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GOVERNMENT OF NEPAL
MINISTRY OF HEALTH
DEPARTMENT OF DRUG ADMINISTRATION

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

CONTENTS

EDITORIAL

Shifting paradigms of The Medicines Regulation in Nepal

Since the promulgation of the Drug Act 2035, Nepal embarked into a kind of license-raj regarding manufacture, sales distribution and import of medicines, that is to say without a product license, import recommendation, marketing authorization of the medicine product, no one could legally carryout any such activities. The Department of Drug Administration, for this matter, remained a major implementer. Up now, we are carrying out these functions in order to assure quality, safety and efficacy of medicines. Several rules were developed and used to implement these legal obligations.

Globally, the medicines regulations gained a reputation of a science. There are several disciplines the regulatory authority should embrace with defined body of knowledge to cope with myriad functions before allowing medicines into the market and after. Widely accepted disciplinary components of regulatory science are listed below(Box 1).

BOX-1: Disciplines of regulatory science

• Basic investigation • Bioengineering • Bioethics • Bioinformatics • Biology • Bio nutrition • Biostatistics • Chemistry • Clinical investigation and clinical trial design • Clinical pharmacology	• discovery and development • Drug disposition and metabolism • Economics • Epidemiology • Genetics • Government/policy • Information technology • Institutional Review Board experience • Law	• Pharmacology (whole animal) • Pharmacy • Protection of human subjects • Public health • Regulatory knowledge • Research pharmacy • Risk assessment and communication • Surveying/methods

• Clinical research operations • Communication • Decision theory • Drug/device	• Medical informatics • Medicine • Metrics • Microbiology • Monitoring and quality assurance Nutrition	• Systems analysis • Systems biology • Technology transfer • Toxicology • Veterinary

Though there is not a single agreed upon definition of regulatory science, many view it as a subset of translational science. The traditional taxonomy of the translational science contains mainly four phases viz: Discovery to candidate health application (T1), Health application to evidence-based practice guidelines (T2), Practice guidelines to health practice (T3) and Practice to population health impact(T4). Similarly, the regulatory science also contains mainly four phases coinciding with that of translational science viz: Preclinical evaluation of safety and efficacy (RS1), Clinical trial design and analysis (RS2), Post marketing review of safety and optimal utilization (RS3) and Health policies, including social aspects of regulatory science (RS4).

Thus, regulatory personnel do need to possess these body of knowledge in order to effectively deliver his/her duties to ensure medicines /devices of quality, safe and efficacious.

Department of drug administration is slowly but continually embracing these principles and disciplines with a shift from adoption of elementary quality requirements to safety and efficacy data, from quality control of finished product to control of quality of manufacturing (GMP inspection), from quality control of finished product and inspection of manufacturing sites in general to more understanding the general processes, and product specific processes involved, from rigid limits to agree upon beforehand set of limits which can be used by manufacturers in a more flexible manner, refocusing from pre-marketing assessment on effective

risk management during the whole life cycle of a medicines, from national to international harmonization collaboration and cooperation approaches(Member of SEARN). SEARN is an acronym used for South East Asian Medicines Regulatory Network.

In conclusion, a paradigm shift is in the making, though it may take several years there is no other option than to adhere, embrace and adopt science-based approaches in regulations in order to ensure quality, safety and efficacy of medicines, and health technology products in the country. the regulatory environment, particularly those regulated and in policy making level need to realize the inevitable shift that the regulation is heading for.

Adieu!!!

Narayan Prasad Dhakal
Chief Editor
Department of Drug Administration

Progress Report OF DDA and Brach Office
Second Quarter FY 2073/074

a) Targeted Activities

S. N	Activities	Unit	Target	Achieve-ment
1	Drug information to the public by different media	Number	6	17
2	Publication of Drug Bulletin of Nepal	Issue	1	1 (100 %)
3	Inspection of domestic Pharmaceutical Industries	Number	33	19
4	Inspection to drug retailers & wholesalers	Number	970	825
5	Drug sample Analysis	Number	250	294
6	Audit of Pharmaceutical Analytical Laboratories	Number	8	6

b) Other target less Activities

S. N	Activities	Achievement
1	Registration of new foreign pharmaceutical industry	6
2	Registration of new medicine (import)	17
3	Renew of import license	712
4	Issue of marketing license	30
5	Issue of product license	190
6	Import license for raw material for domestic industry	107
7	Approval of layout of industry	21
8	Recall of medicine from market	13

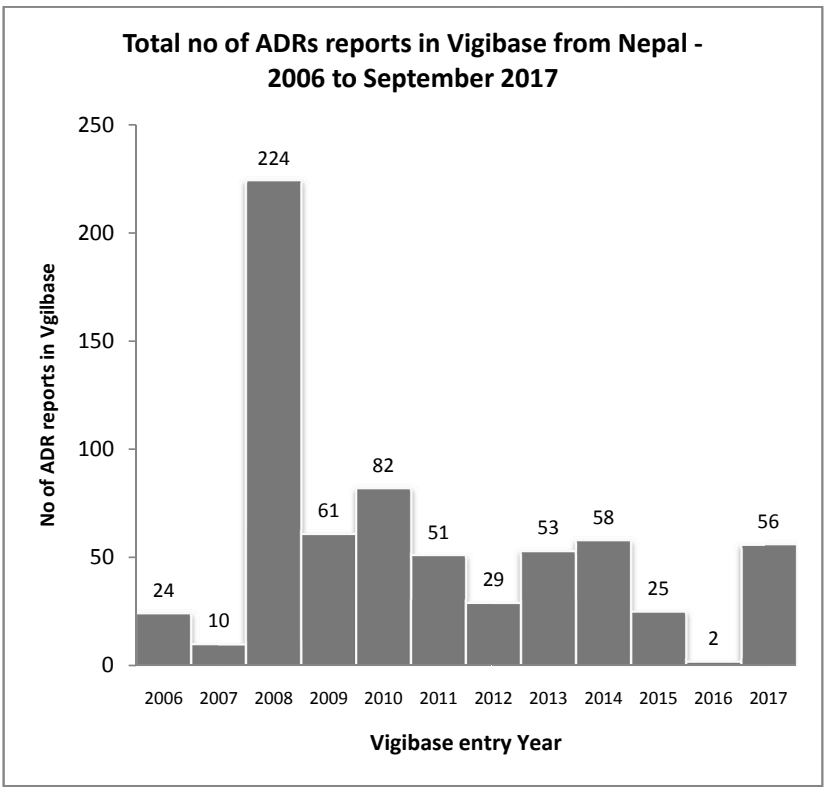
Pharmacovigilance

No drug is 100% safe and free of adverse drug reaction. This fact was realized largely after the thalidomide disaster in 1961, when pregnant mothers were given the drug to treat nausea. The children born from such mothers showed phocomelia (resulting grossly under developed limbs). WHO initiated an international drug monitoring program in 1968 and Swedish government collaborated with this program in 1978 to establish the Uppsala Monitoring Centre.

DDA took a lead to initiate pharmacovigilance program in 2002. In October 2004, the government of Nepal designated DDA to liaise with UMC. Nepal has been reporting adverse drug reaction since 2006 when it finally became a full member of WHO UMC programme. There are currently 10 regional centres which have been sending ADR reports to DDA – the latest ones recognized this year are Dhulikhel hospital and Shree Birendra Hospital.

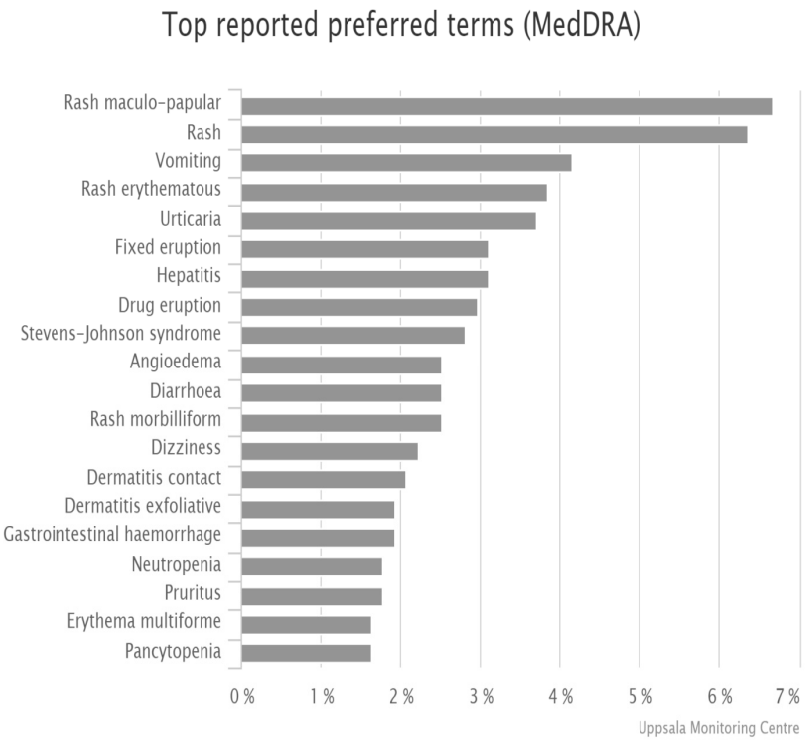
The total number of ADR cases reported from different centres and committed to UMC by DDA in 2017 till September are as follows:

Centre	Contact person	No. of cases
Tribhuwan University Teaching Hospital, IOM	Dr. Sangha Ratna Bajracharya, Dr. Satish Deo	39
Nepal Medical College Teaching Hospital	Dr. Lujaw Tuladhar	11
Manipal Teaching Hospital	Dr. Sudesh Gyawali	2
Civil Service Hospital	Mr. Lavendra Kunwar	2
Norvic International Hospital	Dr. Ajay Chandra	2
Patan Hospital	Mr. Raj Kumar Thapa	1



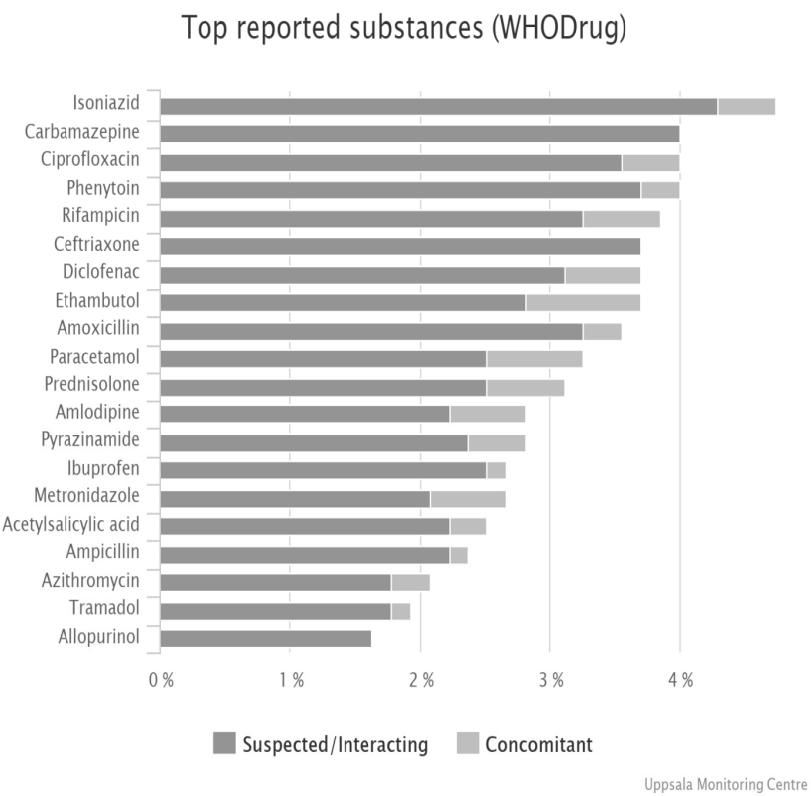
Source : vigilyze.who-umc.org accessed on 9/11/2017

Top reported preferred terms reported by Nepal from 2006 to September 2017



Source : vigilyze.who-umc.org accessed on 9/11/2017

Top reported substances by Nepal from 2006 to September 2017



Source: vigilyze.who-umc.org accessed on 9/11/2017

IMPORTANT INFORMATIONS

Chlorhexidine gluconate

Rare but serious allergic reactions USA

The US Food and Drug Administration (FDA) has warned that rare but serious allergic reactions have been reported with products containing chlorhexidine gluconate. Although rare, the number of reports of serious allergic reactions to these products has increased over the last several years. As a result, the FDA has requested the manufacturers of over-the-counter (OTC) antiseptic products containing chlorhexidine gluconate to add a warning about this risk to the drug facts labels. Chlorhexidine gluconate is mainly available in OTC products to clean and prepare the skin before surgery and before injections in order to help reduce bacteria that potentially can cause skin infections. These products are available as solutions, washes, sponges. Chlorhexidine gluconate is also available as a mouthwash to treat gingivitis and as an oral chip to treat periodontal disease. The FDA has identified 52 cases of anaphylaxis, a severe form of allergic reaction, with the use of chlorhexidine gluconate products applied to the skin. Between January 1969 and early June 2015, the FDA received 43 reported cases worldwide. More than half of these 43 cases were reported after 2010, and after the FDA's public health notice in 1998. These include only reports submitted to FDA, so there are likely additional cases about which we are unaware. The serious allergic reaction cases reported outcomes that required emergency department visits or hospitalizations to receive treatments. These allergic reactions resulted in two deaths. Eight additional cases of anaphylaxis were published in the medical literature between 1971 and 2015 and one case was identified in the National Electronic Injury Surveillance System Cooperative Adverse Drug Event Surveillance (NEISSCADES) database between 2004 and 2013.

Source: WHO Pharmaceuticals Newsletter No. 2, 2017

In Nepal: Health care professionals are advised to be aware of the possibility of developing serious allergic reaction with use of chlorhexidine gluconate containing products.

Codeine

Risk of respiratory depression Malaysia

The National Pharmaceutical Regulatory Agency (NPRA) has reviewed the risk of respiratory depression with codeine and has issued a directive to update the local package inserts of codeine-containing products with this safety issue. Codeine-containing medicines are used to treat pain and reduce cough. Since the year 2000, the NPRA has received 16 ADR reports with 32 adverse events suspected to be related to codeine in Malaysia. Three reports were associated with breathing problems, namely shortness of breath (2) and breathing difficulty (1).

Source: WHO Pharmaceuticals Newsletter No. 2, 2017

In Nepal: Health care professionals are advised to be aware of the possibility of developing respiratory depression with use of codeine containing products.

Fluoroquinolones

Potential risk of persistent and disabling side effects Canada

Health Canada has recommended updating the safety information for all fluoroquinolone products to include information about the risk of persistent and disabling side effects including tendonitis/ tendinopathy, peripheral neuropathy and central nervous system disorders. Fluoroquinolones (ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin and ofloxacin) are antibiotics which are authorized to treat many types of bacterial infections including urinary tract and respiratory infections. Health Canada started a safety review following a review done by the US FDA on systemic fluoroquinolone drugs. The Health Canada safety review focused on serious known side effects that included: tendonitis/tendinopathy, peripheral neuropathy, worsening of myasthenia gravis, hypersensitivity and serious skin reactions, mental disorders, depression and suicide/self-injury, convulsions, cardiovascular disorders, phototoxicity and vision disorders. At the time of the review, Health Canada identified 115 reports of persistent and disabling side effects associated with the use of fluoroquinolones. In 78 of these reports, a probable (29 reports) or possible (49 reports) causal link could be made between the use of fluoroquinolones and persistent disability. In the remaining cases, there was either not

enough information available or it was unlikely that the reports of persistent disability were related to the use of fluoroquinolones. Most of the side effects that were reported in the 115 reports and linked to persistent disability included tendonitis/ tendinopathy, peripheral neuropathy and central nervous system disorders. The side effects of tendinopathy, peripheral neuropathy and central nervous system disorders are included in the current safety information. However, the possibility of persistent duration of these events was not included in the safety information for all fluoroquinolone products. There was little information in the scientific and medical literature on persistent and disabling nature of side effects reported with fluoroquinolone use. Health Canada's review concluded that some of the known side effects, specifically tendonitis/tendinopathy, peripheral neuropathy and central nervous system disorders, already linked to the use of fluoroquinolones, may be persistent and/or disabling.

Source: WHO Pharmaceuticals Newsletter No. 2, 2017

In Nepal: Health care professionals are advised to be aware of the possibility of developing risk of persistent and disabling side effects including tendonitis/tendinopathy, peripheral neuropathy and central nervous system disorders with use of fluoroquinolones.

Furosemide

Risk of dermatitis lichenoid India

The Pharmacovigilance Program of India-Indian Pharmacopoeia Commission (PvPI-IPC) has recommended that the Central Drugs Standard Control Organisation (CDSCO) revise the drug safety label of furosemide to include dermatitis lichenoid as potential adverse drug reaction. Furosemide is a diuretic used to treat oedema and mild to moderate hypertension. Between 2011 and November 2016, the PvPI received four furosemide-dermatitis lichenoid Individual Safety Case Reports (ICSRs). The cases were reviewed by the Signal Review Panel (SRP)-PvPI-IPC and it was concluded that there was a strong causal relationship between furosemide and dermatitis lichenoid in these cases. The PvPI-IPC has reminded health-care professionals that dermatitis lichenoid is a potential adverse drug reaction with furosemide use.

Source: WHO Pharmaceuticals Newsletter No. 2, 2017

In Nepal: Health care professionals are advised to be aware of the possibility of developing respiratory depression with use of codeine containing products.

Hyoscine butylbromide

Risk of serious adverse effects in patients with underlying cardiac disease

The United Kingdom

The Medicines and Healthcare Products Regulatory Agency (MHRA) has updated prescribing information for hyoscine butylbromide (Buscopan®) to help to minimise the risk of serious adverse reactions in patients with cardiac disease. Hyoscine butylbromide, given intravenously or intramuscularly, is indicated in acute muscular spasm, as in renal or biliary colic; in radiology for differential diagnosis of obstruction and to reduce spasm and pain in pyelography; and in other diagnostic procedures where spasm may be a problem (e.g., gastroduodenal endoscopy). The MHRA has received nine reports of patients who died after receiving hyoscine butylbromide injection (including a report from a coroner). In most of these cases, the fatal adverse reaction was reported as acute myocardial infarction or cardiac arrest. Hyoscine butylbromide injection can cause adverse effects including tachycardia, hypotension, and anaphylaxis. These effects can be more serious in patients with underlying cardiac disease (e.g., heart failure, coronary heart disease, cardiac arrhythmia, or hypertension). Several reports have noted that anaphylaxis is more likely to be fatal in patients with underlying coronary heart disease compared with those without.

Source: WHO Pharmaceuticals Newsletter No. 2, 2017

In Nepal: Health care professionals are advised to be aware of the possibility of developing adverse effects including tachycardia, hypotension, and anaphylaxis with use of hyoscine butyl bromide containing products.

Hypnotics/sedatives, anxiolytics and antiepileptics with drug dependence or withdrawal symptoms

Risk of dependence

Japan

The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the package inserts for hypnotics/sedatives, anxiolytics and antiepileptics with dependence, drug dependence or withdrawal symptoms have been updated to underline the risk of dependence such as developing physical dependence with long-term use even within an approved dose range. These medicines are used for the treatment of insomnia, anxiety, tension, depression, sleep disorder and others. They are also used as an anaesthetic premedication. The package inserts for hypnotics/sedatives, anxiolytics, and antiepileptics include "dependence," "drug dependence," or "withdrawal symptoms" (excluding transplacental) as ADRs in the precautions section. PMDA, upon request from the MHLW, investigated whether there was a need to revise the package inserts. Of the drugs subject to investigation, dependence related events were reported with etizolam (720 events in 695 cases), alprazolam (179 events in 171 cases), triazolam (163 events in 158 cases), zolpidem tartrate (129 events in 126 cases), clotiazepam (121 events in 118 cases), and ethyl loflazepate (74 events in 64 cases). These are all benzodiazepine (BZ) receptor agonists. Reports of dependence-related events were limited for barbiturates (BA) and non-BA drugs, and even the most frequently reported pentobarbital calcium had only 17 events in 15 cases. Based on the safety information obtained and reviews and guidelines on Dependence and Withdrawal Symptoms in Japan, the PMDA has determined that the revisions of the package insert were necessary.

Source: WHO Pharmaceuticals Newsletter No. 2, 2017

In Nepal: Health care professionals are advised to be aware of the possibility of developing dependence with use of hypnotics/sedatives, anxiolytics and antiepileptics with drug dependence or withdrawal symptoms.

Itraconazole

Risk of acute generalized exanthematous pustulosis

India

The PvPI-IPC has recommended that the CDSCO revise the drug safety label of itraconazole to include acute generalized exanthematous pustulosis as a potential adverse drug reaction. Itraconazole is used for systemic infections of aspergillosis and candidosis, cryptococcosis, histoplasmosis, sportrichosis, paracoccidioidomycossis, blastomycosis and other rare systemic or tropical mycosis. Between 2011 and November 2016, PvPI received two itraconazole-acute generalized exanthematous pustulosis ICSRs. The cases were reviewed by the SRP-PvPI-IPC and it was concluded that there is a strong causal relationship between itraconazole and acute generalized exanthematous pustulosis in these cases. The PVPI-IPC has reminded healthcare professionals that acute generalized exanthematous pustulosis is a potential adverse drug reaction with itraconazole use.

Source: WHO Pharmaceuticals Newsletter No. 2, 2017

In Nepal: Health care professionals are advised to be aware of the possibility of developing acute generalized exanthematous pustulosis respiratory depression with use of itraconazole containing products.

Low-molecular-weight heparins

Potential risk of bleeding in or around the spinal cord (spinal/ epidural hematoma)

Canada

Health Canada has updated the Canadian safety information of low-molecularweight heparins (LMWH; Fragmin®, Fraxiparine®, Innohep® and Lovenox®) to include information on the recommended length of time between LMWH injection and spinal/epidural anaesthesia or spinal puncture. This length of time can vary, but should be determined by the prescriber in accordance with recommendations in the Canadian safety information. LMWH are prescription drugs which are authorized to treat or prevent blood clots. Health Canada has reviewed information related to the known rare risk of bleeding in or around the spinal cord

(spinal/epidural haematoma) in patients receiving LMWH to prevent blood clots while undergoing spinal/epidural anaesthesia or spinal puncture. The review was initiated because of an update by the US FDA to the safety information for LMWH related to this risk. At the time of the review, Health Canada had received two Canadian cases of bleeding in or around the spinal cord in patients receiving LMWH and undergoing spinal/epidural anaesthesia or spinal puncture. In these two reports, there was not enough information to determine what may have played a role in the bleeding that occurred. This safety review looked at 153 international reports of bleeding in or around the spinal cord in patients receiving LMWH while undergoing spinal/epidural anaesthesia or spinal puncture. In these 153 reports, it was found that a short length of time between LWMH use and the spinal procedure may have increased the risk of bleeding. Health Canada's review concluded that the risk of bleeding may increase if the spinal procedure is carried out soon after injection of LWMH.

Source: WHO Pharmaceuticals Newsletter No. 2, 2017

In Nepal: Health care professionals are advised to be aware of the possibility of bleeding in or around the spinal cord (spinal/epidural hematoma) with the use of low-molecular-weight-heparins.

Menthol containing OTC topical pain relievers

Risk of serious skin burns

Canada

Health Canada has updated the labelling standard for OTC topical pain relievers containing menthol alone or in combination, to inform about this risk. OTC topical pain relievers are applied on the skin to relieve pain in muscles or joints. These products, which may contain menthol, methyl salicylate or capsaicin, either alone or in combination, relieve pain by slightly irritating the skin surface. This irritation reduces the feeling of pain in the underlying joints and muscles. Health Canada has carried out a follow-up safety review, following the safety review in 2013 and based on the additional safety information gathered by Health Canada or obtained by certain manufactures on these products. At the time of the review, Health Canada had received a total of 29 reports of serious skin burns related to the use of OTC topical pain relievers containing

menthol, methyl salicylate or capsaicin in Canada. The products were used as directed in 28 reports; in some reports, other factors may have played a role in the development of burns. In the remaining reports, the product was not used as directed. Of these 29 reports, there were seven reports involving products containing only menthol, two reports involving products containing only methyl salicylate, and one report involving a product containing only capsaicin. There were 19 reports involving products containing multiple ingredients, and most of these contained menthol and methyl salicylate together. The review of the safety information provided by manufacturers identified over 100 additional international reports of serious burns linked to the use of topical pain relievers. The majority of these cases contained menthol, alone or in combination with methyl salicylate. There were no cases of serious burns linked to the use of topical muscle and joint pain relievers containing methyl salicylate or capsaicin alone. In the medical literature, there is only one case of serious skin burns linked to the use of a topical pain reliever product containing menthol and methyl salicylate; however, the product was used inappropriately. Health Canada's current review has established a link between the use of topical pain relievers containing menthol and the risk of rare but serious skin burns; however, there was not enough information to draw the same conclusions for the products containing methyl salicylate or capsaicin alone.

Source: WHO Pharmaceuticals Newsletter No. 2, 2017

In Nepal: Health care professionals are advised to be aware of the possibility of developing skin burns with the use of menthol containing OTC topical pain relievers.

Olanzapine

Risk of Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)

Malaysia

The NPRA has reviewed the risk of Eosinophilia and Systemic Symptoms (DRESS) with olanzapine and issued a directive to update the local package inserts of olanzapine containing products with this safety issue. Olanzapine is used to treat mental health disorders such

as schizophrenia and bipolar disorder. Since the year 2000, the NPRA has received 283 ADR reports with 488 adverse events suspected to be related to olanzapine in Malaysia. There were four reports (0.8%) involving severe cutaneous adverse reactions (SCARs), namely erythema multiforme (3) and DRESS (1).

Source: WHO Pharmaceuticals Newsletter No. 2, 2017

In Nepal: Health care professionals are advised to be aware of the possibility of developing Drug Reaction with Eosinophilia and Systemic Symptoms with the use of olanzapine.

SGLT2 inhibitors

Potential risk of toe amputation

EU

The EMA has informed about a potential increased risk of lower limb amputation in patients taking the sodium glucose co-transporter-2 (SGLT2) inhibitors canagliflozin, dapagliflozin and empagliflozin used for type 2 diabetes. The EMA has also recommended to include a warning of the potential increased risk of toe amputation in the prescribing information for these medicines. Canagliflozin, dapagliflozin and empagliflozin are type 2 diabetes mellitus medicines of the class SGLT2 inhibitors. The review of SGLT2 inhibitors was prompted by an increase in lower limb amputations (mostly affecting the toes) in patients taking canagliflozin in two clinical trials (CANagliflozin cardioVascular Assessment Study: CANVAS and CANVAS-R). The studies, which are still ongoing, involved patients at high risk of heart problems and compared canagliflozin with placebo. As of September 2016, the incidence of lower limb amputation in the CANVAS study was 7 in 1000 patient-years with canagliflozin 100 mg daily and 5 in 1000 patient-years with canagliflozin 300 mg daily, compared with 3 in 1000 patient-years with placebo. (One patient-year is equivalent to 1 patient taking the medicine for 1 year.) The study enrolled around 4300 patients. As of September 2016, the incidence of lower limb amputation in the CANVAS-R study was 8 in 1000 patient-years with canagliflozin and 4 in 1,000 patient-years with placebo. The study enrolled over 5800 patients. The incidences of lower limb amputation given above

for both CANVAS and CANVAS-R are based on interim data, and final incidence rates will depend on analysis of the final study datasets. All patients with diabetes (especially those with poorly controlled diabetes and problems with the heart and blood vessels) are at higher risk of infection and ulcers (sores) which can lead to amputations. The mechanism by which canagliflozin may increase the risk of amputation is still unclear. An increase in lower limb amputations has not been seen in studies with other medicines in the same class, dapagliflozin and empagliflozin. However, data available to date are limited and the risk may also apply to these other medicines. Further data are expected from ongoing studies with canagliflozin, dapagliflozin and empagliflozin.

Source: WHO Pharmaceuticals Newsletter No. 2, 2017

In Nepal: Health care professionals are advised to be aware of the possibility of increased risk of lower limb amputation in patients taking the sodium glucose co-transporter-2 (SGLT2) inhibitors canagliflozin, dapagliflozin and empagliflozin used for type 2 diabetes.

Tramadol-containing products

Risk of serious respiratory depression in children and adolescents

Canada

Health Canada has updated the product information for tramadol containing products to further manage the risk of serious breathing problems. Health Canada has also reminded that tramadol is not recommended for use in patients under 18 years of age. Tramadol is an opioid prescription drug to treat moderate to moderately severe pain in adults. Health Canada has carried out safety review on tramadol, after a safety review of codeine and the risk of serious breathing problems in children. At the time of the review, Health Canada had not received any reports of serious breathing problems related to the use of tramadol in children and adolescents in Canada. This safety review found one international report of respiratory depression in the published literature, linked to the use of tramadol in a 5-year old child. The child was an ultra-rapid metabolizer and this may have played a role. Many studies suggest that differences in how the liver works could affect the risk of side effects experienced by patients using tramadol. These studies help

to confirm that ultra-rapid metabolizer patients may be more at risk of developing respiratory depression with the use of tramadol.

Source: WHO Pharmaceuticals Newsletter No. 2, 2017

In Nepal: Health care professionals are advised to be aware of the possibility of developing serious respiratory depression in children and adolescents with the use of tramadol-containing products.

Warfarin

Risk of calciphylaxis

Malaysia

The NPRA has reviewed the risk of calciphylaxis with warfarin and issued a directive to update the local package inserts of warfarin-containing products with this safety issue. Warfarin is an oral anticoagulant which acts by inhibiting the synthesis of vitamin K-dependent clotting factors II, VII, IX, and X. Since the year 2000, the NPRA has received 341 warfarin related ADR reports with a total of 563 adverse events in Malaysia. Most of the adverse events were reported as skin and subcutaneous tissue disorders (111 cases, 19.7%), nervous system disorders (92 cases, 16.3%) and gastrointestinal system disorders (63 cases, 11.2%). At present, no reports of calciphylaxis have been received locally. One report described a female patient who developed pain and skin necrosis after taking warfarin, however it was not confirmed whether this was calciphylaxis or warfarin-induced skin necrosis (WISN), as no skin biopsy was done.

Source: WHO Pharmaceuticals Newsletter No. 2, 2017

In Nepal: Health care professionals are advised to be aware of the risk of calciphylaxis with the use of warfarin.

Bisphosphonates

Potential risk of osteonecrosis beyond the area of the jawbone: not enough evidence

Canada

Health Canada has reviewed the potential risk of osteonecrosis related

with bisphosphonate use. The review was made due to the product information updates in Europe that warn about the risk of severe bone damage in the outer part of the ear canal. Bisphosphonates (alendronate (Fosamax® and Fosavance®), risedronate (Actonel®), etidronate (Didronel® and Didrocal®), pamidronate, zoledronate (Zometa® and Aclasta®) and clodronate (Clasteon® and Bonefos®)) are prescription drugs which are used for the treatment of bone-related diseases such as:

- osteoporosis;
- Paget's disease of bone;
- bone metastases;
- hypercalcaemia of malignancy; and
- a particular type of blood cell cancer known as multiple myeloma.

At the time of the review, Health Canada received 15 reports of severe bone damage related to the use of those bisphosphonates that do not have a warning about osteonecrosis in Canada. Among these reports, none were related to severe bone damage of the external ear canal. Out of the 15 reports, seven were excluded from the safety review because the bone damage was established before the patient took the bisphosphonate product. For the remaining eight reports, a link between osteonecrosis and the use of the bisphosphonate could not be established. This was either due to lack of information, the existence of other health conditions such as previous bone fracture or the patient being exposed to cortisone. This safety review found 11 patient reports in the scientific literature on the use of bisphosphonates that do not have a warning about severe bone damage. Severe bone damage to the external ear canal was noted in five reports. In the remaining 6 reports, severe damage to other bones was noted. Overall, the review of these 11 cases could not conclude whether bisphosphonate use played a role in the severe bone damage because of other factors such as the patient having other diseases (e.g., diabetes) or receiving other treatments (e.g., cancer treatments). Health Canada’s review of the available information did not establish a link between the use of the following bisphosphonates [risedronate, etidronate and clodronate] and the risk of severe bone damage of the external ear canal or other parts of the body other than the jaw. The review also did not establish a link between the use of [alendronate and clodronate] and the risk of severe bone damage

(in areas other than the outer ear canal and the jaw). Health Canada will continue to monitor safety information involving bisphosphonates.

Source: WHO Pharmaceuticals Newsletter No. 2, 2017

In Nepal: Health care professionals are advised to be aware of the possibility of developing osteonecrosis beyond the area of the jawbone with the use bisphosphonates.

Certain anti-neoplastic, immunosuppressant or immunomodulatory medications

Potential risk of progressive multifocal leukoencephalopathy (PML)

Australia

The TGA has provided advice on the potential risk of progressive multifocal leukoencephalopathy (PML) for health-care professionals who prescribe anti-neoplastic, immunosuppressant or immunomodulatory medications as follows;

- Prescribers of anti-neoplastic, immunosuppressant or immunomodulatory medications should be aware of PML as a potential adverse event.
- Prescribers should consider PML in any immunosuppressed patient presenting with new onset focal neurological deficits.
- Prescribers should be aware that in Multiple Sclerosis (MS) patients, PML can sometimes be confused with an MS relapse, which has the potential to delay PML diagnosis and treatment.
- Prescribers should monitor patients being treated with medicines known to be associated with PML for any new focal neurological signs or symptoms.
- Prescribers should consider testing for anti-John Cunningham Virus (JCV) antibodies in patients prior to starting medicines that have been associated with PML or during treatment if antibody status is not known.
- If a prescriber suspects PML, immunosuppressive medications should be withheld and appropriate investigations ordered

(gadolinium-enhanced MRI and cerebrospinal fluid analysis for JC viral DNA are recommended).

PML can be a complication in those who are exposed to antineoplastic or immunosuppressive therapies such as fludarabine (Fludara®), cyclophosphamide(Endoxan®),azathioprine(Imuran®),mycophenolate mofetil (Cellcept® and Myfortic®), tacrolimus (Prograf®), everolimus (Certican®), sirolimus (Rapamune®) and cyclosporine (Neoral®); and monoclonal antibodies including natalizumab (Tysabri®), rituximab (Mabthera®), alemtuzumab (Mabcampath®), vedolizumab (Entyvio®), brentuximab vedotin (Adcetris®) and Ofatumumab (Azerra®) as well as in those with HIV/AIDs, haematological malignancies (for example, lymphoproliferative disorders) and organ or haemopoietic stem cell transplantation. More recently, PML was reported in patients receiving immunomodulatory therapy, namely fingolimod (Gilenya®) or dimethyl fumarate (Tecfidera®) for the treatment of MS. As of 16 November 2016, the TGA's Database of Adverse Event Notifications (DAEN) includes 30 reports of PML. It should be noted that not all of these reports document confirmed cases. In many of these reports, patients were also receiving chemotherapy and/or had concomitant or previous use of other immunosuppressive/ immunomodulatory medicines or had underlying immunosuppressive conditions. Some of the reports involved patients on treatment for MS. The majority of reports were associated with use of monoclonal antibodies, in particular natalizumab and rituximab. There were 16 reports associated with rituximab and in 12 of these reports it was the sole suspected medication. There were 10 reports associated with natalizumab and in seven of these it was the sole suspected medication. In addition there were smaller numbers of reports that cosuspected multiple medications known to cause immunosuppression or to have previously been associated with PML; fludarabine (4), fingolimod (2), alemtuzumab (1), lefluonmide (1), azathioprine (1), mycophenolic acid (1) and tacrolimus (1).

Source: WHO Pharmaceuticals Newsletter No. 2, 2017

In Nepal: Health care professionals are advised to be aware of the possibility of developing progressive multifocal leukoencephalopathy (PML) with the use such anti-neoplastic, immunosuppressant or immunomodulatory medications.

Rivaroxaban, dabigatran and apixaban

Possible risk of hair loss (alopecia): no link was shown

New Zealand

The Medsafe has updated its original communication on possible risk of hair loss (alopecia) with rivaroxaban, dabigatran and apixaban. These medicines are used in a variety of conditions including:

- Prevention of stroke and systemic embolism.
- Prevention of venous thromboembolism (VTE).
- Treatment of deep vein thrombosis (DVT) and/or pulmonary embolism (PE).
- Prevention of recurrent DVT and/or PE.

Medsafe has stated that during the medicines monitoring period (30 May 2016 to 31 December 2016), no further cases of alopecia were reported to the Centre for Adverse Reactions Monitoring (CARM). The safety concern has been investigated and no link between rivaroxaban, dabigatran and apixaban and hair loss was demonstrated. Medsafe has concluded that the balance of the benefits and risks of harm for rivaroxaban, dabigatran and apixaban remains positive and no further action is required at this time.

Source: WHO Pharmaceuticals Newsletter No. 2, 2017

In Nepal: Health care professionals are advised to be aware of the possibility of developing hair loss (alopecia) with the use rivaroxaban, dabigatran and apixaban.

नेपाल सरकार

स्वास्थ्य मन्त्रालय

औषधि व्यवस्था बिभागको

औषधि फिर्ता (RECALL) गर्ने सम्बन्धि अत्यन्त जरुरी सूचना

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

तपसिल

सि. नं.	औषधिको नाम	ब्याच नं.	Mfg/ Expiry date	कारण	उत्पादकको नाम र ठेगाना
१	Relyte (Oral Rehydration Salt)	POR 699	March 2017/ Feb 2020	Leak test फेल भएको	Curex Pharmaceutical Pvt. Ltd. Kavre, Nepal
२	Panpraz (Pantoprazole tablet)	6193	Oct 2016/ Sep 2018	Dissolution Test फेल भएको	Amtech Med Pvt. Ltd, Kothahari- 9, Morang, Nepal

मिति २०७३/१२/२२ (2017 April 4) गतेको गोरखापत्र दैनिकमा प्रकाशित सूचना

नेपाल सरकार

स्वास्थ्य मन्त्रालय

औषधि व्यवस्था बिभागको

औषधि फिर्ता (RECALL) गर्ने सम्बन्धि अत्यन्त जरुरी सूचना

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

तपसिल

सि. नं.	औषधिको नाम	ब्याच नं.	Mfg/ Expiry date	कारण	उत्पादकको नाम र ठेगाना
१	बिलादी चुर्ण (BILADI CHURNA)	BWC 027	Jan 2016 /Dec 2018	Microbial Test फेल भएको	Divya pharmacy, industrial area, Uttarakhanda, India
२	अभिपत्तिकर चुर्ण (AVIPATTIKAR CHURNA)	A-AVC 067	Feb 2016 /Jan 2018	Microbial Test फेल भएका	Divya pharmacy, industrial area, Uttarakhanda, India
३	अजमोदादी चुर्ण (AJAMODADI CHURNA)	AJC 028	Mar 2016/ Feb 2018	Microbial Test फेल भएका	Divya pharmacy, industrial area, Uttarakhanda, India
४	सितोपलादी चुर्ण (SITOPALADI CHURNA)	SPC 015	Sep 2015/ Aug 2017	Microbial Test फेल भएका	Divya pharmacy, industrial area, Uttarakhanda, India

मिति २०७४/०२/२३ (2017 June 6) गतेको गोरखापत्र दैनिकमा प्रकाशित सूचना

नेपाल सरकार

स्वास्थ्य मन्त्रालय

औषधि व्यवस्था बिभागको

औषधि फिर्ता (RECALL) गर्ने सम्बन्धि अत्यन्त जरुरी सूचना

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तपसिल

सि. नं.	औषधिको नाम	ब्याच नं.	Mfg/ Expiry date	कारण	उत्पादकको नाम र ठेगाना
१	BACTOCLAV	BDAID 0167	Feb 2016/ July 2017	Identification test फेल भएको	Micro lab limited, ankle Taluk, Bangalore, India
२	AMLA CHURNA	AMC 067	Jan 2016/ Dec2017	Microbial Test फेल भएको	Divya pharmacy, Uttarakhanda, India (पतञ्जली आर्युवेदिक केन्द्रबाट बिक्रि वितरण हुने)
३	DIVYA GASHAR CHURNA	A-GHC 131	Mar 2016/ Feb 2018	Microbial Test फेल भएको	Divya pharmacy, Uttarakhanda, India (पतञ्जली आर्युवेदिक केन्द्रबाट बिक्रि वितरण हुने)
४	BAKUCHI CHURNA	BKC 011	Dec2015/ Nov 2017	Microbial Test फेल भएको	Divya pharmacy, Uttarakhanda, India (पतञ्जली आर्युवेदिक केन्द्रबाट बिक्रि वितरण हुने)
५	TRIPHALA CHURNA	A-TP C151	Feb 2016/ Jan 2018	Microbial Test फेल भएको	Divya pharmacy, Uttarakhanda, India (पतञ्जली आर्युवेदिक केन्द्रबाट बिक्रि वितरण हुने)
६	ASWAGANDHA CHURNA	AGC 081	Jan2016/ Dec2017	Microbial Test फेल भएको	Divya pharmacy, Uttarakhanda, India (पतञ्जली आर्युवेदिक केन्द्रबाट बिक्रि वितरण हुने)
७	DIVYA CHURNA	DYC 059	Jan 2016/ Dec 2017	Microbial Test फेल भएको	Divya pharmacy, Uttarakhanda, India (पतञ्जली आर्युवेदिक केन्द्रबाट बिक्रि वितरण हुने)

मिति २०७४/०३/०६ (2017 June 20) गतेको गोरखापत्र दैनिकमा प्रकाशित सूचना

नेपाल सरकार

स्वास्थ्य मन्त्रालय

औषधि व्यवस्था बिभागको

औषधि फिर्ता (RECALL) गर्ने सम्बन्धि अत्यन्त जरुरी सूचना

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तपसिल

सि. नं.	औषधिको नाम	ब्याच नं.	Mfg/ Expiry date	न्यून गुणस्तरीयताको कारण	उत्पादकको नाम र ठेगाना
१	IMUTREX 10 (Methotrexate Tablet IP 10 mg)	GJ 50390	May2015/ Apr 2018	बिना अनुमति Sticker टाँसी बिक्री वितरण गरेको	Cipla Ltd, India
२	FACIN 200 (Ofloxacin 200 mg)	FC 21502	Jan 2015/ Dec 2017	बिना अनुमति मूल्यमा Rubber क्तकउ लगाइ बिक्री वितरण गरेको	Hukam pharmaceutical Pvt. Ltd, Thimi, Nepal
३	FACIN 400 (Ofloxacin 400 mg)	FC 21503	July 2015/ June 2018	मूल्यमा Rubber Stamp लगाई बिक्री वितरण गरेको	Hukam pharmaceutical Pvt. Ltd, Thimi, Nepal
४	PANTAZOLE 40 (Pantoprazole tablet USP)	T-73077	Nov 2016/ Oct 2018	Dissolution Test	Apex Pharmaceuticals Pvt. Ltd, Birgunj, Nepal
५	HARITAKI CHURNA	A-HTC 94	Feb 2016/ Jan 2018	Staphylococcus aureus भेटिएको	Divya Pharmacy, Uttarakhanda, India
६	MOGYL 1000 (Tinidazole Tablet)	T16/ 057	June2016/ May 2019	Assay Test	Simca Laboratories Pvt. Ltd, Byasi, Bhaktapur, Nepal
७	ASHWAGAN-DHADI CHURNA	24	Feb 2016/ 2 years from Mfg Date	Microbial Limit Test	Shree Baidhynath Ayurved Bhawan Pvt. Ltd, India
८	DHATUPAU SHTIK CHURNA	27	Feb 2016/ 2 years from Mfg Date	Microbial Limit Test	Shree Baidhynath Ayurved Bhawan Pvt. Ltd, India

मिति २०७४/०३/०६ (2017 July 10) गतेको गोरखापत्र दैनिकमा प्रकाशित सूचना

नेपाल सरकार

स्वास्थ्य मन्त्रालय

औषधि व्यवस्था बिभागको

औषधि फिर्ता (RECALL) गर्ने सम्बन्धि अत्यन्त जरुरी सूचना

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

तपसिल

सि. नं.	औषधिको नाम	ब्याच नं.	Mfg/ Expiry date	कारण	उत्पादकको नाम र ठेगाना
१	Dextrose Injection IP 50 % (Dextrose anhydrous IP 50 %)	28	Feb 2016/ Jan 2018	Particulate matter test फेल भएको	Hindustan Medicine (P) Ltd. India.
२	V-Glim-2 (Glimepride Tablets)	VG2-014	Aug 2015/ July 2017	Dissolution Test फेल भएको	Vijayadeep Laboratories Ltd, Nepal
३	Prorab 20 (Rabiprazole Sodium Tablet IP)	JR 10276	April 2016/ March 2018	Dissolution Test फेल भएको	Wockhardt limited, India

मिति २०७३/१२/२२ (2017 May 2) गतेको गोरखापत्र दैनिकमा प्रकाशित सूचना

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 जानकारीका 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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औषधि व्यवस्था विभागका शाखा कार्यालय

	कञ्चनबारी, विराटनगर	आदर्शनगर, बेपालगञ्ज	मुरली बजैचा, विरगंज
	०२१-४२०८४५	०८१-५२२०७४	०५१-५२७७५३
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For further infomation, please contact:

Government of Nepal
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