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Scope of the Bulletin

- Pharmaceuticals Stability, quality control formulation, biopharmaceutics
- Policy, legislation, and regulatory control
- Availability and supply
- Administration and dosage
- Choice of therapy, indication, contraindications
- Drug interaction
- Pharmacovigilance, Adverse drug reactions
- Essential drugs

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EDITORIAL

Facts and Myths on generic drugs: a motivated and sponsored dichotomy rather than founded on scientific evidences

Last week we had a policy dialogue to address pharmaceutical procurement and supply chain in federal context. Among many suggestions and views to address access to medicines one issue attracted attention of many experts that was issue of drug quality and prescribing practices in generics. Few of the experts opined generics are substandard and cannot be prescribed with full confidence. They opined to allow brand preference and procurement law should be amended to allow brand procurement. Since procurement policy required all public sector entity to purchase medicines in generic names, because clinician often express their hesitancy in accepting generics as equivalent to their branded versions public procurement entities are unable to serve their demand so is the viability of hospital pharmacy in the country. The issue of the interchangeability based on such perceived opinions need an urgent address and that should be founded on scientific evidences. Since the advent of essential medicines program following the Alma-Ata declaration on primary health care Governments all around the world especially of developing countries have been advocating generic prescription as one of the most effective interventions to ensure access to medicines. WHO and many developed countries are stressing to use generic medicines to reduce health care cost thereby preventing impoverishment through increased health care cost. But the dichotomy of generics verses brand preference still prevails and is influencing health policy makers, regulators, and practitioners all over the world. Is it a myth or founded on facts? Why this is so powerfully debated? Is it motivated due to strong lobby of manufacturers and traders? Or is it founded on scientific evidences? Few of these questions are addressed in the following paragraph.

Let's review what are these myths often raising debates and facts regarding branded and generic named drug products:

Myth#1: The Active Pharmaceutical Ingredients (API) in generics are different from brand-name drugs, and generics go through a less stringent DDA approval process

Fact: Both Branded and Generic products contain same API in same strength and dosage form. Medicines registration guidance 2073 has no difference in DDA approval process for branded and generic products in Nepal, infect majority of

products registered in Nepal are branded generics, only few innovator (branded in true sense) versions are registered.

Myth 2#: Generics somehow work differently in the human body as brand-name drugs.

Fact: Products in brand name are of two types. The innovator and branded generic in Nepalese context. The latter is understood as generic thus the brand preference as advocated by most is not understood as innovator verses generic in Nepal rather one branded generic verse another generic brand. The mechanism of action, route of administration of both branded and generics are same and since they contain same API their pharmacokinetic and pharmacodynamic phenomenon are same.

Myth#3: The standards set for quality in the manufacturing of brand-name drugs are somehow higher than quality standards for the production of generics

Fact: The product standards as set in official pharmacopoeia are applied for both types of products. And for non-pharmacopoeial products Drug advisory committee recommended standards (including that developed by innovator) are applied. Also, based on Biopharmaceutics classification system (BCS) many generics (read branded generics) bioequivalence study reports are required and evaluated prior to marketing authorization.

Myth#4: Generic are sold at a vastly lower price because of their less quality

Fact: Generic manufacturers are able to sell their products for lower prices, not because the products are of lesser quality, but because generic manufacturers generally do not engage in significant research and development expenses. Of Innovator brands and brand-named generics and generic-named products, innovator brands are costlier commensurate with the cost incurred due to long process of product development and development prior to put into market while brand-named generics and generic-named products do not incur such costs and further they need not require high cost for promotion/marketing thus are placed at lower prices but quality parameters applied are similar and comparable in all of these cases.

Myth#5:Brand name drugs are safer than generic drugs

Facts: As mentioned previously we have innovator, brand-named generic and generic-named (very few) products in the country. The safety, efficacy and quality as established during drug development and first-time marketing by the innovator (Brand) is taken as global evidence of safety of generic equivalents also however pharmacovigilance program including post marketing surveillance

help cater current evidences on both innovator brand and generic version. Thus, bioequivalent products are considered similar in safety as well as efficacy.

Myth #6: DDA's enforcement action against the drug company recently demonstrates quality problems with imported and manufactured generic drugs

Fact: Quality problems which may arise during the different level of product life cycle are monitored through Post marketing surveillance and actions sanctions are applied consequently as per the quality evidences. A recent recall actions of brand-named generics shows such products put patients at risk, however this cannot be viewed as an evidence of all brand-named generics of generics in general are of substandard. The innovator brands are also sampled and tested against its specification in order to assure products are available and put off any risk of taking substandard medicines.

Myth#7:DDA does not care about quality concerns over Generic drugs

Fact: DDA applies the requirements set in drug act and rules under it, so that quality safe and efficacious medicines are manufactured, distributed, imported and stored throughout the country. The medicines registration guidance and standards applied for product registration, marketing authorization, and renewal does not discriminate between innovator brand and brand-named generics.

In conclusion, general views upon drug product quality available in Nepal and their prescription are lacking scientific argument rather motivated due to powerful marketing campaign, preconceived brand/product preferences for years. And information available for safety quality and efficacy of innovator(branded) and brand-named generics(including generics) are limited and not reaching the prescribers well. The similarity of Regulatory controls over all products is not well understood and rather misunderstood to have conclusion like brands are better than generics. Nepal's scenario is altogether misunderstood, since Nepali market consist of the brand-named generics, most clinicians are accustomed with preferences of certain brand-named generics with a gross bias against generics. Scientifically, the dichotomy over brand verses generic seems to have ceased but bias against generics over innovator (brand) is still prevails due probably strong promotional exercises by the companies, traders or pharmacists. Thus, it is advised to all clinicians, health professionals, traders to wipe away the misunderstanding on brand verses generic product use and are strongly advocated to use them enhancing better health outcomesand establishing value for money.

Narayan Prasad Dhakal
Chief Editor

REGULATORY NEWS

New approved medicines

The drug evaluation committee within DDA is responsible for studying the quality, safety, efficacy, cost-effectiveness etc. of new medicines that have not been registered in the department and not been published in any listed pharmacopoeias. The committee makes a decision based on the study whether to forward the molecules to Drug Advisory Committee (DAC) or not. The DAC, based on the report/recommendation from the drug evaluation committee makes a decision to approve or reject those medicine for registration. In the 49th meeting of DAC, five medicines have been recommended for registration within DDA which are as follows:

1. **Dulaglutide,** which is used in management of Type-II Diabetes Mellitus.
2. **Cetuximab,** which is an epidermal growth factor receptor inhibitor used for the treatment of metastatic colorectal cancer, metastatic non-small cell lung cancer and head and neck cancer.
3. **Empagliflozin,** which is an drug of the gliflozin class used for the treatment of type 2 diabetes in adults
4. **Luliconazole,** which is an imidazole antifungal drug indicated for the treatment of athlete's foot, jock itch, and ringworm caused by dermatophytes such as *Trichophyton rubrum, Microsporum gypseum* and *Epidermophyton floccosum*
5. **Teneligliptin,** which is a dipeptidyl peptidase-4 inhibitor or gliptin used for the treatment of type 2 diabetes mellitus.

IMPORTANT INFORMATION

Flucloxacillin and concomitant paracetamol
Interaction: Risk of high anion gap metabolic acidosis

The Health Products Regulatory Authority (HPRA) has stated that the SPC and package leaflet for flucloxacillin containing medicinal products will be updated to include information on the risk of high anion gap metabolic acidosis (HAGMA) and concomitant paracetamol therapy. Flucloxacillin containing medicinal products are licensed for the treatment of specified bacterial infections. The Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) recently concluded a review of the risk of HAGMA with flucloxacillin and concomitant paracetamol therapy. Evidence in the literature and a limited number of spontaneous reports seem to support the possibility of the appearance of a specific type of HAGMA (pyroglutamic acidosis) in the presence of flucloxacillin and paracetamol.

Source: WHO Pharmaceuticals Newsletter No. 1, 2018

In Nepal: Health care professionals are warned of the risk of development of high anion gap metabolic acidosis with concomitant use of flucloxacillin and paracetamol.

Iodine-containing contrast agents
Possible risk of hypothyroidism in infants

The Medicines and Medical Devices Safety Authority (Medsafe) has requested that data sheets for iodine-containing contrast agents (ICAs) are updated with information on the risk of hypothyroidism. The data sheets should include information on thyroid function and monitoring, particularly in neonates. ICAs are medicines used to enhance visibility of blood vessels and organs during medical imaging (e.g. CT scans). ICAs can be administered intravascularly or enterally. Medsafe put ICAs under its medicine monitoring programme on 2 March 2017. During the period (2 March to 30 September 2017), one case of hypothyroidism was reported in a premature newborn to the Centre for Adverse Reactions Monitoring (CARM). A thyroidstimulating hormone (TSH) test at three days of age was normal, but TSH was elevated about two weeks after a single dose of ICA. Iodine levels in the urine were high approximately 20 days after ICA was given. The balance of benefits versus harm for ICAs remains positive and no further action is required at this time.

Source: WHO Pharmaceuticals Newsletter No. 1, 2018

In Nepal: Health care professionals are warned of possible risk of hypothyroidism in infants to whom iodine-containing contrast agents have been used.

Long-acting beta agonists (LABAs) and inhaled corticosteroids (ICS)
Removal of Boxed Warning about asthma related deaths

The US FDA has removed the boxed warning about asthma-related deaths from the drug labels of medicines that contain both an inhaled corticosteroids (ICS) and longacting beta agonists (LABAs). LABAs are inhaled medications that are used in the treatment of asthma and chronic obstructive pulmonary disease (COPD). ICS are indicated for the maintenance treatment of asthma as prophylactic therapy in adult and paediatric patients six years of age and older. It is also indicated for asthma patients requiring oral corticosteroid therapy, where adding ICS may reduce or eliminate the need for oral corticosteroids. A FDA review of four large clinical safety trials shows that treating asthma with LABAs in combination with ICS does not result in significantly more serious asthma-related adverse effects than treatment with ICS alone. A description of the four trials has also been included in the warnings and precautions section of the drug labels.

Source: WHO Pharmaceuticals Newsletter No. 1, 2018

In Nepal: Health care professionals are informed of the removal of such boxed warning about asthma related deaths from medicines that contain both an inhaled corticosteroid and long- acting beta agonist by FDA.

Proton Pump Inhibitors (PPIs)

Risk of subacute cutaneous lupus erythematosus (SCLE)

Health Canada has updated the product safety information for all proton pump inhibitors (PPIs) to inform health-care professionals and patients about the rare risk of subacute cutaneous lupus erythematosus (SCLE). PPIs are medications used to reduce stomach acid, treat heartburn and sores in the lining of the stomach. They are available with a prescription and over-the-counter. Health Canada reviewed the potential risk of SCLE after an article indicating the risk of SCLE with PPIs was published in the literature. As of September 30, 2016, Health Canada received two Canadian reports of potential SCLE with PPI use, but there were insufficient information in these reports to show that the patients had all the symptoms suggestive of SCLE or to conclude that the PPI caused the skin reaction. Health Canada reviewed another 18 international reports of potential SCLE with PPI use in the published literature. Other factors may have contributed to the skin reaction, e.g. concomitant medicines. It was noted that, of these patients, 16 recovered when they stopped taking the suspected PPI. SCLE cases have not been reported for all PPIs. However, it is expected that all PPIs could potentially lead to the development of SCLE in some individuals. Health Canada concluded that there is a rare risk of SCLE associated with PPI use.

Source: WHO Pharmaceuticals Newsletter No. 1, 2018

In Nepal: Health care professionals and consumers are warned of the risk of development of subacute cutaneous lupus erythematous with the use of proton pump inhibitors.

Sedative and anaesthetic drugs (other than benzodiazepines and barbiturates)
Risk of neurodevelopmental disorders

Health Canada has updated the product information for specific sedative and anaesthetic drugs (propofol, ketamine, sevoflurane, desflurane, and isoflurane) to warn health-care professionals and patients about the risk of neurodevelopmental disorders. Sedative and anaesthetic drugs are used by health-care professionals during surgical and medical procedures in children and adults. Health Canada carried out a safety review to assess the potential for negative effects on the development of children's brains (i.e. neurodevelopmental disorders) with specific sedative and anaesthetic drugs (propofol, ketamine, sevoflurane, desflurane and isoflurane) used in early childhood or in pregnant women (exposure of the fetus). At the time of the review, Health Canada searched for Canadian and international reports for potential negative effects on the development of children's brains related to the use of sedative and anaesthetic drugs in pregnant women or young children. In the identified reports (39 Canadian and 38 international), two reports of international patients were of interest but there was not enough information to further assess these reports. Published studies in animals suggest that repeated or lengthy exposure (more than three hours) to sedative and anaesthetic medicines during the third trimester of pregnancy or in young animals can cause neurodevelopmental issues, such as problems with learning and memory. In contrast, neurodevelopmental issues were not seen when animals were treated for a shorter period of time (three hours). Published studies, mostly in children up to three years of age, were also found. In these studies, some found no link between the use of these drugs and neurodevelopmental disorders while others found similar results as those seen in the animal studies. However, in studies on children, it was not clear whether the neurodevelopmental disorder was due to the drug or other factors such as illness or the surgery itself. Health Canada's review concluded that repeated or lengthy use (more than three hours) of these sedative and anaesthetic drugs in pregnancy and in children up to approximately three years of age may potentially lead to neurodevelopmental disorders in children.

Source: WHO Pharmaceuticals Newsletter No. 1, 2018

In Nepal: Health care professionals are warned of the risk of neurodevelopmental disorders with the use of sedative and anaesthetic drugs (other than benzodiazepines and barbiturates).

Chlorhexidine
Risk of serious allergic reactions

The Health Sciences Authority (HAS) has informed health-care professionals about the outcome of a review on the known risk of allergic reactions, whilst using chlorhexidinecontaining products. Chlorhexidine is a broadspectrum antiseptic which is effective against gram-positive and gram-negative bacteria on the skin and is widely used to reduce the risk of bacterial infections. This review

was conducted following safety alerts of serious allergic reactions reported with antiseptic products containing chlorhexidine. Fifteen reports of anaphylactic reactions related to chlorhexidine were identified over a span of 36 years (1981 to 2017). There was no increase in trend of serious allergic reactions to chlorhexidine-containing products observed. At the time of the review, HSA did not identify any significant safety signals regarding serious allergic reactions with the use of chlorhexidine in Singapore. Health-care professionals are advised to inform patients to stop using the product and seek immediate medical attention if they experience symptoms of a serious allergic reaction, such as wheezing, swelling of the face, or severe rashes.

Source: WHO Pharmaceuticals Newsletter No. 1, 2018
In Nepal: Health care professionals are warned of the risk of serious allergic illness with the use of chlorhexidine.

Ibuprofen
Study suggests effects on testicular physiology
L'Agence Nationale de Sécurité du Médicament et des Produits de Santé (ANSM) has reminded health-care professionals and patients about the importance of respecting the treatment dosage and duration defined in the marketing authorisation for ibuprofen. The lowest effective dose for the shortest time necessary to address patients' symptoms should be used. Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) used primarily for pain and fever. This reminder follows results of a study conducted in Denmark on the effects of ibuprofen on testicular physiology. Results from a study suggest that ibuprofen taken in large doses for prolonged periods can disrupt testicular physiology. However, testosterone levels observed in study participants remained normal. In addition, no clinical consequences (male fertility disorders, impotence, libido disorders) were found. This study is being analyzed at European level to determine, if further studies are needed. At this stage, these results do not alter the benefit/risk ratio of ibuprofen when used in accordance with its marketing authorization.

Source: WHO Pharmaceuticals Newsletter No. 1, 2018
In Nepal: Health care professionals are informed about the possible effects on physiology due to use of ibuprofen in large doses for prolonged periods.

SGLT2 inhibitor
Risk of non-traumatic amputations of the lower limbs, diabetic ketoacidosis and renal failure
El Instituto de Salud Pública de Chile is updating the safety information brochures for pharmaceutical products containing SGLT2 inhibitors (canagliflozin, dapagliflozin and empagliflozin), to reflect cases of non-traumatic amputations of lower limbs (amputation of toes associated with canagliflozin use), diabetic

ketoacidosis and acute renal failure. SGLT2 inhibitors are used for type 2 diabetes mellitus.

Source: WHO Pharmaceuticals Newsletter No. 1, 2018

In Nepal: Health care professionals are warned of the risk of non-traumatic amputations of the lower limbs, diabetic ketoacidosis and renal failure associated with use of SGLT2 inhibitor.

Antihistamines (first generation, oral sedating)

Potential for fatal respiratory depression in children under two years of age

The Therapeutic Goods Administration (TGA) will work with manufacturers to strengthen warnings in the product information (PI) and consumer medicine information (CMI) for first generation oral antihistamines, to emphasize that they should not be used in children under two years of age due to the potential risk respiratory depression. In addition, TGA will be seeking to include a mandatory warning statement on labels of overthe-counter (OTC) liquid oral formulations of first-generation oral sedating antihistamines about the contra-indication of use in children under two years. The TGA recently reviewed a fatal case of respiratory depression in a 74-day old infant who was treated with OTC promethazine oral liquid. Although the infant's death was not attributed to use of promethazine, the case raised a safety concern. Up until 15 November 2017, the TGA database of adverse event notifications contained 45 reports of adverse events in children aged under two years in which a first-generation oral sedating anti-histamine is listed as the sole-suspected medicine. These reports document a range of adverse events including hypersensitivity reactions, agitation, abnormal movements, vomiting and diarrhoea.

Source: WHO Pharmaceuticals Newsletter No. 2, 2018

In Nepal: Health care professionals and general public are warned of the potential for fatal respiratory depression in children under two years of age with use of antihistamines.

Clarithromycin

Potential risk of heart problems or death in patients with heart disease

The US Food and Drug Administration (FDA) has added a new warning about an increased risk of death in patients with heart disease to the drug labels for clarithromycin (Baxin®). In addition, the FDA has added the results of a clinical trial that indicate this increased risk to clarithromycin drug labels. Clarithromycin is used to treat a variety of infections and is not approved to treat heart disease. The FDA’s recommendation is based on a review of the results of a 10-year follow-up study of patients with coronary heart disease form a large clinical trial that first observed this safety issue. Results from the trial provide evidence of the increased risk compared to placebo. Other observational studies showed mixed findings.

The FDA is unable to determine why the risk of death is greater for patients with heart disease.

Source: WHO Pharmaceuticals Newsletter No. 2, 2018

In Nepal: Health care professionals are informed about the risk of heart problems or death in patients with heart disease with the use of clarithromycin.

Miconazole and warfarin interaction

Reminder of reduced warfarin clearance

TGA has requested that a warning statement about the potential interaction with warfarin is added to product labels for miconazole containing products. In addition, TGA will also work with manufacturers to strengthen warnings in the patient information (PI) and consumer medicines information (CMI) documents. Miconazole is an antifungal medication used to treat ringworm, pityriasis versicolor, and yeast infections of the skin or vagina. Miconazole inhibits one of the main cytochrome P450 isoenzymes involved in warfarin metabolism (CYP2C9), which can result in reduced warfarin clearance and an enhanced anticoagulant effect. This can lead to supratherapeutic international normalised ratio (INR) values and subsequent bleeding complications. Bleeding events can have fatal outcomes. The TGA has reminded health professionals that, while the number of Australian reports of warfarin and miconazole interactions are low, the potential of an interaction can be life-threatening.

Source: WHO Pharmaceuticals Newsletter No. 2, 2018

In Nepal: Health care professionals are warned of the reduced warfarin clearance due to interaction when miconazole has been administered concomitantly.

Dabigatran

Possible risk of gout or gout-like symptoms

Medsafe highlighted a possible risk of gout or gout-like symptoms with the use of dabigatran (Pradaxa®). Dabigatran is used in conditions such as: prevention of stroke and systemic embolism; prevention of venous thromboembolism; treatment and prevention of deep vein thrombosis and/or pulmonary embolism. In September 2017 a report of aggravation of gout after starting treatment with dabigatran was received by the CARM. The patient experienced a marked increase in episodes of gout after starting dabigatran and improved after treatment with dabigatran was stopped, without other interventions. Gout is not a known adverse effect of dabigatran and is not included in the data sheet. A search of the WHO global database for Individual Case Safety Reports, VigiBase to date, revealed 71 reports worldwide of gout or gout-like symptoms, suspected to be associated with dabigatran use. Medsafe is placing this safety concern on the medicines monitoring scheme to obtain further information on these possible adverse reactions. Also, Medsafe calls for reports of cases of gout or gout-like symptoms in patients taking dabigatran.

Source: WHO Pharmaceuticals Newsletter No. 2, 2018
In Nepal: Health care professionals are warned of the risk of gout like symptoms with use of dabigatran.

Direct-acting antivirals (DAAs)
Possible effects on blood glucose control when used in patients with type 2 diabetes
Medsafe investigated the association of direct-acting antivirals (DAAs) and effects on blood glucose control when used in patients with type 2 diabetes. During the medicines monitoring period (13 March 2017 to 31 December 2017), no cases of abnormal glucose levels were reported to the CARM. Effects of the use of DAAs on blood glucose control, when used in patients with type 2 diabetes, could not be confirmed. The balance of benefits and risks of harm for DAAs remains positive and no further action is required at this time. Medsafe will re-investigate this concern should more information become available.

Source: WHO Pharmaceuticals Newsletter No. 2, 2018
In Nepal: Health care professionals are warned of the possible effects on blood glucose control when direct acting antivirals are used in patients with type 2 diabetes.

Sodium-glucose Cotransporter-2 (SGLT2) inhibitors
Potential risk of a rare brain condition (posterior reversible encephalopathy syndrome) in patients who developed diabetic ketoacidosis
Health Canada has reviewed the potential risk of posterior reversible encephalopathy syndrome (PRES) in patients were treated with sodium-glucose cotransporter 2 (SGLT2) inhibitors and developed diabetic ketoacidosis. SGLT2 inhibitors lower blood sugar in adults with type 2 diabetes. At the time of the review, Health Canada had received two unique Canadian reports of PRES in patients treated with SGLT2 inhibitors who had developed DKA. Both reports involved canagliflozin and suggested that PRES could possibly be associated with the medicine. However, other risk factors such as DKA and severe infection could have played a role in the events. Health Canada's review of the available information did not find a link between the use of SGLT2 inhibitors and the risk of PRES in patients who have developed DKA. Health Canada encourages consumers and healthcare professionals to report any adverse effects related to the use of these health products. Health Canada will continue to monitor the safety of SGLT2 inhibitors.

Source: WHO Pharmaceuticals Newsletter No. 2, 2018
In Nepal: Health care professionals are warned of the potential risk of brain conditions in patients who developed diabeteic ketoacidosis when treated with sodium-glucose cotransporter-2.

Amlodipine

1. Risk of Alopecia

The National Coordination Centre - Pharmacovigilance Programme of India (NCC-PvPI), Indian Pharmacopeia Commission (IPC) has made a recommendation to the Central Drugs Standard Control Organisation (CDSCO) requesting that the drug safety label for amlodipine is revised to include alopecia as an adverse drug reaction. Amlodipine is used for the treatment of angina, hypertension and coronary artery disease. Between July 2011 and August 2017, NCCPvPI received seven individual case safety reports (ICSRs) of alopecia with amlodipine use. The cases were reviewed by Signal Review Panel (SRP)- PvPI, IPC and they showed a strong causal relationship between amlodipine and alopecia.

2. Risk of Gingival Hypertrophy

NCC-PvPI, IPC has made a recommendation to CDSCO requesting that the drug safety label for amlodipine is revised to include gingival hypertrophy as an adverse drug reaction. Between July 2011 and March 2018, NCC-PvPI received 44 ICSRs reporting gingival hypertrophy with amlodipine use. The cases were reviewed by the Signal Review Panel (SRP)-PvPI, IPC and they suggested a strong causal relationship between amlodipine and gingival hypertrophy.

Source: **WHO *Pharmaceuticals Newsletter No. 3, 2018***

In Nepal: Health care professionals are warned of the risk of alopecia and gingival hypertrophy with use of amlodipine.

Atypical antipsychotic

Potential risk of DRESS

Health Canada has announced that the product safety information for atypical antipsychotics will be updated to include the risk of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS). Atypical antipsychotics are indicated to treat mental disorders including schizophrenia, bipolar disorder, and depression. Health Canada reviewed safety information for all atypical antipsychotics following voluntary updates by the manufacturers for olanzapine (Zyprexa®) and ziprasidone (Zeldox ®) to include the risk of DRESS in the product safety information. Among 43 international reports of DRESS with the use of atypical antipsychotics, 11 reports met the definition of DRESS, and two reports showed a likely link between DRESS and the reported atypical antipsychotic. Health Canada's review concluded that there may be a link between the risk of DRESS and the use of six other atypical antipsychotics including clozapine, quetiapine, risperidone, aripiprazole, paliperidone, and lurasidone.

Source: WHO Pharmaceuticals Newsletter No. 3, 2018

In Nepal: Health care professionals are warned of the potential risk of DRESS with the use of atypical antipsychotic.

SIGNAL

SGLT-2 inhibitors and genital pruritus

A non-serious event with the potential for noncompliance and/or discontinuation

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Summary

Sodium glucose cotransporter-2 inhibitors (SGLT- 2i) are members of a relatively new class of oral antidiabetic agents which are used in the treatment of type 2 diabetes mellitus as monotherapy or in combination with other agents. Itching in the genital area is a common non-serious adverse reaction for these types of drugs which was known at the time of approval. A joint UMC/Lareb signal detection sprint performed in October 2016, highlighted reports from patients that were retrieved from VigiBase, the WHO global database of individual case safety reports, which revealed that often patientsstop taking these medications because of this adverse event.

A 71 year old female with a history of type 2 diabetes and hypertension was initiated on empagliflozin. The patient was treated for cystitis approximately one month after starting therapy. Also, the patient experienced non-serious events of thrush, burning in the urogenital area, redness in the urogenital area, blistering in the urogenital area and hypoglycaemia. In the course of five days the itching increased up to intolerability. Therapy for the event of cystitis was antibiotics and antifungal cream; therapy of the symptoms in the urogenital area included unspecified ointments without success and a mild-cortisone containing ointment which helped slightly. Empagliflozin was discontinued.

A 60 year old female experienced severe itching, soreness, and reddening of the genital area and an inability to sit while on therapy with dapagliflozin. The patient was diagnosed with candidal mycosis and treated with antifungal cream. The cream did not bring improvement and the patient discontinued dapagliflozin "on her own" in response to the events.

Introduction

Sodium glucose cotransporter-2 inhibitors (SGLT-2i) are members of a relatively new class of oral antidiabetic agents. Three medicines in this class, dapagliflozin, canagliflozin and empagliflozin, are currently marketed for use in the treatment of type 2 diabetes mellitus as monotherapy or in combination with other agents.

SLGT-2i work by inhibiting glucose reabsorption in the kidney and thereby promoting urinary excretion of glucose. Studies have revealed that SGLT-2i have beneficial effects on blood glucose levels, but also they reduce blood pressure and induce weight loss. Given that the action of these agents is independent of both insulin secretion and insulin action, another benefit of these agents is a lower risk of hypoglycaemia.

Given their mechanism of action, one of the major safety concerns for the SLGT-2i is an increased risk of genital infections caused by high levels of glucose in the urine. This safety concern is common enough that it was observed in clinical trials and has been fairly well characterised. Genital infections are largely fungal

in nature, manifesting as mycotic vulvovaginitis in females and mycotic balanitis in males. Such infections have been estimated to affect 5-10% of patients using SGLT-2i and are more common in premenopausal women, patients with a history of genital infections, and obese patients. There was no evidence of a relationship between the incidence of genital infections and the amount of glycosuria observed in the clinical trials. Furthermore, rates of infections are highest in the first few months of treatment.

Reports in VigiBase

During a joint UMC/Lareb signal detection sprint with a focus on patient reports, a total of 99 individual case safety reports which included the MedDRA preferred term (PT) 'pruritus genital' for dapagliflozin, canagliflozin and empagliflozin were identified in VigiBase, the WHO global database of individual case safety reports as of 6 November 2016.

Forty-eight reports of pruritus genital (48.5%) have been received for dapagliflozin, 31 (31.3%) for canagliflozin and 20 (20.2%) for empagliflozin.

67.7% of the reports have been described events in females, 28.3% of the reports for males.

40.4% of the reports originated from the Americas, 36.4% from Europe, and 23.2% from Asia.

The most commonly co-reported MedDRA PT were genital burning sensation (9.1%), pollakiuria (7.1%) and dysuria (5.1%).

Twenty-three of the reports were received from con sumers or non-health professionals (eight of which were classified as “serious”) and 25 were received from physicians (none of which were classified as “serious”). Furthermore, fifty-four (54.5%) of the reports documented that the drug was discontinued secondary to the reported adverse drug reactions.

Literature and Labelling

The summary of product characteristics for each of these products notes that most genital infections were mild to moderate and only rarely resulted in discontinuation. The patient information leaflet notes only that genital infections are common to very common and manifest with irritation, itching, unusual discharge or odour. There is no information provided to the patient to seek medical consultation for treatment of these infections.

Discussion and Conclusion

The aim of communication is to highlight that some events can be characterised as nonserious in the clinical trial setting but may manifest in the post marketing period as severe events which have a large enough impact on the quality of life for the patient that discontinuing the medication is necessary.

Additionally, more guidance by drug developers or regulators on how to manage these effects may be necessary to ensure that patients who receive benefit from taking the medications are able to remain compliant with them.

Source: WHO Pharmaceuticals Newsletter No. 3, 2017

FEATURE

Enhancing Pharmacovigilance in Low and Middle Income Countries using Smart Safety Surveillance

Access to priority medicines and vaccines in low and middle-income countries (LMICs) has improved significantly in the last few years. With the urgent need for novel treatments for diseases such as tuberculosis, malaria and HIV, more and more medicinal products are expected to be released on an accelerated, fast-track basis. However, there has not been a proportionate improvement in pharmacovigilance (PV). This is of great concern, as effective safety monitoring systems are essential to learn about the safety of novel treatments, manage adverse effects and minimize risks. In addition, a lack of functional PV system is a barrier to access as many new products require safety monitoring as a condition to authorization of a license for use.

In 2016, the World Health Organization, (WHO) in collaboration with the Bill and Melinda Gates Foundation (BMGF) launched the Smart Safety Surveillance or Project 3S to help LMICs identify, assess and adequately manage the risks associated with new medicines and vaccines. The 3S approach proposes strengthening of PV systems and practices in LMICs, to support the introduction of new health products through identification, assessment, and management of any risks associated with them. Although the 3S approach was borne out of a WHO-BMGF grant agreement, the approach is equally valid for strengthening PV systems in countries supported by other donors such as UNITAID.

One of the products that will be used as a pathfinder to test the concept of the 3S approach is bedaquiline. Bedaquiline (BDQ), is a new class of medicines against M. Tuberculosis indicated for the use of multi-drug resistant tuberculosis (MDR-TB). The emergence of drug-resistant tuberculosis (TB) is a major threat to global TB care and control, and even more so when there is resistance to multiple drugs. Bedaquiline was approved for use in the treatment of MDR-TB under the United States Food and Drug Administration (U.S FDA) accelerated-approval regulations and conditional under the European Medicines Agency (EMA). Subsequently, the World Health Organization (WHO) issued conditional recommendations for its use through an interim policy guidance published in 2013. One of the conditional requirements is pharmacovigilance and proper management of adverse drug reactions and prevention of drug–drug interactions. So far, WHO estimates that bedaquiline has been introduced and used in over 46 countries worldwide, under various mechanisms of compassionate use, expanded access programmes, donation programmes, import waiver and registered market access.

Armenia and Kyrgyzstan are among 27 countries in the world with a high burden of multidrug-resistant tuberculosis (MDR-TB) and among the 18 high-priority countries for TB in the WHO European Region. In March 2018, representatives from WHO Safety and Vigilance team at Headquarters in Geneva, WHO regional office in Europe, and WHO country offices in Armenia and Kyrgyzstan visited TB clinics and national PV centres in Armenia and Kyrgyzstan to gain insight on existing PV systems and explore how the 3S principles can be applied to strengthen existing systems.

Through various meetings and discussions, WHO has gained an understanding of structural components such as legislations, existence of guidelines and standard operating procedures, human resources and access to information, in both countries. The team also gained a good understanding of the reporting process, analysis and level of decision making was also acquired. WHO representatives also met with a few non-governmental agencies such a Médecins for sans Frontièrs (MSF) and KNCV to clarify roles, activities and future plans under the scope of PV. The team gathered information on areas of PV that require support, so that countries are prepared for the safety monitoring of new medicinal products. WHO, together with the countries, and other partners such as the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK is designing a work plan to address identified gaps and needs, with the aim of strengthening the PV systems in countries.

Source: WHO Pharmaceuticals Newsletter No. 2, 2018

Fifteenth Meeting of the WHO Advisory Committee on Safety of Medicinal Products (ACSoMP)

The WHO Advisory Committee on Safety of Medicinal Products (ACSoMP) has been constituted to provide advice on Pharmacovigilance policy and issues related to the safety and effectiveness of medicinal products. A summary of discussions and key recommendations from the 15th meeting of ACSoMP is provided below.

1. WHO reports

1.1. Safety and Vigilance (SAV):

Medicines WHO's programme of work for 2019−2023:

While the standardized approach to pharmacovigilance will continue, there will be more focus on strengthening capacity to promote the safety of medicines, especially in low- and middle-income countries (LMICs). There is to be a focus on country ownership, but with better quality data, faster detection of signals, reduced costs and reduced mortality and morbidity.

Normative work will be boosted in countries by encouraging more consistent engagement in the work of the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), as well as continuing close collaboration with the Council for International Organizations of Medical Sciences (CIOMS). The pharmacovigilance toolkit is being updated and expanded. Indicators are being prepared to assess how ready countries are to use new pharmacovigilance products, and the WHO-ISoP pharmacovigilance curriculum is being adapted to a more competency-based model. WHO's training will include a module on ICH approaches for countries that are interested in this.

Technical assistance: The short-term (1−2 years) aim is to gather intelligence on a small number of products and build minimum capacity for surveillance support to 4−6 countries that will use the products. A further short-term project is to pilot a WHO undergraduate curriculum on pharmacovigilance in selected countries, while general support to countries will aim to link pharmacovigilance activities to the regulatory function. In the longer term (5 years) the goal is to scale up the number of countries supported for preparedness and ensure alignment with the Global Benchmarking Tool priority countries, supporting pharmacovigilance goals and strengthening work. Particular aims will be to support countries to link pharmacovigilance to regulation, and to strengthen the use of new technical developments – such as the WebRADR (Recognising Adverse Drug Reactions) application and electronic health records.

Significant dates: The 41st annual meeting of national pharmacovigilance centres which will take place in Geneva on 5-9 November 2018 will mark the 50th anniversary of the WHO Programme for International Drug Monitoring (PIDM) and the 40th anniversary of the Uppsala Monitoring Centre (UMC) which has provided technical support for the programme since 1978. The year 2018 also marks the 70th anniversary of the creation of WHO.

Summary of Discussions/Recommendations

- A future meeting of the Advisory Committee should include a session on capacity-building. The Advisory Committee called for more emphasis on building competency in pharmacovigilance for medical products.
- In planning and implementing training curricula, WHO should consider the work of ICH, universities, and of professional societies.
- While there is to be a focus on national ownership, a regional approach to pharmacovigilance could be supported where relevant.
- Because of all the data in assessment reports on various products, sharing these reports amongst various stakeholders would greatly increase knowledge to help guide future safety and vigilance efforts. The Advisory Committee agreed to propose protocols to further encourage access to the data that already exist.
- WHO should help direct people to pharmacovigilance data that are publicly available.

1.2. WHO Collaborating Centre for International Drug Monitoring

Milestones: The Uppsala Monitoring Centre (UMC) reported on research milestones, including:

- Investigating variations in risk between the sexes and between different subgroups of patients;
- A pilot study on detecting systematic medication errors in VigiBase, identifying 10 potential safety issues;
- A project in collaboration with Australia's Therapeutic Goods Administration (TGA) and the United Kingdom's Medicines and Healthcare products Regulatory Agency (MHRA) to develop and refine methods for de-identifying case narratives through the use of deep neural networks;
- Completion of the Innovative Medicines Initiative's Web-RADR project;
- Complementing the BLIS methodology for predicting indications in electronic medical records with cluster analysis that grouped related medical events, followed by a pilot study;
- Finalization of four modules on signal detection and causality assessment for the UMC distance learning course.

UMC collaboration: It was reported that collaboration is expanding with a number of partner agencies. UMC now has joint user group meetings and training sessions with the MSSO, the maintenance organization for the Medical Dictionary for Regulatory Activities (MedDRA). Most reports to UMC still come from the United States Food and Drug Administration (FDA), but in 2017 about 10% of reports came from China with large and increasing numbers also from India and the Republic of Korea. Many countries are requesting help in developing skills for data analysis and not just data collection. UMC is therefore increasingly focusing its training in this area.

Summary of Discussions/Recommendations

- Now that database system differences, which caused difficulties in the past, are no longer the main problem, UMC should focus more on encouraging countries to work together.
- More work is needed to help countries understand what actions to take when a signal is announced.
- Since UMC functions as the lead WHO technical partner for the PIDM, it is important that ACSoMP plays a role in guiding the work of UMC by reviewing UMC workplans and submitting comments to the UMC board. UMC will continue to share the workplans with WHO, and through WHO, with ACSoMP for input and advice.
- As the situation in many countries is changing fast, there is a need for a long-term strategic view of pharmacovigilance in order to guide investment for change in 10 years' time. In that regard, ACSoMP should consider having a bigger role in reviewing the workplan of WHO's SAV team (and its collaborating centres).
- Institutions responsible for carrying out pharmacovigilance around the world should be helped to have the capacity to do data analysis and make decisions as to what their data show.
- Efforts should be strengthened to help countries obtain tools to make safety reporting easy. The United Arab Emirates used its own resources to launch the generic version of the WEB-RADR app, Zimbabwe also launched an ADR reporting app.
- As other actors develop apps for data reporting, UMC, a WEB-RADR partner, was urged to complete its development of an interface platform so that data from all sources can be gathered.
- Although there are considerable safeguards on data use, commercial enterprises are able to use online search data to build user profiles. Advice should be developed on data privacy, proposing how and when pharmacovigilance data may be used.

2. The Smart Safety Surveillance (3S) project

Background: WHO and the Bill and Melinda Gates Foundation (BMGF) have introduced "Smart Safety Surveillance" (or 3S), which is a risk-based approach to pharmacovigilance (PV) for new products that have not been introduced into reference regulatory markets and therefore no longer possible to draw on the experience of those markets. The 3S project, which was described at the fourteenth meeting of the Advisory Committee, will include piloting a set of key pharmacovigilance principles using selected new products in selected countries.

Aim of the 3S project: The aim is to establish the proof of concept for strategies for building or strengthening pharmacovigilance systems in LMICs. The strategies are to assess product launches over the coming 10 years, the time frame for product launches, anticipated/potential risks with the products, and capacity for pharmacovigilance in launch countries. Key objectives are to strengthen the functionality of pharmacovigilance systems, to build capacity to analyse safety data, to improve regulatory decisions, and to support collaboration between public health and pharmacovigilance programmes. Key principles of 3S are to leverage product introduction, to focus surveillance initially on areas identified during development and on products with a high-risk profile, to undertake active surveillance to a targeted period of time, to use current standards for safety, and to leverage and build on current harmonization platforms.

Products: Three products have so far been selected for the pilot project – the tuberculosis medicine bedaquiline (BDQ), the malaria medicine tafenoquine (TFQ), and the rotavirus vaccine Rotavac. A shortlist of priority countries has been drawn up and assessments of these are under way in order to select the final set of countries for the pilot. Discussions have been held with WHO's programmes on tuberculosis, malaria and HIV both to fine-tune details of the pilots and to define criteria for selecting countries. A Project Advisory Group has been set up and includes the chairpersons of ACSoMP and the Global Advisory Committee on Vaccine Safety. In addition, the United Kingdom's Medicines and Healthcare Products Regulatory Agency (MHRA) has received a grant from the BMGF to provide technical support to 3S.

Summary of Discussions/Recommendations

- Experience gained during 3S could be used to address other issues in resource limited settings (such as substandard products). Although the project is geared to individual countries, there may be implications at a regional level.
- Committee members expressed overall support for 3S and for its pilots. Although the activities are centred around specific medicinal products, the purpose of the project would be to build sustainable systems and capacity for pharmacovigilance.

- Although different countries are expected to have different approaches to pharmacovigilance, and with a different focus and priority, the underlying principles must be the same.
- 3S must ensure that patients' privacy is protected when data are gathered.
- Cultural sensitivities will be important, as will the readiness of industry to become involved and the extent of collaboration with WHO and national disease programmes.
- As the 3S project evolves, thought should be given to the future role of UMC and what more it could do.

2.1. Bedaquiline (BDQ)

One of the pilot projects of 3S will focus on the introduction of the new tuberculosis (TB) medicine bedaquiline (BDQ).

Background: Bedaquiline (BDQ) is the first representative of a new class of medicines expected to address the high unmet medical need for new treatment options for pulmonary multidrug-resistant tuberculosis (MDRTB). FDA has granted accelerated approval to Sirturo (bedaquiline) tablets in the treatment of pulmonary multi-drug resistant tuberculosis (MDR-TB) as part of combination therapy in adults in 2012. Bedaquiline (BDQ) was authorized in the European Union (EU) in 2013 with a conditional marketing authorization under the trade name Sirturo with the marketing authorization holder (MAH) Janssen-Cilag International. The European Medicines Agency (EMA) recommended granting conditional marketing authorization because, although the data supplied by the applicant showed that the medicine's benefits outweighed its risks, the data are not yet comprehensive. Therefore, additional studies on the use of BDQ should be conducted by the MAH with the final analysis of the data in November 2021. The authorized indication (EMA, FDA) of BDQ is for the treatment of adults with MDR-TB of the lungs, to be always used in combination with other anti-TB medicines.

Conditions of use: WHO issued an interim guidance which provides advice on the inclusion of bedaquiline in the combination therapy of MDR-TB in accordance with the existing WHO Guidelines for the Programmatic Management of Drug-resistant TB (2011 Update).

BDQ as a 3S Project 'candidate': The decision to include BDQ in the 3S pilot project is based on the selection criteria that were developed by WHO (Safety & Vigilance and WHO Global TB Programme (GTB), and under the advice of the WHO ACSoMP. In brief:

- BDQ is being introduced conditionally, as a pilot phase, in some low and middle income countries (LMICs) at the same time as its introduction in high income countries (HICs) with an orphan status. Since MDR-TB incidence is

low in HICs, the medicine has been licensed under the orphan-drug approval process; thus LMICs do not have much data on BDQ from HIC to lean on. Monitoring BDQ, within the 3S project in LMICs, will provide the much needed data on BDQ for LMIC-specific use, about the QT prolongation impact of the medicine in the treatment , all other hitherto unknown adverse events and the implementation of patient inclusion and monitoring in every day practice.

- Nearly 60% of all MDR-TB patients live in LMICs in Asia and Africa. It is critical that robust data on BDQ are available quickly in these settings through 3S and other projects, to support the scale up of BDQ, from pilot to full-access programmes in LMICs.
- Phase II and Phase III trials are unlikely to provide an exhaustive understanding of the safety profile of a medicine, particularly for harms and drug-drug interactions (DDI) that are uncommon, and therefore surveillance of the kind proposed by this initiative will add to current knowledge.

Summary of Discussions/Recommendations

- In many countries data on new medicines are not shared and ways need to be found to encourage sharing.
- National TB programmes should be urged/supported by WHO to collect data and to share these with national regulators, other countries and ultimately with the WHO global database, for mutual learning.

2.2. Tafenoquine (TFQ)

Background:

P. vivax malaria has a significant public health and economic impact, with millions of clinical infections, primarily in South and South East Asia, Latin America and the horn of Africa. At present primaquine (PRQ) is the only treatment approved for the radical cure (prevention of relapse) of vivax malaria. PRQ is administered as a once-a-day oral dose for 14 days and it is widely accepted that the long dosing leads to reduced compliance and hence reduced clinical efficacy. Alternative treatments with less frequent dosing regimens are needed.

Tafenoquine (TFQ) is an 8-aminoquinoline derivative with activity against the P. vivax lifecycle, including hypnozoites. It has the potential to provide alternative treatment in P. vivax infections which can be administered as a single dose. Co-administration with another blood schizonticide (chloroquine) will be required for treatment of P. vivax malaria as this combination targets both blood and liver stages of infection.

GlaxoSmithKline (GSK) has applied to the Australian Therapeutics Good Administration (TGA) seeking approval of single-dose tafenoquine treatment for the radical cure (prevention of relapse) of P. vivax malaria. GSK also plans to

progress regulatory filings in other countries in 2018. Approval of TFQ by TGA will likely facilitate registrations in other malaria-endemic countries in the region. However, as there is no prior experience with TFQ in any country for preventing relapse of P. vivax malaria, LMICs will not have sufficient post-marketing safety data when TFQ is introduced in their settings and will need to collect and analyse their own data on TFQ for this indication.

Summary of Discussions/Recommendations

- LMICs within the 3S project must be prepared and supported to monitor TFQ to provide the much-needed post-marketing data on TFQ.

2.3. Pharmacovigilance readiness of 3S pilot countries

Indicators: To carry out a baseline assessment of preparedness, a list of indicators was drawn up and approved by ACSoMP in May 2017. The 21 structural indicators aim to show the presence of key pharmacovigilance structures, systems and mechanisms; 15 process indicators aim to show the extent of pharmacovigilance activities; and a set of outcome and impact indicators is used to identify results of interventions and changes as a measure of impact (such as new legislation or restructuring). The status of public health programmes is also considered. Each set of indicators (structural, process, outcome) covers five areas, namely: 1) Policy, law and regulation, 2) System structure and stakeholder coordination, 3) Signal generation and data management, 4) Risk assessment and evaluation, and 5) Risk management, plus communication and commensurate resources needed for the pharmacovigilance system.

Summary of Discussions/Recommendations

- The systematic approach to organizing the project was welcomed.
- On BDQ, there are four issues that need resolution – data need to be collected, data must be shared with the national authorities, national authorities need to share data with VigiBase, and clarification is needed on who is responsible for analysis.
- Ideally all safety data should be chanelled through the national PV system to the global database. If an non-governmental organization (NGO) collects data, on behalf of a marketing authorization holder (MAH), a first step could be to urge the NGO to share its data promptly with the government and arrange for the government to share with WHO/UMC.
- It is important for each country to receive all data on products available in that country. As capacity increases and the country is able to analyse its data, it will also benefit from the data that are in VigiBase. The national regulator and pharmacovigilance centre are accountable for the safety of the patients in their country.

- The 3S project anticipates several levels of pharmacovigilance: with only minimal resources, reporting can be strengthened and encouraged, but in countries with more resources, more advanced pharmacovigilance functions could be implemented.
- Since India has some ongoing studies on Rotavac as well as spontaneous reporting, the aim of the Rotavac pilot is to verify safety and build reassurance.
- The core principle for using key products is to strengthen country pharmacovigilance systems and not only to acquire more data.
- The WHO TB programme's active TB drug safety monitoring and management (aDSM) database collates data from settings with poor or nonexistent pharmacovigilance systems. The data in aDSM are in a format that can be easily transferred to other databases.
- WHO should work on proposals to support data sharing between National TB treatment programmes and the Regulator/National PV Centres.

3. Data access

3.1. Proposed access policy for VigiBase

Background: The WHO Collaborating Centre in Uppsala, (UMC) in Sweden manages the global ICSR database, Vigibase, on behalf of WHO and its Member States participating in the WHO Programme for International Drug Monitoring (PIDM). The original agreement between WHO and the Swedish government only mentioned WHO PIDM use of the data, but subsequent WHA and ICDRA recommendations have requested greater openness. As a result, in 2012 ACSoMP had discussed a proposal about making VigiBase data available to the general public. This led to VigiAccess, for broad, high-level public access to summary information from Vigibase. More recently, academic and industry groups, as well as some training organizations who work with WHO, have requested various levels of access. UMC has prepared a proposal on data access policies. The proposal was presented to the committee for review and advice.

The draft data access policy drew attention to the fact that VigiBase information was collected "for the sole purpose of carrying out the pharmacovigilance activities agreed on within the WHO Programme for International Drug Monitoring (PIDM)" and was intended to strengthen capacity for pharmacovigilance and promote the safe use of medicines. The draft policy identified six groups of stakeholders for Vigibase pharmacovigilance data, namely:

- UMC itself and its Signal Review Panel;
- Approved national authorities of WHO Member States who are members of the PIDM;
- academia;
- marketing authorization holders;

- the general public;
- participants in training activities organized by UMC or other WHO collaborating centres within the PIDM.

In addition, the policy proposed five general principles for data use, namely:
- VigiBase contains anonymized information transferred from Member States. Confidential patient and reporter details should be removed before transfer to VigiBase.
- No onward transfer of the ICSRs in VigiBase is allowed.
- Only anonymized information may be made public.
- All attempts to re-identify data subjects from VigiBase data are prohibited.
- Access to VigiBase data requires signature of a valid user licence agreement, including acceptance of a statement on the nature, confidentiality and limitation of use of the data.

Three levels of access (public, intermediate and extensive) were proposed, to balance transparency and patient confidentiality, access to information, academic interest and towards pharmacovigilance obligations of various stakeholders. ACSoMP members were requested to comment on the scope and content of the proposed policy and the proposed levels of access.

Summary of Discussions/Recommendations

- ACSoMP members were generally positive about the proposed policy which would facilitate data access and give clear guidelines.
- Each country supplying data has to comply with its own national laws on data protection as well as the terms of the policy.
- Access to some data fields will need to be blocked. In the EU, to strengthen anonymity, if there are fewer than three reports on an issue, they are described as EU or non-EU with no indication of country.
- The EMA reported that it does not give access to academic enquirers unless they give evidence of ethics approval. All academic requests should go through some kind of process to ensure that the request is serious and the project is worthwhile.
- Enquirers who want to have data from a specific country should be directed to ask the relevant authority in that country as UMC is concerned only with global data and not country-specific data.
- ACSoMP gave their overall approval to the proposed access policy. The proposal will be formally presented to Member States in the upcoming WHO Annual Meeting of Representatives of National Pharmacovigilance Centres for comments and consideration.

3.2. Regional data platforms

Background:

Some groups of countries have expressed interest in operating their own regional pharmacovigilance databases with more comprehensive data on regional issues. One argument is that regional databases could encourage countries to contribute data to the global database. In addition, some regional groupings have asked to have access to the full data held by each country in the group including the case narratives. However, such an arrangement would require all countries of a region to have contractual agreements with each other. For instance, not only would sufficient case details for efficient analysis need to be provided, but collaboration agreements between countries would be required for data-sharing to take place, a data access policy would need to be agreed by all, and there would need to be agreement on the process for granting controlled access.

If this were to go ahead, each country in a region would continue to have its own data in its own VigiFlow/other national database, and submit the data to VigiBase. Instead of seeing only a certain limited level of data from other countries via the VigiLyze interface, as today, the proposal is that each country in a defined regional group could in future access a more detailed set of data from countries in the group.

Additionally, some countries with limited capacity for data management have requested all reports from all companies on all medicines. The concern is that countries that have done little data collection and use so far may be overstretched if they receive all global MAH reports.

Summary of Discussions/Recommendations

- The sharing of data as requested by regions is technically feasible. Countries would be able to join their own regional consortium and submit data in order to use regional data. The EMA's Eudravigilance database was described as a model for this. Another example is VigiFlow, originally developed for Swissmedic, to cater for reporting and data sharing between regional centres in the country.
- Any such request by regional groupings for VigiBase data would need to be made at the highest level. This issue should be taken forward by UMC in consultation with WHO.
- There are different views in countries in some regions, so WHO is attempting to obtain ministerial approval from each country before going ahead with this.
- It would be important to know if a country's laws permit the requester to hold the data being requested, in a regional database.

- Since generics manufacturers are the predominant suppliers of medicines to many resource limited countries, safety data from such companies would be particularly relevant in some regional databases.
- It was agreed that a subgroup of ACSoMP members should draw up a short policy statement setting out the issues of collection and management of global MAH data and making some draft proposals that ACSoMP members could then review and contribute to. This topic could be discussed at the WHO meeting of national pharmacovigilance centres.

4. Pharmacovigilance of HIV medicines during pregnancy

4.1. Update on toxicity monitoring of dolutegravir

Members of ACSoMP received a presentation on "Enhancing toxicity monitoring and active safety surveillance during pregnancy for new antiretroviral (ARV) medicines". As the world is moving towards 30 million people receiving antiretroviral treatment (ART) in 2020, there is a need to transition to optimized ART regimen. With dolutegravir, there are remaining gaps: in efficacy data with regard to use with TB drugs, and in safety data in pregnancy and breastfeeding, and in children. It is necessary to look at population-level data over long term use and review any unexpected complications that may arise.

The HIV programme is learning from past experience with some other ARV medicines which resulted in serious adverse complications that led to policy changes in the use of ARVs (WHO 2010 introduction of tenofovir to replace stavudine, and of efavirenz in 2013 to replace nevirapine in preferred 1st line). As a result, in July 2017 WHO issued new technical guidance on transitioning to new ARVs, with programmatic considerations including a section on monitoring of toxicity. The guidance presents approaches for routine HIV patient monitoring, active ARV toxicity monitoring (CNS, IRIS, long-term toxicities), surveillance through ARV pregnancy registry and surveillance for congenital anomalies as well as monitoring of mother–infant pairs during breastfeeding.

Among countries that have started transitioning to dolutegravir, Brazil has implemented a pharmacovigilance programme. As of August 2017, approximatively 52 000 patients were receiving DTG (with an average of 8000 new patients per month) and, of these, some 36 000 had started ART with DTG. The active toxicity monitoring programme included 45 000 patients and found that 3% referred to experiencing an adverse event, although only 79 patients interrupted DTG because of such an event. Regarding safety during pregnancy, very few countries use DTG in 1st line treatment during pregnancy (example, Botswana), while other countries substitute DTG to another ARV, or use DTG ONLY in exceptional clinical situations. The WHO Guidelines released in 2016 cautioned that there were insufficient data for using DTG during pregnancy or breastfeeding and

recommended efavirenz (EFV) in combination with tenofovir (TDF) + lamivudine (3TC) or emtricitabine (FTC) as the preferred option in pregnancy. The main sources of data during pregnancy are the Antiretroviral Pregnancy Registry in the USA, the European Pregnancy and Pediatric HIV cohort collaboration, and an active birth outcomes surveillance study - TSEPAMO study, conducted by the Botswana-Harvard AIDS Institute Partnership in Botswana where DTG is used in first-line regimen.

WHO and the Tropical Disease Research (TDR) Programme have established a WHO registry for the Epidemiological Surveillance of Drug Safety during Pregnancy AND a central repository for safety evaluation of dolutegravir (general population) to pool data from programmes and studies to get bigger samples more rapidly and be able to analyze toxicity data. A data entry interface for supporting countries to enter their data into the WHO registry for the Epidemiological Surveillance of Drug Safety during Pregnancy was presented to ACSoMP as well as the list of tools available. It includes: a list of standard variables, data dictionary, data entry programme, user guide, newborn surface examination video. WHO has issued important surveillance recommendations –

- to invest in standard and active monitoring of toxicity to generate data and inform future treatment policies, and
- to share data between studies and types of sites into WHO/TDR platforms with a multi country approach to learn quickly and globally.

Source: WHO Pharmaceuticals Newsletter No. 3, 2018

REGULATORY NOTICES

नेपाल सरकार

स्वास्थ्य तथा जनसंख्या मन्त्रालय

औषधि व्यवस्था विभागको

TRAMADOL एकल तथा समिश्रित औषधिहरुको

विक्रिवितरण सम्बन्धि अत्यन्त जरुरी सूचना !!!

हाल बजार अनुगमनका क्रममा TRAMADOL एकल तथा समिश्रित औषधिहरुको दुरुपयोग अत्यधिक मात्रामा बढिरहेको पाईएको तथा सो औषधि हालै केही मुलूकमा नियन्त्रित औषधिको सूचिमा समेत राखिसकेकाले औषधि सल्लाहकार समितिको मिति २०७५/३/२९ गते बसेको ४९ औं बैठकले ती बनावटका औषधिहरु सीमित स्थानहरुवाट मात्र विक्रिवितरण गर्ने र सो को प्रभावकारी नियमन गर्न गराउन अस्पताल फार्मेसी (सरकारी तथानिजी) मार्फत मात्र चिकित्सकको प्रेष्क्रृप्सनको आधारमा रेकर्ड राखी उपलव्ध गराउने सिफारिस गरेको छ। सो व्यवस्था कार्यान्वयनका लागि आगामी भाद्र १५, २०७५ देखि औषधि उत्पादक तथा आयातकर्ताहरुलाई आवश्यक व्यवस्था मिलाउन सूचित गरिन्छ साथै, हाल अस्पताल फार्मेसी बाहेक खुद्रा औषधि पसलमा विक्रिवितरण हुनबाँकी रहेका ती औषधिहरु सम्वन्धित थोक विक्रेतालाई फिर्ता गर्नुहुन र भाद्र १५, २०७५ देखि ती औषधिहरु खुद्रा औषधि पसलबाट विक्रिवितरण नगर्नु/नगराउनुहुन मिति २०७५/४/२४ को विभागिय निर्णयानुसार सम्वन्धित सबैलाई सूचित गरिन्छ।

नेपाल सरकार

स्वास्थ्य तथा जनसंख्या मन्त्रालय

औषधि व्यवस्था बिभागको

औषधि फिर्ता (RECALL) गर्ने सम्बन्धि अत्यन्त जरुरी सूचना

यस विभागबाट बजार अनुगमनको क्रममा संकलन गरिएका औषधिहरुको नमुना परिक्षण गर्दा तपसिल बमोजिमका उत्पादकहरुबाट उत्पादित तपसिल ब्याच न. का औषधिहरु न्यून गुणस्तर भएको पाइएकोले ती औषधिहरु औषधि ऐन २०३५ को दफा १४ बमोजिम बिक्रि वितरण रोक्का गरि बजारबाट तुरुन्त फिर्ता (RECALL) गर्न र सोको विवरण यस विभागमा १५ दिन भित्र पेश गर्न सम्बन्धित उद्योग तथा आयतकर्ता तथा तिनका आधिकारिक प्रतिनिधिहरुको जानकारीको लागि यो सूचना प्रकासित गरिएको छ साथै उक्त औषधिहरु सिफारिस, बिक्रि वितरण तथा प्रयोग समेत नगर्नर नगराउनु हुन सम्बन्धित सबैलाई अनुरोध छ।

तपसिल

सि.न.	औषधिको नाम	ब्याच. न	Mfg/ Expiry date	कारण	उत्पादकको नाम र ठेगाना
१.	Cip 500 (Ciprofloxacin tablets IP)	17/10	Aug 2017/ Jul 2019	Non-compliance to IP 2014 w.r.t. dissolution test	Pharmaco Industries Pvt. Ltd., Ramkot, Kathmandu

मितिः २०७४/०२/१० गते (May 24, 2018) गतेको गोरखापत्र राष्ट्रिय दैनिकमा प्रकाशित सूचना

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औषधि फिर्ता (RECALL) गर्ने सम्बन्धि अत्यन्त जरुरी सूचना

यस विभागबाट बजार अनुगमनको क्रममा संकलन गरिएका औषधिहरुको नमुना परिक्षण गर्दा तपसिल बमोजिमका उत्पादकहरुबाट उत्पादित तपसिल ब्याच न. का औषधिहरु न्यून गुणस्तर भएको पाइएकोले ती औषधिहरु औषधि ऐन २०३५ को दफा १४ बमोजिम बिक्रि वितरण रोक्का गरि बजारबाट तुरुन्त फिर्ता (RECALL) गर्न र सोको विवरण यस विभागमा १५ दिन भित्र पेश गर्न सम्बन्धित उद्योग तथा आयतकर्ता तथा तिनका आधिकारिक प्रतिनिधिहरुको जानकारीको लागि यो सूचना प्रकासित गरिएको छ साथै उक्त औषधिहरु सिफारिस, बिक्रि वितरण तथा प्रयोग समेत नगर्नर नगराउनु हुन सम्बन्धित सबैलाई अनुरोध छ ।

तपसिल

सि.न.	औषधिको नाम	ब्याच. न	Mfg/ Expiry date	कारण	उत्पादकको नाम र ठेगाना
१.	Nirogi Churna 100 g	1840	Sep 2016/ Aug 2019	Non-compliance w.r.t. bacterial count	Mudgal Ayurved Bhawan, Hapur, Ghaziabad, India.
२.	Talishadi Churna 60 g	20-A	Aug 2016/ Jul 2018	Non-compliance w.r.t. bacterial count	Shree Baidyanath Ayurved Bhawan Pvt. Ltd., Allahabad, Kolkata.
३.	Triphala Churna 60 g	319	Aug 2016/ Jul 2018	Non-compliance w.r.t. fungal count	
४.	Dhatupaushtik Churna 60 g	180	Aug 2016/ Jul 2018	Non-compliance w.r.t. total aerobic microbial count	

मितिः २०७४/०२/२५ गते (June 08, 2018) गतेको गोरखापत्र राष्ट्रिय दैनिकमा प्रकाशित सूचना

नेपाल सरकार

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औषधि व्यवस्था बिभागको

औषधि फिर्ता (RECALL) गर्ने सम्बन्धि अत्यन्त जरुरी सूचना

यस विभागबाट बजार अनुगमनको क्रममा संकलन गरिएका औषधिहरुको नमुना परिक्षण गर्दा तपसिल बमोजिमका उत्पादकहरुबाट उत्पादित तपसिल ब्याच न. का औषधिहरु न्यून गुणस्तर भएको पाइएकोले ती औषधिहरु औषधि ऐन २०३५ को दफा १४ बमोजिम बिक्रि वितरण रोक्का गरि बजारबाट तुरुन्त फिर्ता (RECALL) गर्न र सोको विवरण यस विभागमा १५ दिन भित्र पेश गर्न सम्बन्धित उद्योग तथा तिनका आधिकारिक प्रतिनिधिहरुको जानकारीको लागि यो सूचना प्रकासित गरिएको छ साथै उक्त औषधिहरु सिफारिस, बिक्रि वितरण तथा प्रयोग समेत नगर्नर नगराउनु हुन सम्बन्धित सबैलाई अनुरोध छ

तपसिल

सि.न.	औषधिको नाम	ब्याच. न	Mfg/ Expiry date	कारण	उत्पादकको नाम र ठेगाना
१.	RL 500 ml (Ringer Lactate Solution for Injection IP)	CSL 7085	May 2017/ Apr 2019	Non-compliance to IP 2018 w.r.t. physical appearance	Eurolife Healthcare Pvt. Ltd, India
२.	RL 500 ml (Ringer Lactate Solution for Injection IP)	CSL 7084	May 2017/ Apr 2019	Non compliance to IP 2018 w.r.t. bacterial endotoxin test	
३.	RL 500 ml (Ringer Lactate Solution for Injection IP)	CSL 7127	May 2017/ Apr 2019		
४.	RL 500 ml (Ringer Lactate Solution for Injection IP)	CSL 7115	May 2017/ Apr 2019		

मितिः २०७५/०३/२८ गते (July 12, 2018) गतेको गोरखापत्र राष्ट्रिय दैनिकमा प्रकाशित सूचना

नेपाल सरकार

स्वास्थ्य तथा जनसंख्या मन्त्रालय

औषधि व्यवस्था विभागको

औषधीको आम उपभोक्तालाई जानकारी

- मान्यता प्राप्त स्वास्थ्यकर्मीकों पुर्जा अनुसार मात्र औषधीको प्रयोग गर्नुहोस्;
- औषधीको प्रयोग सम्बन्धि सम्पूर्ण जानकारी लिने जस्तै, औषधि कसरी प्रयोग गर्ने, औषधी घरमा कसरी भण्डारण गर्ने, औषधि सेवन गर्दा खान नहुने खाध तथा अन्य औषधि, कुनै मात्रा छुटेमा के गर्ने, औषधिको नकारात्मक असरहरु (side effects), तथा औषधी प्रयोग गर्दा अपनाउनु पर्ने सावधानीहरु;
- औषधी बच्चाको पंहुचबाट टाढा राख्नुहो ;
- आफु गर्भवती भएमा सो को बारे स्वास्थ्यकर्मीलाई जानकारी दिनुहोस;
- औषधी प्रयोग गर्दा जीउ चिलाएमा, छालामा डाबरहरु आएमा, श्वास फेर्न गाह्रो भएमा वा यस्तै अन्य लक्षण देखा परेमा तुरुन्त औषधी प्रयोग गर्न छाडी स्वस्थाकर्मीलाई सम्पर्क राख्नुहो;
- यदि एन्टिबायोटिक औषधी सेवन गर्न लाग्नु भएको छ भने तोकिएको मात्रा र अबधिसम्म प्रयोग गर्नुहोस र गरानुहोस;
- औषधी खरिद गर्ने औषधि पसलको ब्यबसायीको मान्यता प्रमाणपत्र हेर्ने गर्नुहोस;
- औषधी खरिदगर्दा अनिवार्य बिल लिने बानी गर्नुहोस् ।

स्वस्थथकर्मी, औषधि सिफारिसकर्ता, औषधी उत्पादक, पैठारि कर्ता तथा व्यबशायीलाई जानकारी

- बिभागमा दर्ता नभएका औषधिको बिक्रि वितरण नगर्ने तथा बिल बिजक बिना कुनैपनि औषधिको खरिद बिक्रि नगरौ ;
- चिकित्सकहरुले वा स्वास्थ्यकर्मीहरुले ब्यबसायिक मर्यादा र आचरणमा बसी औषधिको सिफारिश गर्ने गरौ र कुनै औषधी कम्पनिबाट कुनै लाभ वा अवसरको संभौता गर्नु भएको छ भने पारदर्शी गर्ने गरौ;
- मूल्य नभएको तथा बिभागबाट मूल्य स्वीकृत नभएको औषधी को बिक्रि बितरण गर्ने नगरौ;
- उधोग तथा औषधी वितरकले दिने मभबा दयलगक पारदर्शी गर्ने गरौ र यसबाट उपभोक्तालाई लाभान्वित गरौ;
- Physician sample को दुरुपयोग नगरौं;
- औषधीको स्तर खुलाई मात्र औषधिको उत्पादन र बिक्रि वितरण गर्ने गरौ;
- लागु तथा मनोदिपक र एन्टिबायोटिक औषधिहरुको समुचित प्रयोग गर्ने बनि बसालौ र अरुलाई पनि सिकाउ;
- औषधि दर्ता भएनभएको जानकारी यस विभागबाट जानकारी लिऔ;
- थोक बिक्रेताले खुद्रा बिक्रेतालाई कारोबार गर्दा आधिकारिक बिल तथा अधावादिक दर्ता रहेको औषधी पसलमा मात्र गर्ने र
- लागु तथा मनोदिपक औषधीहरु को अनिवार्य रुपमा चिकित्सकको सिफारिसको आधारमा पारदर्शी रेकर्ड राखेर मात्र बिक्रि वितरण गर्ने गरौ ।

औषधि प्रयोग गर्दा ध्यान दिनुपर्ने कुराहरू:

- मान्यता प्राप्त स्वास्थ्यकर्मीको पूर्जामा मात्र औषधि प्रयाग गर्ने ।
- औषधिको प्रयोग सम्बन्धि पूर्ण जानकारी लिने ।
- औषधिको सेवन तोकिएको समयमा, तोकिए बमोजिमको फरकमा, तोकिएको समयसम्म प्रयोग गर्ने ।
- औषधि बालबच्चाको पहुँचबाट टाढा राख्ने ।
- यदि कुनै औषधि सेवन गर्न भूलेमा सम्झने बित्तिक्कै सेवन गर्ने तर अर्को मात्रा सेवन गर्ने समय नजिक भएमा सेवन नगरी अर्को मात्रा सेवन गर्ने ।
- आफू गर्भवती भएमा सो बारे स्वास्थ्यकर्मीलाई जानकारी दिने ।
- औषधि प्रयोग गर्दा जिउ चिलाएमा, छालामा डाबरहरु आएका, स्वास फेर्न गाह्रो भएमा वा यस्तै अन्य लक्षण देखा परेमा तुरन्त औषधि प्रयोग गर्न छाडी स्वास्थ्यकर्मीलाई सम्पर्क राख्ने ।

एण्टिबायोटिक औषधि प्रयोग गर्दा मान्यता प्राप्त स्वास्थ्यकर्मीको सल्लाहमा तोकिएको अवधि र समयभित्र प्रयोग गरौं र गराऔं ।

औषधि सम्बन्धि थप जानकारीका लागि तल उल्लेखित ठेगानामा सम्पर्क राख्नुहोला ।

औषधि व्यवस्था विभाग

मदनभण्डारी पथ-४, बिजुलीबजार, काठमाडौं

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