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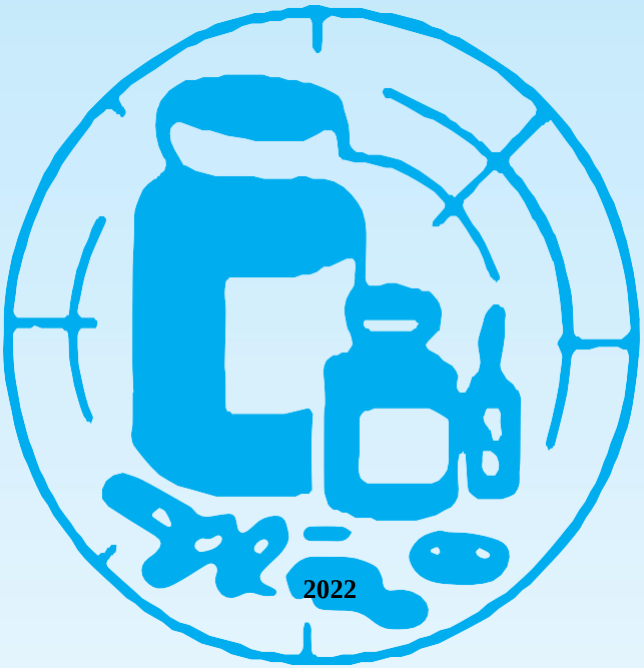

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GOVERNMENT OF NEPAL
MINISTRY OF HEALTH AND POPULATION
DEPARTMENT OF DRUG ADMINISTRATION

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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

Good Pharmacy Practice (GPP): A step towards improvement of Pharmaceutical care and Pharmacy Services

The health of the public is fundamental to the happiness and welfare of all people. Barriers to good health include poor access to quality medical products, lack of access to trained health professionals and care, an inadequate health workforce, unaffordable cost of care and poor standards of education of health-care professionals.

Medicines are an essential and critical part of health-care services in the country. The potential benefit of medicines is often not fully realized. There is a gap between the proven efficacy of medicines demonstrated in clinical trials and their actual effectiveness in practice. The reasons for this gap include problems with medicine selection and dosages, improper administration of medicines and lack of adherence by patients to prescribed treatment, medicine–medicine and medicine–food interactions, and adverse medicine events.

To address these medication-related needs, pharmacists working in communities' pharmacies and hospitals are entrusted with greater responsibility for the outcomes of medicines use. As health-care professionals, pharmacists play an important role in improving access to health care and in closing the gap between the potential benefit of medicines and the value for money.

In 1992, the International Pharmaceutical Federation (FIP) developed standards for pharmacy services under the heading "Good pharmacy practice in community and hospital pharmacy settings". It was then submitted to WHO Expert Committee on Specifications for Pharmaceutical Preparations in 1994. Following the recommendations of the WHO Expert Committee and the endorsement of the FIP Council in 1997, the FIP/WHO joint document on good pharmacy practice (GPP) was published in 1999 in the thirty-fifth report of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (WHO Technical Report Series, No. 885).

Realizing the benefits of such standards, DDA first issued sales and distribution code in 2071. These early interventions did draw attentions among professionals but practices could not be improved as desired. Having realized this, DDA has currently put its effort to revise and implement all new version of GPP and GSDP as part of codes on sales and distribution code 2080. After a wide consultation and public

opinion call it is now improved and put forward to drug advisory committee for necessary endorsement. With the aim of safeguarding the health of citizens by ensuring the availability of safe, effective and quality medicines together with increasing the quality of Pharmacy services the draft code will be implemented throughout pharmacies operated in both public and private settings. We assume these practices if observed in all pharmacy settings, can be game-changer interventions for accurate medication, dispensing, patient counseling, facility design, quality control and ethical conduct. The Draft Drug Sales and Distribution Codes 2080 has all the necessary provisions needed to be fulfilled and obtain certification of Good Pharmacy practices from the Department.

While Good Pharmacy Practice (GPP) sets the benchmark for quality patient care, its successful implementation is not without challenges. Department play a pivotal role in ensuring the successful implementation of GPP across Pharmacies. By setting standards, conducting inspections enforcing corrective actions and providing guidance, Department ensures that Pharmacies adhere to GPP principles. This oversight not only safeguards patients but also contributes to the overall wellbeing of society by fostering a culture of excellence and accountability within health care ecosystem. Collaboration among regulatory agency, professional associations, councils and all other stakeholder is essential driving force of the successful implementation of these practices.

Narayan Prasad Dhakal
(Director General)
Chief Editor

1. आ.व. २०७९/८० प्रथम त्रैमासिकको प्रगति विवरण

अनुगमन, मुल्यांकन तथा कानुन कार्यान्वयन महाशाखा अन्तर्गत मुख्य कार्यहरु:

औषधि पसल/फार्मेसी निरीक्षण :

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पहिलो त्रैमासिक लक्ष्य	४५०	१२५	१२५	१२५	८२५
पहिलो त्रैमासिक प्रगति	१९९	१०२	१६८	७४	५४३
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उद्योग निरीक्षण :

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2. REGULATORY NEWS

Valacyclovir
Potential risk of drug reaction with eosinophilia and systemic symptoms (DRESS)
Canada. Health Canada has announced that the product safety information for valacyclovir containing products will be updated to include the potential risk of drug reaction with eosinophilia and systemic symptoms (DRESS). DRESS is a rare, but serious, and potentially life threatening drug reaction that includes fever, rash, elevated white blood cell count, and can affect one or more organs.

Valacyclovir is indicated for the treatment of cold sores (herpes labialis), shingles (herpes zoster) and treatment, suppression or reduction of the transmission of genital herpes.

Health Canada reviewed information provided by the manufacturer of Valtrex®, data from the Canada Vigilance database, and the published literature. Health Canada reviewed 115 cases (three Canadian, 112 international) of DRESS in patients taking valacyclovir, of which 26 cases (international) met the criteria for further assessment. Of the 26 case reports, four cases, including three published in the scientific literature, were assessed to be "probably" linked to the use of valacyclovir. Twenty-one cases, including one death, were found to be possibly linked, and one case was unlikely to be linked to the use of valacyclovir. In 25 of the 26 cases, patients were also taking other medications known to cause DRESS. Health Canada's review concluded that there may be a link between the use of valacyclovir containing products and the potential risk of DRESS.
Source: WHO Pharmaceuticals Newsletter No.3, 2022

Metformin
Risk of reduced vitamin B12 levels

United Kingdom. The MHRA has announced that the product information for metformin containing medicines have been updated to state that vitamin B12 deficiency is a common adverse drug reaction of metformin and may affect up to 1 in 10 people who take it.

Metformin is indicated for the treatment of type 2 diabetes mellitus and prevention of type 2 diabetes in patients with a high risk of developing it.

Vitamin B12 deficiency is a known adverse drug reaction of metformin, and the

current literature has suggested that the frequency of this adverse drug reaction is higher than previously thought.

The product information has also been updated to note that the risk of this adverse reaction increases with an increase in metformin dose and treatment duration, and in patients with risk factors known to cause vitamin B12 deficiency. Healthcare professionals are advised to test vitamin B12 levels in those presenting with anemia or neuropathy, and that periodic vitamin B12 monitoring should be considered in patients with risk factors for vitamin B12 deficiency.

Source: WHO Pharmaceuticals Newsletter No.3, 2022

Iopamidol, Iohexol, Iomeprol
Risk of acute coronary syndrome, accompanying an allergic reaction

Japan. The MHLW and the PMDA have announced that the product information for Iopamidol, Iohexol and Iomeprol should be revised to include the risk of acute coronary syndrome accompanying an allergic reaction.

Iopamidol, Iohexol and Iomeprol are iodinated contrast media used for X-ray imaging.

Cases of acute coronary syndrome accompanying an allergic reaction were reported in Japan with the use of several iodinated contrast media products. A causal relationship between iodinated contrast media and acute coronary syndrome was evaluated and a reasonably possible causal relationship was found with the use of Iopamidol (2/14 cases) Iohexol (4/6), and Iomeprol (2/2). There are no cases reported for other iodinated contrast media such as amidotrizoate, Iotroxate and Iodixanol. In addition, there was no evidence to support a class effect for iodinated contrast media. It was concluded that acute coronary syndrome is a clinically significant adverse reaction for Iopamidol, Iohexol and Iomeprol.

Source: WHO Pharmaceuticals Newsletter No.4, 2022

Cholinesterase inhibitors
Risk of QT interval prolongation and torsade de pointes
Canada. Health Canada has announced that the product safety information for cholinesterase inhibitors (donepezil-, rivastigmine- and galantamine-containing products) will be updated to strengthen the information on the risk of QT interval prolongation and torsade de pointes.

These cholinesterase inhibitors are indicated for the treatment of dementia associated with Alzheimer's disease and/or Parkinson's disease.

Health Canada reviewed 53 case reports (one Canadian, 52 international) of QT interval prolongation and torsade de pointes in patients taking cholinesterase inhibitors and found that:

• For donepezil (35 reports), two cases were found to be probably linked, 30 cases were possibly linked, two cases were unlikely to be linked and one case could not be assessed. Four deaths were reported (two of which were determined to have a possible link and two unlikely to be linked).

• For galantamine (10 reports including one Canadian), three cases were found to be probably linked, five cases were possibly linked, one case was unlikely to be linked and one case (Canadian) could not be assessed. One death was reported and was unlikely to be linked.

• For rivastigmine (eight reports), seven cases were found to be possibly linked and one case was unlikely to be linked.

Health Canada also reviewed 20 articles published in the scientific literature which contained limited evidence. In conclusion, Health Canada's review supported a link between the use of all three cholinesterase inhibitors and the risk of QT interval prolongation and torsade de pointes.

Health-care professionals are advised that this risk is increased in patients with a history of certain heart conditions; a history or family history of QT interval prolongation; low levels of certain electrolytes, such as magnesium, potassium or calcium in the blood; or taking certain medications that can affect heart rhythm at the same time as the cholinesterase inhibitors.

Source: WHO Pharmaceuticals Newsletter No.4, 2022

Ramucirumab

Risks of thrombotic microangiopathy (TMA)

Japan. The MHLW and the PMDA have announced that the product information for ramucirumab (Cyramza®) should be revised to include the risk of thrombotic microangiopathy (TMA).

Ramucirumab is a monoclonal antibody that blocks VEGFR2 and is indicated for

solid tumors including gastric and colorectal cancer.

Seventeen cases of TMA reported in Japan were evaluated, of which six cases were assessed to have a reasonably possible causal relationship between the drug and event. It was concluded that TMA is a clinically significant adverse reaction for ramucirumab.

Source: WHO Pharmaceuticals Newsletter No.4, 2022

Methadone
Potential risk of hypoglycemia

Canada. Health Canada has announced that the product safety information for methadone will be updated to include the potential risk of hypoglycemia (low blood sugar).

Methadone is indicated for the relief of severe pain in patients who have previously used opioids, or as a substitute in patients with opioid dependence.

Health Canada reviewed the available information by searching national and international databases, and the published literature. The review looked at 19 cases of hypoglycemia in adults after methadone use, of which 12 cases have a probable or possible link between methadone use and the risk of hypoglycemia. Six published studies reporting cases of hypoglycemia after methadone use were assessed and a possible link was also found.

Source: WHO Pharmaceuticals Newsletter No.2, 2022

Parenteral iron products
Risk of fetal bradycardia and Kounis syndrome
Australia. The TGA has announced that the product information for parenteral iron products has been updated class-wide to include information about fetal bradycardia and Kounis syndrome, which is the concurrence of acute coronary syndromes with conditions associated with mast cell activation. Both conditions can have serious clinical implications.

There are four parenteral iron products marketed in Australia: ferric carboxymaltose (Ferinject®) and ferric derisomaltose (Monofer®) are indicated for iron deficiency where oral administration is ineffective or contraindicated, or where there is a need to deliver iron rapidly; iron polymaltose (Ferrosig

injection®) is for the treatment of iron deficiency anaemia when oral iron therapy is contraindicated, enteric absorption of iron is defective, or when patient noncompliance or persistent gastrointestinal intolerance makes oral therapy impractical; and iron sucrose (Venofer®) is for the treatment of iron deficiency anaemia in patients undergoing chronic haemodialysis and who are receiving supplemental erythropoietin therapy.

Hypersensitivity is a class effect that is well documented in the product information of all parenteral iron products. The TGA concluded that fetal bradycardia and Kounis syndrome are biologically plausible as a result of hypersensitivity reactions.

Source: WHO Pharmaceuticals Newsletter No.1, 2022

Somatropin
Removal of contraindication to diabetes mellitus

Japan. The MHLW and the PMDA have announced that the product information for somatropin preparations (Genotropin®, Growject®, Humatrope® and Norditropin®) should be revised to remove the contraindication in patients with diabetes mellitus.

Somatropin is a recombinant human growth hormone and is indicated for growth hormone deficient short stature without epiphyseal closure. In Japan, administration of all somatropin preparations to patients with diabetes mellitus was a contraindication from the time of initial approval in 1988.

The MHLW and the PMDA reviewed overseas (the US, EU, Canadian, and Australian) package inserts, clinical practice guidelines and standard textbooks, which do not contraindicate somatropin in patients with diabetes mellitus, but provide a special caution instead. In the serious Japanese cases reporting changes in glucose metabolism following somatropin administration, the reactions eventually improved and were adequately controlled by the temporal discontinuation of somatropin or initiation of antidiabetic drugs. Published literature and post-marketing surveillance studies (Japanese and overseas) reported several cases of patients with concurrent diabetes mellitus in which exacerbation of diabetes mellitus was not observed following administration of somatropin.

While removing the contraindication, some precautions should be added for use of somatropin in patients with diabetes mellitus, glucose intolerance, or diabetes mellitus risk factors. Close monitoring of blood glucose and HbA1c is required during administration of somatropin, as well as dosage adjustment of antidiabetic

drugs if needed.

Source: WHO Pharmaceuticals Newsletter No.3, 2022

Bortezomib
Risks of Guillain-Barré syndrome (GBS), demyelinating polyneuropathy

Japan. The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the product information for bortezomib should be revised to include the risk of GuillainBarré syndrome (GBS) and demyelinating polyneuropathy.

Bortezomib is indicated for the treatment of multiple myeloma and mantle cell lymphoma.

Cases of GBS or demyelinating polyneuropathy reported in Japan and internationally were evaluated. There was one Japanese case of GBS and eight international cases. Two of the cases were assessed to have a reasonably possible causal relationship between bortezomib and GBS. There were 20 international cases of demyelinating polyneuropathy. Thirteen of these cases were assessed to have a reasonably possible causal relationship between bortezomib and demyelinating polyneuropathy. It was concluded that GBS and demyelinating polyneuropathy are clinically significant adverse reactions for bortezomib.

Source: WHO Pharmaceuticals Newsletter No.4, 2022

3.SAFETY OF MEDICINES

Selective Serotonin Reuptake Inhibitors (SSRIs)
Risk of suicidality

Singapore. The HSA has reminded health-care professionals of the risk of suicidality for selective serotonin reuptake inhibitors WHO Pharmaceuticals Newsletter No. 4, 2022 • 12 Safety of Medicines (SSRIs), where an increased risk is observed particularly in patients less than 25 years of age although a causal association remains to be conclusively established.

SSRIs are used for the treatment of depression, anxiety and other mood disorders. Although none of the registered SSRIs are approved specifically for the treatment of depression in children and adolescents below 18 years old, they are used off-label in this patient population.

Based on data from the electronic medical records, over the past five years, an increasing trend in the prescriptions of SSRIs was observed (around 4% increase from 2017 to 2020, followed by 9.1% increase from 2020 to 2021). Also, the proportion of patients less than 25 years of age are increasing among the patients prescribed SSRIs: the annual proportion of children or adolescents (<18 years) was stable at around 3.4% from 2017 to 2020 and increased to 4.1% in 2021, while those of young adults (18-24 years) steadily increased over the years from 11.2% in 2017 to 15.5% in 2021.

Health-care professionals are encouraged to refer to the available patient educational materials on SSRIs during medication counseling to their patients and/or caregivers. The materials include warnings on suicidality and mental state worsening and risks in young people aged below 25 years.

Source: WHO Pharmaceuticals Newsletter No.4, 2022

Benzodiazepines
Potential risk of abuse, dependence and withdrawal

New Zealand. The Medsafe has reminded prescribers of the recent update to the product information for benzodiazepines regarding the potential risks of abuse, dependence and withdrawal, even when taken at recommended dosages.

New Zealand dispensing data shows that diazepam and lorazepam are the most dispensed benzodiazepines. The total amount of these medicines that were dispensed for all indications has increased in the period between 2016 and 2020 which may suggest frequent and/or long-term use.

Between August 1969 and March 2022, the CARM received 23 case reports of withdrawal and/or dependence with the use of benzodiazepines. Clonazepam (nine cases) was the most frequently reported benzodiazepine, followed by lorazepam (five), diazepam (three) and triazolam (three).

Health-care professionals are advised to counsel patients about the risks of benzodiazepines when initiating treatment, regularly review the ongoing need for treatment, and gradually taper benzodiazepines following continuous or high-dose use to reduce the risk of withdrawal reactions.
Source: WHO Pharmaceuticals Newsletter No.3, 2022

Pembrolizumab
Potential risk of cholestasis
Saudi Arabia. The SFDA has identified a safety signal for pembrolizumab (Keytruda®) and the potential risk of cholestasis.

In 2021, the SFDA detected the signal by reviewing the medical literature. The SFDA extracted and reviewed ICSRS that were most complete (completeness score of >0.8) from the local and WHO global databases. WHO causality assessment criteria were applied on the extracted cases and most of cases were assessed to have a positive association (out of 33 ICSRs: one case was assessed to be certain, 10 probable, and seven possible cases). The investigation concluded that the current available evidence is sufficient to support the relationship between pembrolizumab and cholestasis.

This signal needs further investigation to confirm the risk, and health-care professionals should be aware of this potential adverse reaction.
Source: WHO Pharmaceuticals Newsletter No.3, 2022

Finasteride
Potential risk of suicidal ideation
Singapore. The Health Sciences Authority (HSA) has reminded health-care professionals of the potential risk of suicidal ideation with the use of finasteride following results of a recent pharmacovigilance study that suggests younger patients with alopecia may be more vulnerable to the risk of suicide ideation.

Finasteride is indicated for the treatment of benign prostatic hyperplasia and androgenic alopecia.

In the study, disproportionality analysis was used to assess whether suicidality or psychological adverse events (AEs) were more frequently reported for finasteride than would be expected by chance alone by comparing them against similar reports for all other drugs in VigiBase (WHO global database of ICSRs). The study identified 356 reports of suicidality and 2,926 reports of psychological AEs in users of finasteride, reported from 1993 to 2019. Among the reports with data available, the majority (99%) occurred in males, and 71% occurred in individuals aged between 18 and 44 years. Significant disproportionality signals for suicidality (reporting odds ratio [ROR], 1.63; 95% CI, 1.47- 1.81) and psychological AEs (ROR, 4.33; 95% CI, 4.17- 4.49) were identified in finasteride users.

Health-care professionals are advised to consider the potential risk of psychological adverse events when assessing the benefit-risk of finasteride for their patients

Source: WHO Pharmaceuticals Newsletter No. 4, 2022

Olaparib

Potential risk of Pneumocystis Jirovecii Pneumonia (PJP)

Saudi Arabia. The Saudi Food & Drug Authority (SFDA) has released a safety signal concerning olaparib (Lynparza ®) and the potential risk of Pneumocystis Jirovecii Pneumonia (PJP). PJP (formerly Pneumocystis carinii) is a lung infection caused by the fungal organism Pneumocystis jirovecii.

Olaparib is indicated as monotherapy for the treatment of adult patients with deleterious or suspected deleterious germline BRCAmutated (BRCAm) and human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer, who have previously been treated with chemotherapy.

In 2021, the SFDA detected the signal and reviewed all the evidence available. SFDA has examined the local and WHO global databases, which resulted in identifying four ICSRs. The SFDA used the WHO causality assessment criteria, and one ICSR was supportive of the association. The disproportionality of the number of observed and expected ICSRs (IC=1.1) together with one case report published in the literature were supportive for an association, too.

Health-care professionals should be aware of this potential risk, and it is advisable to monitor any signs or symptoms of PJP in treated patients.

Source: WHO Pharmaceuticals Newsletter No. 3, 2022

Umbralisib
Possible increased risk of death with lymphoma investigated

USA. The US FDA is investigating the risk of death in patients treated with umbralisib (Ukoniq®). Enrollment of new patients in ongoing clinical trials of umbralisib has been suspended until the review is complete.

Umbralisib is PI3 kinase inhibitor used to treat adults with marginal zone lymphoma (MZL) and follicular lymphoma (FL) when the disease has returned or it did not respond to prior treatment(s).

Initial findings from a clinical trial evaluating umbralisib used for the treatment of chronic lymphocytic leukemia (CLL) indicate a possible increased risk of death and serious adverse events in patients taking umbralisib.

Health-care professionals should review patients' progress on umbralisib and discuss with them the risks and benefits of continuing the treatment in the context of other available treatments.
Source: WHO Pharmaceuticals Newsletter No.3, 2022

Colchicine
Risk of fatality if overdose

New Zealand. The Medsafe has issued a warning reminding the public of the high risk of fatality with colchicine overdose and that there are no effective treatments available for severe colchicine poisoning.

Colchicine is indicated for the treatment of acute gout when nonsteroidal anti-inflammatory drugs are contraindicated, ineffective or not tolerated.

Although colchicine has a narrow therapeutic index with the well-defined separation between therapeutic and toxic doses, some clinical guidelines may refer to unapproved dosing schedules for colchicine.

From January 2016 to January 2021, the National Poisons Centre (NPC) received 56 cases related to colchicine poisoning.

The main reasons of the poisoning were child exploratory behavior, therapeutic error and intentional self-poisoning.

Health-care professionals should communicate with patients about the importance of storing medicines out of sight and reach of children and ensure patients know

when and how to take colchicine.

Source: WHO Pharmaceuticals Newsletter No.4, 2021

Aflibercept
Potential risk of Fournier's gangrene

Saudi Arabia. The SFDA has released a potential safety signal concerning Fournier's gangrene associated with the use of aflibercept.

Aflibercept is indicated for the treatment of neovascular (wet) age-related macular degeneration and metastatic colorectal cancer.

The SFDA reviewed five case reports, two of which supported the association, and the literature.

Source: WHO Pharmaceuticals Newsletter No.1, 2022

First-generation oral sedating antihistamines
Risk of serious harm in children

Australia. The TGA has warned that first-generation oral sedating antihistamines, including those available over the-counter (OTC), should not be used for the treatment of cough, cold and flu symptoms in children under six years and for any indication in children under two years of age.

First-generation oral sedating antihistamines include products containing diphenydramine and pheniramine. These medicines can cause children serious harm, or even death, and there is little if any evidence that they are effective in treating cough, cold and flu symptoms. Warnings on use in children have been introduced in the labelling since 2020.

Up until 24 May 2022, 226 cases reporting the use of first generation oral sedating antihistamines in newborns, infants and children were received by TGA. The reports included a range of adverse events, including hypersensitivity reactions, vomiting, hallucination, tremor and abnormal movement. Of the 226 cases, 20 related to off-label use, misuse or overdose in children four years and under.

The TGA's independent Advisory Committee on Medicines (ACM) reinforced the importance of health professionals providing thoughtful diagnosis, advice and treatment of allergy, cold and flu symptoms in children. They also reiterated that it is inappropriate to use antihistamines for sleep and behaviour disturbance, especially in children and adolescents.

Source: WHO Pharmaceuticals Newsletter No.3, 2022

4. SIGNAL

A signal is defined by WHO as reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously.

Methotrexate and muscle spasm

Rosa María Papale, Argentina and Mónica Tarapués, Ecuador

Summary

Methotrexate is a structural analogue of folic acid. As a folic acid antagonist, it blocks the synthesis of purines by inhibiting numerous regulatory enzymes. It produces an intense anti-inflammatory action and inhibits cell division. A screening of VigiBase, the WHO global database of individual case safety reports (ICSRs), identified the association of the MedDRA Preferred Term (PT) 'muscle spasm' with methotrexate. A qualitative analysis of 47 cases was undertaken with a completeness score of over 0.70. The similarity of characteristics with respect to time to onset, the biological plausibility, the improvement after drug withdrawal, all provide evidence of this association. The muscle spasms could be associated with methotrexate, especially in patients on long term low doses. Prescribers and patients need to be aware that muscle spasms could be present with the use of methotrexate. This adverse reaction could impair the patients' quality of life, especially long□ term users with chronic diseases.

Introduction

Methotrexate was granted US FDA approval in December 1953. Since then, it has been used via oral, intramuscular, intravenous, subcutaneous, intrapleural, and intrathecal routes of administration. Methotrexate acts by inhibiting enzymes responsible for nucleotide synthesis. It is used for the treatment of several neoplasmic conditions, such as acute leukaemia, lymphomas, osteosarcoma, breast cancer, and in autoimmune diseases, such as rheumatoid arthritis and psoriasis. In addition, it is used to treat gestational choriocarcinoma, chorioadenoma, hydatiform mole, and

advanced mycosis fungoides.1,2

Muscle spasm covers several overlapping concepts of true spasm and cramps. Spasms are involuntary muscle contractions. When these are prolonged and painful, they are often referred to as cramps. Muscle cramps are sustained, painful contractions of muscle which occur in individuals with or without medical conditions. Muscle cramps are common in the general population and can be disabling. This description distinguishes muscle cramps from other painful muscle disorders that either do not include shortening of the muscle, e.g., myositis and myalgia, or that include involuntary shortening of muscle but do not cause pain, e.g., myotonia and tetany.3 Myalgia and arthralgia are listed in the Summary of Product Characteristics (SPC) of methotrexate as rare adverse drug reactions (ADRs).4,5 Other drugs such as diuretics may cause muscle spasm through dehydration or an electrolyte imbalance, especially hypokalaemia, hypocalcaemia, or hypomagnesemia. Muscle spasm can accompany myopathy, which has been associated with numerous drug classes, including antimalarials and statins. Other medications can cause muscle spasms, including beta-agonists, acetylcholinesterase inhibitors (often used for the treatment of myasthenia gravis), cimetidine, steroids, morphine, penicillamine, cardiotropic medications, antiretrovirals, and psychotropic medications.6,7

Reports in VigiBase

As of May 2020, there were 397 reports for the MedDRA Preferred Term ‘muscle spasms’ associated with methotrexate. Due to the large number of cases, a completeness score over 0.7 was set for this analysis so as to identify the causality patterns that strengthen the signal. In the present case series, 47 cases were evaluated.

The reports came from 18 countries, most of them in Europe but also from the Americas, Africa, and Asia. There were 30 females and 17 males. The age was recorded for 45 patients, ranged from 13 to 87 years (median 57); 31 were adults. Thirty-six cases (76%) were reported by health professionals (20 by physicians and 16 by pharmacists). Sixteen cases were considered serious, mainly under the criterion of other medically important condition (10 cases). The last report was received in March 2020.

Thirty three of the cases had a narrative; their characteristics are summarized in Table 1.

The most frequent therapeutic indication was rheumatoid arthritis (17 cases), followed by psoriasis or psoriatic arthritis.8 There were also cases with neoplastic indications (6) and with polymyositis, meningitis, and Crohn's Disease (one of each). In 13 reports the therapeutic indications were not given. Methotrexate was administered orally in 26 (55%) patients, parenterally in 8 patients (6 intravenous and 2 intrathecal), and subcutaneously in four patients. The time to onset was highly variable in the whole group, ranging from one day to six years. However, 26 patients received a weekly dose: 17 orally, 4 subcutaneously, and 5 were unknown. In this subgroup of 26 patients, the time to onset, reported for 14, ranged from 1 day to 18 months, with a median of 29 days. A daily dose was reported for five patients who developed muscle spasms on the day of administration.

Methotrexate was the only suspected drug in 28 patients, and in 18 others, it was the only drug reported. Adalimumab was reported as a co suspected drug in five patients, but methotrexate WHO Pharmaceuticals Newsletter No. 1, 2022 • 32 Signal was the last medication taken for two patients, and the other three patients were on chronic methotrexate treatment when adalimumab was administered. Etanercept was a co-suspected drug in two patients. Dates were available for only one patient who was a chronic user of methotrexate and etanercept was recently administered. Proton pump inhibitors (PPIs), were reported in five patients as co suspected (lansoprazole (1), pantoprazole (2), and esomeprazole (2)). In additions PPIs were reported as concomitant medication, in eight patients but only four had dates that suggest that the PPI administration came before the ADR and was concurrent with the use of methotrexate. Esomeprazole was used after the occurrence of the ADR in one patient. Non-steroidal anti-inflammatory drugs (NSAIDs) were concomitant drugs for three patients (diclofenac (2), naproxen (1)) . Three cases reported concomitant statins, (atorvastatin and simvastatin).

Another ADR, decreased levels of calcium and magnesium was reported for one patient. Diarrhoea or vomiting were reported at the same time as muscle spasms in seven patients. The LLT term used for 31 patients was

muscle cramps, and for some patients the location of the cramps was reported as a limb, legs, hand, or foot. The reported LLT was muscle spasms for 16 patients some of which were described as a cervical or back muscle spasm. The intensity of this ADR for a 63 year-old male patient, reported by a pharmacist, was described as "very intense, disabling and painful on the arms or the legs, with frequency variable, 1 to 3 times a day". . Methotrexate and pantoprazole were reported as suspected drugs. This patient also had concomitant diltiazem, digoxin, and paracetamol. Methotrexate was first used subcutaneously for rheumatoid arthritis. After about six months, the patient presented with muscle cramps, and five months later methotrexate was changed to an oral route. The patient was reported as not recovered.

Another 65 year-old patient, reported by a pharmacist, had muscle cramps that occurred at night following the administration of methotrexate (15 mg a week) for rheumatoid arthritis, with a latency of 14 days after increasing the dose. The dose was subsequently reduced to 7.5 mg a week and the patient felt better with fewer complaints. Only methotrexate was reported as suspected. The concomitant medications were carbasalate, diclofenac, misoprostol, amlodipine, isosorbide dinitrate, folic acid, metoprolol, alendronic acid, and simvastatin. The patient had never had a muscle disorder in association with simvastatin. The national centre mentioned that the official product information of methotrexate only describes myalgia.

Positive dechallenge was reported for 21 patients. Methotrexate was stopped in 18 patients, of whom 16 were reported as recovered, 1 was recovering, and 1 was recovered with sequelae. In the remaining three patients the dose was reduced, and the reported outcome was recovered. Individual causality assessment was undertaken for 16 patients, (10 using the Naranjo algorithm and 6 using the UMC/WHO global introspection method). The reported result was 'possible', for 15 patients and not assessable by the UMC/WHO method for the remaining patient.

Rechallenge was undertaken in 8 of the 47patients, and in three there was a positive rechallenge; however, there were no narratives for these patients. The outcome was reported as unknown for the other rechallenged patients, although they reported some interesting details. For example, a 57 year-old man, whose physician described muscle cramps and increased blood

creatine phosphokinase with the use of methotrexate and lansoprazole. In the narrative, the physician wrote: “This patient is being followed for non-erosive rheumatoid arthritis. Treatment with methotrexate 10 mg/week was introduced in February. The patient reports from the start of his treatment disabling muscle cramps preventing any sporting activity. He has also been treated with lansoprazole since February. This patient was also on hydrochlorothiazide- irbesartan, stopped in November of the same year, but without improvement in muscle symptoms”. It is worth noting that the rechallenge had an unknown outcome. However, with the dates given in the original report, it is possible to deduce that the rechallenge was without the lansoprazole, because at the beginning in February the patient was exposed to both drugs, but for the rechallenge, only methotrexate was reintroduced.

A 33 year-old woman, reported by a physician, with pain, muscle spasm, and tetany was rechallenge. The suspected drugs were methotrexate and adalimumab (both subcutaneous, weekly) and opipramol (daily, oral). The medical history included former smoker, adiposity, allergic bronchial asthma, depression, onychomycosis, bilateral gonalgia, and psoriatic arthritis. The starting date for methotrexate was January and for adalimumab, March of the same year. The muscle cramps began on 30 April and the tetany on 4 May. Complete tetany of the right leg, which was not resolved by administration of tetrazepam was reported for this patient. The patient was reported as rechallenged with an unknown outcome.

Literature and labelling

The main risks with the use of methotrexate are related to haematological toxicity, and reduced immunity in the presence of infections. However, neither the SPC in the US nor in Europe describe muscle spasm or cramps as ADRs. Myalgia, WHO Pharmaceuticals Newsletter No. 1, 2022 • 33 Signal arthralgia, osteonecrosis, and osteoporosis are listed as musculoskeletal ADRs.

There are several special warnings and precautions for use of methotrexate regarding potential interactions with other drugs. There is a warning for the concomitant use with NSAIDs, because it has been found to decrease the tubular secretion of methotrexate and possibly to increase its toxicity.

Likewise, there is a precaution in the concomitant use of omeprazole and pantoprazole because of their potential impact on methotrexate elimination .5 However, there are no warnings regarding concomitant use of statins or adalimumab, or other drugs that can cause musculoskeletal disorders.

There are no case reports about muscle cramps in the literature, although there are two case reports about musculoskeletal ADRs. One describes two cases of acute diffuse muscular pain following initiation of weekly low dose oral methotrexate in rheumatoid arthritis (women 70 and 49 years old).8 The other report concerns a 59-year-old man with a folliculotropic cutaneous T-cell lymphoma taking low dose pulse methotrexate (15 mg intramuscularly, once a week), at the same time as being treated with pantoprazole (20 mg/day, orally). After the first injection of methotrexate the patient presented with generalized myalgia and bone pain. The symptoms recurred over the following four methotrexate cycles. Pantoprazole was replaced by ranitidine and the muscle symptoms disappeared. The report mentioned a positive rechallenge, during which a laboratory test showed an elevation in the serum concentration of the 7-hydroxymethotrexate, which the authors interpreted as an interaction in renal elimination, rather than a metabolic interaction.9

Discussion

Muscle spasms or cramps may sometimes overlap with myalgia, and myalgia has already been identified as an ADR. Nevertheless, this analysis presents a group of patients who suffered from spasm or cramp, with most cases reported by physicians. For that reason, it is plausible to think the muscle spasm or cramp is a worrisome clinical event that may prevent some patients from performing daily activities.

Methotrexate inhibits aminoimidazole caboxamide ribonucleotide transformylase (AICART). This inhibition leads to the accumulation of AICART ribonucleotide, which inhibits adenosine deaminase, leading to an accumulation of adenosine triphosphate and adenosine in the extracellular space, stimulating adenosine receptors. This action is well known as the basis for its anti-inflammatory properties, however, this also acts on the skeletal muscle by the adenosine monophosphate-activated protein kinase (AMPK). Hence, the potential action of the methotrexate on

the skeletal muscle is a concern. Recent research suggests that methotrexate could reduce the threshold for AMPK activation by AICART. AMPK has recently emerged as a novel target for the treatment of pain, with the exciting potential for disease modification. AMPK activators inhibit signalling pathways that are known to promote changes in the function and phenotype of peripheral nociceptive neurons and promote chronic pain.2,10–12

The literature suggests that muscle spasms could be associated with peripheric neuropathy and hypothyroidism, which were not identified in this case series due to the intrinsic limitations of spontaneous reporting. Other causes could be electrolyte imbalances, and calcium and magnesium imbalances were reported for one patient. It is well known that hypokalaemia can be associated with muscle cramps or other muscle disorders, however, hypokalaemia was not reported for any of the patients.

The concomitant drugs found in the case reports raise concerns about an incomplete profile of methotrexate interactions. Some drugs, such as adalimumab, or statins, could be strongly associated with the muscle ADRs, however, it is not possible to rule out the suspected role of methotrexate as its administration fits the same timeframe. Also, results with animal models and some pharmacokinetics studies suggest that other drugs such as NSAIDs and PPIs can decrease renal elimination and tubular secretion. Some studies that have analysed this interaction with low and high doses of methotrexate concluded that the elevation in methotrexate concentration as a consequence of the interaction has a low clinical impact, however, it is important to carefully assess the risk-benefit balance before deciding to prescribe it, and to follow-up the patients, especially those who are long-term users of methotrexate.5,13,14

Conclusion

Muscle spasms or muscle cramps are not currently mentioned in the SPC for methotrexate, and this ADR could have an impact on the quality of life of patients undergoing treatment with methotrexate. Patients, as well as physicians, should be aware of these ADRs to avoid a reaction that could affect the quality of life of patients. For this reason, it is reasonable to consider an in-depth clinical analysis when the patient mentions these

complaints, especially patients on low doses.

Table 1. Summary characteristics of 47 cases in VigiBase of muscle cramps in association with methotrexate with a completeness score over 0.70.

Characteristic	47 cases with completeness score over 0.70
Age (mean / range)	53 years / 13-87
Patient sex distribution	30 females / 17 males, ratio 2:1
Top ten countries	Netherlands (15), France (6), Canada (5), Australia (2), Republic of Korea (2), Sweden (2), Croatia (2) Germany (2), Italy (2), Costa Rica (1)
Reporters	Physician (26), Pharmacist (10), Consumer (7), Other Healthcare Professional (4)
Single suspected drug	28 reports (59%)
Single reported drug	18 reports
Time-to-onset	1 day to 6 years
The action taken with the drug /outcome	25 cases with drug withdrawn / 16 recovered, 1 recovered with sequelae, 1 recovering, and 1 outcome unknown. 4 cases with dose reduced / 3 recovered and 1 not recovered. 12 cases with the drug not changed / 3 recovered, 1 recovered with sequelae, 7 not recovered and 1 outcome unknown. 6 drug action unknown / 3 recovered and 3 outcomes unknown

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Source:WHO Pharmaceuticals Newsletter No. 1, 2022

5.REGULATORY NOTICES

नेपाल सरकार

स्वास्थ्य तथा जनसंख्या मन्त्रालय

औषधि व्यवस्था बिभागको

औषधिको विक्रीवितरण तथा प्रयोग सम्बन्धि अत्यन्त जरुरी सूचना

प्रकाशित मितिः २०७५/०५/१३

यस विभागबाट अनुगमन/निरीक्षणका क्रममा देहाय उत्पादकबाट उत्पादित देहाय ब्राण्डको औषधिको विक्रीवितरण तथा प्रयोग भएको पाइएकोमा विभागको अभिलेख अनुसार सो ब्राण्डको औषधिको औषधि पैठारी दर्ता प्रमाणपत्र (अनुसूची ४ ड) र औषधि पैठारी सिफारिस पत्र (अनुसूची ७) को नवीकरण अद्यावधिक नदेखिएकोमा सो सम्बन्धि थप अनुसन्धान भईरहेको हुँदा उक्त ब्राण्डको औषधिको तत्काल विक्री वितरण तथा प्रयोग नगर्न/नगराउनु हुन सरोकारवाला सबैलाई जानकारीका लागि यो सूचना प्रकाशित गरिएको छ ।

तपसिलः

सि. नं.	औषधिको ब्राण्ड नाम	औषधिको जेनेरिक नाम	उत्पादकको नाम र ठेगाना	आधिकारिक आयातकर्ताको नाम र ठेगाना
1.	Aronem 1gm IV Inj.	Meropenem USP 1 gm	ACI Limited, Narayangunj, Bangladesh.	Ways International Pharma Division, Kathmandu- 23.

नेपाल सरकार

स्वास्थ्य तथा जनसंख्या मन्त्रालय

औषधि व्यवस्था विभागको

विदेशी औषधि उद्योग निरिक्षण/अडिट सम्बन्धी अत्यन्त जरुरी सूचना

प्रकाशित मिति : २०७९।०६।०४

विदेशी औषधि उद्योग तथा ताँहाका उत्पादनहरु दर्ताको लागि उद्योग निरिक्षण गरि पाऊँ भनि हालसम्म विभागमा दर्ता भई आएका आवेदनहरु मध्ये औषधि पैठारी सम्बन्धिको प्रावधान वमोजिमका उत्पादनहरु बाहेकको लागि आएका, आवश्यक कागजात पेश नभएका र WHO-GMP Guideline वमोजिमका पुर्वाधार रहेको भनि पर्याप्त आधार आवेदन साथ प्राप्त कागजातबाट पुष्टि नभएका आवेदनहरु तथा एउटै उद्योगको सम्बन्धमा आएका दुई वा सो भन्दा बढी आवेदनहरु लगायत हालसम्मका छनोटमा नपरेका सबै आवेदन हरु रद्द गर्ने र सम्पुर्ण नयाँ आधिकारीक कागजात सहित नयाँ सुची बनाई Audit कार्य कार्यान्वयन गर्न मिति २०७९।०२।२६ गतेको नेपाल सरकार (सचिव स्तर) को निर्णय भएकोले सम्बन्धित सबैले सोहि बमोजिम गर्नु गराउनुहुन यो सुचना प्रकाशित गरिएको छ।

२०७९/०६/०४

बरिष्ठ औषधि व्यवस्थापक

नेपाल सरकार

स्वास्थ्य तथा जनसंख्या मन्त्रालय

औषधि व्यवस्था विभाग

औषधि फिर्ता (Recall) गर्ने सम्बन्धी अत्यन्त जरूरी सूचना

प्रकाशित मितिः २०७८/०६/१३

यस विभागबाट बजार अनुगमनको क्रममा संकलन गरिएका औषधिको नमुना परिक्षण गर्दा तपसिल बमोजिमको उत्पादकबाट उत्पादित तपसिलको ब्याच नं. को औषधि न्यून गुणस्तर भएको पाइएकोले औषधि ऐन, २०३५ को दफा १४ बमोजिम सो औषधि बिक्रि वितरण रोक्का गरि बजारबाट तुरुन्त फिर्ता (Recall) गर्न र सोको विवरण यस विभागमा पेश गर्न सम्बन्धित उद्योगलाई जानकारीको लागि यो सूचना प्रकाशित गरिएको छ । साथै उक्त औषधि सिफारिस, बिक्रि वितरण तथा प्रयोग समेत नगर्न र नगराउन् हुन सम्बन्धित सबैलाई अनुरोध छ ।

तपसिलः

सि. न.	औषधिको नाम	ब्याच. न.	Mfg./Exp. Date	कारण	उत्पादकको नाम र ठेगाना
1.	LEVOSAFE-500 (Levofloxacin 500mg Tablets IP)	LVT11017	Jan-2021/ Dec-2022	Does not Comply to IP 2018 with respect to Dissolution Test	Qmed Formulation Pvt. Ltd., Chhaling-5, Bhaktapur, Nepal
2.	ZEFIX-100 (Cefixime 100 mg Dispersible Tablets IP)	ZX 0220	Nov-2020/ Oct-2022	Does not Comply to IP 2018 with respect to Disintegration Test	Lomus Pharmaceuticals Pvt. Ltd., Gothatar, Kathmandu, Nepal

नेपाल सरकार

स्वास्थ्य तथा जनसंख्या मन्त्रालय

औषधि व्यवस्था बिभागको

Hand sanitizer फिर्ता (Recall) गर्ने सम्बन्धी अत्यन्त जरुरी सूचना

प्रकाशित मिति : २०७९/०७/३०

यस विभागबाट निम्न उत्पादक र ब्याच नं. को Hand sanitizer को नमुना श्री राष्ट्रिय औषधि प्रयोगशाला, काठमाडौंमा परिक्षण गर्दा न्यून गुणस्तर (बिषाक्त **METHANOL**) भएकोले उक्त ब्याच नं. को Hand sanitizer औषधि ऐन २०३५ को दफा १४ बमोजिम बिक्रि वितरण रोक्का गरि बजारबाट तुरुन्त फिर्ता (Recall) गर्न र सोको विवरण यस बिभागमा पेश गर्न सम्बन्धित उद्योग, आयातकर्ता तथा तिनका प्रतिनिधिहरुका जानकारीको लागि यो सूचना प्रकाशित गरिएको छ। साथै उक्त Hand sanitizer सिफारिस, बिक्रि वितरण तथा प्रयोग समेत नगर्न र नगराउनु हुन सम्बन्धित सबैलाई अनुरोध छ।

तपसिल :

सि. नं.	औषधिको नाम	ब्याच. नं.	Mfg./Exp. Date	कारण	उत्पादकको नाम र ठेगाना
1.	**GHC HAND SANITIZER, 500ML**	CARE-11-22	Jan, 2022-Dec, 2024	**Doesn't comply** as per standard for instant Hand Sanitizer (Alcohol Based) 2076 with respect to Identification test, assay test. **(positive for the presence of Ethyl Alcohol (2%v/v) & Methyl alcohol (67%v/v)**	**Global Healthcare** Kunjpura, Karnal-132 023, India

नेपाल सरकार

स्वास्थ्य तथा जनसंख्या मन्त्रालय

औषधि व्यवस्था विभागको

औषधि फिर्ता (Recall) गर्ने सम्बन्धी अत्यन्त जरुरी सूचना

प्रकाशित मिति : २०७९/०७/२९

यस विभागबाट निम्न उत्पादक र ब्याच नं. का औषधिहरुका नमुना संकलन गरि राष्ट्रिय औषधि प्रयोगशाला, काठमाडौंमा परिक्षण गर्दा देहायका औषधिहरुको न्यून गुणस्तर भएकोले उक्त ब्याच नं. का औषधिहरु औषधि ऐन २०३५ को दफा १४ बमोजिम बिक्रि वितरण रोक्का गरि बजारबाट तुरुन्त फिर्ता (Recall) गर्न र सोको विवरण यस विभागमा पेश गर्न सम्बन्धित उद्योग तथा तिनका प्रतिनिधिहरुका जानकारीको लागि यो सूचना प्रकाशित गरिएको छ। साथै उक्त औषधिहरुको सिफारिस, बिक्रि वितरण तथा प्रयोग समेत नगर्न र नगराउनु हुन सम्बन्धित सबैलाई अनुरोध छ।

तपसिल :

सि.नं.	औषधिको नाम	ब्याच. नं.	Mfg./Exp. Date	कारण	उत्पादकको नाम र ठेगाना
1.	**Myvit-C** (Ascorbic Acid) (Vitamin-C) IP 500mg	TMS-046	May, 2021-April, 2023	**Doesn't comply** as per company's finished product specification with respect to description	**Curex Pharmaceuticals Pvt.Ltd,** Banepa-10, Kavre, Nepal
		TMS-047	Jun., 2021-May, 2023		
		TMS-049	Jun., 2021-May, 2023		
		TMS-051	Jun., 2021-May, 2023		

नेपाल सरकार

स्वास्थ्य तथा जनसंख्या मन्त्रालय

औषधि व्यवस्था विभागको

औषधि फिर्ता (Recall) गर्ने सम्बन्धी अत्यन्त जरुरी सूचना

प्रकाशित मिति : २०७८/०७/०६

यस विभागबाट बजार अनुगमनको क्रममा संकलन गरिएका औषधिको नमुना परिक्षण गर्दा तपसिल बमोजिमको उत्पादकबाट उत्पादित तपसिलको ब्याच न. को औषधि न्यून गुणस्तर भएको पाइएकोले सो औषधि औषधि ऐन २०३५ को दफा १४ बमोजिम बिक्रि वितरण रोक्का गरि बजारबाट तुरुन्त फिर्ता (Recall) गर्न र सोको विवरण यस विभागमा पेश गर्न सम्बन्धित उद्योग तथा सम्बन्धित उद्योगको अधिकारिक आयातकर्ता तथा तिनका प्रतिनिधिहरुको जानकारीको लागि यो सूचना प्रकाशित गरिएको छ। साथै उक्त औषधि सिफारिस, बिक्रि वितरण तथा प्रयोग समेत नगर्न र नगराउनु हुन सम्बन्धित सबैलाई अनुरोध छ।

तपसिलः

सि.न.	औषधिको नाम	ब्याच. न.	Mfg./Exp. Date	कारण	उत्पादकको नाम र ठेगाना
1.	PYRIMIDE (Nimesulide Tablets 100mg)	19130070	Jan-2019/ Dec-2021	Does not comply to Analytical Profile No.: NIMES 075/076/AP051 with respect to Dissolution Test	ALKEM LABORATORIES LTD., Kumrek, Rangpo, East Sikkim, India

नेपाल सरकार

स्वास्थ्य तथा जनसंख्या मन्त्रालय

औषधि व्यवस्था बिभागको

औषधि फिर्ता (Recall) गर्ने सम्बन्धी अत्यन्त जरुरी सूचना

प्रकाशित मिति : २०७५/०७/२७

यस विभागबाट बजार अनुगमनको क्रममा संकलन गरिएका औषधिका नमुना परिक्षण गर्दा तपसिल बमोजिमको उत्पादकहरुबाट उत्पादित तपसिलको ब्याच नंाको औषधिहरु न्यून गुणस्तर भएको पाइएकोले सो औषधिहरु औषधि ऐन २०३५ को दफा १४ बमोजिम बिक्रि वितरण रोक्का गरि बजारबाट तुरुन्त फिर्ता (Recall) गर्न र सोको विवरण यस विभागमा पेश गर्न सम्बन्धित उद्योग तथा तिनका प्रतिनिधिहरुका जानकारीको लागि यो सूचना प्रकाशित गरिएको छासाथै उक्त औषधिहरुको सिफारिस, बिक्रि वितरण तथा प्रयोग समेत नगर्न र नगराउनु हुन सम्बन्धित सबैलाई अनुरोध छ ।

तपसिलः

सि.नं.	औषधिको नाम	ब्याच. नं.	Mfg./Exp. Date	कारण	उत्पादकको नाम र ठेगाना
1.	BIOCAL-D (Calcium Carbonate & Vitamin D3 Tablets BP)	BD2104	March-2021/ Feb-2023	Does not comply with respect to Assay test of Vitamin D3	Biogain Remedies Pvt. Ltd., Tilottama-16, Rupandehi
2	Asvit (Vitamin-C Tablets IP)	AS2121	Aug-2021/ Jul-2023	Does not comply with respect to Friability test	Lomus Pharmaceuticals Pvt. Ltd., Gothatar, Kathmandu

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स्वास्थ्य तथा जनसंख्या मन्त्रालय

औषधि व्यवस्था बिभागको

औषधि फिर्ता (Recall) गर्ने सम्बन्धी अत्यन्त जरुरी सूचना

प्रकाशित मिति : २०७५/०५/१२

यस विभागबाट बजार अनुगमनको क्रममा संकलन गरिएका औषधिका नमुना परिक्षण गर्दा तपसिल बमोजिमको उत्पादकहरुबाट उत्पादित तपसिलको ब्याच नं. को औषधि न्यून गुणस्तर भएको पाइएकोले सो औषधि औषधि ऐन २०३५ को दफा १४ बमोजिम बिक्रि वितरण रोक्का गरि बजारबाट तुरुन्त फिर्ता (Recall) गर्न र सोको विवरण यस विभागमा पेश गर्न सम्बन्धित उद्योग तथा तिनका प्रतिनिधिहरुका जानकारीको लागि यो सूचना प्रकाशित गरिएको छ । साथै उक्त औषधिको सिफारिस, बिक्रि वितरण तथा प्रयोग समेत नगर्न र नगराउनु हुन सम्बन्धित सबैलाई अनुरोध छ ।

तपसिलः

सि.नं.	औषधिको नाम	ब्याच. नं.	Mfg./Exp. Date	कारण	उत्पादकको नाम र ठेगाना
१.	Zincomin-DT (Zinc Dispersible Tablets IP)	ZDT2-28	May-2021/ April-2023	Doesnot comply with respect to disintegration test	Nova Genetica Pvt.Ltd., Khani khola-7, Naubise, Dhading

औषधि प्रयोग गर्दा ध्यान दिनुपर्ने कुराहरू:

- मान्यता प्राप्त स्वास्थ्यकर्मीको पूर्जामा मात्र औषधि प्रयोग 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 तुरुन्त 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 जानकरीका लागि तल उल्लेखित ठेगानामा सम्पर्क राख्नुहोला ।

औषधि व्यवस्था विभाग

मदनभण्डारी पथ-४, बिजुलीबजार, काठमाडौं

पोष्ट बक्स नं. १००३८, फोन नं.: (०१)-४७८०२२७/४७८०४३२, फ्याक्स नं. ०१-४७८०५७२

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