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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

A responsive regulatory to address COVID Pandemic

The government of Nepal has been acting concertedly to contain spread of the COVID 19 disease through various public health measures which are proven to be effective as well as monitoring and expanding health system capacity to ensure it can meet population needs. Access to essential health care services has been ensured even during the most fearful of the phases of the pandemic. Department of Drug Administration (DDA) took the lead in this endeavor mainly assessing medicines availability, new interventions or approaches in tackling the disease and authorization of such newer therapeutics of prospects.

In response to the ongoing crisis and exempting the future of the pandemic, most needed legal tools were reviewed and amendments were made so that legal rational authority is vested like; provisions to issue emergency use authorization and conduct clinical trials for the medicines including vaccines. In order for maintaining the supply chain of essential medicines, and vaccines were eased for the import permission especially used in the COVID-19 treatment. DDA coordinated and worked in tandem with Domestic manufactures to introduce promising therapeutics early like issuance of emergency use authorization license for remdesivir and favipiravir(for clinical study). The development of standards to introduce quality alcohol based hand-sanitizer and issuance of manufacturing as well as import licenses was lauded from all section of the society since local manufacturing made it possible for the consumers to get quality products at a time the commodity was in high demand throughout the world.

To avoid shortages of medicines and medical equipment supply, an online monitoring form was generated and shared with importers and manufacturers for real time stock balance. Besides, regular virtual meetings with stakeholders were

held to track unhindered availability of medicines and medical supply in the country. DDA also carried out active inspections all over the country to ensure quality medicines and vaccines are moving in the market round the clock. Several perpetrators of substandard and falsified hand-sanitizers were brought to legal and administrative actions.

As we know, vaccination is a simple, safe and effective way to protect against harmful infectious diseases, several vaccine solutions were in the making and were emerging to be approved for emergency use. DDA took track of them and devised legal and procedural tools to introduce as early as possible. Code on Emergency Use of Drugs or Vaccines, 2077 was prepared and implemented in warp speed. Till date DDA has issued Emergency Use Authorization to nine COVID-19 vaccines.

In this greatest public health challenge of a generation, a responsive regulatory is a must to tackle the spread and providing effective therapies to treat and contain extent of disease progression. Also, responsive mechanism and upfront actions are desired for effective surveillance of substandard and falsified medicines. The pandemic is not yet over, and we never know for sure how long it will last and what comes next, regulatory preparedness to act responsively is to go on.

Narayan Prasad Dhakal
(Director General)
Chief Editor

1. Emergency Use Authorization (EUA) of Vaccines for Use in Nepal

SN	Name of Vaccine	Manufacturer	Type of Vaccine	EUA Date by DDA
1	ChAdox1 nCoV-19 Corona Virus Vaccine (Recombinant) COVISHIELD	Serum institute of India	Replication-deficient chimpanzee adenovirus vector encoding the SARS-CoV-2-Spike (S) glycoprotein	2077/10/02
2	Inactivated SARS-CoV-2 Vaccine Vero Cell	Beijing institute of Biological Products Co., Ltd., China under Sinopharm	Whole Inactivated Virus	2077/11/04
3	COVAXIN™	Bharat Biotech International Ltd, India	Whole Inactivated virus	2077/12/06
4	Sputnik-V	FSBI N.F, Gamaleya National Research Center of Epidemiology and Microbiology, Russia	Human Adenovirus Vector	2078/01/07
5	CoronaVac	SINOVAC LIFE SCIENCES CO., LTD., China	Whole Inactivated Virus	2078/02/21
6	AZD1222 Vaxzervria	AstraZeneca	Replication deficient adenoviral (CHAdOx1) vector vaccine	2078/03/15
7	Janssen AD26COV2.S Vaccine	Janssen- Cilag International NV, Belgium	Adenovirus type 26 vector	2078/03/16
8	Pfizer-BioNTech COVID-19 mRNA Vaccine (COMIRNATY)	Pfizer-BioNTech	mRNA	2078/05/23
9	Moderna COVID-19 mRNA	Moderna	mRNA	2078/05/30

Updated- 2078/06/01

2. 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 recommendation 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 medicines for registration. In the 51th meeting of DAC, 7 medicines have been recommended for registration within DDA which are as follows:

S. No.	Name of Molecule
1.	Idarucizumab
2.	Gadobutrol
3.	Bifonazole
4.	Palanosetron
5.	Cinacalcet
6.	Benfotiamine
7.	Influenza (Nasal) Vaccine

3. Analytical Method Validation

Analytical Method Validation committee that has been formed by Department of Drug Administration has been working for validation of analytical methods for non-pharmacopoeial products submitted to Department for the registration of the products. In the 51th meeting of Drug Advisory Committee (DAC), 22 methods have been approved from Drug Advisory Committee.

S.No.	Product Name	Analytical Profile No./Status
1.	Esomeprazole Fast Releasing Tablet	Esmo FR 076/077/AP 061
2.	Iron Polymaltose Complex & Folic acid capsule	IPFC 076/077/AP 062
3.	Amlodipine & Ramipril Tablet	Amlo Rami 076/077/AP 063
4.	Salbutamol Sulphate & Bromhexine HCl Syrup	Salb Brom 076/077/AP 064
5.	Sodium Picosulphate Tablets	Sodp 076/077/AP 065
6.	Linezolid & Dextrose Injection	Linez 076/077/AP 066

7.	Enrofloxacin Oral Solution (Veterinary)	Enrof 076/077/AP 067
8.	Moxifloxacin Eye Ointment	Moxif 076/077/AP 068
9.	Metronidazole & Diloxanide furoate suspension	Metr Dilo L 076/077/AP 069
10.	Progesteron SR tablet	Prog SR 076/077/AP 070
11.	Esomeprazole Sodium for Injection	Esmo I 076/077/AP 071
12.	Ambroxol Hydrochloride Syrup	Ambrx 076/077/AP 073
13.	Cefpodoxime Proxetil and Potassium Clavulanate Tablet	Cefpo Clav 076/077/AP 074
14.	Cefpodoxime Proxetil and Potassium Clavulanate Dispersible Tablet	Cefpo Clav DT 076/077/AP 075
15.	S (-) Amlodipine and Hydrochlrothiazide tablet	Amlo Hydro 076/077/AP 076
16.	Rivaroxaban tablets	Riva 076/077/AP 077
17.	Metronidazole and Furazolidone bolus (Veterinary)	Metr Fur 076/077/AP 078
18.	Norfloxacin oral powder (veterinary)	Norf 076/077/AP 079
19.	Levofloxacin oral solution 10% w/v (veterinary)	Levo V 077/078/AP 081
20.	Favipiravir Tablet	Favi 077/078/AP 083
21.	Dextromethorphan HBr, chlorpheniramine Maleate & Phenylephrine HCl syrup	Dex Chlor Phen 077/078/AP 085
22.	Bromhexine HCl, Chlorpheiramine Maleate & Phenylephrine HCl Syrup	Brom Chlor Phen 077/078/AP 087

4. REGULATORY MATTERS

Methimazole

Risk of vasculitis

Canada. Health Canada has announced that it is working with the manufacturers to update product safety information of methimazole (Tapazole®) to include information about the risk of inflammation of the blood vessels (vasculitis).

Methimazole is indicated to treat hyperthyroidism and overactive thyroid gland.

Triggered by updates made by the US Food and Drug Administration (FDA) to the product safety information for methimazole related to the risk, Health Canada reviewed the potential risk of vasculitis with the use of methimazole.

Health Canada reviewed 13 international case reports of vasculitis in patients receiving methimazole, where 11 reports showed a possible link to methimazole use. Also, Health Canada assessed 22 articles from the published literature and found that many of them suggested a potential risk of vasculitis with methimazole use although the frequency was very rare.

Health Canada concluded that there is a link between the risk of vasculitis and the use of methimazole.

Source: WHO Pharmaceuticals Newsletter No.3, 2020

In Nepal: Health care professionals are warned of the risk of vasculitis with the use of Methimazole.

Propylthiouracil

Potential risk of birth defects

Canada. Health Canada has announced that it is working with the manufacturers, to update product safety information for propylthiouracil (Propyl-Thyracil®), to inform health-care professionals and patients about the potential risk of birth defects.

Propylthiouracil is indicated for hyperthyroidism, several radioiodine therapies, thyroid storm and, to control an overactive thyroid gland.

Triggered by international reports of birth defects linked with propylthiouracil use in pregnant women, Health Canada reviewed the potential risk of birth defects in babies whose mothers were treated with propylthiouracil during pregnancy. The review included 12 reports of birth defects, where seven reports were found to have possible link between the use of propylthiouracil and the birth defects. Also,

22 relevant published studies were found, but the review of the studies did not find sufficient evidence.

Health Canada's reviews could not confirm or exclude a link between the risk of birth defects in babies and use of propylthiouracil in women during pregnancy.

Source: WHO Pharmaceuticals Newsletter No.3, 2020
In Nepal: Health care professionals are warned of the Potential risk of birth defects with the use of propylthiouracil.

Pegfilgrastim

Increased risk of thrombocytopenia

Japan. The MHLW and the PMDA have announced that the package insert for pegfilgrastim (G-Lasta®) should be revised to include an increased risk of thrombocytopenia as a precaution.

Pegfilgrastim is indicated to prevent chemotherapy-induced febrile neutropenia.

Thirty cases involving thrombocytopenia in patients with pegfilgrastim have been reported in Japan during the previous three years, including one case for which a causal relationship between the drug and event could not excluded. No patient mortalities have been reported.

A pharmacoepidemiological study on the association between pegfilgrastim and decreased platelet counts was conducted in Japan. The relative risk of decreased platelet counts was statistically significant in patients with pegfilgrastim.

The MHLW and PMDA have concluded that precaution for thrombocytopenia should be added in the package insert.

Source: WHO Pharmaceuticals Newsletter No.3, 2020
In Nepal: Health care professionals are warned of the increased risk of thrombocytopenia with the use of pegfilgrastim.

SGLT2 inhibitors

Risk of diabetic ketoacidosis

United Kingdom. The MHRA has advised health-care professionals to interrupt sodium-glucose co-transporter 2 (SGLT2) inhibitor treatment in patients who are hospitalised for major surgical procedures or acute serious medical illnesses, and to monitor ketones during the period.

SGLT2 inhibitors are indicated to treat adults with diabetes to improve glycaemic control. In UK, available SGLT2 inhibitors are canagliflozin, dapagliflozin, empagliflozin and ertugliflozin.

A detailed European review in 2016 confirmed diabetic ketoacidosis as a rare risk for the SGLT2 inhibitors.

In 2019, a new European review recommended that warnings should be updated to include routine monitoring of ketones in patients hospitalized for surgery or acute illness. Testing of ketones in blood is recommended rather than measuring ketone bodies in urine because SGLT2 inhibitors may diminish the excretion of ketone bodies in urine. The review of the evidence did not identify a specific type of surgery as being linked to an increased risk of diabetic ketoacidosis.

Health-care professionals should restart treatment with the SGLT2 inhibitor once ketone values are normal and the patient's condition has stabilized.

Source: WHO Pharmaceuticals Newsletter No.3, 2020
In Nepal: Health care professionals are warned of the risk of diabetic ketoacidosis with the use of SGLT2 inhibitors.

SSRI, SNRI

Potential risk of sexual dysfunction

Ireland. The HPRA has announced that the SmPC and the PL for medicines containing selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs) will be updated to advise of the possible symptoms of sexual dysfunction which may persist following discontinuation of product.

SSRIs and SNRIs are indicated to treat major depressive disorder and anxiety disorders. SSRI containing medicinal products include citalopram, escitalopram, fluvoxamine, fluoxetine, paroxetine, sertraline; SNRI containing medicinal products include duloxetine, venlafaxine, desvenlafaxine and milnacipram.

After reviewing evidence from EMA database of adverse reactions and literature, the EMA's PRAC considered that the product information for SSRI and SNRI medicinal products should be amended to warn about the possibility of sexual dysfunction, which may persist following discontinuation of the medicinal products.

Source: WHO Pharmaceuticals Newsletter No.3, 2020
In Nepal: Health care professionals are warned of the potential risk of sexual dysfunction with the use of SSRI, SNRI.

Tofacitinib

Risk of venous thromboembolism and serious and fatal infections

United Kingdom. The MHRA has alerted health-care professionals that tofacitinib (Xeljanz®) is associated with a dose-dependent increased risk of serious venous thromboembolism; and is also known to increase the risk of serious and fatal infections such as pneumonia, cellulitis, herpes zoster and urinary tract infections.

Tofacitinib is indicated to treat rheumatoid arthritis, psoriatic arthritis and ulcerative colitis.

In an ongoing trial to assess the use of tofacitinib in ulcerative colitis, cases of pulmonary embolism and deep vein thrombosis were also observed. As a new recommendation, maintenance treatment for ulcerative colitis at the 10mg twice-daily dose is not recommended in patients with known risk factors for venous thromboembolism such as previous venous thromboembolism, myocardial infarction, heart failure, hypertension and diabetes, unless there is no suitable alternative treatment.

Also, tofacitinib increases the risk of serious and fatal infections, with rates of infections greater in older patients. Health-care professionals should only consider use of tofacitinib in patients older than 65 years if there is no suitable alternative treatment available.

Source: WHO Pharmaceuticals Newsletter No.3, 2020

In Nepal: Health care professionals are warned of the risk of venous thromboembolism and serious and fatal infections with the use of tofacitinib.

5. SAFETY OF MEDICINES

Benzodiazepines, opioids

Risk of potentially fatal respiratory depression

United Kingdom. The MHRA has reminded that benzodiazepines and opioids can both cause fatal respiratory depression, and when co prescribed, additive effects on the central nervous system increase the risks of sedation, respiratory depression, coma and death.

Benzodiazepines and opioids are indicated to treat anxiety, insomnia, agitation, seizure, muscle spasms and pain relief.

The MHRA recently received a report of death by respiratory arrest of a man given the benzodiazepine clonazepam and among other drugs, the opioid methadone.

Health-care professionals should only prescribe benzodiazepines and opioids together if there is no alternative. If co-prescribed, the lowest doses for the shortest duration should be used and patients should be carefully monitored. Also, health-care professionals should advise patients of the symptoms of respiratory depression and sedation, and the need to seek immediate medical attention if these occur.

Source: WHO Pharmaceuticals Newsletter No.3, 2020

In Nepal: Health care professionals are warned of the risk of potentially fatal respiratory depression with the use of Benzodiazepines, opioids.

Aminophylline

Risk of urinary retention

Malaysia. The National Pharmaceutical Regulatory Agency (NPRA) has reported the case of urinary retention in a 75-year-old male patient after treatment with intravenous aminophylline for acute exacerbation of chronic obstructive pulmonary disease (COPD).

Aminophylline is a combination of theophylline and ethylenediamine. Theophylline exerts bronchodilatory effect and is used for the treatment of COPD. Two products containing aminophylline are registered in Malaysia.

The NPRA has received 46 case reports with 76 adverse events associated with

aminophylline use, two of which were linked to urinary retention. On the other hand theophylline has one report each for urinary retention and difficulty in urination. As of February 2020, WHO's Vigibase contains 25 and 30 reports of urinary retention suspected to be cause by aminophylline and theophylline respectively.

The dosage for aminophylline should be reduced in the elderly population. Patients on aminophylline therapy should be monitored for symptoms of urinary retention or difficulty urinating.

Source: WHO Pharmaceuticals Newsletter No.4, 2020

In Nepal: Health care professionals are warned of the risk of urinary retention with the use of aminophylline.

Flucloxacillin

Risk of renal toxicity

New Zealand. Medsafe has announced that flucloxacillin can injure the kidneys as well as the liver. Both interstitial nephritis and hepatitis are listed in the flucloxacillin data sheets.

Flucloxacillin is beta-lactam antibiotic and generally indicated to treat infections caused by susceptible Gram positive bacteria.

The CARM has received 39 reports of liver-related reactions and 13 reports of kidney-related reactions, suggesting that interstitial nephritis may be an under recognized reaction to flucloxacillin. Of the 13 reports of renal reactions, the majority occurred in patients aged over 70 years.

Early recognition of flucloxacillin-induced interstitial nephritis and prompt treatment reduces the risk of long-term renal impairment.

Source: WHO Pharmaceuticals Newsletter No.4, 2020

In Nepal: Health care professionals are warned of the risk of renal toxicity with the use of flucloxacillin.

Levothyroxine

Risk of myocardial infarction

Malaysia. The NPRA has reported a case of non-ST segment elevation myocardial infarction (NSTEMI) in an 80- year-old female patient after

treatment with levothyroxine for subclinical hypothyroidism. After levothyroxine was withdrawn, the reaction subsided and patient gradually recovered.

Levothyroxine is indicated as a substitution therapy in hypothyroidism. Six products containing levothyroxine are registered in Malaysia. The risk of developing myocardial infarction following levothyroxine use is documented in the product information.

The NPRA has received 223 local ADR reports with 571 adverse events suspected to be related to levothyroxine. There is one report associated with NSTEMI, as above-mentioned. The WHO's Vigibase revealed five reports of NSTEMI and 27 reports of acute myocardial infarction suspected to be associated with levothyroxine.

Health-care professionals should exercise extra caution when initiating levothyroxine in elderly patients and in patients with underlying cardiovascular disease. In those, the lowest possible dose should be initiated followed by gradual increase.

Source: WHO Pharmaceuticals Newsletter No.4, 2020

In Nepal: Health care professionals are warned of the risk of myocardial infarction with the use of levothyroxine.

Water (for injection)

Risk of haemolysis

Australia. The Therapeutic Goods Administration (TGA) has reminded health-care professionals that water for injection can cause haemolysis resulting in patient harm including death, if large quantities are inadvertently administered intravenously without being rendered isotonic.

Water for injection is indicated for dissolving or diluting injectable therapeutic substances for parenteral administration. Water for injection is hypotonic. It is contraindicated for intravenous administration if it is not adjusted to isotonicity by the addition of suitable solutes.

The TGA is aware of international reports of mix-ups between 1 L bags of water for injection and other 1 L bags including sodium chloride 0.9% and glucose 5%.

All registered injection products in Australia with a volume of 100 mL or more are required to include a statement on the label to indicate if the injection is

hypotonic, hypertonic or isotonic.

Health-care professionals should check the label to ensure there is no confusion between water for injection and other intra venous bags.

Source: WHO Pharmaceuticals Newsletter No.4, 2020

In Nepal: Health care professionals are warned of the risk of haemolysis with the use of water (for injection).

6. 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.

Everolimus and osteonecrosis of the jaw (ONJ)

Anna Hegerius, Uppsala Monitoring Centre

Summary

Osteonecrosis of the jaw (ONJ) is a rare but potentially serious and painful condition, originally associated with the use of bisphosphonates. In recent years ONJ has been linked to several other drugs, including the mTOR inhibitor everolimus, used to treat advanced malignancies and to prevent transplant rejection. During a UMC signal detection sprint, held in December 2018, the MedDRA preferred term 'osteonecrosis of jaw' was highlighted for the drug everolimus in VigiBase, the WHO global database of individual case safety reports (ICSRs). As of 3 February 2020, there were 117 reports for this drug–adverse drug reaction (ADR) combination in VigiBase.

ONJ is not labelled for everolimus, but related terms such as stomatitis, jaw pain, oral pain, impaired wound healing and mucositis are. Among the cases in VigiBase and the scientific literature, the vast majority concern patients with concurrent or past therapy with drugs known (or suspected) to cause ONJ, which makes it difficult to identify the offending drug. However, there are a few case reports where neither drugs nor risk factors associated with ONJ were involved, implicating everolimus as an independent cause of ONJ. In 15 of the VigiBase cases, the reaction abated when the drug was withdrawn.

The exact pathophysiology of ONJ remains unclear, but several theories have been proposed and the mechanism is likely multi-factorial. Factors that may cause ONJ are: bone remodelling (osteoclast) inhibition, bone infection/inflammation, angiogenesis inhibition, soft tissue toxicity, and immunity dysfunction. Considering the mechanism of action of everolimus, it is reasonable to assume that it may be involved in the development of ONJ.

Based on current data, the risk of ONJ due to everolimus treatment alone seems very low. However, combined with other drugs with a potential to cause ONJ and risk factors such as diabetes or dental surgery, everolimus may act as a trigger. Further studies in this area are required considering the increasing population of patients at risk of ONJ and the adverse impact on the quality of

life for those affected.

Introduction

The antineoplastic agent everolimus is indicated for the treatment of various cancers (breast, pancreatic, gastrointestinal, lung, and renal) and is also used as an immunosuppressant to prevent transplant rejection. In breast cancer treatment, everolimus is combined with the aromatase inhibitor exemestane. Everolimus inhibits the activity of mammalian target of rapamycin (mTOR), a serine-threonine kinase involved in cell growth and metabolism, resulting in a decrease of both hypoxia-inducible factors and vascular endothelial growth factor (VEGF) levels, which reduces tumour growth and angiogenesis. Furthermore, the mTOR and VEGF pathways play a key role in regulating bone homeostasis and immune responses.1, 2 Everolimus and temsirolimus (the other drug in the same class) are derivatives of sirolimus.

Osteonecrosis of the jaw (ONJ) is characterised as oral lesions of exposed necrotic bone that persist for at least eight weeks, with no previous history of radiation or metastasis to the area. This oral condition is rare but potentially serious and very painful. A number of drugs are known to cause ONJ but it can also occur spontaneously.3 The condition was first described in 2003, in a case report including 36 patients who had been treated with two different bisphosphonates,4 and was later determined to be a drug class effect. In the following years, other drugs were also associated with the development of ONJ, such as the monoclonal antibodies denosumab and bevacizumab and the tyrosine kinase inhibitor sunitinib. More recently the mTOR inhibitor everolimus has also been implicated as a risk factor for ONJ.5 Hence the term 'Medication Related Osteonecrosis of the Jaw' (MRONJ) was established in 2009 by the American Association of Oral and Maxillofacial Surgeons (AAOMS).3 In addition to the use of antiresorptive and antiangiogenic agents, several other risk factors for ONJ have been identified. These include dental surgery (e.g. tooth extraction), poor oral health, diabetes, smoking, and concomitant use of steroids.6, 7

The combination of antiangiogenics and antiresorptives is known to increase the risk of ONJ development,[8, 9] but little is known about the risk of developing ONJ with antiangiogenics alone.

Reports in VigiBase

During a UMC signal detection sprint held in December 2018, the MedDRA preferred term 'osteonecrosis of jaw' was highlighted for the drug everolimus in

VigiBase, the WHO global database of individual case safety reports (ICSRs).

As of 3 February 2020, there were 117 reports for this drug–adverse drug reaction (ADR) combination in VigiBase. Based on the overall reporting of adverse reactions for everolimus, and of the adverse reaction ONJ in VigiBase, the expected value for the number of reports on the combination was 35, and the association was highlighted as disproportionally reported, by IC analysis[10].

The reports came from 15 countries across four continents: Europe (76 reports), the Americas (16), Asia (23), and Australia (1). More female than male patients were affected (75% women), since the most common indication for everolimus in the case series was breast cancer, and the age range was 29-82 years, with a median of 64 years. Physicians and other health professionals accounted for 95% of the reports and the rest were submitted by pharmacists and consumers/non-health professionals. More than 90% of the cases were serious, including six fatalities (5%), but all were not caused by the ONJ.

In 18 cases, everolimus was the only reported drug, and in 26 cases it was the only suspected drug. The most frequently co-reported drugs were exemestane (54 cases), zoledronic acid (54), denosumab (38), capecitabine (11) and fulvestrant (11). Zoledronic acid and denosumab are both known to cause ONJ. Exemestane is a potent oestrogen lowering agent, and a reduction in bone mineral density and an increased fracture rate has been observed. Fulvestrant is an oestrogen receptor antagonist and may also cause osteoporosis, but there is no long-term data on the effects on bone. Most co-reported reactions were malignant neoplasm progression (13 cases), stomatitis (12),

fatigue (11), pain (10) and metastasis to bone (9). Stomatitis and metastasis to the bone (if located in the jaw) may have contributed to the ONJ.

The vast majority of the patients were administered everolimus due to breast cancer (73 cases) or renal cancer (28 cases), and the dose varied between 5 and 20 mg per day, with 10 mg being the most common daily dose. Most cases had a reasonable time to onset, with a median of 31 weeks, which is shorter than the median time to onset for bisphosphonate-related ONJ (108 weeks) but longer than the median time to onset for non- antiresorptive medications (20 weeks).[11, 12] In 15 cases the reaction abated when the drug was withdrawn.

Since several other drugs are known to cause ONJ, all cases with drugs that have ONJ labelled were excluded from the case series. This resulted in 27 remaining cases, but some of them could also be excluded since the narratives revealed that the patients had taken other ONJ-causing drugs. Some cases had a medical history that may have contributed to the development of ONJ, e.g. stomatitis, dental issues or bone metastasis.

A selection of reports is presented in Table 1. Case 1 concerns a female patient with metastatic breast cancer who developed ONJ five weeks after initiating everolimus (and exemestane) treatment. Both drugs were withdrawn and the patient was recovering when the report was sent. According to a later publication of this case, the patient had no relevant past dental history and metastasis was ruled out. The patient was treated with cephalosporin for two weeks and after two months her condition had improved.[13]

In case 2, a female patient received everolimus for advanced breast cancer and after nine days experienced a range of adverse reactions including aphthae, throat pain and difficulty swallowing. She was also diagnosed with ONJ and had no relevant medical history or concomitant medication.

Everolimus treatment was continued and most of the adverse reactions persisted, except for the aphthae which resolved after laser therapy. The time to onset was very short in this case, but not implausible.[12] The reporter assessed the events as suspected to be related to the drug.

Case 3 describes a female patient with metastatic breast cancer who received everolimus for 19 days and then stopped the drug for one month due to a tooth extraction. The treatment was then resumed but again stopped after only two days due to ONJ onset. The reporter suspected the drug to have caused the adverse reaction since the patient had recovered substantially two weeks after drug withdrawal. However, tooth extraction is also a trigger event for ONJ.

Case 4 concerns a female patient with recurrent breast cancer, treated with everolimus and a few other drugs (see Table 1) who developed ONJ. The time to onset is unknown but the patient was recovering after the drug had been withdrawn. The patient had no related medical history nor past drug therapy.

Case 5 presents a female patient of unknown age who developed ONJ during

treatment with everolimus for advanced breast cancer. The time to onset is unknown, but the drug was withdrawn and the stomatitis resolved; the outcome of the ONJ was unknown.

Table 1. Characteristics of a selection of case reports in VigiBase of everolimus in association with osteonecrosis of jaw (ONJ)

Case	Reporter	Age/ Sex	Suspected (S) or concomitant (C) drugs	Reactions (MedDRA preferred terms)	Time to onset	Action taken
1	Other health professional	76/F	Everolimus (S) Exemestane (C)	Osteonecrosis of jaw	5 weeks	Drug withdrawn, recovering
2	Other health professional	61/F	Everolimus (S)	Osteonecrosis of jaw, aphthous ulcer, oropharyngeal pain, dysphagia, furuncle, hepatotoxicity etc.	9 days	Dose not changed, not recovered
3	Physician	55/F	Everolimus (S) Exemestane (C) Pantoprazole (C) Prednisone (C) Tramadol (C) Colecalciferol (C)	Osteonecrosis of jaw	7 weeks*	Drug withdrawn, recovering
4	Physician	75/F	Everolimus (S) Exemestane (S) Capecitabine (S) Cyclophophamide (S) Fulvestrant (S)	Osteonecrosis of jaw	Unknown	Drug withdrawn, recovering Rechallenge, outcome unknown
5	Other health professional	75/F	Everolimus (S)	Osteonecrosis of jaw, stomatitis	Unknown	Drug withdrawn, outcome unknown for

						everolimus, recovered for stomatitis

*The patient was treated with the drug for 19 days, halted treatment for a month due to a tooth extraction, and then resumed treatment for only two days before the ONJ occurred and the drug was withdrawn.

Literature and labelling

ONJ is not labelled for everolimus (or temsirolimus) in the most recent Summary of Product Characteristics (SPC) in the United Kingdom but related terms such as stomatitis, jaw pain, oral pain, impaired wound healing and mucositis are.[14] ONJ has not been observed in clinical trials, but gingival swelling and jaw pain have been.[6] Osteonecrosis is labelled for sirolimus, and since everolimus mimics sirolimus, it is reasonable to assume that it might have a similar effect.

In addition to the cases in VigiBase, there are several case reports in the literature where everolimus is suspected of causing or contributing to ONJ. However, in some of these cases, it is difficult to establish a causal link since the patient had also taken other drugs known to cause ONJ, for example bisphosphonates.[15-17] Even though many years may have passed since a patient was administered a bisphosphonate, these drugs accumulate in bone and the effect may last more than 10 years,[18] which makes it reasonable to assume that previous intake of these drugs may still be relevant for the development of ONJ.

However, in addition to case 1 above, there are a few other published case reports where bisphosphonates or monoclonal antibodies were not involved, implicating everolimus as an independent cause of ONJ. One case concerns a female breast cancer patient with no medical history of radiation, and metastasis to the mandible was ruled out. The patient had a tooth extracted four months prior to the ONJ diagnosis, which may have contributed to the onset.[19] Another case describes a male patient who had taken everolimus for 1.5 years (after a kidney transplant) when he was diagnosed with ONJ. He had no recent dental trauma, but he had taken steroids, which may also have contributed to the adverse reaction.[20]

There are also case reports where the other mTOR inhibitor temsirolimus has been combined with denosumab or bevacizumab, resulting in ONJ, and the authors describe a potential synergistic effect.[21,22]

Furthermore, US FDA reviewed all ONJ cases in FAERS on the drugs suspected to cause ONJ. This study was the first to show that the mTOR inhibitors everolimus and temsirolimus were also associated with the risk for ONJ, with 84 and 28 cases respectively. However, compared to other drugs, the risk of mTOR induced ONJ was low (<5%).[23]

The exact pathophysiology of ONJ has still not been fully understood but several theories have been proposed and the mechanism is likely to be multi- factorial. Factors that may cause ONJ are: bone remodelling (osteoclast) inhibition, bone infection/inflammation, angiogenesis inhibition, soft tissue toxicity, and immunity dysfunction.[24] In relation to everolimus, pre-clinical studies have shown that inhibition of mTOR decreases the maturation of osteoclasts and increases their apoptosis, which may explain how osteonecrosis may occur.[1] Furthermore, when VEGF activity is inhibited, the healing of bone is impaired[6]. The immunosuppression caused by everolimus explains the impaired wound healing and the infection susceptibility of treated patients. However, although infection and inflammation are often present when ONJ is diagnosed, it has not been established whether infection precedes or follows necrosis.[25]

The wide range of time to onset of ONJ can be explained by several factors, for example the potency, route of administration, and cumulative dose of the drug used.[26] One study showed that ONJ caused by non-antiresorptive medications had an earlier time to onset, a higher proportion of cases lacking a trigger event, and greater likelihood of healing and shorter healing time, compared to ONJ caused by bone targeting agents, and the diagnosis of ONJ is often delayed.[12] There is a risk of underdiagnosis of ONJ due to lack of awareness, strict diagnostic criteria, and the fact that early signs and symptoms of the condition are similar to the clinical presentation of stomatitis, which is a very common side effect of everolimus and most other drugs that may also cause ONJ.[6] This means that there is probably under-reporting of ONJ; one study concluded that the occurrence of ONJ in renal cancer patients receiving bisphosphonates and

targeted agents might be underestimated.[8]

Discussion and conclusion

Among the cases in VigiBase, the vast majority concerned patients with concurrent or past therapy with drugs known (or suspected) to cause ONJ, which makes it difficult to identify the offending drug. Furthermore, exemestane and fulvestrant (often co-administered with everolimus), may also play a part in the development of ONJ considering their mechanism of action. Some patients also had potential risk factors such as diabetes and tooth extractions. There are a few case reports of ONJ in patients who neither taken other suspected drugs nor had any known risk factors. Based on current data, the risk of ONJ due to everolimus treatment alone, seems very low. However, combined with other drugs with the potential to cause ONJ and risk factors such as diabetes or dental surgery, everolimus may act as a trigger. Although it is impossible to conclude what role everolimus played in each reported case, VigiBase data and published case reports still point to a potential causal association where the drug may at least have contributed to the development of ONJ. Further studies in this area are required considering the increasing population of patients at risk of ONJ, the seriousness of this condition, and the adverse impact on the quality of life for those affected.

Close collaboration between medical doctors and dentists, as well as information to patients at risk, are important aspects for the prevention, prompt recognition and treatment of ONJ.[2]

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Source: WHO Pharmaceuticals Newsletter No.5, 2020

७. आ. व. २०७७/७८ मा कारवाही भएका उद्योगहरुको विवरण

क्र. स.	उद्योगको नाम	कारवाही
१.	MDH Pharmaceuticals Pvt. Ltd., भक्तपुर	मिति २०७७/०७/१७ को विभागीय निर्णयानुसार virok pure palm hand sanitizer gel 50 ml को उत्पादन अनुमति पत्र सुधार नभए सम्म निलम्बन गरिएको। veterinary oral liquid section मा hand sanitizer को उत्पादन रोक्का राखिएको ।मिति २०७८/०३/१० गतेको विभागीय निर्णयानुसार सो उद्योगमा External Preparation कक्षको व्यवस्था कायम भएको भनि प्रतिबेदन प्राप्त भएकोले उक्त उद्योगको Hand Sanitizer को रोक्का राखिएको उत्पादन कार्य फुकुवा गरिएको छ ।
२.	Supreme Chemicals, पर्सा	मिति २०७७/०८/२४ को विभागीय निर्णयानुसार निरीक्षण प्रतिबेदनमा औल्याईएका कैफियतहरु सुधार नगरे सम्म उत्पादन कार्य रोक्का राखिएको ।
३.	Shree Ram Pharmaceuticals Pvt. Ltd, पर्सा	मिति २०७७/०८/२४ को विभागीय निर्णयानुसार निरीक्षण प्रतिबेदनमा औल्याईएका कैफियतहरु सुधार नगरे सम्म उत्पादन कार्य रोक्का राखिएको ।
४.	Amtech Med Pvt. Ltd.,बिराटनगर	मिति २०७७/१०/८ गतेको विभागीय निर्णयानुसार उक्त उद्योगको WHO GMP तथा औषधि उत्पादन कुशल अभ्यास संहिता २०७२ बमोजिमको प्रमाणपत्र निलम्बन गरिएको। मिति २०७७/१२/०३ गते स्थलगत रुपमा निरीक्षण गरि प्राप्त प्रतिबेदनमा छलफल गर्दा CAPA अनुरुप कैफियतहरुमा सुधार भएको देखिएकोले उक्त उद्योगको WHO GMP तथा औषधि उत्पादन कुशल अभ्यास संहिता २०७२

		बमोजिमको प्रमाणपत्र निलम्बन फुकुवा गरिएको मिति २०७८/०१/०९ गतेको विभागीय निर्णयानुसार जानकारी गराईन्छ ।
५.	Shiv Pharmaceuticals Laboratories, धरान	मिति २०७७/१०/१३ को विभागीय निर्णयानुसार निरीक्षण प्रतिबेदनमा औल्याईएका कैफियतहरु सुधार नगरे सम्म Small Volume Parenterals, Sterile powder for Injections, Sterile Ophthalmic and Otic Preparations उत्पादनहरुको उत्पादन कार्य रोक्का राखिएको। Small Volume Parenterals, Sterile powder for Injections, Sterile Ophthalmic and Otic Preparations उत्पादनहरुको विभागबाट जारी भएको उत्पादन अनुज्ञा पत्र तथा बिक्रि वितरण दर्ता प्रमाण पत्र निलम्बन गरिएको छ ।
६.	Rhododendron Biotech Pvt. Ltd., ललितपुर	मिति २०७७/१०/१९ को विभागीय निर्णयानुसार प्रतिबेदनमा औल्याईएका कैफियतहरु सुधार नगरे सम्म उत्पादन कार्य रोक्का राखिएको। यस विभागबाट सो उद्योगलाई प्रदान गरिएका उत्पादनहरुको उत्पादन अनुज्ञा पत्र तथा बिक्रि वितरण दर्ता प्रमाण पत्र हाल लाई निलम्बन गरिएको छ ।
७.	Time Pharmaceuticals Pvt. Ltd.	मिति २०७७/११/२८ को विभागीय निर्णयानुसार प्रतिबेदनमा औल्याईएका कैफियतहरु सुधार नगरे सम्म sterile manufacturing area (Eye/Ear Drops बर्ग) उत्पादनहरुको उत्पादन कार्य रोक्का राख्न। यस विभागबाट सो उद्योगलाई प्रदान गरिएका Sterile Eye/Ear Drops उत्पादनहरुको उत्पादन अनुज्ञा पत्र हाल लाई निलम्बन गरिएको छ ।

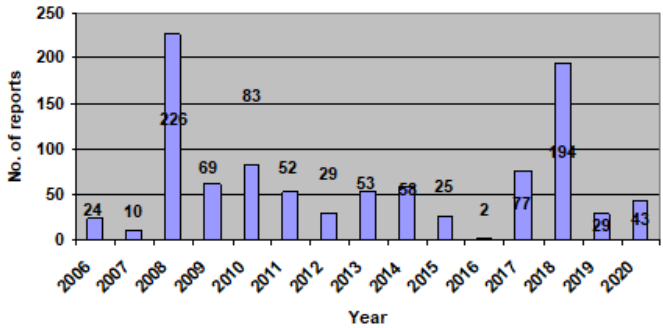
८.	लाइभ केयर फर्मासिउटिकल्स प्रा. लि.	मिति २०७८/०३/०१ गते यस विभागका निरीक्षण टोलीले सो उद्योगको स्थलगत निरीक्षण अनुगमन गरी प्राप्त प्रतिबेदनमा सो उद्योगले Tiamulin Hydrogen Fumarate (Tiamuliv 80) भेटेरिनरी औषधि यस विभागमा दर्ता नै नगरी उत्पादन तथा बिक्रि वितरण गरेको देखिएकोले सो उद्योगलाई यस विभागबाट जारी गरेको उत्पादन अनुज्ञापत्रहरु, बिक्रि वितरण दर्ता प्रमाणपत्रहरु र पैठारी सिफारिस पत्रहरु औषधि ऐन २०३५ को दफा २० को उपदफा ४ (क) बमोजिम १० (दश) दिनको लागि निलम्बन गरिएको मिति २०७८/०३/१६ गतेको विभागीय निर्णयानुसार जानकारी गराइन्छ।

8. ADR Reporting in Nepal in 2020

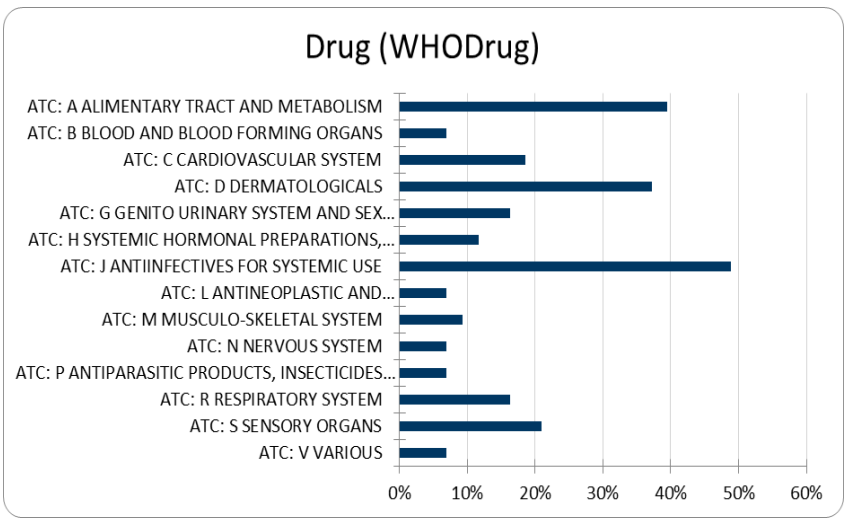
Pharmacovigilance plays a prominent role in establishing the safety profile of marketed drugs. Recognizing the importance and benefits of pharmacovigilance as an important tool towards safety monitoring and rational use of medicines Government of Nepal (GoN) initiated the pharmacovigilance program in 2002. With the initiation of this program GoN is attempting to have its own database for safety monitoring of medicines. Department of Drug Administration (DDA) acts as the focal point to liaise with the Uppsala Monitoring Centre (UMC) WHO Collaborating Centre for International Drug Monitoring in Sweden. Nepal now is a full member country of UMC. At present, there are fifteen regional centres (Manipal Teaching Hospital, Tribhuvan University Teaching Hospital, Nepal Medical College Hospital, KIST Medical College, B.P. Koirala Institute of Health Science, Civil Service Hospital, Patan Hospital, Norvic Hospital, Nepal Army Hospital, Dhulikhel Hospital, Nepal Cancer Hospital and Research Center, College of Medical Sciences - Teaching Hospital, Nepal Medicity Hospital, Nepal Tuberculosis centre, and Chitwan Medical college and teaching hospital) which report ADR to DDA. The adverse drug reactions reported by the regional hospitals are received in the DDA via Vigiflow online (web based) and are then forwarded to the UMC.

The National database contains about 967 ADR reports. 43 ADR reports have been sent to Uppsala by DDA in 2020.

Graph 1: Number of ADR Reports received in National database



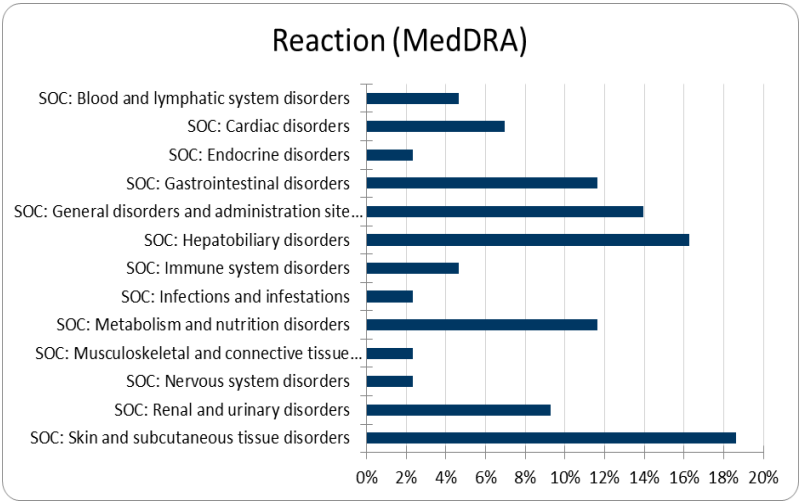
Graph 2: Top reported medicine class in the year 2020



Medicine Class with ATC

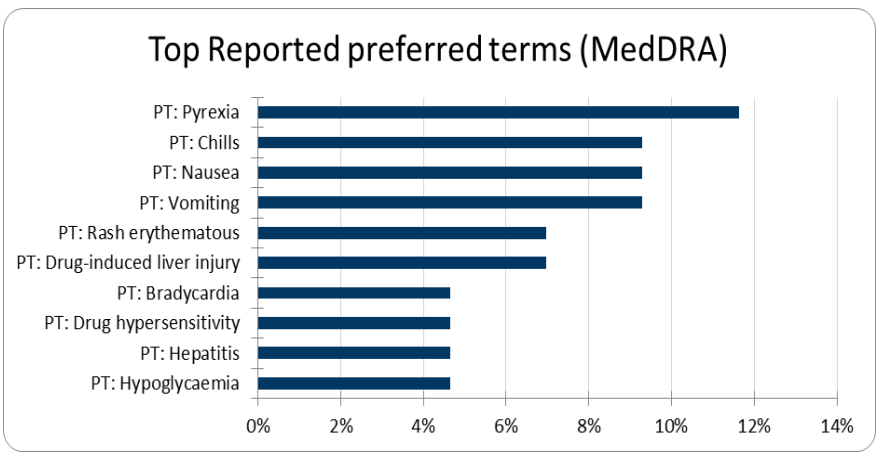
Source: Data retrieved from Vigiflow/Vigilyze software (Nepal)

Graph 3: Adverse drug reaction affecting different body system



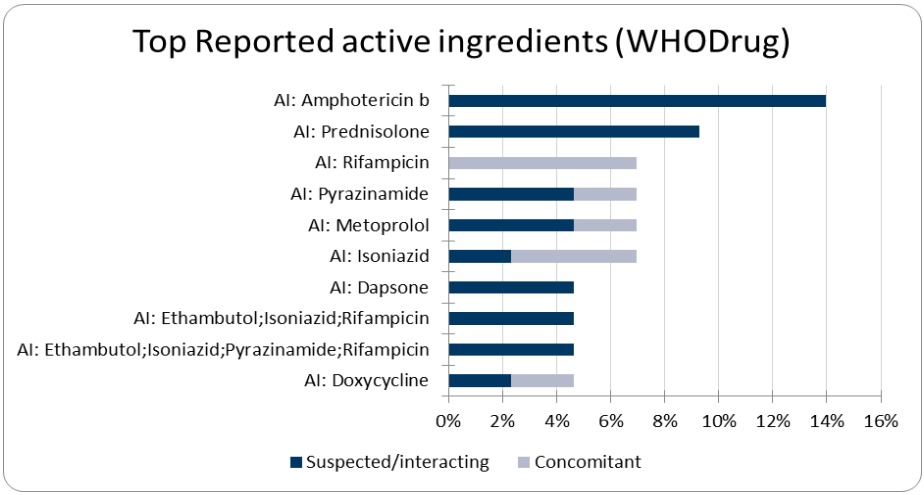
Source: Data retrieved from Vigiflow/Vigilyze software (Nepal)

Graph 4: Top reported adverse drug reaction



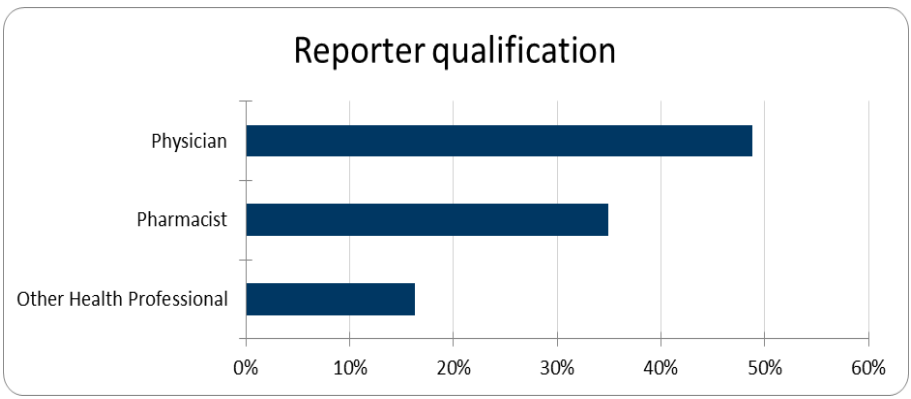
Source: Data retrieved from Vigiflow/Vigilyze software (Nepal)

Graph 5: Top reported drugs in 2020



Source: Data retrieved from Vigiflow/Vigilyze software (Nepal)

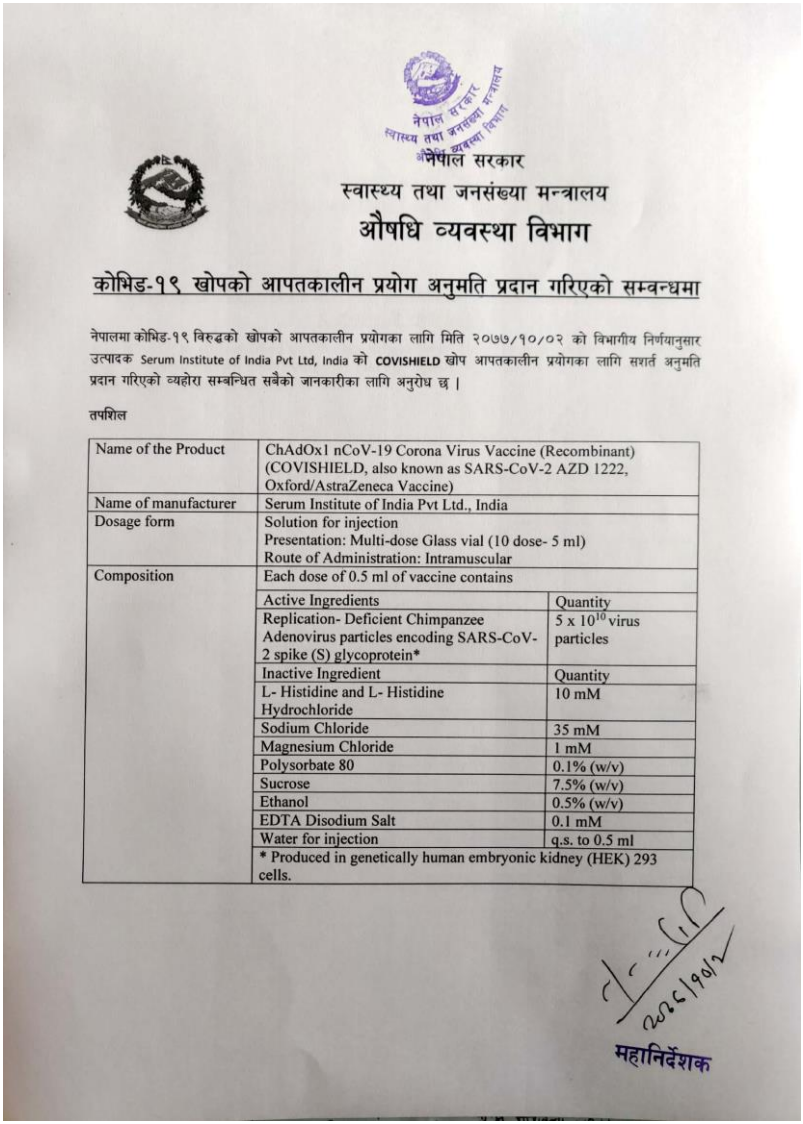
Graph 6: Reporter Qualification



Source: Data retrieved from Vigiflow/Vigilyze software (Nepal)

DDA has been working towards addition of more hospitals as regional centres for ADR reporting. A comprehensive program and adequate continued funding will be needed for the effective implementation and sustainability of the ongoing pharmacovigilance program and for promoting the awareness in ADR reporting.

9. REGULATORY NOTICES



नेपाल सरकार
स्वास्थ्य तथा जनसंख्या मन्त्रालय
औषधि व्यवस्था विभाग

कोभिड-१९ खोपको आपतकालीन प्रयोग अनुमति प्रदान गरिएको सम्बन्धमा

नेपालमा कोभिड-१९ विरुद्धको खोपको आपतकालीन प्रयोगका लागि मिति २०७७/१०/०२ को विभागीय निर्णयानुसार उत्पादक Serum Institute of India Pvt Ltd, India को **COVISHIELD** खोप आपतकालीन प्रयोगका लागि सशर्त अनुमति प्रदान गरिएको व्यहोरा सम्बन्धित सबैको जानकारीका लागि अनुरोध छ ।

तपशिल

Name of the Product	ChAdOx1 nCoV-19 Corona Virus Vaccine (Recombinant) (COVISHIELD, also known as SARS-CoV-2 AZD 1222, Oxford/AstraZeneca Vaccine)	
Name of manufacturer	Serum Institute of India Pvt Ltd., India	
Dosage form	Solution for injection Presentation: Multi-dose Glass vial (10 dose- 5 ml) Route of Administration: Intramuscular	
Composition	Each dose of 0.5 ml of vaccine contains	
	Active Ingredients	Quantity
	Replication- Deficient Chimpanzee Adenovirus particles encoding SARS-CoV-2 spike (S) glycoprotein*	5×10^{10} virus particles
	Inactive Ingredient	Quantity
	L- Histidine and L- Histidine Hydrochloride	10 mM
	Sodium Chloride	35 mM
	Magnesium Chloride	1 mM
	Polysorbate 80	0.1% (w/v)
	Sucrose	7.5% (w/v)
	Ethanol	0.5% (w/v)
	EDTA Disodium Salt	0.1 mM
	Water for injection	q.s. to 0.5 ml
	* Produced in genetically human embryonic kidney (HEK) 293 cells.	

२०७८/१०/२

महानिर्देशक

Government of Nepal
Ministry of Health and Population
Department of Drug Administration

Regarding the permission for Emergency Use Authorization of Covid-19 vaccine

It is to notify to all concerned that the conditional permission has been granted for Emergency Use Authorization of **Covid-19 Vaccine (Vero cell), Inactivated vaccine** manufactured by Beijing Institute of Biological Products Co., Ltd. (BIBP), China under Sinopharm against COVID-19 in Nepal as per the departmental decision dated 16th Feb 2021.

Name of the Product	SARS-CoV-2 Vaccine (Vero Cell), Inactivated
Name of manufacturer	Beijing Institute of Biological Products Co., Ltd. (BIBP), China under Sinopharm
Dosage form	Solution for injection Each 0.5 ml vaccine contains 6.5 U of inactivated SARS-CoV-2 antigen Route of Administration: Intramuscular
Composition	Each dose of 0.5 ml of vaccine contains
	Active Ingredients
	SARS-CoV-2 (inactivated)
	Inactive Ingredient
	Disodium hydrogen phosphate, Sodium chloride, Sodium dihydrogen phosphate , Aluminum hydroxide

17th Feb 2021

Director General

नेपाल सरकार
स्वास्थ्य तथा जनसंख्या मन्त्रालय
औषधि व्यवस्था विभाग

विदेशी उद्योग निरीक्षण सम्बन्धि अत्यन्त जरुरी सुचना !!!

यस विभागको चालू आ.व. ०७७/७८ को वार्षिक कार्यक्रममा विदेशी औषधि उद्योगको WHO GMP Audit गर्ने कार्यक्रम रहेको र कोभिड-१९ महामारी र सृजित परिस्थितिको मुल्यांकन पश्चात मात्र उक्त कार्यक्रम तय गरिने हुँदा औषधि पैठारी सम्बन्धि यस विभागको २०७२ श्रावणदेखि लागू भएको प्रावधान अनुसार इच्छुक उद्योगहरुले आफ्ना आधिकारिक पैठारीकर्ता मार्फत विभागबाट तोकिएका आवश्यक कागजात सहित आवेदन दिन सकिने व्यहोरा जानकारी गराईन्छ । यस पूर्व आवेदन दिएकाहरुको हकमा Updated Site Master File लगायतका तोकिएको आवश्यक कागजातहरु सहित मिति २०७७ साल चैत्र १५ गते भित्र अध्यावधिक गर्न गराउनुहुन यो सुचना प्रकाशीत गरिएको छ । कागजातहरु अध्यावधिक नभएका/नपुग भएका उद्योगहरुलाई निरीक्षण सूचीमा नराखिने समेत जानकारीको लागि अनुरोध छ ।

पुनश्चः तोकिएको आवश्यक कागजातहरुको विवरण यस विभागको website: www.dda.gov.np बाट अथवा विभागको श्री अनुगमन, मुल्यांकन तथा कानुन कार्यन्वयन महाशाखाबाट प्राप्त गर्न सकिनेछ ।

२०७७/११/१८ .
वरिष्ठ औषधि व्यवस्थापक

नेपाल सरकार
स्वास्थ्य तथा जनसंख्या मन्त्रालय
औषधि व्यवस्था विभाग
प्रशासन शाखा

फोन नं.: ४७८०२२७, ४७८०४३२
फ्याक्स नं.: ९७७-१-४७८०५७२
पोष्ट बक्स नं. १००३८
ई-मेलः info@dda.gov.np
काठमाडौ, नेपाल

पत्र संख्या :०७७/०७८
चलानी नं.: ९८८८

मितिः २०७७/०८/३०

विषयः औषधि उत्पादनमा प्रयोग हुने मुख्य कच्चापदार्थ लगायत अन्य पदार्थहरु दर्ता सम्बन्धी अत्यान्त जरुरी सूचना।

नेपाल सरकारद्वारा नेपाल राजपत्रमा मिति २०७७/०८/२९ मा औषधि दर्ता नियमावली, २०३८ को तेश्रो संसोधन सम्बन्धमा प्रकाशित भएको सूचना अनुसार **औषधि उत्पादनमा प्रयोग हुने मुख्य कच्चापदार्थ, सहायक कच्चापदार्थ, प्याकेजिङ्ग मेटेरियल्स, औषधि विश्लेषण गर्न प्रयोग हुने सन्दर्भ रसायनजस्ता पदार्थ पैठारी गर्न चाहने व्यक्तिले औषधि दर्ता (तेश्रो संसोधन) नियमावली, २०७७ मा** उल्लेख भए अनुसारका कागजातहरु संलग्न गरी त्यस्तो पदार्थ पैठारी गर्नको लागि उक्त नियमावलीको अनुसूचीमा उल्लेखित ढाँचामा विभाग समक्ष दरखास्त दिन सरोकारवाला सबैमा जानकारीको लागि यो सूचना प्रकाशन गरिएको छ। नेपाल राजपत्रमा २०७७/०८/२९ मा प्रकाशित भएको औषधि दर्ता (तेश्रो संसोधन) नियमावली, २०७७ यस विभागको वेबसाइटमा समेत राखिएको छ।

भरत भट्टराई
महानिर्देशक
महानिर्देशक

नेपाल सरकार
स्वास्थ्य तथा जनसंख्या मन्त्रालय
औषधि व्यवस्था विभागको

औषधि फिर्ता (Recall) गर्ने सम्बन्धी अत्यन्त जरुरी सूचना

प्रकाशित मिति: २०७७/११/१३

यस विभागबाट बजार अनुगमनको क्रममा संकलन गरिएका औषधिहरुको नमुना परिक्षण गर्दा तपसिल बमोजिमको उत्पादकबाट 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 उद्योगको जानकारीको लागि यो सूचना प्रकाशित गरिएको छ। साथै उक्त औषधि 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.	FEXHIST (Fexofenadine Hydrochloride Oral Suspension)	LFH76001	Aug.2019/ Jul. 2021	Does not comply as per Analytical Profile No. Fex 073/74 AP 009 with respect to pH	Prime Pharmaceuticals Pvt. Ltd., Birgunj-32, Parsa, Nepal
2.	Gastogel Suspension 200ml	GSL7051	Jun.2020/ May.2023	Does not comply as per product specification with respect to Description and pH	Bhaskar Herbaceuticals Pvt. Ltd., Chorni-1, Birgunj, Parsa, Nepal
3.	Lipilage 10 (Atorvastatin Tablets IP)	LIP 28	Jul.2019/ Jun.2021	Does not comply as per IP 2018 with respect to assay and content uniformity	CTL Pharmaceuticals Pvt. Ltd., Byasi, Bhaktapur, Nepal
4.	Irgonol-200 (Itraconazole Capsules)	JY19002	Jul.2019/ Jun.2021	Does not comply as per USP 2020 with respect to dissolution	Magnus Pharma Pvt. Ltd., Rampur Tokani, VDC-2, Bara, Nepal
5.	Inox (Itraconazole Capsules BP)	INC 947	Feb.2020/ Jan.2022	Does not comply as per BP 2020 with respect to dissolution	Amtech Med Pvt. Ltd., Katahari-4, Morang, Nepal
6.	Inox (Itraconazole Capsules BP)	INC 946	Nov.2019/ Oct.2021	Does not comply as per BP 2020 with respect to dissolution	Amtech Med Pvt. Ltd., Katahari-4, Morang, Nepal
7.	Itac (Itraconazole Capsules 100mg)	IT1902	Aug.2019/ Jul.2021	Does not comply as per USP 2020 with respect to dissolution	Biogain Remedies Pvt. Ltd., Patthardada, Rupandehi, Nepal
8.	Syntran-200 (Itraconazole Capsules BP)	FSYC 67002	Oct.2019/ Sep.2021	Does not comply as per BP 2020 with respect to dissolution	Arya Pharmalab Pvt. Ltd., Chhatapipara, Bara, Nepal

नेपाल सरकार

स्वास्थ्य तथा जनसंख्या मन्त्रालय

औषधि व्यवस्था विभाग

कोभिड-१९ को खोपको आपतकालीन प्रयोगका लागि दर्ता अनुमति सम्बन्धी अत्यन्त जरुरी सूचना

औषधि ऐन, २०३५(तेस्रो संशोधन सहित) को दफा ९क को कार्यान्वयनको लागि तथा कोभिड-१९ महामारीको रुपमा फैलिएको सङ्क्रामक रोगको रोकथाम, नियन्त्रण वा निर्मूल गर्न विश्व स्वास्थ्य संगठनमा सूचीकृत भएका वा सम्बन्धित मुलुकको औषधि नियामक निकायले दर्ता गरेका वा त्यस्ता नियामक निकायले अनुमति प्रदान गरेका खोपको उत्पादक सूचीकरण र खोपको आपतकालीन प्रयोगको दर्ता गर्ने प्रयोजनको लागि यो सूचना प्रकाशित गरिएको छ ।

विभागले कोभिड-१९ खोपको आपतकालीन प्रयोगका लागि दर्ता गर्दा नेपाल सरकारबाट स्वीकृत भएको औषधि वा खोपको आपतकालीन प्रयोग सम्बन्धि संहिता, २०७७ र "कोभिड-१९ विरुद्ध प्रयोग हुने खोपको प्राप्ति र प्रयोग सम्बन्धी" अवधारणापत्रलाई आधार मानिनेछ।

यस विभागमा दर्ता रहेका वा दर्ता गरी आयात गर्ने मनशाय राखु हुने उत्पादक वा सो का आधिकारीक आयातकर्ताले सम्बन्धित उत्पादकको तर्फबाट आवश्यक कागजातहरुसहितको विवरणहरु खुलाई खोपको आपतकालीन प्रयोगको दर्ता अनुमतिका लागि यस विभागमा यथाशिघ्र आवेदन पेश गर्नहुन सम्बन्धित सबैलाई सुचित गरिन्छ ।

२०८१ श्रा २९

महानिर्देशक

USAID FROM THE AMERICAN PEOPLE

Government of Nepal
Ministry of Health and Population
Department of Drug Administration

usp

Invitation to manufacturers in Nepal to submit an Expression of Interest (EOI) for Technical Assistance

First Date of publication: February 07, 2021

To support national and global efforts to increase access to the affordable quality assured products for Maternal, Neonatal and Child Health (MNCH) and Family Planning (FP), the Department of Drug Administration (DDA), with technical assistance from the Promoting the Quality of Medicines Plus (PQM+) program implemented by **United States Pharmacopeia (USP)** and with funding from the **U.S. Agency for International Development (USAID)**, invites Nepali pharmaceutical manufacturers to submit an Expression of Interest (EOI) for evaluation of their manufacturing sites to assess compliance with Good Manufacturing Practices (GMP) for production of essential medicines for MNCH and FP products to attain the WHO Prequalification requirement.

1. PROCEDURE FOR THIS INVITATION TO SUBMIT EOI

The current invitation is published in accordance with the provision of Drug Act 2035 to prevent the misuse or abuse of drugs and allied pharmaceutical substances and false or misleading information relating to the efficacy and use of drugs and to control the production, sale, distribution, export, import, storage and consumption of those drugs which are not safe for public consumption, efficacious and of standard quality.

The assessment of manufacturers under this invitation will include inspection of manufacturing site, review of product data, and information of current manufacturer and comparison of the data and information to internationally accepted standards such as the World Health Organization (WHO) GMP and National GMP requirements. In collaboration with the DDA, PQM+ program will provide the needed technical assistance to address the areas of improvement within the mandate and period of performance of PQM+ program.

Interested manufacturers in Nepal are therefore encouraged to submit their expression of interest for technical assistance to manufacture products listed under item 2 below.

2. PRODUCTS INCLUDED IN THIS INVITATION

The purpose of this invitation is to invite manufacturers to participate in the technical assistance program to increase the supply of quality assured essential medicines to meet WHO-recommended quality standards. Following list of finished products is selected based on The Treatment of Diarrhoea-A manual for physicians and other senior health workers (WHO), National list of essential medicines of Nepal and on the basis of their benefits and appropriateness for use in the treatment of child and maternal health problems. The products of interest are:

2.1. Amoxicillin tablet (scored), 125mg, 250mg
2.2. Oxytocin injection, 5/10 IU
2.3. Zinc sulfate dispersible tablet, 10 mg, 20mg
2.4. Azithromycin tablet 500 mg

3. QUALITY ASSESSMENT PROCEDURE FOLLOWING SUBMISSION OF AN EXPRESSION OF INTEREST BY MANUFACTURER

The assessment in response to the EOI will be conducted to determine whether the pharmaceutical product manufacturers of products listed above meet the quality standards recommended by WHO and is manufactured in compliance with GMP norms. The procedure for evaluation will include:

a. Evaluate the production and quality control status of the manufacturer
b. Assess product data and information on safety, efficacy and quality submitted by the manufacturer including the product formulation, manufacturing and testing data and results
c. Assess the manufacturing site's compliance status with GMP norms, consistency in production and quality control of starting materials, packaging materials with specific emphasis on active pharmaceutical ingredient(s) and finished product.
d. Sample and test the products.

4. TECHNICAL ASSISTANCE TO MANUFACTURERS OF SELECTED PHARMACEUTICAL PRODUCTS FOLLOWING SUBMISSION OF AN EXPRESSION OF INTEREST

After assessment of manufacturing site by PQM+, a review of product data and information will be conducted comparing the data and information to internationally accepted standards such as WHO-GMP and National GMP requirements. In partnership with PQM+, DDA will provide the needed technical assistance to address any discovered deficiencies in order to ensure the quality of products meeting the internationally accepted quality standards.

PQM+, in collaboration with DDA, reserves the right to prioritize the manufacturers to receive technical assistance based on the assessment and existing compliance level to ensure effective support to those selected pharmaceutical companies.

5. DEADLINE AND SUBMISSION PROCEDURE FOR EOI

A covering letter expressing the manufacturer's interest in receiving technical assistance for the manufacture of selected finished pharmaceutical products should be submitted to PQM+ within on or before March 08, 2021 (5:00 PM) to PQM+ Nepal, House no 405, Prasuti Griha Marga, Ward no 11, Babarmahal, Kathmandu, Nepal or via e-mail at usp.nepal@usp.org

A preliminary assessment questionnaire will be sent to interested manufacturer upon request. The filled questionnaire should be submitted along with the expression of Interest.

नेपाल सरकार

स्वास्थ्य तथा जनसंख्या मन्त्रालय

औषधि व्यवस्था विभागको

औषधीको आमउपभोक्तालाई जानकारी

- मान्यताप्राप्त स्वास्थ्यकर्मीको पुर्जा अनुसार मात्र औषधीको प्रयोग गर्नुहोस ;
- औषधीको प्रयोग सम्बन्धि सम्पूर्ण जानकारी लिने जस्तै, औषधि कसरी प्रयोग गर्ने, औषधी घरमा कसरी भण्डारण गर्ने, औषधि सेवनगर्दा 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 राख्नुहोस ;
- 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 राख्नुहोस ;
- यदि एन्टिबायोटिक औषधी सेवन गर्न लाग्नु भएको छ भने तोकिएको मात्रा र अवधिसम्म प्रयोग गर्नुहोस र गरानुहोस ;
- औषधी खरिद गर्ने औषधि पसलको व्यवसायीको मान्यता प्रमाणपत्र हेर्ने गर्नुहोस ;
- औषधी खरिद गर्दा अनिवार्य बिल लिने बानी गर्नुहोस ।

स्वास्थ्यकर्मी, औषधि सिफारिसकर्ता, औषधी उत्पादक, पैठारिकर्ता तथा व्यबशायीलाई जानकारी

- विभागमा दर्ता नभएका औषधिको बिक्रिवितरण नगर्ने तथा बिल बिजकबिना कुनै पनि औषधिको खरिद बिक्रि नगरौ ;
- चिकित्सकहरुले वा स्वास्थ्यकर्मीहरुले व्यवसायिक मर्यादा र आचरणमा बसी औषधिको सिफारिश गर्ने गरौ र कुनै औषधी कम्पनिबाट कुनै लाभ वा अवसरको सम्झौता गर्नु भएको छ भने पारदर्शी गर्ने गरौ ;
- मूल्य नभएको तथा विभागबाट मूल्य स्वीकृत नभएको औषधीको बिक्रि-बितरण गर्ने नगरौ ;
- उद्योग तथा औषधी वितरकले दिने deal bonus पारदर्शी गर्ने गरौ र यसबाट उपभोक्तालाई लाभान्वित गरौ ;
- Physician sample को दुरुपयोग नगरौं ;
- औषधीको स्तर खुलाई मात्र औषधिको उत्पादन र बिक्रिवितरण गर्ने गरौ ;
- लागू तथा मनोद्विपक र एन्टिबायोटिक औषधिहरुको समुचित प्रयोग गर्ने बानि बसालौ र अरुलाई पनि सिकाउ ;
- औषधि दर्ता भए नभएको जानकारी यस विभागबाट जानकारी लिऔ ;
- थोक बिक्रेताले खुद्रा बिक्रेतालाई कारोबार गर्दा आधिकारिक बिल तथा अद्यावधिक दर्ता रहेको औषधी पसलमा मात्र गर्ने र
- लागु तथा मनोदिपक औषधीहरुको 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 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

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