NEWSLETTER

PAKISTAN NATIONAL PHARMACOVIGILANCE CENTRE
Drug Regulatory Authority of Pakistan
GOVERNMENT OF PAKISTAN
Telecom Foundation Complex, Sector G-9/4, Islamabad.

TABLE OF CONTENTS

Global Therapeutic Goods Safety Information.

1. Triptans: Risk of headache due to medication overuse 3
2. Glucagon-like peptide-1 (GLP-1) receptor agonist:risk of diabetic ketoacidosis 3
3. Magnesium Sulfate: risk of skeletal adverse effects for neonates 4
4. Codeine, dihyrocodeine and tramdol-contraindicated in children: risk of severe respiratory depression. 4
5. Non-steroidal anti-inflammatory drugs (NSAIDS): risk of cardiovasular adverse events. 5
6. Proton pump inhibitors (PPIs): risk of rebound acid hypersecretion (RAHS). 5
7. Cyproterone: risk of meningioma. 6
8. Rivaroxaban and other direct-acting oral anticoagulants (DOACs): increased risk of recurrent thrombotic events. 6
9. Tocilizumab: risk of hepatotoxicity. 7

National Therapeutic Goods Safety Information.

10. Domperidone: risk of serious cardiac adverse events in children 9
11. Detection of NDMA in Rantidine 9

1. Triptans: Risk of Headache Due to Medication Overuse.

Ministry of Health, Labour and Welfare (MHLW) and Pharmaceuticals and Medical Devices Agency (PMDA), Japan have announced that the package inserts for triptans such as sumatriptan, naratriptan, eletriptan, zolmitriptan and rizatriptan should be revised to include headache caused by medication overuse as an adverse drug reaction.

In previous three fiscal years, six cases of headaches due medication overuse have been reported in Japan. For all of the six cases, a causal relationship between the drug and event could not be excluded. Although only a small number of cases of headaches due to medication overuse have been reported in patients treated with triptans in Japan, the MHLW and PMDA have concluded that revision of the package insert is necessary based on the results of the investigation of the currently available evidence and in consultation with expert advisors.

Triptans (selectiveserotonin-agonists) are selective 5-HT1 receptor agonists, indicated in migraine attacks. These drugs act by causing vasoconstriction primarily in the cranial blood vessels. These include sumatriptan, eletriptan, and zolmitriptan etc.

Based on the above information, healthcare professional are advised to use all the triptans drugs with caution and report any suspected adverse drug reaction to Pakistan National Pharmacovigilance Centre, Drug Regulatory Authority of Pakistan.

Reference:
Revision of Precautions,
MHLW/PMDA, 4 June 2019
(www.pmda.go.jp/english/)

2.Glucagon-like peptide-1 (GLP-1) receptor agonists: Risk of diabetic ketoacidosis.

The Medicine and Health Product Regulatory Agency (MHRA) of United Kingdom has requested that the Summaries of Product Characteristics and Patient Information Leaflets for Glucagon-like peptide-1 (GLP-1) receptor agonists (liraglutide and dulaglutide) should be updated to include advice on reducing insulin dosage using a stepwise approach and monitoring of blood glucose to minimize the risk of diabetic ketoacidosis.

Serious and life-threatening cases of diabetic ketoacidosis have been reported in association with exenatide, liraglutide, and dulaglutide, particularly after rapid reduction or discontinuation of concomitant insulin. An EU review of these reports concluded that the cases could be attributed to abrupt discontinuation or dose reduction of insulin while initiating GLP-1 receptor agonist therapy, resulting in a poor glycaemic control.

Glucagon-like peptide-1 (GLP-1) receptor agonists (also known as GLP-1 mimetic therapies) such as liraglutide and dulaglutide etc. are used in adults with type 2 diabetes to improve glycaemic control. GLP-1 receptor agonists act by stimulating insulin secretion from the pancreas in a glucose-dependent manner, as well as slowing gastric emptying and suppressing glucagon secretion.

Keeping in view the aforesaid information, health-care professionals are advised that if the insulin dose is to be reduced, a stepwise approach is recommended. Also, they should monitor for signs and symptoms of diabetic ketoacidosis and risk factors with patients. Suspected adverse drug reaction with these drugs should be reported to Pakistan National Pharmacovigilance centre.

Reference:
Drug Safety Update, MHRA,
19 June 2019 (www.gov.uk/mhra/)

3. Magnesium sulfate: Risk of skeletal adverse effects in neonates.

The Medicine and Health Product Regulatory Agency (MHRA) of United Kingdom (UK) has announced that the product information for products containing magnesium sulfate would be updated to warn of skeletal adverse effects observed with administration for more than five to seven days during pregnancy.

In 2013, the United States Food and Drug Administration (US FDA) issued safety recommendation against use of magnesium sulfate for more than 5–7 days when used as a tocolytic (medications used to suppress premature labor), which is not an approved indication in UK. FDA in the said safety communication informed that administration of magnesium sulfate injection to pregnant women longer than 5-7 days may lead to low calcium levels and bone problems (skeletal problem) in the developing baby or fetus, including thin bones, called osteopenia, and bone breaks, called fractures. Therefore, such prolonged exposure of magnesium sulfate as tocolytic may result in significantly higher cumulative doses than those encountered with use of magnesium sulfate when used for eclampsia or foetal neuroprotection.

The MHRA informed that it is not aware of any reports in the UK of skeletal adverse effects (bone problems) or relevant biochemical effects in the neonate following use of magnesium sulfate. However, considering that there is an increase in the usage in the UK, MHRA decided to update product labels, based on the recommendations from the Paediatric Medicines Expert Advisory Group.

Magnesium sulfate is indicated for the prevention of further seizures associated with eclampsia in pregnancy and for the treatment of magnesium deficiency in hypomagnesemia. It is also used in emergency treatment of serious arrhythmias, especially in the presence of hypokalaemia.

Based on this information, healthcare professionals are advised to consider monitoring neonates for abnormal calcium and magnesium levels and skeletal adverse effects if maternal treatment with magnesium sulfate is prolonged or repeated. Healthcare professionals are also advised to report any suspected adverse drug reaction with magnesium sulfate to Pakistan National Pharmacovigilance Centre, Drug Regulatory Authority of Pakistan.

Reference:
Drug Safety Update, MHRA,
17 May 2019 *(*www.gov.uk/mhra *)*

4.Codeine, dihydrocodeine, tramadol Contraindication in children: Risk of serious respiratory depression.

Ministry of Health, Labour and Welfare (MHLW) and Pharmaceutical and Medical Device Agency (PMDA) of Japan have announced that the package inserts for products containing codeine, dihydrocodeine or tramadol should be revised to include contraindications in children under 12 years of age (for all uses), and patients under 18 years of age when used for pain relief after tonsillectomy or adenoidectomy, due to the risk of serious respiratory depression.

In Japan there were four reports of morphine like toxic symptoms such as respiratory depression in patients using codeine, dihydrocodeine or tramadol. Mortality has not been reported. MHLW and PMDA have reviewed available safety information and concluded that the revision of package inserts is necessary.

In January, 2018, the United States Food and Drug Administration (US FDA) had also updated the prescribing information of codeine and hydro codeine cold preparation. The use of these drugs was limited to adult of 18 years or older and was contraindicated for the treatment of cough in any paediatric population.

Codeine, and dihydrocodeine are available in combination for treatment of cough and pain. Tramadol is an opiate analogue and is used in severe acute and chronic pain, during diagnostic measures and for surgical pain.

Healthcare Professional are advised to not use codeine, dihyrdocodeine or tramadol containing drugs in children under 12 years of age (for all uses), and patients under 18 years of age when used for pain relief after tonsillectomy or adenoidectomy. Any suspected adverse drugs reaction should be reported to Pakistan National Pharmacovigilance Centre.

Reference:

Revision of Precautions,
MHLW/PMDA, 9 July 2019
(www.pmda.go.jp/english/)

5. Non-steroidal anti-inflammatory drugs (NSAIDs): risk of cardiovascular adverse events.

Medicine and Medical Devices Safety Authority (Medsafe) of New Zealand has announced that all non-steroidal anti-inflammatory drugs (NSAIDs) increase the risk of a cardiovascular adverse event.

NSAIDS are generally indicated to reduce pain, decrease fever and decrease inflammation. NSAIDs reduce inflammation by inhibiting the production of cyclo-oxygenase (COX), an important enzyme in prostaglandin synthesis. There are two major forms of the COX enzyme: COX-1 and COX-2. While COX-1 is present in most tissues all the time, COX-2 is expressed in response to inflammation. Both forms catalyse the conversion of arachidonic acid, via intermediates, to thromboxane A2 (pro-thrombotic) and prostacyclin (anti-thrombotic).

Since the Medicines Adverse Reactions Committee (MARC) previously discussed the cardiovascular safety of diclofenac in 2013 and ibuprofen in 2015, several new studies on the cardiovascular safety of NSAIDs have been published.

Medsafe presented a report on the recent literature of cardiovascular safety of NSAIDS in the recent meeting of MARC. These studies include two key clinical trials, and two large observational studies using healthcare databases. In addition, there have been two meta-analyses of older studies and a case-control study nested in a cohort derived from European electronic healthcare databases that examines the risk of hospital admission for heart failure exacerbation in new users of NSAIDs.

MARC after reviewing these studies concluded that it is currently not possible to differentiate or rank NSAIDs by their individual cardiovascular risk profiles. MARC recommended that: all NSAIDs should be avoided in patients with established cardiovascular disease; patients should be informed about the risk of cardiovascular disease with NSAID, even those without a history of cardiovascular disease; and If required, use NSAIDs at the lowest effective dose for the shortest duration possible.

Reference:

Prescriber Update, Vol. 40,
No.2, Medsafe, June 2019
*(*www.medsafe.govt.nz/)

6. Proton pump inhibitors (PPIs): Risk of rebound acid hyper-secretion (RAHS).

Medicine and Medical Devices Safety Authority (Medsafe) of New Zealand has announced that rebound acid hyper-secretion (RAHS) has been reported in patients after stopping prolonged treatment with proton pump inhibitors (PPIs).

Proton pump inhibitors (PPIs) includes omeprazole, lansoprazole, esomeprazole and

pantoprazole etc. These are used to inhibit gastric acid secretion and have several indications such as the short-term treatment of benign duodenal and gastric ulcers and the eradication of Helicobacter Pylori in combination with anti-bacterial. Rebound acid hyper secretion **(**RAHS**)** is the recurrence of symptoms due to an increase in gastric acid secretion above pre-treatment levels after stopping PPI therapy. Symptoms of RAHS may include heartburn, regurgitation or dyspepsia.

Medsafe recommended a "step down" approach for people taking a PPI who are no longer experiencing symptoms and/or do not require long-term treatment. For many people, short-term PPI use (4-8 weeks) is appropriate. Stepping down involves gradually reducing the dose over time, before stopping the medicine completely. Alternative treatments, such as histamine H2-receptor antagonists or antacids, may be useful to manage rebound symptoms.

Reference:
Prescriber Update, Vo. 40,
No.2, Medsafe, June 2019
*(*www.medsafe.govt.nz/*)*

7. Cyproterone: risk of meningioma.

The Pharmacovigilance Risk Assessment Committee (PRAC) of European Medicines Agency (EMA) has started a review of medicines containing cyproterone. The review will investigate the risk of meningioma, a rare, usually non-malignant tumour of the membranes covering the brain and spinal cord with these medicines.

Cyproterone is a steroidal anti-androgen, indicated for the treatment of a range of conditions, including excessive hair growth, prostate cancer, acne, and in hormone replacement therapy.

The risk of meningioma with cyproterone daily doses of 10 mg or more has been known since 2008 and information was included in the prescribing information for these medicines along with a warning that cyproterone should not be used in people who have or have had a meningioma tumour. However, there was no information at the time on the magnitude of the risk and how the risk could change with different doses. A recent study in France has now suggested that the risk of meningioma, although still very low, may be greater in those taking high doses of cyproterone for a long period. The PRAC will examine available evidence and make recommendations.

Healthcare professionals are advised to report any suspected adverse drug reaction with cyproterone to Pakistan National Pharmacovigilance Centre. Drug Regulatory Authority of Pakistan is aware of the PRAC's review of cyproterone and will take necessary action in Pakistan, based upon the result of the review.

8. Rivaroxaban and other direct-acting oral anticoagulants (DOACs).

The Medicine and Health Product Regulatory Agency (MHRA) of United Kingdom has announced that a clinical trial has shown that there is an increased risk of recurrent thrombotic events associated with rivaroxaban use compared to warfarin, in patients with antiphospholipid syndrome and a history of thrombosis.

A clinical trial (TRAPS study) compared rivaroxaban to warfarin in patients with antiphospholipid syndrome and a history of thrombosis, and at high risk for thromboembolic events (patients who persistently tested positive for all 3 antiphospholipid tests). The trial was terminated prematurely after the enrolment of 120 patients due to an excess of thromboembolic events among patients in the rivaroxaban arm. It showed that use of rivaroxaban in patients with antiphospholipid syndrome could be associated with increased rates of recurrent thrombotic events compared to therapy with warfarin. There have been no completed clinical trials for use of

other DOACs such as apixaban, edoxaban and dabigatran in patients with antiphospholipid syndrome, therefore available data for these medicines are limited. However, available data suggest that other DOACs may also be associated with asimilarly increased risk of recurrent thrombotic events as with use of rivaroxaban.

Direct-acting oral anticoagulants (DOACs) are indicated for the treatment and prevention of venous thromboembolism, and prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation with one or more risk factors. DOACs available are rivaroxaban, apixaban, edoxaban and dabigatran.

MHRA advised healthcare professionals that direct-acting oral anticoagulants (DOACs) are not recommended in patients with antiphospholipid syndrome, particularly high-risk patients (those who test positive for all 3 antiphospholipid tests — lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2 glycoprotein I antibodies). Healthcare professionals were also advised to review whether continued treatment with a DOAC is appropriate for patients diagnosed with antiphospholipid syndrome, particularly high-risk patients, and consider switching to a vitamin K antagonist such as warfarin

Healthcare professionals are advised to use direct-acting oral anticoagulants (DOACs) with cautions in patients with antiphospholipied syndrome and report any suspected adverse drug reaction to Pakistan National Pharmacovigilance Centre.

Reference:
Drug Safety Update, MHRA,
19 June 2019 (www.gov.uk/mhra)

9. Tocilizumab: Risk of Hepatotoxicity

The Therapeutic Goods Administration (TGA) of Australia, has announced that serious drug-induced liver injuries, including acute liver failure, hepatitis and jaundice, have been observed with the administration of tocilizumab. Tocilizumab is known to cause transient or intermittent mild to moderate elevation of hepatic transaminases. The current Product Information does not recommend treatment in patients with elevated alanine aminotransferase (ALT) or aspartate aminotransferase (AST).

The Medicine and Health Product Regulatory Agency (MHRA) has also announced that serious liver injury has been reported in patients treated with tocilizumab with an onset ranging from two weeks to more than five years after initiation. Liver injury includes acute liver cumulative failure and hepatitis, and some cases required liver transplantation.

Furthermore, a recent European Union review found that treatment was associated with severe liver injury. The review of data from clinical trials, non-interventional studies, spontaneous reports, and the published literature identified eight cases of tocilizumab related drug-induced liver injury worldwide.

Tocilizumab, is an immunosuppressive drug, mainly used for the treatment of rheumatoid arthritis (RA), giant cell arthritis in adults and systemic juvenile idiopathic arthritis, a severe form of arthritis in children. It is a humanized monoclonal antibody against the interleukin-6 receptor (IL-6R).

The TGA in its recommendation advises patients treated with tocilizumab to be closely monitored for liver adverse events and advised to seek immediate medical advice if they have signs or symptoms of hepatotoxicity such as jaundice, dark urine, itch, loss of appetite, nausea or vomiting. TGA is also reviewing the data on hepatotoxicity with the said drug and may recommend changes to prescribing information in this regard. MHRA advised healthcare professions to measure ALT and AST levels before starting treatment with tocilizumab and monitored every four to eight weeks for the first six months of

treatment followed by every 12 weeks thereafter.

Based on the above information, healthcare professionals are advised to closely monitor patients using for liver function during and before initiation of treatment with tocilizumab. Any suspected adverse drug reaction with said drug should be reported to Pakistan National Pharmacovigilance Centre.

Reference:
Drug Safety Update, MHRA,
17 July 2019 *(*www.gov.uk/mhra*)*
Medicines Safety Update, TGA,
11 July 2019 ***(***www.tga.gov.au***)***

10. Domperidone: Risk Of Serious Cardiac Adverse Events in Children Under 12 Years of Age.

Domperidone is a drug prescribed for the relief of nausea and vomiting. It is available as tablets, oral suspension and suppositories. It facilitate gastric emptying and decreases small bowel transit time by increasing oesophageal and gastric peristalsis and by lowering oesophageal sphincter pressure. The drug has been under close monitoring by International regulatory authorities because of its side effects, including its rare but potentially serious cardiac effects. It is not currently a legally marketed human drug in USA and is not approved for sale. Due to the persistence of undesirable effects, Belgium initiated a European reassessment of the benefit / risk ratio of domperidone, in 2013, of which France was a rapporteur. France and Belgium were in charge of the evaluation. The European Medicines Agency (EMA) and the Agency for the Safety of Medicines and Health Products (ANSM), France now confirmed the risk of serious cardiac adverse events associated with the use of domperidone including QT prolongation, Torsade De Pointes, Serious Ventricular Arrhythmias and Sudden Cardiac Death.

As part of the re-evaluation of the benefit-risk balance of domperidone conducted by the European Medicines Agency (EMA) in 2014, an efficacy study for children under 12 years of age was requested. The results of this study, presented this year, showed no difference in efficacy compared to placebo. Because of this lack of efficacy and its undesirable effects, the use of domperidone is therefore restricted to adults and adolescents over 12 years old and weighing more than 35kg. ANSAM France has also issued dear healthcare professional letter related to restriction of domperidone to adults/ adolescents.

Based on the above new update, the case was presented in 290th meeting of Registration Board which after deliberation decided that manufacturers/ importers of domperidone containing drugs should update their prescribing information and patient information as per the recommendation of EMA. Most recently, Secretary, Registration Board also issued an advisory to all the manufactures/importers of domperidone for implementation of the said update in Pakistan.

Healthcare professionals are advised to use domperidone only for the relief of nausea and vomiting symptoms and its use should be restricted to adults and adolescents over 12 years of age and weighing more than 35kg. The dose should be limited to 10 mg up to 3 times daily, with a maximum dose of 30 mg per day and the treatment duration should be as short as possible. Domperidone containing drugs are now contraindicated especially in cases of hepatic insufficiency, in certain situations at risk of prolongation of QT (cardiac pathologies, drug interactions) and in case of children under 12 years of age or weighing less than 35kg. Healthcare professionals are advised to report suspected adverse drug reactions to Pakistan National Pharmacovigilance Centre.

Reference:
Minutes of 290th meeting of Registration Board.

11. Detection of NMDA in Ranitidine Medicines.

In September, 2019, the United States Food and Drug Administration (US-FDA) informed about detection of very low levels of nitrosamine impurity called N-nitrosodimethylamine (NDMA) in ranitidine medicines (Zantac). The European Medicine Agency (EMA) in September, 2019 also started review of ranitidine medicines after tests showed that some of these products contained NDMA. Neither the source of material nor the quantity of NDMA found was mentioned by both the agencies in their press release. Both the

agencies ,at first, informed that they are evaluating any possible risk to patients due low level of NDMA. Later on, Health Canada on 17th September, 2019 requested companies to stop distributing ranitidine drugs in Canada, while it assesses the NDMA. A company namely Novartis AG's Sandoz also voluntarily recalled its product containing ranitidine in Canada and stopped its worldwide distribution. In addition, multiple recalls and halt on distribution of generic version of ranitidine were initiated around the world including United States. EMA's human medicines committee (CHMP) subsequently requested marketing authorisation holders for human medicines containing chemically synthesised active substances to review their medicines for the possible presence of nitrosamines and test all products at risk as a matter of precaution.

Last year, similar situation arises when in July, 2018, NDMA was detected by EMA in valsartan active substance manufactured by Zhejiang Huahai Pharmaceuticals of China. Subsequently, valsartan medicines were recalled in the European Union. Accordingly, the Drug Regulatory Authority of Pakistan in July, 2018, also triggered a recall of all valsartan containing medicines having the same source of active substance as of EMA and also issued a list of manufacturers who have purchased valsartan raw material from the same source.

Ranitidine is a H2 (histamine-2) blocker which decreases the amount of acid created by the stomach. It is used to treat heartburn, gastric and intestinal ulcers and treatment of gastroesophageal reflux disease. NDMA is classified as a probable human carcinogen, based on results from laboratory tests. NDMA is a known environmental contaminant and found in water and foods, including meats, dairy products, and vegetables and is not expected to cause harm when ingested invery low levels.

In greater public interest and in order to protect patients from risk associated with detection of low levels of NDMA in ranitidine containing products as per alert of FDA and EMA, the DRAP at first advised to halt the distribution/sale/utilization of ranitidine containing medicines in Pakistan followed by its recall and suspension of production of all dosage forms.

There are multiple medicines in the market that are approved for same or similar uses as ranitidine. Due to recall of the said drug in Pakistan, healthcare professionals are advised to switch to alternative medicine that are approved for the same indication.

Reference:

EMA Press release 13th and 26th September, 2019
https://www.ema.europa.eu/en
FDA Medwatch Alert of 12 September, 2019
https://www.fda.gov/
DRAP news section
www.dra.gov.pk