascular risks factors, and were followed for a median of 2.1 years; HF was included in a composite secondary endpoint. 12.8% of participants had prior HF.[11] The events were more frequent in patients with diabetes and HF.[24] In a large trial assessing the effect of alogliptin on cardiovascular outcomes in 5,380 patients followed for a median of 18 months, 28% of the participants had HF at baseline; HF was not part of the primary composite outcome or secondary outcomes. Although the heterogeneity of sub-groups is mentioned, no specific details are provided.[25]

Prior HF was the strongest predictor of hospitalization during the study, followed by impaired kidney function. In the EXAMINE study, the risk increase for hospitalization due to HF associated with alogliptin was apparently less clear in spite of the percentage of patients with prior HF, the higher use of ß-blocking agents, and the more frequent medical controls with treatment adaptations in EXAMINE might be one of the potential explanations.[26]

Mechanisms of the hypothesized effect of DDP4 inhibitors on HF are unknown. As previously mentioned, DPP4 cleaves not only GLP-1 and GIP, but also other cardioactive peptides, such as substance P, brain natriuretic peptide (BNP), neuropeptide Y, CXCL12, bradykinin, and related peptides.[6-7] BNP is increased in HF, being both a diagnostic and prognostic marker.[9,10] It has also been suggested that DPP4 is abnormally increased in patients with T2DM and these increased DPP4 levels are independently associated with asymptomatic left ventricular both diastolic and systolic dysfunction in T2DM patients which have a higher risk of presenting left ventricular dysfunction.[27] Neuropeptide Y (NPY1-36) is released from sympathetic neurons; DPP4 removes the N-terminal from NPY1-36 to generate NPY3-36, which binds to Y2 receptors that have relative antagonist properties to Y1 receptor activation. Any decrease in the DPP4 mediated generation of NPY3-36 would decrease the activity of Y2 inhibitory autoreceptors; and so augment sympathetic and parasympathetic neurotransmitter release.[28] A clinical study in 53 patients found that peptide Y is augmented in diabetic patients.[29]

Linagliptin also has significant inhibitory activity on the human M1, M2 and M3 muscarinic receptors, with half minimal inhibitory concentration (IC_{50}) values of 295 to 1000 nM (more than 22 times the clinical peak concentration (Cmax), which has not been considered clinically relevant.[1,2] In animal models a relationship between B-adrenergic and M2 muscarinic receptors and diminished ventricular contractility has been suggested.[30]

In spite of their inherent limitations, spontaneous reports from VigiBase® add observational data in support of the association cardiac failure-linagliptin/ (DPP4i) as a drug-related effect in some patients with risk factors (e.g. old age), underlying concomitant conditions or pre-existing cardiac failure and/or other concomitant medication. The pair linagliptin-cardiac failure should be considered as a signal, and deserves further clinical and pharmacoepidemiological investigation.

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Response from Boehringer Ingelheim

Thank you for the opportunity to provide our comments. Boehringer Ingelheim completed a cumulative assessment of HF on 14 February 2014 following an internally detected signal after publication of the results for the saxagliptin and alogliptin cardiovascular outcome trials (CVOT) in September 2013.

A cumulative review of linagliptin and linagliptin+metformin fixed dose combination (FDC) reports entered in the Boehringer Ingelheim global drug safety database until 27AUG2014 was undertaken using the narrow MedDRA v17.0 SMQ cardiac failure. Data from clinical trials, epidemiologic studies and the published literature were also reviewed.

92 events (87 serious) in 83 reports were identified in association with linagliptin; no reports were identified in association with the linagliptin+metformin FDC. Forty-six events in 42 reports were from clinical trials, 32 events in 28 reports were spontaneous, 3 events in 3 reports were from Health Authorities and 11 events in 10 reports were from observational studies. The main reason for seriousness was hospitalization alone or associated with life-threatening or fatal reports. Forty six patients were female (55%), 35 were male (42%) and 2 did not report gender.

The 78 reports which provide age range between 39 and 92 years with most (75%) over 60. Twenty one patients (25%) were older than 80.

All of the reports were individually assessed and had a plausible alternative explanation, factors (e.g. temporality) that make a causal relationship to linagliptin unlikely or insufficient information for a more full causal assessment.

A dechallenge is described in 28 reports: 12 positive, 7 negative and 2 unknown outcomes. Four rechallenges are described: 2 negative, one unknown outcome. Only one positive rechallenge was described, in a patient with end stage renal and chronic cardiac failure with critical coronary occlusion. In 4 reports the patient recovered while linagliptin continued unchanged. Six reports were not temporally related to linagliptin; one patient had viral cardiomyopathy 5 months after discontinuation, another with pre-existing chronic renal failure experienced HF 3 months after discontinuation, 3 had evidence of worsening of pre-existing HF prior to starting linagliptin and one event occurred on the day that linagliptin was started, when hyperthyroidism was also diagnosed.

Time to onset was reported in 71 of the 92 events. Thirty eight events (54%) were <6 months, and 11 (15%) events occurred more than 1 year after starting linagliptin.

Of the 15 ICSRs identified on the Vigibase database, 14 are included in the search results. Case 15 is not because the Preferred Term Nocturnal dyspnoea is not in the narrow cardiac failure SMQ definition. In addition to the information presented, case 1 reported a patient in a Boehringer Ingelheim sponsored trial in patients with renal impairment. The patient was taking furosemide for congestive heart failure (CHF) and spironolactone and metolazone was added 3 months before linagliptin was started indicating worsening or instability of the disease prior to linagliptin.

The evaluation of HF is complex in the type 2 Diabetes Mellitus (T2DM) population. As stated in the article above, the risk factors for HF would be expected to be higher in the T2DM population compared with non- diabetics. An assessment was conducted of past or concomitant conditions that are known risk factors for HF. Seventy seven patients (93%) had at least one risk factor and 55 patients (66%) had 3 or more risk factors. Six patients did not have at least one risk factor for HF and all 6 reports had limited or no medical history provided.

Hypertension may be the single most important modifiable risk factor for HF.[1] Fifty eight patients (70%) reported hypertension.

Obesity and insulin resistance are also important risk factors for cardiac failure.[1] Using the international classification of body mass index (BMI)[2], of 54 patients reporting a BMI, 12 (22%) were pre-obese and 27 (50%) were obese. Only 10 reports described patients with normal BMI and the 5 underweight patients had renal failure.

Linagliptin does not require dose alteration in patients with renal insufficiency and may be more

likely to be used in this patient population than other DPP-4 inhibitors. Thirty six patients (43%) reported renal insufficiency, acute or chronic renal failure or diabetic nephropathy which are recognised risk factors for HF.[1]

The reported incidence rate of HF in patients with T2DM varies across studies largely reflecting differences in ascertainment and adjustment approaches.[3] A study conducted in multiple countries across Europe and North Africa estimated an annual incidence rate of CHF requiring hospitalisation of 10 per 1000 persons.[4] In the US, the CDC reported the annual age-adjusted hospital discharge rate with HF as first-listed diagnosis in diabetes patients to be 13.4 per 1000 in 2006.[5] Another US study estimated a crude incidence rate of about 11.8 per 1000 PY.[6]

The incidence rate of patients with unadjudicated narrow MedDRA SMQ cardiac failure events for linagliptin is 5.8 per 1000PY (N=9060).[7] Pooled analysis of safety data from 23 randomized clinical trials (N=5488 linagliptin, 3290 placebo) showed same overall incidence of cardiac disorders (3.3% and 3.3%, respectively).[7] Using the narrow MedDRA SMQ cardiac failure, the frequency was 0.5% (linagliptin) and 0.2% (placebo).[8] This frequency in patients with a history of cardiac failure was 5.1% (linagliptin) and 5.5% (placebo).[7] External adjudication of events of hospitalization for HF in 8 randomized, double-blind studies, (N=2039 linagliptin, 1275 placebo) showed 9 (0.4%) and 5 (0.4%) patients respectively were adjudicated to have HF. Further adjudicated analyses will be available when the large ongoing CVOTs CAROLINA and CARMELINA complete.

It is not possible to demonstrate a direct causal effect of linagliptin with HF due to the confounding of the reports with risk factors for the condition and the known relatively high background incidence in the T2DM population. In addition, the observed incidence rate in the clinical trials appears to be within the published range. Data does not demonstrate an increased frequency in patients with previous HF. Boehringer Ingelheim concluded that linagliptin is not casually associated with HF however this topic will continue to be closely monitored and the linagliptin CVOTs CAROLINA and CARMELINA will provide important further information.

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Temsirolimus and Myocardial infarction

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Summary

Temsirolimus is a selective inhibitor of mTOR (mammalian target of rapamycin). Temsirolimus binds to an intracellular protein (FKBP-12), and the protein/temsirolimus complex binds and inhibits the activity of mTOR that controls cell division. It is indicated for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC) who have at least three of six prognostic risk factors, and also for the treatment of adult patients with relapsed and/or refractory mantle cell lymphoma (MCL). After the elimination of duplicates there are currently (6 May 2014) 17 ICSRs in the WHO Global ICSR Database, VigiBase® of myocardial infarction (MI) in association with temsirolimus. The reports are from Austria, Canada, Germany, Greece, Japan, and the United States. The association has an IC value of -0.18 with an IC_{025} value of -0.86. Temsirolimus was the only drug suspected in eight of the 17 cases. The outcome of the MI was stated in nine reports. Five of these patients were reported as recovered or recovering and the outcome was fatal in three reports. In the remaining case, the patient recovered from the MI but died from other causes. In another three reports, the outcome of the MI was unknown but the patient died from other causes in one case and the cause of death was unknown in the other two cases.

Case reports in VigiBase® suggest that there is a possible signal for the association of temsirolimus and MI. Temsirolimus was the only drug suspected in almost half of the cases. Although there are alternative explanations for MI in some reports and advanced disease may make a contribution in others, the use of temsirolimus appears to be a possible signal. Temsirolimus is known to induce high levels of cholesterol and particularly triglycerides and this is a plausible mechanism for the development of MI in some patients. Time to onset is consistent with a drug-induced effect and although onset is very short in some cases, this may be explained by the presence of free fatty acids. Finally, although the IC value is negative, there are compelling reasons why the IC is not a reliable indicator of disproportionality in this association.

Introduction

Temsirolimus is a selective inhibitor of mTOR (mammalian target of rapamycin). Temsirolimus binds to an intracellular protein (FKBP-12), and the protein/temsirolimus complex binds and inhibits the activity of mTOR that controls cell division. In addition to regulating cell cycle proteins, mTOR can regulate translation of the hypoxia-inducible factors, HIF-1 and HIF-2 alpha. These transcription factors regulate the ability of tumours to adapt to hypoxic microenvironments and to produce the angiogenic factor vascular endothelial growth factor (VEGF). The anti-tumour effect of temsirolimus, therefore, may also in part stem from its ability to depress levels of HIF and VEGF in the tumour or tumour microenvironment, thereby impairing vessel development. It is indicated for the first-line treatment of adult patients with advanced renal cell carcinoma (RCC) who have at least three of six prognostic risk factors, and also for the treatment of adult patients with relapsed and/or refractory mantle cell lymphoma (MCL). The most serious reactions observed with temsirolimus in clinical trials are hypersensitivity/infusion reactions (including some life-threatening and rare fatal reactions), hyperglycaemia/glucose intolerance, infections, interstitial lung disease (pneumonitis), hyperlipaemia, intracranial haemorrhage, renal failure, intestinal perforation, wound healing complication, thrombocytopenia, neutropenia (including febrile neutropenia), and pulmonary embolism. The adverse reactions (all grades) experienced by at least 20% of the patients in RCC and MCL registration studies include anaemia, nausea, rash (including rash, pruritic rash, maculopapular rash, pustular rash), decreased appetite, oedema asthenia, fatigue, thrombocytopenia, diarrhoea, pyrexia, epistaxis, mucosal inflammation, stomatitis, vomiting, hyperglycaemia, hypercholesterolemia, dysgeusia, pruritus, cough, infection, pneumonia, and dyspnoea.[1]

Myocardial infarction (MI) is myocardial necrosis resulting from inadequate blood supply. MI 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.[2] MI is commonly known as a heart attack and most often occurs as a result of a blood clot that blocks one of the coronary arteries.[3] Abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, alcohol, lack of consumption of fruits and vegetables, and lack of regular physical activity account for most of the risk of myocardial

infarction worldwide in both sexes and at all ages in all regions.[4]

Reports in VigiBase®

As of 6 May 2014 there are 21 ICSRs of MI in association with temsirolimus in the WHO Global ICSR Database, VigiBase® (Table 1). After the elimination of one duplicate and three of four quadruplicate reports, the reports were submitted from the United States (9 reports), Germany (4 reports), and Austria, Canada, Greece and Japan (1 report each). The patients ranged in age from 51 to 78 years with a median of 64 years in the 11 cases which provided the information. There were 13 males and three females in the 16 reports which contained these details.

Temsirolimus was the only drug suspected in eight of the 17 cases. There were other drugs also suspected in the remaining nine cases and they were mostly drugs probably being used for the same indication as temsirolimus and included erlotinib, bortezimib, gemcitabine, lenalidomide, interferon alfa-2a and vinorelbine in six individual reports and everolimus, sorafenib and sunitinib in another report. Diltiazem and simvastatin were also each suspected drugs in the other two cases. Concomitant drugs were reported in 11 of the 17 cases and together with the suspected drugs and information about the patients, this indicated a patient population which, apart from cancer, had significant morbidity including hypertension and/or angina pectoris (5 cases), gastroesophageal reflux disease (5 cases), asthma (3 cases) and hyperlipidaemia (3 cases) and required pain management (5 cases), nausea control (4 cases), NSAIDs (3 cases) and antiplatelet therapy (3 cases). Temsirolimus was reported to have been administered intravenously or by injection, as expected, in all 13 cases which provided this information. The indication for use was stated in 16 reports and included RCC in 11 reports and MCL, oligodendroglioma, multiple myeloma, pancreatic cancer and neuroendocrine tumour in one report each.

Time to onset was reported in 11 of the reports and ranged from 1 day to 9 months (median 2.5 months).

The outcome of the MI was stated in nine reports. Five of these patients were reported as recovered or recovering and the outcome was fatal in three reports. In the remaining case, the patient recovered from the MI but died from other causes. In another three reports, the outcome of the MI was unknown but the patient died from other causes in one case and the cause of death was unknown in the other two cases. In the six cases with recovery, temsirolimus was either withdrawn or the course discontinued in four cases and the fate of the drug was unknown in the other two cases. In the three cases where the outcome of the MI was death, the drug was withdrawn or discontinued in two cases and the fate of the drug was unknown in the other case.

Other reactions were reported in all but one case. These included respiratory reactions such as pulmonary oedema, pleural effusion, respiratory insufficiency or dyspnoea in six cases, pneumonia in four cases, renal reactions such as renal failure or azotaemia in four cases and gastrointestinal reactions such as nausea, anorexia, diarrhoea or vomiting in four cases. Most of these reactions are listed as adverse reactions in the product information.[1] The respiratory reactions may be accompanying symptoms of myocardial infarction.

Literature and Labelling

The product literature does not refer to MI. The only cardiac disorder that was reported in clinical trials was pericardial effusion which was reported uncommonly. Vascular disorders such as venous thromboembolism (including deep vein thrombosis and venous thrombosis), thrombophlebitis and hypertension were reported commonly. There are also no reports in the literature which link MI with temsirolimus. In a phase I clinical trial of temsirolimus and bevacizumab in the treatment of salivary duct carcinoma, however, one of the two patients treated died as a result of an MI although it was considered unrelated to the study drugs.[5]

Discussion

Case reports in VigiBase® suggest that there is a possible signal for the association of temsirolimus and MI. Temsirolimus was the only drug suspected in eight of the 17 cases. There were other drugs suspected in the remaining nine cases although except for the presence of tyrosine kinase inhibitors in two cases, these other suspected drugs were all different and overall do not appear to be a more likely cause. While MI is listed in the product information as common in association with sorafenib (Case 10), it was used two years before onset and appears an unlikely cause. MI is also listed as common in association with lenalidomide but the dates of administration are unknown so it is difficult to assess this association. Four other suspected drugs (bortezomid, gemcitabine, interferon alfa-2a and vinorelbine) have MI listed in the product information but the relationship is considered rare or not known.

Time to onset ranged from 1 day to 9 months (median 2.5 months). Assuming that the mechanism involves the development of atheroma then four of the reports, in particular, which describe a time to onset of one month or less, would appear to be inconsistent with such a mechanism. On the other hand, the seven reports

which describe onset between 2 and 9 months would be consistent with this mechanism. As noted above, however, although coronary atherosclerosis is the most likely explanation for MI, other mechanisms are possible. Hypertriglyceridaemia and hypercholesterolaemia were reported in close to 20% of patients in clinical trials with Grade III or IV hypertriglyceridaemia reported as high as 6% in one Phase II study.[1,6] Lipids, particularly triglycerides, can be broken down to free fatty acids (FFAs). MI is nearly always associated with the presence of higher FFA levels. These high levels may cause adverse effects on heart metabolism resulting in arrhythmias and poor cardiac function.[7] It is also possible that high levels of lipids could accelerate the development of an MI in a susceptible patient. One of the patients in this series (Case 19) recorded a triglyceride level of 2600 mg/dL after temsirolimus treatment (500 mg/dL is considered very high8) although it was not clear from the report whether temsirolimus was still being taken at this time.

There are some reports where there are other alternative explanations. In Case 3, the patient had pre-existing increased cholesterol; in Case 5, the patient had pre-existing angina pectoris and possibly hypertension; in Case 7, the patient had pre-existing hypercholesterolaemia and angina pectoris; in Case 10, the patient had pre-existing hypertension and thrombotic disease; in Case 12, the patient had pre-existing angina pectoris or hypertension; in Case 13, the patient had pre-existing thrombotic disease with a history of percutaneous transluminal coronary angioplasty; in Case 14, disease progression appears a likely explanation; and in Case 20, the patient had pre-existing thrombotic disease and angina pectoris and/or hypertension. It is also possible that the presence of advanced disease in other cases may have contributed to the MI.

Dechallenge is not particularly suggestive of a signal. However, for a drug which is indicated for periodic administration by injection, this is not a particularly meaningful parameter. Moreover, for an acute, singular event such as MI, the response to drug withdrawal is also not meaningful as recovery or otherwise will be dependent on other factors such as the severity of the event, the overall state of health of the patient and the speed of treatment rather than drug withdrawal.

The IC value is negative (IC -0.18, IC_{025} -0.86) which means that the temsirolimus-MI combination is reported less frequently than expected. There are, however, exceptional circumstances with respect to the association with MI. MI has been reported over 90,000 times but half of these reports have arisen from just five drugs with almost 20,000 reports for rofecoxib (IC=4.84), almost 16,000 reports for rosiglitazone (IC=5.12), 6,000 reports for celecoxib (IC=3.51), over 3,500 reports for valdecoxib (IC=4.69) and over 2,000 reports for the combination of rosiglitazone and metformin (IC=5.15). The IC values for these five combinations are all very high and the IC for most other combinations is reduced and is not a reliable indicator of disproportionality in this association. In an attempt to investigate the disproportionality of temsirolimus and MI without this masking effect, the IC was computed after the exclusion of these five drug-event combinations from the data. After this exclusion the IC increased to 0.68 (IC_{025} = 0.02).

Conclusion

In summary, there are 17 reports associating MI with the use of temsirolimus. Temsirolimus was the only drug suspected in eight of the 17 cases. Although there are alternative explanations in some and advanced disease may make a contribution in others, the use of temsirolimus appears to be a signal. Temsirolimus is known to induce high levels of cholesterol and particularly triglycerides and this is a plausible mechanism for the development of MI in some patients. Time to onset is consistent with a drug-induced effect and although onset is very short in some cases, this may be explained by the presence of free fatty acids. Finally, although the IC is negative, there are compelling reasons why the IC is not a reliable indicator of disproportionality in this association.

Table 1. Case overview of reports in VigiBase® of myocardial infarction in association with temsirolimus

Case	Age/ Sex	Other suspected (S) or concomitant (C) drugs	Reactions (WHO-ART)	Outcome
1	57/F	Erlotinib (S)	Myocardial infarction, dehydration, nausea	Unknown
2*	51/M	Bortezomib (S)	Myocardial infarction, agranulocytosis, hypotension, hypoxia, respiratory insufficiency, sepsis, tachycardia	Unknown but died
3	-/M	Atorvastatin, cimetidine, eszopiclone, naproxen, paracetamol/hydrocodone bitartrate, prochlorperazine, salbutamol, senna alexandrina, zoledronic acid (all C)	Myocardial infarction, cardiac failure, respiratory insufficiency	Recovering

4	-/M	None	Myocardial infarction	Recovered
5	71/M	Diltiazem (S) Budesonide, bumetanide, carbasalate, carvedilol, glyceryl trinitrate, isosorbide mononitrate, nifedipine, pantoprazole, salbutamol, sodium bicarbonate/ potassium chloride/macrogol (all C)	Myocardial infarction, pneumonia	Recovering
6	-/M	Ondansetron, oxycodone, sulfamethoxazole/trimethoprim (all C)	Myocardial infarction, GI haemorrhage, pleural effusion, renal failure	Unknown but died from other
7	-/M	Acetylsalicylic acid, glyceryl trinitrate, rabeprazole (all C)	Myocardial infarction, cardiac failure	Unknown
8*	-/M	Bortezomib (S) Amoxicillin, fluticasone propionate/ salmeterol xinafoate, gabapentin, metoprolol, oxycodone, valacic- lovir (all C)	Myocardial infarction, agranulocytosis, pleural effusion, pneumonia, respiratory insufficiency, sepsis	Died
9	-/F	None	Myocardial infarction, urinary incontinence	Unknown
10	75/M	Everolimus, sorafenib, sunitinib (all S) Allopurinol, doxazosin, paracetamol, ramipril, zoledronic acid (all C)	Myocardial infarction, anorexia, anuria, arrhythmia, ascites, azotaemia, bradycardia, cardiac arrest, dyspnoea, fatigue, hypotension, pericardial effusion, stomatitis, trigeminal neuralgia, troponin t increased	Died
11*	51/M	Bortezomib (S)	Myocardial infarction, anaemia, azotaemia, coma, granulocytopenia, pleural effusion, pulmonary oedema, rigors, skin discolouration, thrombocytopenia	Unknown but died
12*	51/M	Bortezomib (S) Amoxicillin, fluticasone propionate/salmeterol xinafoate, gabapentin, metoprolol, oxycodone, valacic- lovir (all C)	Myocardial infarction, anaemia, azotaemia, coma, granulocytopenia, multiple organ failure, pleural effusion, pneumonia, pulmonary oedema, respiratory distress syndrome, sudden death, sepsis, thrombocytopenia	Unknown but died
13#	62/M	Gemcitabine (S) Dexamethasone, dimetindene, fondaparinux, ondansetron, ranitidine (all C)	Myocardial infarction, hypoxia, multiple organ failure, pneumonia, sepsis, thrombocytopenia, klebsiella infection**	Recovered from MI but died from other
14	70/F	Lenalidomide (S) Dexamethasone, omeprazole (both C)	Myocardial infarction, cardiac failure, disease progression**	Died
15#	62/M	Gemcitabine (S) Dexamethasone, dimetindene, fondaparinux, ondansetron, ranitidine (all C)	Myocardial infarction, fever, hypoxia, multiple organ failure, pneumonia, sepsis, thrombocytopenia, klebsiella infection**	Died
16	59/M	Interferon alfa-2a (S) Diclofenac (C)	Myocardial infarction, renal failure	Died
17	67/M	None	Myocardial infarction, pulmonary oedema, vomiting	Recovered
18	-/-	None	Myocardial infarction, angina pectoris	Unknown
19	64/M	Simvastatin (S)	Myocardial infarction, diabetes mellitus, myalgia, medicine ineffective, hypertriglyceridaemia, hypercholesterolaemia	Unknown
20	57/M	Vinorelbine (S) Acetylsalicylic acid, atenolol, enoxaparin, escitalopram, lisinopril, magnesium, megestrol (all	Myocardial infarction, anorexia, diarrhoea, embolism pulmonary, fall, gait abnormal, hypokalaemia, oedema peripheral	Unknown but died
21	78/M	Dexchlorpheniramine, etodolac, morphine, oxycodone, prochlorperazine (all C)	Myocardial infarction, pneumonia bacterial**	Recovered

**Cases 2, 8, 11 and 12 are quadruplicates, #Cases 13 and 15 are duplicates, **MedDRA terms*

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CAVEAT DOCUMENT

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

Uppsala Monitoring Centre (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®.

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