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

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

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No. 4, 2013

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

In addition to the usual features, this issue includes the summary of discussions from the tenth meeting of the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP).

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## Feature
- Tenth Meeting of the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) ........................ 24
Almitrine-containing medicines

Oral almitrine to be withdrawn by EU Europe. The Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CM DH), a medicines regulatory body representing the European Union (EU) Member States, has endorsed the recommendation by the European Medicines Agency’s (EMA’s) Pharmacovigilance Risk Assessment Committee (PRAC), that permission to market oral medicines containing almitrine should be withdrawn across the EU. As the PRAC recommendation was endorsed by consensus by the CMDh, it will now be implemented directly by the Member States where oral almitrine is authorised, according to an agreed timetable.

Almitrine is a stimulant of the part of the brain responsible for the breathing reflex. In the EU, it is authorised in France, Poland and Portugal to be taken orally for the treatment of chronic respiratory failure (inability of the lungs to take in oxygen and get rid of carbon dioxide properly), which is associated with hypoxaemia (lower than normal levels of oxygen in the blood). These conditions pose a particular problem in patients with lung conditions known as chronic obstructive pulmonary disease (COPD), where the airways and air sacs inside the lungs become damaged or blocked.

The safety review of oral almitrine was requested by the French medicines agency, the National Agency for the Safety of Medicine and Health Products (ANSM), because of concerns about side effects and a view that the available evidence did not support the use of the medicine in the current management of COPD.

The PRAC concluded that there is a clear association between oral almitrine treatment and potentially serious and long-lasting peripheral neuropathy (damage to the nerves in the hands and feet) and significant weight loss that further weakens patients. The PRAC noted that cases continue to be reported even after additional precautions on the use of the medicines were put in place. Furthermore, oral almitrine is no longer included as a recommended therapy in international treatment guidelines for the management of COPD. The CMDh agreed with the PRAC conclusion that the benefits of these medicines do not outweigh their risks, and adopted a final position that the marketing authorisations should be withdrawn throughout the EU.

Health-care professionals are advised the following:

- Patients being treated with oral almitrine should have their treatment reviewed at the next scheduled appointment, and appropriate alternative treatments should be considered.
- Pharmacists should refer patients presenting a new or repeat prescription to their treating physician.
- Prescribers and pharmacists will be sent a letter giving them further information on the withdrawal of oral almitrine.

Reference:

Codeine

Restricted use as analgesic in children and adolescents under 18

UK. The Medicines and Healthcare products Regulatory Agency (MHRA) announced that the use of codeine for analgesia in children and adolescents under 18 has been restricted after a European safety review. The review was triggered by case reports of children who received codeine for pain control after tonsillectomy or adenoidectomy (or both) for obstructive sleep apnoea and who developed rare, but life-threatening adverse events, including death.

Codeine is converted to morphine in the liver by the CYP2D6 enzyme. There are many genetic variations of CYP2D6, which affect the extent of this conversion in individuals. Different plasma morphine concentrations in patients’ blood leads not only to different levels of pain relief, but also to a variable and unpredictable risk of side effects due to morphine’s action on the brain and respiratory centre.

The MHRA advised Health-care professionals that:

- Codeine should only be used to relieve acute moderate pain in children older than 12 years and only if it cannot be relieved by other painkillers such as paracetamol or ibuprofen alone
- Codeine is now contraindicated in:
  - all children age 0–18 years who undergo tonsillectomy or adenoidectomy (or both) for obstructive sleep apnoea
  - all patients of any age known to be CYP2D6 ultra-rapid metabolisers
- Codeine is not recommended for use in children whose breathing might be compromised, including those with: neuromuscular disorders; severe cardiac or respiratory conditions; upper respiratory or lung infections; multiple trauma; or extensive surgical
procedures. Morphine toxicity may be increased in these settings

- In children age 12–18 years, the maximum daily dose should not exceed 240 mg. This may be taken in divided doses up to four times a day at intervals of no less than 6 hours. It should be used at the lowest effective dose for the shortest period. Duration of treatment should be limited to 3 days and if no effective pain relief is achieved, treatment should be reviewed by a physician
- Information should be given to parents and caregivers on how to recognise the signs and symptoms of morphine toxicity, and advice should be given to stop giving the child codeine and to seek medical attention immediately if the child shows these signs or symptoms, which include: reduced levels of consciousness; somnolence; respiratory depression; ‘pin-point’ pupils; lack of appetite; constipation; or nausea and vomiting
- Codeine should not be used by breastfeeding mothers because it can pass to the baby through breast milk and potentially cause harm

(See WHO Pharmaceuticals Newsletters No.5, 2012 for use in certain children after tonsillectomy and/or adenoidectomy - risk of rare, but life-threatening adverse events or death in the USA).

**Reference:**

**Cyproterone and ethinylestradiol containing medicinal products**

**Benefits of Diane 35 and its generics outweigh risks in certain patient groups**

**Europe.** The CMDh endorsed the recommendation of the EMA’s PRAC, which concluded that the benefits of Diane 35 (cyproterone acetate 2 mg / ethinylestradiol 35 micrograms) and its generics outweigh the risks, provided that several measures are taken to minimise the risk of thromboembolism. These medicines should be used solely in the treatment of moderate to severe acne related to androgen sensitivity or hirsutism in women of reproductive age. Furthermore, Diane 35 and generics should only be used for the treatment of acne when alternative treatments, such as topical therapy and antibiotic treatment, have failed.

Since Diane 35 and its generics act as hormonal contraceptives, women should not take these medicines in combination with other hormonal contraceptives. Concomitant use of Diane 35 and its generics with another hormonal contraceptive will expose women to a higher dose of oestrogen and increase the risk of thromboembolism.

The risk of thromboembolism occurring with these medicines is low and well known. However, to minimise this risk, further measures should be implemented in addition to the updated product information. These include providing educational materials to prescribers and patients highlighting the risks of thromboembolism, for example a prescriber checklist to ensure that the risks, together with the signs and symptoms, are discussed with the patient.

The review of Diane 35 and its generics was triggered by the French medicines agency, the National Agency for the Safety of Medicine and Health Products (ANSM), following its decision to suspend Diane 35 and its generics in France within three months. The French decision followed a national review of the medicine by ANSM. This review highlighted serious thromboembolic events and extensive off-label use of these medicines as a contraceptive only.

Despite the PRAC recommendation, ANSM proceeded with the suspension of the marketing authorisation of these medicines in France. Once the European Commission has adopted its decision, all EU Member States where Diane 35 and its generics are authorised must follow it and ensure that all agreed risk-minimisation measures, including changes to the information to prescribers and patients, are implemented.

(See WHO Pharmaceuticals Newsletter for review of Diane 35 and other medicines started extensive off-label use of these medicines as a contraceptive as hormonal contraceptives, women should not take these medicines in combination with other hormonal contraceptives. Concomitant use of Diane 35 and its generics with another hormonal contraceptive will expose women to a higher dose of oestrogen and increase the risk of thromboembolism.

**Diclofenac**

**New contraindications and warnings after a Europe-wide review of cardiovascular safety**

**UK.** The Medicines and Healthcare products Regulatory Agency (MHRA) announced that available data indicate that the cardiovascular risk with diclofenac is similar to that of the selective COX-2 inhibitors and that, consistent with COX-2 inhibitors, diclofenac is now regulated by the Medicines and Healthcare products Regulatory Agency (MHRA) as a COX-2-selective non-steroidal anti-inflammatory drug (NSAID) and is no longer available for use in the UK.

**Reference:**

**Diclofenac**

**New contraindications and warnings after a Europe-wide review of cardiovascular safety**

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**Reference:**
contraindicated in those with: ischaemic heart disease; peripheral arterial disease; cerebrovascular disease; or established congestive heart failure (New York Heart Association [NYHA] classification II–IV). Health-care professionals are advised that patients with these conditions should be switched to an alternative treatment at their next routine appointment. The new treatment advice applies to systemic formulations (ie, tablets, capsules, suppositories, and injection available both on prescription and via a pharmacy, P); it does not apply to topical (ie, gel or cream) formulations of diclofenac.

It is also advised that diclofenac treatment should only be initiated after careful consideration for patients with significant risk factors for cardiovascular events (eg, hypertension, hyperlipidaemia, diabetes mellitus, smoking).

An increased risk of heart attack and stroke with some non-selective non-steroidal anti-inflammatory drugs (NSAIDs)—such as diclofenac—is well recognised, particularly with long-term use of high doses and in patients who are already at high risk. Warnings for health-care professionals and patients have been included in the product information and in the British National Formulary for some years.

The European Medicines Agency’s Pharmacovigilance Risk Assessment Committee has recently recommended updates to the treatment advice for diclofenac in light of the findings of a Europe-wide review of the cardiovascular safety of NSAIDs. The review found further evidence that the arterial thrombotic risk with diclofenac is similar to that for the selective COX-2 inhibitors.

Diclofenac is available to buy in a pharmacy without a prescription at low doses (up to 75 mg/day) for short-term use (3 days) in the UK. Pharmacists are advised to take the following steps when supplying diclofenac without prescription:

- Ask questions to exclude supply for use by people with established cardiovascular disease and people with significant risk factors for cardiovascular events
- Advise patients to take diclofenac only for 3 days before seeking medical advice
- Advise patients to take only one NSAID at a time

(See WHO Pharmaceuticals Newsletters No.6, 2012 for need for updated treatment advice for diclofenac in follow-on review in EU).

Reference:

Hydroxyethyl starch intravenous infusion

Suspension of licences in UK and new boxed warning in the US

UK (1). The Medicines and Healthcare products Regulatory Agency (MHRA) announced that the licences for all hydroxyethyl starch (HES) products have been suspended.

HES products are synthetic colloid solutions used for plasma volume expansion in a range of clinical settings. In the UK, marketed HES products are: Volulyte®, Tetraspan®, Venofundin®; and Voluven®.

The EU Pharmacovigilance Risk Assessment Committee has reviewed the balance of benefits and risks of HES products in different patient groups. The review concluded that there is a clear indication of harm when HES is used for fluid resuscitation, and no evidence of a greater benefit, compared with crystalloid solutions. The risks HES products pose to patients are considered to outweigh the benefits in all clinical settings. Although a formal EU regulatory position has not been finalised, on the advice of the Commission on Human Medicines, the licences and therefore use of HES products is being suspended in the UK.

Health-care professionals are advised that:

- There is clear evidence of harm from increased renal dysfunction and mortality associated with the use of HES, and overall the risks outweigh the benefits
- There is no evidence that infusion solutions containing HES for plasma volume expansion provide additional clinically relevant benefit to patients compared with crystalloids in any indication
- HES should not be used for plasma volume expansion. An alternative resuscitation fluid should be selected according to clinical guidelines
- A recall of all remaining HES stock has been issued

USA (2). The U.S. Food and Drug Administration (FDA) concluded that Hydroxyethyl starch (HES) solutions should not be used in critically ill adult patients, including patients with sepsis and those admitted to the ICU, and a Boxed Warning to include the risk of mortality and severe renal injury is warranted. In addition, The US FDA reviewed a meta-analysis of studies conducted in patients undergoing open heart surgery in association with cardiopulmonary bypass and determined that an additional warning about excessive bleeding is needed in the Warnings and Precautions Section of the package insert.

HES solutions are used for the treatment of hypovolemia when plasma volume expansion is desired. Recent
data have associated the use of these products with an increased risk of severe adverse events when used in certain patient populations.

In the US, recommendations for health-care professionals include the following:
- Do not use HES solutions in critically ill adult patients including those with sepsis, and those admitted to the ICU.
- Avoid use in patients with pre-existing renal dysfunction.
- Discontinue use of HES at the first sign of renal injury.
- Need for renal replacement therapy has been reported up to 90 days after HES administration. Continue to monitor renal function for at least 90 days in all patients.
- Avoid use in patients undergoing open heart surgery in association with cardiopulmonary bypass due to excess bleeding.
- Discontinue use of HES at the first sign of coagulopathy.

Reference:

Ketoconazole

Risk of potentially fatal liver toxicity
Canada. The manufacturers of ketoconazole, in collaboration with Health Canada, have revised the Product Monograph (PM) regarding the risk of potentially fatal liver toxicity. Ketoconazole has been associated with rare cases of serious hepatotoxicity including liver failure and death. This risk was also observed in patients with no pre-existing liver disease and no serious underlying medical conditions. Hepatotoxicity and death have been reported to occur at recommended doses and with treatment courses longer than 10 days.

The Warnings’ sections of the PM was updated to include the following additional instructions:
- Ketoconazole tablets are indicated for the treatment of serious or life threatening systemic fungal infections and should not be considered for mild to moderate infections.
- Oral ketoconazole has been associated with hepatic toxicity, including cases with fatal outcomes.
- Liver function tests should be performed in all patients before starting treatment, at week 2 and 4, and monthly thereafter.
- Treatment should be stopped if liver parameters are elevated (> 3 times the normal limit) or if patients develop clinical signs or symptoms consistent with liver disease such as anorexia, nausea, vomiting, jaundice, fatigue, abdominal pain, dark urine, or pale stools.

Health-care practitioners are advised to consider the risk of fatal liver toxicity with ketoconazole when prescribing antifungal treatment for patients who are already at risk for liver toxicity. It is also advised that patients using ketoconazole concurrently with potentially hepatotoxic drugs should be carefully monitored, especially in those expected to be on prolonged therapy or at risk for hepatotoxicity.

Reference:

Olmesartan medoxomil

Label changes to include sprue-like enteropathy
USA. The US FDA warned that olmesartan medoxomil (Benicar®, Benicar HCT®, Azor®, Tribenzor®, and generics) can cause intestinal problems known as sprue-like enteropathy. Symptoms of sprue-like enteropathy include severe, chronic diarrhea with substantial weight loss. FDA has approved changes to the labels of these drugs to include this concern. Sprue-like enteropathy has not been detected with angiotensin II receptor blockers (ARB) other than olmesartan.

Olmesartan medoxomil is ARB approved for the treatment of high blood pressure, alone or with other antihypertensive agents.

Health-care professionals are recommended to tell patients to contact them if they develop severe, chronic diarrhea with substantial weight loss while taking an olmesartan-containing product, even if it takes months to years for symptoms to develop. Patients should contact their health-care professional right away if they take an olmesartan-containing product and experience severe diarrhea, diarrhea that does not go away, or significant weight loss.

References:

Strontium ranelate

Recommendation to restrict the use and further review started
Europe. The CHMP recommended a restriction in the use of strontium ranelate (Protelos® and Osseor®), following an assessment of data showing an increased risk of serious heart problems. The CHMP recommended that the drug should only be used to treat severe osteoporosis in postmenopausal women at high risk of fracture and severe osteoporosis in men at
increased risk of fracture. Additional measures, including restrictions in patients with heart or circulatory problems, were also recommended to minimise the heart risks of these medicines.

The CHMP recommendation is based on the advice of the PRAC, which evaluated strontium ranelate as part of a routine benefit-risk assessment. During the assessment, data from clinical studies in post-menopausal women were evaluated, showing a higher risk of heart attack with the drug than with placebo, with no observed increase in mortality risk. Given the other serious risks (blood clots and rare serious skin reactions) previously identified with the medicine, the PRAC concluded that certain restrictions in the use of the medicine should be in place for the benefit-risk balance to remain favourable and that a further in-depth evaluation of the benefits and risks of the medicine was needed.

The CHMP agreed with the PRAC’s recommendations and this opinion will be sent to the European Commission for a legally binding decision. A further wide-ranging evaluation of the benefits and risks of strontium ranelate will now be conducted by PRAC and CHMP. In the meantime, the current recommendations are intended to minimise the risk of serious heart problems.

Health-care professionals are advised the following:
• Strontium ranelate should only be used for the treatment of severe osteoporosis in postmenopausal women at high risk of fracture and severe osteoporosis in men at increased risk of fracture.
• Strontium ranelate is contraindicated in patients with a current or past history of ischaemic heart disease, peripheral arterial disease, or cerebrovascular disease, or in patients with uncontrolled hypertension.
• Treatment with strontium ranelate should only be started by a physician experienced in the treatment of osteoporosis.
• Physicians should base their decisions to prescribe strontium ranelate on an assessment of the individual patient’s risks. The patient’s risk of developing cardiovascular disease should be evaluated before and at regular intervals during treatment.
• Treatment should be stopped if the patient develops ischaemic heart disease, peripheral arterial disease or cerebrovascular disease or if hypertension becomes uncontrolled.

(See WHO Pharmaceuticals Newsletter No. 3, 2013 for risk of serious cardiac disorders in UK).

Reference:

Retigabine

Restricted use is recommended due to risk of retinal pigmentation

Europe. The CHMP recommended restricting the use of the anti-epileptic medicine retigabine (Trobalt®) only to those patients for whom other anti-epileptic medicines have proved inadequate or have not been tolerated. This follows a careful evaluation of cases of pigmentation of the skin, nails, lips and eye tissues, including the retina reported in patients taking part in long-term studies. Retigabine was authorised as add-on treatment in adults with partial-onset seizures.

The CHMP recommended that patients currently being treated with retigabine should be reviewed at a routine (non-urgent) appointment. The balance of benefits and risks should be re-evaluated, and patients should be informed of the latest safety information. The CHMP also recommended that a comprehensive eye examination should be performed at the start of treatment (for new patients) and at least every six months during treatment. If retinal pigment or vision changes are detected, treatment with the drug should only be continued after a careful re-assessment of the balance of benefits and risks.

In its assessment, the CHMP took into account not only the importance of retinal pigmentation, as it could possibly result in impaired vision, but also considered that uncontrolled epilepsy is a serious condition which may be life-threatening if left untreated. The CHMP therefore concluded that the drug remains a valuable alternative option for patients whose epilepsy cannot be controlled by other medicines.

Reference:

Varenicline tartrate and bupropion hydrochloride

Revision to the Product Monograph of non-nicotine smoking cessation aids

Canada. Pfizer Canada Inc. and Valeant Canada LP, in collaboration with Health Canada, informed of revisions to Product Monograph (PM) for non-nicotine smoking cessation aids varenicline tartrate (Champix®) and bupropion hydrochloride (Zyban®).

Varenicline tartrate is a smoking cessation pharmacological treatment to be used in conjunction with
smoking-cessation counselling. Bupropion hydrochloride is a smoking cessation pharmacological treatment to be used in conjunction with behavioural modification. In addition, Bupropion hydrochloride is indicated for use with nicotine replacement therapy.

The following key statements have been added to the PMs for the class of non-nicotine smoking cessation aids:

• Prior to a decision to prescribe a non-nicotine treatment, varenicline tartrate or bupropion hydrochloride, thorough consideration should be given to the treatment option of nicotine replacement therapy.

• In many cases, nicotine replacement therapy should be tried before prescribing these drugs.

These revisions to the PMs are based on continuing post-marketing surveillance and mechanisms of action of non-nicotine products. The PM revisions and this communication are intended to reinforce the importance of a discussion with patients about the expected potential benefits and risks associated with the use of smoking cessation therapies.

(See WHO Pharmaceuticals Newsletters No. 1, 2013 and No. 4, 2011 for risk of certain cardiovascular adverse events in the USA).

Reference:

Zolpidem containing products

Lower recommended doses required

USA. The US FDA approved label changes specifying new dosing recommendations for zolpidem products (Ambien®, Ambien CR®, and Edluar® and Zolpimist™), which are widely prescribed sleep medications. FDA has approved that the bedtime dose be lowered because of the known risk of next-morning impairment with these drugs.

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

References:
Insulin glargine

Data do not indicate an increased risk of cancer

Europe. The EMA completed a review of new data on the cancer risk with insulin glargine-containing medicines (Lantus® and Optisulin®). The CHMP concluded that the data do not show an increased risk of cancer and that the balance of the medicine’s benefits and risks remains unchanged. Insulin glargine is an injectable insulin used to treat diabetes in patients aged two years or older.

In 2009, the publication of four registry studies raised concerns of a possible link between insulin glargine and cancer, particularly breast cancer. Following the publication, the CHMP carried out an indepth review and concluded, that, due to some limitations in the way the studies were conducted, a link between insulin glargine and cancer could not be confirmed or excluded from the results. In addition, the Committee noted that the results of the studies were not consistent. The CHMP requested that the company that markets the medicine provide further data. The company subsequently carried out further studies and submitted the results to the CHMP for review.

Based on the assessment of the population-based studies, the CHMP concluded that overall the data did not indicate an increased risk of cancer with insulin glargine, noting that there is no known mechanism by which the insulin glargine would cause cancer and that a cancer risk has not been seen in laboratory studies. As for all medicines, the Agency will continue to assess any new data that become available in this area, as part of the routine monitoring of the medicine.

(See WHO Pharmaceuticals Newsletter No. 4, 2009 for risk of cancer to be investigated in EU and in the USA).

Reference:

Olanzapine Pamoate

Investigating two deaths following injection

USA. The US FDA is investigating two unexplained deaths in patients who received an intramuscular injection of the antipsychotic drug olanzapine pamoate (Zyprexa Relprevv®). The patients died 3-4 days after receiving an appropriate dose of the drug, well after the 3-hour post-injection monitoring period required under the drug’s Risk Evaluation and Mitigation Strategy (REMS). Both patients were found to have very high olanzapine blood levels after death.

Under the REMS, patients are required to receive olanzapine pamoate injection at a REMS-certified health care facility, to be continuously monitored at the facility for at least 3 hours following an injection, and to be accompanied home from the facility. The drug’s label contains warnings about the risk of post-injection delirium sedation syndrome (PDSS), a serious condition in which the drug enters the blood too fast following an intramuscular injection, causing greatly elevated blood levels with marked sedation (possibly including coma) and/or delirium.

The US FDA provided this information to health-care professionals while it continues its investigation. If therapy with olanzapine pamoate is started or continued in patients, health-care professionals are recommended to follow the REMS requirements and drug label recommendations.

Patients and caregivers are recommended to talk to their health-care professional(s) about any questions or concerns.

References:

Renin-angiotensin-system (RAS)-acting agents

Review started of combined use of renin-angiotensin-system-acting agents

Europe. The EMA announced to start a review of the risks of combining certain medicines to block separate stages of the renin-angiotensin system (RAS) in the treatment of hypertension and congestive heart failure. The RAS is a hormone system that controls blood pressure and the volume of fluids in the body, and medicines that act on this system are collectively known as ‘RAS-acting agents’.

The review was started due to concerns that combining several RAS-acting agents could increase the risk of hyperkalaemia, low blood pressure and kidney failure, compared with using one RAS-acting agent alone. In addition, using multiple RAS-acting agents may not be more beneficial than a single RAS-acting agent in terms of reducing overall mortality. The evidence is based on a number of published studies, including a recent meta-analysis of 33 clinical studies involving over 68,000 patients published in the British Medical Journal.

There are three main types of RAS-acting agent: angiotensin-receptor blockers (ARBs, sometimes known as sartans), angiotensin-converting-enzyme inhibitors (ACE
inhibitors) and direct renin inhibitors (such as aliskiren).

The current review follows a previous EMA review of medicines containing aliskiren, which concluded in February 2012 that the combination of aliskiren with an ACE inhibitor or ARB could increase the risk of side effects affecting the heart and blood vessels or the kidneys. The CHMP decided that the combination of aliskiren with an ACE inhibitor or ARB is not recommended in any patient and should be contraindicated in patients with diabetes or moderate to severe kidney impairment, since they are at greater risk.

The EMA will evaluate the impact of the latest available evidence on the benefit-risk balance of combining RAS-acting agents in the treatment of hypertension and congestive heart failure.

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

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

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

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

### Agomelatine and QT prolonged

**Dr. Raquel Herrera Comoglio, Argentin**

**Summary**

Agomelatine is a synthetic analogue of the hormone melatonin used to treat major depressive disorder. QT prolongation is a proarrhythmic cardiac repolarization disturbance that can be congenital or induced by stressors, especially several drugs. Many drugs including antiarrhythmic agents, antipsychotics and antidepressants have been associated with QT prolongation.

On 25 January 2013, there were nine Individual Case Safety Reports (ICSRs) reporting the combination between agomelatine and QT prolonged in the WHO Global ICSR Database, VigiBase™. This possible association is not listed in the product information for agomelatine and only one published case report was found in a literature search. The ICSRs from VigiBase present cases in which agomelatine has been suspected as the cause of QT prolongation in patients with risk factors (female gender, congenital Long QT Syndrome), co-administration of other agents previously associated with QT prolongation, or intentional overdose. The analysis of these case reports suggests that agomelatine might prolong the QT interval in patients with predisposing risk factors or overdose.

**Introduction**

Agomelatine is a synthetic analogue of the hormone melatonin that regulates various circadian rhythms including sleep-wake cycles. It is used as an anti-depressant with a novel mechanism of action. It acts as a potent melatonin receptor agonist drug (MT₁ and MT₂), and similarly to currently used antidepressant drugs, mianserin and mirtazapine, it also binds to and inhibits 5-HT₂C receptor subtypes. Agomelatine was approved by centralized procedure as an antidepressant agent in the EU in February 2009, and in Australia late 2010; it has not been approved in the USA to date.¹,²,³,⁴

In in vitro assays, CYP1A2 was responsible for the major metabolism of agomelatine, whereas CYP2C9 and CYP2C19 were found likely to be of potential relevance only at higher agomelatine concentrations. The concomitant use of potent CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin) is contraindicated.

The prolongation of cardiac repolarization in Long QT Syndrome (LQTS) is reflected in the surface electro-cardiogram, expressed as the QT interval corrected by the heart rate (QTc).⁵ QT lengthening can result from several factors: some medications, congenital LQTS, clinically significant bradycardia or heart disease, electrolyte imbalance (hypokalaemia, hypomagnesaemia or hypocalcaemia), and/or pharmacokinetic/pharmacodynamic interactions.⁶,⁷,⁸ Long QTc can lead to a life-threatening polymorphic ventricular...
tachycardia known as Torsade de Pointes (TdP) that may cause sudden death, but this relationship is not always straightforward.\(^8\)

Long QTc can be congenital or acquired. Drug therapy is the most common cause of the acquired Long QT Syndrome (aLQTS). Virtually all drugs that cause aLQTS reduce the delayed rectifier potassium current (IKr) and prolong the cardiac action potential; case series support the idea that genetic variants in ion channels can increase the risk.\(^8\) Some drugs prolong QTc in a dose-dependent manner; others do so at any dose. Most patients that develop drug-induced TdP have underlying risk factors. Female sex is the most common.

The most common class of drugs implicated in aLQTS is QT prolonging anti-arrhythmic drugs; in particular IKr blockers such as sotalol, dofetilide, quinidine and ibutilide, but this proarrhythmia can also occur with non-cardiovascular drugs, especially antipsychotics and antidepressants.\(^8,9,10,11,12,13\)

The effects of agomelatine on QT interval were evaluated in two specific premarketing studies. The first study included only 13 subjects and agomelatine did not seem to cause any clinically meaningful changes in cardiac depolarization. The second study was conducted in response to regulatory requirements and included 56 subjects (28 males and 28 females). The results showed that single doses of agomelatine 50 mg and 400 mg fulfilled the demands set out in the CHMP/ICH/2/04 “Note for guidance on the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs”.\(^2,4\)

**Reports in VigiBase**

Up to 25 January 2013, a total of nine Individual Case Safety Reports (ICSRs) of agomelatine and QT prolonged were submitted to the WHO Global ICSR Database, VigiBaseTM. The IC value for the combination was 2.38 and the IC\(_{0.25}\) 1.29. An overview of these case reports’ main characteristics is displayed in Table 1.
Table 1. Characteristics of retrieved ICSRs for agomelatine and QT prolonged in VigiBase™

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/Gender</th>
<th>Suspected drugs/daily dose</th>
<th>Concomitant drugs/daily dose</th>
<th>Time to onset from the start of therapy</th>
<th>Other reported ADRs in addition to QT prolonged (WHO-ART preferred terms)</th>
<th>QT prolongation outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>58/F</td>
<td>Agomelatine 50 mg</td>
<td>Fentanyl 25 µg Ramipril 10mg</td>
<td>17 days</td>
<td>-</td>
<td>Recovered</td>
</tr>
<tr>
<td>1</td>
<td>39/F</td>
<td>Agomelatine 25 mg</td>
<td>Bisoprolol 2.5 mg</td>
<td>8 days</td>
<td>-</td>
<td>Recovered</td>
</tr>
<tr>
<td>2</td>
<td>58/F</td>
<td>Agomelatine 25 mg, increased to 50 mg Venlafaxine 75 mg increased to 300 mg</td>
<td>Ramipril 10mg Fentanyl 25 µg Fentanyl 50 µg</td>
<td>17 days from the 25 mg dose and 7 days from 50 mg dose</td>
<td>Medicine ineffective (at 25 mg dose)</td>
<td>Recovered</td>
</tr>
<tr>
<td>3</td>
<td>76/F</td>
<td>Escitalopram 5 mg Agomelatine 25 mg</td>
<td>Lansoprazole Hydrochlorothiazide/ Irbesartan 150 mg</td>
<td>8 days</td>
<td>Convulsions grand mal Vomiting Constipation</td>
<td>Died</td>
</tr>
<tr>
<td>4</td>
<td>45/F</td>
<td>Agomelatine 25mg, increased to 50 mg (decreased to 25mg after ADR)</td>
<td>Amisulpride 200 mg</td>
<td>Approximately 3 months</td>
<td>Fracture Impulse control disorder</td>
<td>Not recovered</td>
</tr>
<tr>
<td>5</td>
<td>28/M</td>
<td>Agomelatine 25 mg Agomelatine 700mg</td>
<td>Chlorprothixene 30 mg Prothipendyl Diclofenac Acetylsalicylic acid</td>
<td>1 day (after overdose)</td>
<td>Intentional overdose Suicide attempt Somnolence</td>
<td>Recovered</td>
</tr>
<tr>
<td>6</td>
<td>Around 55/F</td>
<td>Agomelatine 350 mg</td>
<td>Trimipramine 3000 mg Lorazepam 90 mg Zopiclone 150 mg</td>
<td>Same day as overdose</td>
<td>Condition aggravated Coma Somnolence Multiple drug overdose (MedDRA term)</td>
<td>Recovered</td>
</tr>
<tr>
<td>7</td>
<td>32/F</td>
<td>Agomelatine Ibuprofen Ziprasidone Pregabalin Lamotrigine Venlafaxine</td>
<td>-</td>
<td>1 day</td>
<td>Coma Intentional overdose</td>
<td>Recovered</td>
</tr>
<tr>
<td>8</td>
<td>45/F</td>
<td>Quetiapine 600 mg Agomelatine 25 mg</td>
<td>Lorazepam 6 mg Diazepam 60 mg Zolpidem 80 mg</td>
<td>10 months</td>
<td>Migraine aggravated Agitation Insomnia Dizziness Diarrhoea Sleep disorder Condition aggravated</td>
<td>Reported as not recovered, ECG normal during hospitalization</td>
</tr>
</tbody>
</table>
All ICSRs are from Europe, most come from Germany (seven out of nine, including one report from literature), one from Italy and one from Spain. The ICSRs were entered into VigiBase from July 2010 to April 2012.

The reporters are physicians, except for one from literature and one from a consumer. Case 2 and case 0 (from a German physician) seem to be duplicates. The case has also been published in a review, which provides more precise and thoroughly documented data. Due to this we will consider only eight cases. Seven out of eight cases concerned female patients and there was one male patient. There was only one patient older than 60 years (a 76 year old woman), the male patient was 28 years old and the other patients were aged in the range 32-58 years.

The 76 year old woman died after 16 days of concomitant therapy of escitalopram and agomelatine at lowest doses. Both drugs had been added to non psychotropic therapy (irbesartan/hydrochlorothiazide and lanoprazole) and had been administered for 14 days, when QT prolongation was diagnosed. In five of eight cases the patients recovered from QT prolongation.

All eight cases mentioned concomitant drugs. Two patients had a medical history of congenital LQTS, and both were on beta-blocker therapy (bisoprolol and metoprolol respectively). Although seven cases reported concomitant administration of other drugs associated with QT prolongation, agomelatine was the only suspected medication in four cases. Concomitant medication included psychotropic drugs in seven cases. No ICSRs mentioned any antiarrhythmic, antibiotic, antiemetic, antineoplastic or any other non psychotropic drugs previously known to cause QT prolongation as concomitant medication.

Agomelatine was added to previous non psychotropic therapy in three cases. In case 1, agomelatine was added as the only psychotropic medication eight days prior to the reaction. In the other two cases agomelatine was added in combination with another psychotropic agent to previous non psychotropic therapy. In case 3 (time to onset: eight days), agomelatine was prescribed together with escitalopram to a female patient on previous therapy not associated with QT prolongation. In case 5, agomelatine 25 mg was prescribed on an unspecified date; the patient ingested a massive dose of agomelatine together with two antipsychotics, chlorprothixene and prothipendyl, in a suicide attempt the day before the adverse reaction was detected.

Agomelatine was added to previous therapy with agents known/reported as potential QT-prolonging agents in two cases. In case 2 (report from the literature), agomelatine was prescribed to a patient on previous therapy with venlafaxine, together with a fentanyl and ramipril long-term therapy. In case 4, agomelatine was prescribed to a patient with congenital LQTS on previous therapy with amisulpride and metoprolol. On the other hand, in case 8, quetiapine 600 mg was prescribed to a female patient on long-term therapy with agomelatine (nine months).

Seven cases reported concomitant psychotropic therapy with antidepressants or antipsychotics. In three of the seven cases agomelatine was the only suspected drug, although administered concomitantly with amisulpride, chlorprothixene, prothipendyl and trimipramine. References from the literature and product information report QT prolongation in association with venlafaxine, escitalopram, amisulpride, chlorprothixene, prothipendyl, trimipramine, ziprasidone and quetiapine.

There are three cases reporting overdose (two reported as intentional overdose, one of them also states suicide attempt, the third is reported with the MedDRA term multiple drug overdose). Case 5, a 28 year old male patient, attempted suicide by taking one packet of acetylsalicylic acid, 30 tablets of chlorprothixene, pro-thipendyl and one packet of agomelatine (700 mg) in one day; previous concomitant administration of diclofenac is mentioned. Case 7, a 32 year old woman, ingested unspecified overdoses of psychotropic medicines (agomelatine, ziprasidone, pregabalin, lamotrigine, venlafaxine) together with ibuprofen, and all medicines were reported as suspected. In case 6, the patient ingested 90 mg of lorazepam, 150 mg of zopiclone, 3000 mg of trimipramine and 350 mg of agomelatine. All three patients recovered from QT prolongation, two patients recovered after one day, and one patient recovered after two days. Although all three patients took other drugs that have previously been associated with QT prolongation, agomelatine was reported as the only suspected drug in two cases (cases 5 and 6).

**Literature and Labelling**

A PubMed search, using terms “agomelatine” and “QT prolongation” retrieved only one result, a case report describing case 2 in this case series. The same case was also mentioned in an article from 2011.

QTc prolongation is not mentioned in the EMA Product Information, or in the EMA Public Assessment Report, as an adverse effect of agomelatine.

**Discussion and Conclusion**

Drug-induced LQTS can be caused by cardiovascular and non-cardiovascular drugs. The cardiovascular side effects of older antidepressants, such as tricyclic anti-
Depressants, are well established and are known to be linked to their capacity to inhibit cardiac and vascular ion channels. Other newer antidepressant agents, such as selective serotonin reuptake inhibitors, mirtazapine and venlafaxine, also share antagonistic properties with regard to voltage-dependent ion channels in different tissues.

Agomelatine, similarly to mianserin and mirtazapine, has a serotonin 5-HT2C antagonist effect. Both mianserin and mirtazapine can prolong the QTc interval.

Drug-induced LQTS results from the association of predisposing factors to a drug acting as an environmental stressor. Predisposing factors include female sex, congenital LQTS, electrolyte disturbances and high drug levels.

In the reviewed ICSRs, exposure to normal doses of agomelatine was the only suspected cause of QTc prolongation in two patients with congenital LQTS. Overdose of agomelatine was reported as the only suspected cause of QT prolongation in patients with multiple drug intentional overdoses. All patients were on previous therapy with other agents. The role of concomitant medication and risk factors is discussed below:

In case 0 (likely a duplicate of case 2), agomelatine was prescribed to a 58 year old female patient treated with fentanyl and ramipril; a causal link is supported by time to onset, (17 days), risk factors, and reversibility of the adverse reaction. Case 2 (from literature) reports that agomelatine was prescribed to a 58 year old female patient on treatment with venlafaxine, ramipril and fentanyl. Both antidepressants, venlafaxine and agomelatine, were reported as suspected to cause the QTc prolongation. For concomitant drugs, no other pharmacodynamic interactions seem to be likely, and fentanyl, an opioid agent, has also been suggested to have neutral or even some protective effect against QTc prolongation. The patient started therapy with venlafaxine and a borderline QTc interval prolongation was diagnosed. Increased doses did not worsen the effect on QT, and QTc was normalized on venlafaxine 75 mg. Venlafaxine was later stopped because of lack of effect.

Agomelatine was first started, concomitantly with venlafaxine, at 25 mg and after 10 days augmented to 50 mg. QTc interval prolongation was found 17 days after initiation of agomelatine therapy and seven days after the dose change to 50 mg. It increased to 477 milliseconds at day 31 (day 21 of 50 mg dosage). The dose of agomelatine was reduced and the QTc interval prolongation normalized seven days after the dose reduction. The dose effect on QTc interval supports a causal relationship. It is unclear whether the effect could be caused by both agents in a synergistic manner when administered concomitantly, but the reaction did remain under agomelatine therapy when venlafaxine had been already stopped.

In case 1, agomelatine was administered to a female patient with congenital LQTS treated with bisoprolol. The time to onset (eight days) and the underlying condition support a causal relationship with agomelatine.

In case 3, a female patient died after the introduction of an antidepressant therapy with low dose escitalopram and 25 mg of agomelatine. Both antioxidants and hydrochlorothiazide/irbesartan. A review found that escitalopram has a small effect on the QTc interval and a prolonged QTc was seen in 2 to 14% of escitalopram overdose cases, without serious cardiac sequelae.

In this ICSR, in addition to the suspected co-administered escitalopram, a female gender and hypothetical (but not reported) electrolyte disturbances (possibly caused by hydrochlorothiazide and vomiting) are risk factors for QT prolongation, and may have played a role in the fatal outcome. Concerning pharmacokinetic interactions, irbesartan as well as all proton-pump inhibitors (PPIs) may inhibit CYP2C9 which metabolizes escitalopram (together with CYP2D6) and also plays a minor role in agomelatine’s metabolism. Irbesartan has a modest affinity for CYP1A2, suggesting that the theoretical potential for drug interactions is likely to be quite low for the main CYP metabolizing agomelatine, but it has been shown to inhibit tolbutamide methylhydroxylation more potently, suggesting that it could play a role in inhibiting CYP2C9 agomelatine metabolism.

It has been observed that patients can present different responses to diverse QT-prolonging drugs. In case 4, agomelatine was given to a patient treated with amisulpride for psychoaffective disorder and with metoprolol for congenital LQTS. Treatment with amisulpride dated from the previous year (2010), and QT prolongation was reported as caused by agomelatine only. In case 8, where quetiapine 600 mg was added to agomelatine, it cannot be ruled out that agomelatine played some role in the QT prolongation.

Concerning cases reporting intentional overdose, the possible causality of agomelatine overdose is confounded by concomitant ingestion of other agents known to be QT prolonging. In case 5, chlorprothixene (also overdosed) and prothipendyl can both cause QT prolongation, therefore an additive effect is likely; as well as in the other two cases, where both patients also ingested other agents known to be QT prolonging (3000 mg of trimipramine in case 6 and an unspecified dose of ziprasidone in case 7). In spite of this confounding, due to overdoses of agomelatine, the role played by agomelatine cannot be ruled out. The analysis of these ICSRs suggests that agomelatine might prolong the QT interval in patients with predisposing risk factors or overdose.
References


Agomelatine has no binding interaction with the hERG potassium channels, whose inhibition can lead to prolonged QT interval. Based on these in vitro results, it seems unlikely that agomelatine could prolong QT intervals.

During the agomelatine development program, two specific studies were performed to evaluate cardiovascular safety in healthy volunteers. The first was a cross-over randomized, double blind, placebo-controlled study in 13 volunteers, exposed to single dose of 100 and 200mg of agomelatine, versus placebo. The administration of 100 or 200mg of agomelatine did not significantly prolong the ventricular repolarisation time.

The second (“thorough QT/QTc study”), was carried out according to the ICH E14 Guideline. It was a cross-over randomized study in 56 healthy young volunteers (28 males and 28 females) exposed to single oral maximal therapeutic (50mg) and supra-therapeutic (400mg) doses of agomelatine, placebo and single oral 400mg dose of moxifloxacin (positive control). The absence of effect on QT/QTc interval observed in the first study was confirmed in the second, even at supra-therapeutic dose up to 400mg of agomelatine.

From Market Authorisation (19-FEB-2009) to 19-FEB-2013 (PSUR 6 data-lock point), 11 cases of Electrocardiogram QT prolonged and 1 case of Long QT syndrome were reported to the MAH, i.e. a reported incidence of 1.4 case / 100 000 patient-years.

Out of these 12 cases, 6 occurred in a context of over- dose:

- 5 occurred in a multiple drug overdose, with a drug likely to induce of favor a conduction disorder concomitantly taken with agomelatine (trimipramine twice, bupropion, chlorprothixene and venlafaxine).
- 1 case occurred in association with severe alcohol poisoning.

In these cases, the suspected amount of agomelatine varied from 350mg to 3500mg. In the Summary of Product Characteristics (SmPC) of agomelatine, a case of ingestion of 2450mg without subsequent cardiovascular abnormalities was reported.

These 6 cases represented 4.2% of the 142 cases of agomelatine overdose received since Market Authorisation (68 cases of agomelatine overdose and 74 cases of multiple drug overdoses). No cardiac safety concern raised from the analysis of the 136 other cases of agomelatine overdose.

The remaining 6 cases of prolonged QT not occurring in a context of drug overdose are as follows:

- Medical history/context:
  - 2 cases in patients with medical history of congenital / Long QT syndrome
  - 1 case in a patient concomitantly treated with Quetiapine, for which prolonged QT is listed.
  - 1 case in an elderly patient, in a context of diabetic hyperosmolar coma
  - 2 cases (1 case in a context of atrioventricular node ablation, in a patient treated with amiodarone) were poorly documented (e.g. missing ECGs). The role of agomelatine was subsequently difficult to assess.

- 3 cases of positive dechallenge were observed, with no case of positive or negative rechallenge.

- Outcome: 3 patients recovered, 3 were not recovered at the time of the report

These 6 cases were reviewed by Prof. Christian Funck-Brentano, independent Cardiologist and Clinical Pharmacologist. Out of these 6 cases, 3 were assessed as not related to agomelatine:

- In 1 case, the patient was concomitantly treated with amisulpride, a drug known to prolong QT and cause Torsades de Pointes
- In 1 case, the patient was concomitantly treated with quetiapine, a drug known to prolong QT/QTc by 5 to 15 ms
- In 1 case, there was in fact no clinically significant QTc change, using the Fridericia correction formula, a formula which is widely accepted as limiting the biases introduced by the Bazett formula

Two poorly documented cases were considered as not assessable.

In the remaining case, no document is available in support of the diagnosis of QT prolongation (heart rate, corrected QT not provided): the patient presented with hyperglycemic hyperosmolar nonketotic syndrome. Severe potassium deficit often occurs in hyperglycaemic hyperosmolar state and, although no indication is given in the report on kalemia, it is likely that QT prolongation, if any, was due to hypokalemia. The presumed cause of the hyperglycemic hyperosmolar nonketotic coma was not indicated and could have multiple origins.

Overall, the role of agomelatine in these 12 cases seems to be unlikely. Based on the current clinical data and review of cases received from postmarketing surveillance, QT prolonged was not considered as a signal for agomelatine. This event will remain under close monitoring.
Tapentadol and Aggressive reaction
Dr. Ian Boyd, Australia

Summary
Tapentadol is a centrally acting synthetic analgesic combining opioid and non-opioid (noradrenaline reuptake inhibition) activity in a single molecule. In the WHO Global Individual Case Safety Report (ICSR) Database, VigiBase™, there are currently (25 January 2013) 12 ICSRs from four countries of aggressive reaction in association with tapentadol. The association has an IC value of 1.26 with an IC₀₂₅ value of 0.33. The outcome was stated in 10 reports. The patients were reported as recovered or recovering in nine cases and not recovered in one case. The drug was reported to have been withdrawn in eight of the cases where recovery was documented, as well as in the ICSR where the patient had not recovered.

The association of aggressive reaction with tapentadol appears to be a signal. Tapentadol was the only drug suspected in 10 of the 12 cases, the time to onset is suggestive of a drug-induced effect and the observation of recovery after dechallenge in eight of the 12 cases is highly supportive of the signal. In addition, the observation in the product information that other psychiatric reactions occurred commonly and uncommonly in clinical trials suggests that a mechanism for the development of another psychiatric reaction such as aggressive reaction may be possible. The fact that aggressive reaction has been reported in VigiBase at a similar level to some of these reactions is also suggestive of a signal.

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

Tapentadol is indicated for the management of moderate to severe chronic pain unresponsive to non-narcotic analgesia.

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

Aggressive reaction, or aggression, is one of a number of ill-defined behaviour and socialisation disturbances. Aggression can be either proactive or reactive. Proactive aggression is goal-oriented requiring neither provocation nor anger. It can be directed towards possessing objects or dominating people. Reactive aggression involves angry outbursts in response to provocation. However, regardless of its psychiatric definition, an aggressive reaction is a clinical judgment.

Reports in VigiBase
As of 25 January 2013 there are 12 Individual Case Safety Reports (ICSRs) of aggressive reaction in association with tapentadol in the WHO Global ICSR Database, VigiBase™ (Table 1). The association has an IC value of 1.26 with an IC₀₂₅ value of 0.33. The ICSRs were submitted from the United States (eight cases), Germany (two cases), Switzerland and the United Kingdom (one each). The patients ranged in age from 57 to 80 years with a median of 62 years in the seven cases which provided this information. The gender distribution was four females and seven males in the 11 cases with this information.
Tapentadol was the only drug suspected in 10 of the 12 cases. Other drugs were taken in eight cases while concomitant drugs (not suspected) were reported in six cases and included drugs involved in a pain management setting such as paracetamol, tramadol, morphine and NSAIDs. This indicates a patient population with significant morbidity, also indicated by the use of antihypertensives, acetylsalicylic acid, antidiabetics, hypolipidaemics and antidepressants. Tapentadol was reported to have been administered orally, as expected, in 11 cases. The indication for use was included in 11 ICSRs and included treatment for pain in each case.

Time to onset was reported in only three of the ICSRs and ranged from one to two days after the drug was administered. The outcome was stated in 10 ICSRs. The patients were reported as recovered or recovering in nine cases and not recovered in one case. In eight of the cases where recovery was documented, the drug was reported to have been withdrawn as well as in the other report where the patient had not recovered.

Other reactions were described in all 12 ICSRs. In 10 of those ICSRs, other neuropsychiatric effects were described including confusion (four cases), hallucination, speech disorder (both three cases), agitation and increased sweating (both two cases). Interestingly, serotonin syndrome was reported in three cases and the aggressive reaction may have

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### Table 1. Case overview of ICSRs in VigiBase™ of aggressive reaction in association with tapentadol

<table>
<thead>
<tr>
<th>Case</th>
<th>Age/Gender</th>
<th>Other suspected (S) or concomitant (C) drugs</th>
<th>Reactions (WHO-ART preferred terms)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60/ F</td>
<td>Tricyclic antidepressants, gabapentin, zolpidem, lorazepam, paroxetine, olanzapine, fentanyl (all C)</td>
<td>Aggressive reaction, mental deficiency, nervousness, confusion, abdominal pain</td>
<td>Recovered</td>
</tr>
<tr>
<td>2</td>
<td>-/M</td>
<td>None</td>
<td>Aggressive reaction, hallucination</td>
<td>Recovered</td>
</tr>
<tr>
<td>3</td>
<td>80/ F</td>
<td>Sitagliptin, simvastatin, metamizole, etoricoxib, leucovorin, insulin aspart, acetylsalicylic acid (all C)</td>
<td>Aggressive reaction, hallucination, confusion, delusion</td>
<td>Recovering</td>
</tr>
<tr>
<td>4</td>
<td>-/F</td>
<td>Corticosteroids (S)</td>
<td>Aggressive reaction, weight increase, urinary incontinence, oedema generalised, pruritus, coma, non-drug allergy, hypotension, dyspnoea, cardiac arrest</td>
<td>Recovered</td>
</tr>
<tr>
<td>5</td>
<td>-/M</td>
<td>Tizanidine, fluoxetine, bupropion (all S)</td>
<td>Aggressive reaction, serotonin syndrome, hypertension, depersonalization, rigors</td>
<td>Unknown</td>
</tr>
<tr>
<td>6</td>
<td>62/M</td>
<td>Acetylsalicylic acid, lisinopril, metoprolol, levothyroxine, tamsulosin, simvastatin, metformin, sitagliptin (all C)</td>
<td>Aggressive reaction, speech disorder, dyskinesia, convulsions grand mal</td>
<td>Not recovered</td>
</tr>
<tr>
<td>7</td>
<td>63/M</td>
<td>None</td>
<td>Aggressive reaction, serotonin syndrome, confusion, hallucination, agitation, abnormal behaviour, sweating increased, fever, speech disorder, ataxia</td>
<td>Recovered*</td>
</tr>
<tr>
<td>8</td>
<td>57/F</td>
<td>Etoricoxib, venlafaxine, paracetamol/tramadol hydrochloride, tramadol, one (unknown) concomitant drug with name under assessment (all C)</td>
<td>Aggressive reaction, somnolence, dizziness, medicine ineffective, suicide ideation</td>
<td>Recovered</td>
</tr>
<tr>
<td>9</td>
<td>62/M</td>
<td>Pantoprazole, ramipril, bisoprolol, pentaerithrityl tetranitrate, simvastatin, torasemide, clopidogrel, acetylsalicylic acid, metformin (all C)</td>
<td>Aggressive reaction, constipation</td>
<td>Recovered</td>
</tr>
<tr>
<td>10</td>
<td>-/-</td>
<td>None</td>
<td>Aggressive reaction, anxiety</td>
<td>Unknown</td>
</tr>
<tr>
<td>11</td>
<td>-/M</td>
<td>None</td>
<td>Aggressive reaction, serotonin syndrome, confusion, hyperkinesia, ataxia, speech disorder</td>
<td>Recovered</td>
</tr>
<tr>
<td>12</td>
<td>63/M</td>
<td>Glyceryl trinitrate, isosorbide mononitrate, acetylsalicylic acid, folic acid, metoprolol, paracetamol, testosterone, levothyroxine, carbamazepine, morphine, one (unknown) concomitant drug with name under assessment (all C)</td>
<td>Aggressive reaction, agitation, sweating increased, diarrhoea</td>
<td>Recovered</td>
</tr>
</tbody>
</table>

*The outcome was stated as unknown but in the causality table it was stated that the reaction abated after drug withdrawal.
been a manifestation of serotonin syndrome. There is a precaution in the Australian Product Information concerning serotonin syndrome which notes that isolated cases of serotonin syndrome have been reported in association with tapentadol but a causal association has not been established. However, in the ICSRs reviewed here, only one of the cases in which serotonin syndrome has been reported documents the use of a serotonergic drug which might precipitate the occurrence of the syndrome. There is also another case (case 12) which lists three of the cardinal symptoms of serotonin syndrome but again, a concomitant serotonergic drug is not listed so an undiagnosed case of serotonin syndrome appears unlikely.

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

Discussion and Conclusion
Case reports in VigiBase are suggestive that there is a signal for the association of tapentadol and aggressive reaction. Tapentadol was the only drug suspected in 10 of the 12 cases. Time to onset was reported in three of the ICSRs and in each of those, onset occurred within two days of the initiation of tapentadol therapy, consistent with a drug-induced effect.

Dechallenge is also suggestive of a signal. The outcome was stated in 10 ICSRs. The patients were reported as recovered or recovering in nine cases and not recovered in the other case. In eight of the cases where recovery was documented, the drug was reported to have been withdrawn as well as in the other report where the patient had not recovered.

Three of the ICSRs describe serotonin syndrome and it is possible that aggressive reaction may be a component of serotonin syndrome. However, the absence of a concomitant serotonergic drug in two of these cases would make the diagnosis of serotonin syndrome uncertain.

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

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

References
Response from Grünenthal GmbH and Janssen Pharmaceuticals, inc.

The medical concept of aggression has been reviewed during the routine signal detection activities for tapentadol. Based on the integrated analysis including data from the clinical development program and post-marketing case reports for tapentadol and literature reports, there has not been sufficient evidence for an association between tapentadol and aggressive reactions.

Clinical Experience
To date, only 0.03% subjects treated with tapentadol experienced aggression or anger during the clinical development program. All these events were non-serious, with mild or moderate intensity, and did not lead to a change of the safety profile of tapentadol.

Postmarketing Experience
A cumulative review of the MedDRA SMQ Hostility/Aggression (narrow scope) in the MAHs’ safety databases was performed. Most of the retrieved cases contained the MedDRA Preferred Terms (PT) Aggression or Anger. In addition, a few cases included PTs Hostility, Homicidal Ideation, and Violence-related symptom.

Two thirds of the reports were very sparsely documented, lacking a description of the event itself and circumstances under which it occurred, as well as tapentadol therapy details. In the remaining cases aggression was reported together with one or more of the following underlying disorders such as: bipolar disorder, anxiety, depression, posttraumatic stress disorder, and/or concomitant medication known to cause aggressiveness (tricyclic antidepressants, benzodiazepines) or alcohol use. These confound the causality assessment for tapentadol (data on file).

Based on the available review of post-marketing cases, it can be concluded that the currently available information is not supportive of tapentadol induced aggression and/or hostility.

Discussion and Conclusion
Tapentadol is a centrally acting analgesic, combining mu-opioid agonist and noradrenaline reuptake inhibitor activity in a single molecule. Aggression, as a behavior and socialization disturbance, is not known so far to be caused by morphine as the prototypical opiate. An opioid class effect for aggression has not been established as well. To date, only one publication could be found which discussed the relationship between opioids and aggressive responding as possible; however this claim has not been confirmed to date. Noradrenaline reuptake inhibitors have not shown to cause such adverse reaction either.

Some other psychiatric disorders constitute adverse drug reactions for tapentadol, such as: restlessness, perception disturbances, agitation, thinking abnormal. However, the labeling of these events as adverse drug reactions for tapentadol is not sufficient factor to draw the conclusion that aggressive reaction is also expected, as it would constitute a more specific psychiatric disorder. As such, it might not be triggered by above mentioned reactions, but can be a standalone event.

Based on available up-to-date information on tapentadol, there is no pattern observed in occurrence of aggression and/or hostility in patients treated with this substance. Information from the clinical development program and post-marketing case reports do not contain sufficient evidence for an association between events listed in Hostility/Aggression SMQ and tapentadol.

Nevertheless, the medical concept of aggression will be further monitored and targeted questions will be implemented in the follow up of spontaneous case reports, in order to obtain relevant missing information.

Reference
CAVEAT DOCUMENT

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

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

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

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

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

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

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

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

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

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

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

Omission of this statement may exclude the responsible person or organization from receiving further information from VigiBase.
Tenth Meeting of the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP)
Geneva, Switzerland
17 - 19 April 2013

The WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) has been constituted to provide advice on pharmacovigilance (PV) policy and issues related to the safety and effectiveness of medicinal products. The tenth meeting of ACSoMP started with a brief acknowledgement from the Secretariat of various important recommendations issued by the Committee these last 10 years, the several new projects initiated by WHO under the advice of the Committee, notably, the assessment of the safety of some antimalarial medicines, guidelines on PV methodologies for various public health programmes, developing a set of indicators and metrics for assessing PV functions and systems in countries, to name a few. The tenth meeting brought to the Committee's attention some current topics such as PV of biotherapeutics, safety of medicines in the elderly, harmonization of PV activities in low and middle income countries (LMIC) etc. The summary of these discussions are presented below.

Core support to the WHO safety and vigilance programmes:
The Uppsala Monitoring Centre (UMC) has supported WHO for more than 30 years as a WHO Collaborating Centre with primary operative responsibility for the WHO Programme for International Drug Monitoring. The UMC handles the safety information management chain (which starts with collecting information into a global repository), and focuses on multiple critical tasks such as signal detection, tools development and maintenance, data housing, trainings. Additional collaborating centres have come up more recently, to address specific areas of work such as Training and Advocacy for PV in Africa (Ghana, 2009), medication errors and the role of PV centres (Morocco, 2010), pharmacovigilance in education (Lareb, Netherlands, 2013). The WHO Collaborating Centre in Oslo supports by developing the normative tool, the ATC classification system for medicinal products and by assigning 'Defined Daily Doses' (DDD) to these products.

The Committee noted that in the coming years WHO and the Collaborating Centres should focus on a more enhanced interaction between the regulatory activities and the PV systems, for the use and implementation of the knowledge acquired through pharmacovigilance. The Committee recommended strengthening links between PV Centres and Patient Safety programmes. The Committee suggested that such linking might be a priority for the coming years, particularly given the large public health burden of medication errors and the potential for their prevention.

Pharmacovigilance of medicines in the elderly: how can WHO prepare for this challenge?
The group reviewed issues with adverse drug reaction (ADR) reporting systems for this population, signal detection methodologies, approaches to risk management, and stakeholder collaboration, and concluded that:

PV should be more present in a visible manner in the WHO initiative on ‘Ageing and Life Course’. WHO should develop a comprehensive paper on pharmacovigilance problems in the elderly, and solutions to address those problems. A small sub-group of the Committee should be created to:

1. Draft an explanatory document why elderly is a vulnerable group with respect to medicines use
2. Leverage / consolidate available information to help national PV centers create programmes and action plans for monitoring the safety of medicines in the elderly
3. Support WHO to develop a policy document on the importance of monitoring the safety and safe use of medicines in the elderly.
WHO Pharmacovigilance indicators

WHO uses a three-tiered approach for monitoring country pharmaceutical situation: Level I indicators measure the existence and performance of core national pharmaceutical structures and processes. Level II indicators measure key outcomes of these structures and processes in the areas of access, product quality and rational use. Level III indicators assess specific components of the pharmaceutical sector, health system, or national medicines policy in more depth. Consistent with this approach, the current set of PV indicators are categorized into Level III. A global and stepwise consultative process has been followed in identifying the PV indices.

The Committee noted the revisions to the document since its last meeting, in particular the section on indicators for public health programmes. A framework for the implementation of the indicators was discussed. WHO HQ and UMC would work closely with countries in the assessment of PV in their settings (systems, structures, processes...). In the long term a database would be established, to consolidate the PV situation worldwide. Ideally, countries will use the indicators as a self-assessment tool, for evaluating the progress and evolution of PV in their settings. The WHO PV indicators manual will remain a work in progress, with each new version reflecting the lessons learnt in the course of implementation of the tool in the countries.

Safety monitoring of medicines in malaria treatment

The Committee listened to various groups in WHO and to Medicines for Malaria Venture (MMV) on their initiatives to collect data on the safety and safe use of antimalarials. A pregnancy register is being implemented by WHO in seven countries as a platform for improving maternal/child care. The registry will support the option of prospective monitoring of birth defects due to artemesinin combination therapy (ACT) and other medicines used in pregnancy. Cohort Event Monitoring (CEM), an active surveillance method was developed by WHO to support safety monitoring of products within public health programmes. CEM is being implemented in six countries in Africa, to monitor ACTs. CEMFlow, the IT solution accompanying CEM has been developed by the Uppsala Monitoring Centre as a platform for data entry and analysis, with different stratification of events and different examination of events by causality grading. Other initiatives similar to CEM include the 9-year cohort-based active surveillance programme in Senegal. Three forms of artesunate amodiaquine (AS-AQ) are being monitored: loose pills, co blister and fixed dose combination of the As-AQ. The ASAQ study in Cote D'Ivoire by MMV is another example and should be concluded by Oct 2013 when 15,000 patients will have been enrolled. MMV is also implementing INESS (INDEPTH Effectiveness and Safety Studies of Anti-malarial drugs) in four African countries. The Committee discussed the differences in methodology across these initiatives.

The original purpose of the WHO-CEM was to introduce a method that best serves the need of public health programmes, to have robust safety data with new medicines in vulnerable populations and to be able to quantify this data. Loss to follow up is a challenge with this method in the malaria programme where patients do not return to the clinics once the symptoms of malaria have resolved. This is not an issue in HIV and TB treatment programmes since patients are automatically assigned for return visits as part of care. The group came to the conclusion that the principles of the CEM method are sound; but the methodologies need to be standardized across various CEM efforts.

The Committee recommended that the experience to date with CEM should be reviewed, and the lessons learnt should be documented. A 'WHO CEM protocol' tag could be used to identify studies that implement CEM in a manner consistent with the original WHO perspective of the method.

Global Vaccine Safety Initiative (GVSI)

The GVSI is WHO’s implementation mechanism for the Global Vaccine Safety Blueprint. This strategic plan endorsed by the World Health Assembly as part of the Global Vaccine Action Plan has three main goals: 1/ to establish at least minimum capacity for the safety monitoring of vaccines in all countries, 2/ to establish an enhanced capacity for pharmacovigilance in vaccine-producing countries and where new products are made available, and 3/ to establish a global vaccine safety support structure. The two main bodies supporting WHO’s Global Vaccine Safety activities are the GVSI, which aligns and supports the implementation of activities under the Blueprint framework and the Global Advisory Committee on Vaccine safety (GACVS), which is WHO’s main advisory body for vaccine scientific issues.

The Committee acknowledged the rapid progress in implementing the GVSI and the efforts to create national data management systems that will facilitate access to AEFI (Adverse Events Following Immunization) information, for both the national programs and the regulatory authorities.
The Committee encouraged efforts to align capacity building for pharmacovigilance of medicines and vaccines.

**African Medicines Registration Harmonization**

The African Medicines Registration Harmonization (AMRH) initiative was launched in 2009, to address serious gaps in regulatory capacity for this function in the African region. In the long term, the initiative aims to build capacity for mutual recognition and/or centralized registration of medicines in the region. The New Partnership for Africa's Development (NEPAD) is tasked with securing political support for the AMRH initiative. The World Bank manages the budget and WHO provides technical oversight and leadership.

The Committee, whilst acknowledging the AMRH initiative, expressed concern over the absence of any post-registration monitoring activities within the initiative. The Committee had the following comments:

a) The AMRH is likely to lead to improved access to medicines in Africa by speeding up the pace at which medicines are registered

b) The AMRH does not focus on post-registration surveillance of the registered medicines even though post-market surveillance is an essential component of drug registration

c) The increased access to medicines, most of which may be used on long-term basis by patients with chronic conditions, non-communicable diseases and also by vulnerable groups, will be accompanied by an increase in drug-related morbidity and mortality

d) The problem of substandard/spurious/falsely labelled/falsified and counterfeit medical products (SSFFCs) remains a serious problem and calls for urgent attention and investment in view of its negative impact on public health

e) There are very few rigorous national pharmacovigilance systems in Africa to address the above issues; nearly 50% of the PV systems have been established only recently and do not have the experience to address the broad range of challenges that are bound to accompany improved access to medicines.

The Committee called on donors, governments and technical agencies to ensure that the AMRH is accompanied by schemes for post-market surveillance of the registered medicines. The Committee noted that post-market surveillance and pharmacovigilance require only modest investments, but will contribute to the overall benefit of governments, donors, the pharmaceutical industry and most importantly patients. The Committee called on all stakeholders to mobilize the needed resources to ensure that the AMRH is developed simultaneously with a robust, well-funded post-marketing programme.

**Harmonization of safety data submission**

Medicines-safety is a joint responsibility of regulatory authorities, the medical community in the larger sense and of the pharmaceutical industry. The latter has to comply with the requirements of every country in which a company holds a marketing authorization for a product. The lack of harmonization of PV data submission in low and middle income countries (LMIC) has meant that companies have to comply with countless different reporting requirements; this results in inefficiency and, the loss or late submission of crucial safety information to the authorities.

Countries outside the ICH region have started efforts for harmonization (ex. East Africa), however regional harmonization that differs from ICH standards will not lead to a global solution unless the results achieved are at least “ICH-compatible”. Different options do exist, for harmonizing data management, Vigiflow is one such data management option developed by UMC. Vigiflow integrates E2B standards. Currently 22 countries in Sub-Saharan Africa have access to Vigiflow, and have thus already the possibility to collate the individual case safety reports (ICSRs) in their country in an E2B compatible database.

Other non-ICH countries have different systems other than Vigiflow but these are still E2B compatible databases. The UMC has developed a gateway that allows the immediate automated electronic exchange of XML files in E2B format between compatible databases.

A seamless exchange of ICSRs between industry and Medicines Regulatory Authorities is thus possible with the implementation of such tools. These tools could be promoted, as part of a harmonization package for PV in LMIC. However it must be acknowledged that harmonizing the format is not enough: content, quality, adequate staffing and uniform timelines for reporting are also key.
PV training course on post marketing activities for regulators in low and middle income countries (LMIC)

The Committee recognized that in order to be relevant for regulators, the basic PV courses (such as those offered by the UMC) need to include the principles of benefit/harm assessment, evaluation and enforcement of risk management plans, and the use of safety data for regulatory decision making. The US FDA’s one week course for regulators includes regulatory decision making in the post marketing setting. Resources to monitor medicine safety during all the different steps of its life need to be developed, linking this to the impact on public (and patient) safety. The Committee agreed that any effort in this regard for regulators in LMIC should build on the US FDA experience.

The Committee noted that PV should be seen as a whole with its broadest mandate, with its wide scope of strengthening health system and health care, and regulatory decision making. The Committee encouraged WHO to develop a training package on PV for regulators in LMIC.

WHO/ UMC proposal for public access to information from VigiBase

In 2002 the International Conference of Drug Regulatory Authorities (ICDRA) agreed that WHO should make information from the UMC database available to third parties. This was further endorsed by the Advisory Committee on the Safety of Medicinal Products (ACSoMP) at its meeting in Geneva, in 2011 when a proposal for the release of VigiBase data was submitted to the Committee. In partial implementation of these recommendations and based on feedback from National Centres, the UMC ‘Signal’ documents have been made available to a wider audience since 2012; these are now published regularly in the WHO Pharmaceuticals Newsletter.

The UMC has been working on the steps towards the release of VigiBase data to the public. The same level of access will be provided to all users. A simple, user friendly search mask will allow the user to obtain an overview on the whole VigiBase dataset and search for products/active ingredients. All therapeutic agents registered in VigiBase can be searched, including vaccines. However, the data will be presented as statistics only. No line listings and no individual case safety reports (ICSRs) will be provided. A disclaimer with the explicit information that ‘patients should not discontinue their medication if they think they are suffering from an ADR, but should consult their HCP and report the suspected ADR’, as well as the UMC Caveat Document will precede the actual access to VigiBase. This will include checking a “I have read und understood” tick box. The Caveat Document will have to be rewritten in a language that is easily understood by the general public.

The Committee commended the progress in making VigiBase accessible to the public, and noted that from the experience of other stringent regulatory authorities, it is clear that the benefits of transparency outweigh the potential problems associated with open access to data.

The impact of the new EU PV guidelines –definitions and technical procedures for ICSR reporting

In its current form, the legislation requires PV to go beyond the WHO definition of PV, to include also the management of benefits and risks of medicines on the market, powered by tools that help embrace the evidence hierarchy to benefit public health. PV has to be considered all along the product lifecycle. Robust PV builds on 3 pillars: Scientific methods, Resources and Law. Projects such as the EU PROTECT underpin the good science; while resources include fees, datasets; and a new law is in the pipeline. The PV and Risk Assessment Committee (PRAC) focuses on processes outlined in the EU PV legislation. The PRAC outcomes will be used to provide binding regulatory decisions.

A proposal for a recommendation on medication errors and the scope of PV to address this was presented to the Committee and approved:

Key drivers to maximize patient safety include optimization of healthcare delivery and optimization of medicines regulation including pharmacovigilance. In this context all aspects of medicines regulation may be relevant and the naming, labelling and information for users of products are particular areas impacting on the risk of medication errors. Risk management can play a critical role in ensuring evidenced based planning of data collection and risk minimization and this has the potential to reduce the burden of harm from medication errors. Likewise, the collection of near-miss reports, and of reports of suspected adverse reactions due to medication errors, the collation and analysis of these reports, including coding, definitions and other data management issues are important and their
optimization has major potential for reducing the harm from medication errors. The committee recommended that WHO should build on the outputs of the EC funded Monitoring Medicines Project and bridging between patient safety initiatives and pharmacovigilance (including naming and labelling issues) should be a priority for the WHO programme. The Committee further recommended to explore the development and harmonization of relevant terminology, event classification and technical work at the interface of pharmacovigilance and patient safety. Finally, the Committee recommended that national pharmacovigilance should include medication errors within their mandates.

The Committee also noted that EMA reporting of ICSRs to UMC is likely to start in 2016; until then national Centres will continue reporting to UMC. It was agreed that a WHO-EMA joint communication on reporting to UMC until 2016 and then to the EMA (that will then report to UMC) should be prepared, posted on EMA website, and shared at the National Centres meeting.

Pharmacovigilance for biotherapeutics: Presentation by members of the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA)

Biotherapeutics are either innovator biotherapeutic agents (novel, patent protected products that are authorized based on a full registration dossier), biosimilars (or Similar Biotherapeutic Products (SBP), the name given by WHO), that are similar in terms of quality, safety and efficacy to an already licensed reference product, or non-comparable biotherapeutic products that have not been approved in accordance with WHO SBP standards. The complex production process and manufacturing chain, delayed adverse drug reactions (ADRs), immunogenicity, relative instability of the products and traceability are some of the aspects requiring special consideration in the PV of biotherapeutics. These problems are compounded by additional challenges such as inconsistent PV systems, naming and prescribing practices that vary across countries (for example, use of INN versus trade names), changes in manufacturing processes that may lead to a significant change in clinical effectiveness, inappropriate substitution (therapy switch) and prescription. The IFPMA requested WHO to

- take action on clearer, harmonized and distinguishable naming of biotherapeutics
- advance guidance and training of stakeholders on processes and systems for PV of biotherapeutics
- add specific advice on treatment with biotherapeutics to the PV Toolkit

The Committee noted that similar problems exist, also for small molecules. Even electronic record systems may not provide more information other than just the INN. Recording trade names is already recommended in ICSR reporting guidance, but might need to be further emphasized. Bar codes can be helpful to identify the product, however they are available only on the original package.

The WHO Drug Dictionary (WHO-DD) allows entering more details on a product than just trade name and INN. Thus more complete information will then be used by all WHO-DD users. UMC is ready to discuss improvements to the WHO-DD entries, to assist better traceability of biotherapeutics and SBPs.

Anatomical Therapeutic and Chemical (ATC) classification and the Defined Daily Dose (DDD) for medicinal products

ATC/DDD is a tool set for coding medicinal products and for quantifying and comparing drug utilization within and across facilities, countries etc. It could be used for studying trends in use of medicines and patterns of ADRs across therapeutic classes. However the tool remains relatively unknown and under-utilized. ATC/DDD can help determine drug / classes of drugs to monitor in a facility. It was first used to alert policy makers to the over-use of antibiotics. Since DDD can provide information on volume of medicines used, together with ADR reports, it can help also determine ADR rates.

The Committee recommends inviting a member of the WHO International Working Group for Drug Statistics Methodology at the next ACoMP and other relevant PV events, to discuss the utility of ATC DDD in terms of patient safety.
**Adverse events reporting for medical devices**

More than 20,000 different types of medical devices exist. However, there are few relevant regulations on medical devices. The need for training and capacity building is very high, all the more in LMIC: these countries face lack of capacity and human resources, very weak techno-vigilance/post marketing surveillance, and regulations are considered a barrier to access. Another key problem is the absence of a well-recognized nomenclature for medical devices. Potential areas of collaboration with the medicines PV network were discussed, including adverse events (AE) reporting, techno-vigilance/post marketing surveillance, format for reporting complaints by end-users, patient safety systems.

The Committee noted / recommended the following:

*Medical devices are important in the diagnosis, prevention, and treatment of diseases. Attention to the safety and safe use of medical devices is essential for optimizing their role in health care.*

*Monitoring adverse events, medical errors related to medical devices, and device malfunction are important for understanding the safety and safe use of medical devices in actual practice.*

*The development of robust systems for monitoring the safety and safe use of medical devices should be pursued. The ADR reporting systems for medicines have existed for several decades and would serve as useful models. In the interest of patient safety, as a minimum, knowledge exchange should occur between the pharmacovigilance and devices networks.*

*Data on the burden of adverse events due to medical devices should be made available. Also, a nomenclature on medical devices should be developed.*

**Strategies for monitoring the safety of new TB medicines**

PV will be included in the revised international standards for TB care in the post 2015 strategy. Stop TB has developed a plan for new drugs, including assistance to national regulatory authorities (NRAs) for fast approval, PV and surveillance. Several anti-TB drugs are in the pipeline: 4 repurposed drugs, 6 new ones, including 3 new classes. The 2 main new drugs are: bedaquilline (BDQ), and delamanid (in process). 7 countries representing 60% of multidrug resistant TB (MDRTB) cases are interested in registering BDQ. Challenges include finding the optimal regimen for use, evaluating cost effectiveness, ensuring proper surveillance and PV, especially in accelerated approval as with BDQ. BDQ presents some serious concerns, in part because its $\frac{1}{2}$ life is in months. PV tools to study drug interaction would thus be very important. Active PV will be recommended for this drug with a need to follow-up safety aspects, including hepatotoxicity, cardiotoxicity and mortality.

*The Committee welcomed the appearance of new TB drugs, acknowledged the willingness of Stop TB to carry on specific PV efforts, and emphasized the need for PV systems to accompany the roll-out of new TB medicines, building on existing systems and capacities.*

**Substandard and falsified medicines**

Substandard/spurious/falsely labelled/falsified and counterfeit (SSFFC) medical products are a global threat. Inter-country collaboration is needed to tackle this threat. WHO has developed a simplified tool for reporting SSFFCs (Rapid Alert) and a database that stores the reports. The project started as a pilot with 10 countries trained in the use of these tools; more countries are now receiving training in the full roll out of the project. SSFFCs are difficult to identify, particularly if they have some (and not a complete absence of) therapeutic effect. SSFFC products that are toxic are detected more easily. Another issue is the fragmented reporting of incidents, as it is difficult to engage the right stakeholders. The system needs to be extremely rapid, as a warning system. Synergies do exist between the SSFFC and PV disciplines. PV can be another set of ‘eyes and ears’ for SSFFC, just as laboratory networks could be.

**How can PV Centres contribute to drug quality surveillance systems?**

Drug quality related issues may be due to manufacturing or post manufacturing issues. The role of PV systems in drug quality issue needs to be defined. Standard ways of looking at ADR do not always work for drug quality issues. For example, PV does not include field investigation, and does not engage field epidemiologists who are able to analyze the information with a rapid turnaround. The timing of the response and information management are critical for drug quality issues. This is a challenge with non-serious ADRs that are due to drug quality problems; PV reporting requirements for
non-serious ADRs can limit timely identification of these poor quality products. But there are examples in countries, such as in China, where the ADR monitoring system also monitors quality issues, with an automatic system to signal quality issues requiring laboratory testing. The UMC has developed an algorithm to detect poor quality and SSFFC products based on lack of efficacy reports in the pharmacovigilance database. The algorithm needs to be validated by countries, to see if these ‘clusters of potential SSFFCs’ detected by the UMC algorithm are real SSFFC cases.

*The Committee commented that not all quality problems can be identified through the PV systems. However it is important that both communities (PV and SSFFC networks) coordinate efforts, to complement each other’s work. As a first step, the PV Community could be more proactive, in engaging with the SSFFC networks, including the collection of reports of lack of therapeutic effect. WHO should send a letter to all PV centres, urging them to collect and share reports of decreased therapeutic effect with WHO.*

**Update on toxicity monitoring for ARVs**

The HIV department is in the process of revising and publishing the WHO 2013 "Consolidated Guidelines on the use of antiretroviral drugs for treating and preventing HIV infection - Recommendations for a Public Health Approach”. The department commissioned several systematic reviews on ARV toxicity to support and inform the Guidelines Development Committee’s review of evidence and recommendations, including reviews on toxicity with tenofovir, nevirapine and efavirenz. The reviews highlighted the need for more research on sensitive toxicity issues, including renal toxicity with tenofovir and appropriate lab monitoring of renal functions, use of tenofovir in populations with risk factors, safety of efavirenz and nevirapine in pregnancy and young children, toxicity associated with the long term use of ARVs. WHO is supporting work in four countries (Côte d’Ivoire, Kenya, Lao PDR and Viet Nam), with Targeted Spontaneous Reporting (TSR). Also a CEM project is ongoing in Tanzania, and PV training and capacity building have been provided in Ukraine. WHO will organize a technical review meeting of country experiences and a technical report will be published by the end of 2013.

The Committee emphasized that PV should help more in the update of guidelines, as it not only identifies, but also quantifies the risk (e.g. renal failure with TNF). The Committee encouraged WHO-HIV to consider on-going work of prospective cohorts such as the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D).

**PV training modules**

A sub group of ACSoMP has been developing a PV curriculum that considers the whole field of PV, and proposes theoretical chapters as well as practical hands-on exercises. The full Committee was presented with the table of contents, and next steps, including plans for publishing the course content. The document will be completed in 2013. The Committee noted that this is an evolving document and its contents will reflect the expanding scope of PV as it develops. Monitoring and Evaluation (M&E) of PV is also included in the curriculum (with links to the WHO manual of PV indicators), to provide education and training on how to monitor and evaluate a PV system.

**Toolkit**

The Pharmacovigilance Toolkit has been developed as a PV resource repository for low and middle income countries, to support their efforts to develop a good quality, standard PV system. The WHO Collaborating Centre (CC) for Advocacy and Training in Pharmacovigilance, Ghana has been leading the work on the Toolkit, with support from WHO. A short update was presented focusing on progress and new features. In particular, a link with Vaccines is in the pipeline, a toolkit manager has been hired for everyday management of the toolkit and to respond to FAQs from countries, promotional materials and a business plan are being developed, to advocate and improve the use and maintenance of the Toolkit.