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GOVERNMENT OF NEPAL
MINISTRY OF HEALTH AND POPULATION
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

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Editorial

Addressing the Availability of Life Saving Medicines

Access to safe, quality, effective medicines at affordable prices is the fundamental rights of the people. The Constitution of Nepal has pronounced the access to basic health care as the fundamental rights of the Nepalese people. At the same time it has given emphasis that no one should be barred from getting medical service at the situation of emergency.

The Sustainable Development Goal (SDG) has envisioned to transforming the world by 2030. It has set up seventeen goals of which Goal 3 states to ensure healthy lives and promote well-being for all ages. Strategy 3.8 of Goal 3 states – "Achieve Universal Health Coverage, including financial risk protection, access to quality essential health-care services and access to safe, effective, quality and affordable essential medicines and vaccines for all."

Nepal Health Sector Strategy (NHSS), 2015-2020 is propelling Nepal's health sector towards Universal Health Coverage through four key strategic directions among which "equitable access to health services" is one of the strategies. Rests are quality health services, health system reform and multi-sectoral approach. National Health Policy, 2019 envisioned the healthy, happy and awakened citizen.

So, when we talk about the Constitution, SDG, NHSS or National Health Policy, the focus is the better health of Nepalese people. There are many components for quality health service of which availability of medicines at affordable price is the vital one. There is no doubt that the medicines play a pivotal role in the prevention, diagnosis and treatment of diseases. Without this the whole health system will jeopardize.

It is estimated that domestic production meets the forty five percent of the total demands and rest from the import, India and third countries. Most of the medicines are available in the market but most of the lifesaving medicines become short shortage from time to time. It's really a painful

to DDA. The objectives of the DDA is not only to regulate the market but to make available necessary medicines for the benefit of the patients. It is a widely accepted principle that the patients are in the center and all healthcare providers, be it health institutions or health care professionals , and the regulators are revolving around them. So, no one should be the barrier to the fundamental rights of the patients to get the right treatment.

The Department is receiving feedbacks from doctors, government and private hospitals, teaching hospitals, etc regarding the shortage and unavailability of medicines especially life- saving medicines which are of low cost. The media are also publishing the news on shortage of such medicines from time to time. It seems that availability of life-saving medicines has now become a public affairs and cross cutting issue. Realizing this graving situation, the Department has taken initiative to address the unavailability such medicines. It has already published a public notice on national daily newspaper, Gorkhapatra and Kantipur, on 2076/04/03 requesting all concerned doctors, hospitals, etc for feedback. The Department has received the feedbacks from almost all sectors which is very encouraging. The Drug Advisory Committee, from its 50'th meeting held on 2076/05/03, has recommended that the Department should make available life- saving and other essential medicines through facilitating the registration procedure. The Department is actively working on the feedback and the recommendation of DAC and the decision will be taken very soon.

It is very painful when the patients and their caretakers run here and there, even to out of the country, to search for the medicines to save their lives. Let's take it as of our own pains. The Department looks forward the cooperation from the domestic manufacturers and importers to make available such life-saving medicines throughout the year so that patients and their caretakers should not take any further pain for saving their lives. Because life is precious and it shouldn't be put in risk due to unavailability of medicines.

Pan Bahadur Kshetry
Act. Director General

REGULATORY NEWS

A. **ACTIVITES OF DEPARTMENT OF DRUG ADMINISTRATION**

Department of drug administration (DDA) is responsible for the implementation of the Drugs Act 1978 and its regulations. The various administrative and regulatory activities carried out by DDA and its branch offices in Biratnagar, Birgunj and Nepalgunj during April to July 2019 are given below.

1. Number of registered Pharmacy outlets (upto Ashar 2076 as updated on DAMS)

	Wholesaler						Retailers						
District	Allopathy	Veterinary	Ayurved	Homeo	Unani	Total	Allopathy	Veterinary	Ayurved	Homeo	Unani	Total	Grand total
PROVINCE NO 1													
Jhapa	106	23	5	2	0	136	605	173	90	38	0	906	1042
Panchthar	2	0	0	0	0	2	41	13	14	2	0	70	72
Ilam	1	0	0	0	0	1	54	36	13	7	1	111	112
Taplejung	0	0	0	0	0	0	18	3	6	0	0	27	27
Terathum	0	0	0	0	0	0	21	8	3	3	0	35	35
Sankhuwasabha	0	0	0	0	0	0	42	12	6	4	1	65	65
Bhojpur	0	0	0	0	0	0	26	5	1	1	0	33	33
Dhankuta	1	1	0	1	0	3	53	20	10	3	1	87	90
Sunsari	99	22	9	3	0	133	672	154	100	31	3	960	1093
Morang	217	50	18	8	0	293	977	204	170	56	9	1416	1709
Solukhumbu	0	0	0	0	0	0	11	0	0	0	0	11	11
Okhaldhunga	0	0	0	0	0	0	24	5	1	2	0	32	32
Udaypur	9	2	0	0	0	11	113	41	36	3	0	193	204
Khotang	0	0	0	0	0	0	22	3	3	0	1	29	29
PROVINCE NO 2													
Siraha	57	6	5	0	0	68	338	62	87	8	0	495	563
Saptari	50	5	4	0	0	59	360	62	82	22	1	527	586
Mahottari	26	2	0	0	0	28	97	25	71	10	0	203	231
Sarlahi	27	1	1	0	0	29	175	52	144	8	0	379	408
Dhanusha	99	12	3	0	0	114	335	48	202	9	0	594	708
Bara	14	3	2	1	0	20	195	59	41	3	0	298	318
Parsa	247	29	15	3	2	296	356	57	40	9	0	462	758
Rautahat	27	7	2	0	0	36	156	43	181	6	0	386	422

PROVINCE NO 3													
Makawanpur	17	4	2	0	0	23	135	46	25	5	0	211	234
Sindhuli	2	0	0	0	0	2	42	15	15	1	0	73	75
Ramechhap	3	0	0	0	0	3	28	9	5	1	0	43	46
Dolkha	1	0	0	0	0	1	35	7	5	0	0	47	48
Chitawan	123	45	7	0	0	175	549	194	113	25	0	881	1056
Rasuwa	0	0	0	0	0	0	8	2	1	0	0	11	11
Nuwakot	5	0	0	0	0	5	72	42	6	1	0	121	126
Dhading	9	1	0	0	0	10	94	33	9	3	0	139	149
Sindhupalchok	0	0	0	0	0	0	48	11	0	0	0	59	59
Kavre	13	8	0	0	0	21	123	38	16	5	0	182	203
Bhaktapur	54	5	2	0	0	61	313	22	35	1	0	371	432
Lalitpur	101	22	1	0	0	124	533	31	54	6	0	624	748
Kathmandu	645	93	31	4	0	773	2430	93	306	42	0	2871	3644
GANDAKI PROVINCE													
Kaski	131	6	5	0	0	142	524	62	74	16	0	676	818
Syangja	6	1	0	0	0	7	98	17	23	3	0	141	148
Tanahu	8	1	0	0	0	9	118	33	42	11	0	204	213
Gorkha	2	0	0	0	0	2	81	12	6	0	0	99	101
Lamjung	1	0	0	0	0	1	69	10	12	1	0	92	93
Manang	0	0	0	0	0	0	0	0	0	0	0	0	0
Mustang	0	0	0	0	0	0	2	0	0	0	0	2	2
Parbat	1	2	0	0	0	3	42	14	11	0	0	67	70
Myagdi	1	1	0	0	0	2	23	4	5	0	0	32	34
Baglung	12	2	1	0	0	15	80	6	11	2	0	99	114
Nawalparasi *	8	2	1	0	0	11	235	75	54	7	0	371	382
PROVINCE NO 5													
Palpa	4	2	0	0	0	6	88	35	15	3	0	141	147
Rupandehi	157	19	12	2	1	191	667	120	86	28	0	901	1092
Arghakhanchi	5	0	0	0	0	5	79	9	7	0	0	95	100
Gulmi	6	0	0	0	0	6	99	18	15	6	0	138	144
Kapilvastu	18	1	1	1	0	21	141	32	33	6	0	212	233
Rolpa	0	0	0	0	0	0	38	3	7	0	0	48	48
Pyuthan	11	0	0	0	0	11	55	14	12	2	0	83	94
Dang	72	1	3	0	0	76	448	93	97	17	0	655	731
Banke	156	11	5	0	0	172	510	115	66	29	0	720	892
Bardiya	4	1	0	0	0	5	189	95	48	36	0	368	373
Rukum *	9	0	0	0	0	9	57	8	14	1	0	80	89
KARNALI PROVINCE													
Salyan	4	0	0	0	0	4	60	7	6	8	0	81	85
Surkhet	27	3	0	0	0	30	143	36	24	8	0	211	241
Dailekh	0	0	0	0	0	0	33	6	4	8	0	51	51
Jajarkot	1	0	0	0	0	1	23	8	5	5	0	41	42
Jumla	5	0	0	0	0	5	25	7	5	0	0	37	42

Humla	1	0	0		0	1	6	0	0	1	0	7	8
Mugu	0	0	0	0	0	0	14	3	4	2	0	23	23
Dolpa	0	0	0	0	0	0	14	1	0	1	0	16	16
Kalikot	1	0	0	0	0	1	15	1	0	4	0	20	21
SUDURPASCHIM PROVINCE													
Bajhang	1	0	0	0	0	1	23	1	12	0	0	36	37
Bajura	1	0	0	0	0	1	21	2	7	0	0	30	31
Achham	9	0	0	0	0	9	83	3	16	1	0	103	112
Doti	6	0	0	0	0	6	43	3	16	1	0	63	69
Kailali	119	13	5	0	0	137	545	133	105	60	0	843	980
Darchula	0	0	0	0	0	0	9	1	4	0	0	14	14
Baitadi	0	0	0	0	0	0	43	7	20	3	0	73	73
Dadeldhura	15	0	0	0	0	15	34	6	23	0	0	63	78
Kanchanpur	18	1	0	0	0	19	221	80	31	12	0	344	363
Grand Total	**2775**	**408**	**140**	**25**	**3**	**3351**	**14099**	**2708**	**2811**	**597**	**17**	**20232**	**23583**

*** Nawalparasi east/west and Rukum east/west have not been separated in DAMS software. So these districts have been kept as in earlier structure without repetition in relevant provinces.**

2. Pharmaceutical Industries upto Ashadh 2076

Category	Allopathy	Veterinary	Ayurved/Herbal
Foreign	373	16	35
Domestic	73	12	80

3. Pharmaceutical Products for marketing authorization upto Ashadh 2076

Category	Total Brand
Foreign	9940
Domestic	9166

4. Major activities carried out in FY 2075/76 (2018-2019)

1. Awareness on the rational use of medicines by different media
2. Regular publication of Drug Bulletin of Nepal (DBN).
3. Audit/inspection of domestic drug industries for WHO Good Manufacturing Practice (GMP) compliance.
4. Inspection of retail & wholesale pharmacies for compliance.
5. Post marketing quality analysis of drugs available in market.
6. Inspection of Foreign Manufacturers before registration of products.
7. Conducting examination of veterinary drug sellers' training.

8. Audit of domestic manufacturer laboratory for compliance of Good Laboratory Practice (GLP)
9. Take legal and administrative action for violation of regulatory standards.
10. Recall of medicine from market those failed to quality standard.
11. Target Vs Achievement, FY 2075/76

S. N	Activities	Unit	Target	Achievement	
				Num.	%
1	Drug information to the public by different media	Num.	30	42	140
2	Publication of Drug Bulletin of Nepal		3	3	100
3	Conducting examination of veterinary drug sellers' training		2	2	100
4	Inspection of domestic Pharmaceutical Industries		87	87	100
5	Inspection to drug retailers& wholesalers		2913	3404	117
6	Drug sample Analysis		1000	1018	102
7	Audit of Pharmaceutical Analytical Laboratories		30	30	100
8	Inspection of Foreign Companies	Times	5	5	100

Other activities

S. N	Activities	Achievement
1	Registration of new foreign pharmaceutical Industry	39
2	Registration of new medicine (import)	244
3	Renew of import license	3590
4	Issue of marketing license	787
5	Issue of product license	1366
6	Import license for raw material for domestic industry	1321
7	Registration of new pharmacy	893
8	Renew of pharmacy	4571
9	Renew of professional license	575
10	Deregistration of pharmacy	336
11	Recall of medicine from market due to inferior quality	21
12	Training on ISO 17025 certification	1

13	Analytical Method Validation for non-pharmacopoeial products	34
14	Interaction program with stakeholders	5
15	Training on BA/BE & TDM	2
16	Development of SOP for Pharmacovigillance	1
17	Seminar on Rational Use of Medicines in different Provinces	3
18	Training on legal procedure for Drug Inspectors	1

5. List of foreign manufacturers registered during FY 2075/76

1. Abaris Healthcare Pvt Ltd, India
2. Abbvie SPL, Italy
3. Acme Generics LLP Bangladesh
4. Aeropharm GMBH, Germany
5. Affy Parenterals, India
6. Aristo Pharma Ltd. Bangladesh
7. Belco Pharma India
8. BF Biosciences Limited, Pakistan
9. Brown Laboratories Ltd. India
10. Faes Farma, Spain
11. Fresenius Kabi Oncology Ltd., Kisapura India
12. Hetero Labs Limited, Telengana, India
13. Incepta Vaccine Limited, Ziraba Dhaka, Bangladesh
14. Intas Pharmaceutical Ltd., Namthang South Sikkim, India
15. Jawa Pharmaceutical Pvt. Ltd., India
16. Laboratories Galderma, Albay, France
17. Lek SA, Poland
18. Lupin Limited East Sikkim, India
19. Medisol Life Science Pvt. Ltd., India
20. Mylan Laboratories Ltd. Nasik, India
21. Neovil Biotech GMBH, Germany
22. Octapharma, Sweden
23. Olive healthcare Pvt. Ltd. India
24. Premium Serums & Vaccines Pvt. Ltd., India
25. Pure and Cure Health Care Pvt. Ltd., India
26. Reliance Life Science Pvt. Ltd. India
27. Reliance Lifesciences, Navi Mumbai, India
28. Roche SPA, Segrate, Italy

29. Salutas Pharma GMBH, Germany
30. Sandoz Pvt. Ltd., India
31. Selmore pharmaceutical Pvt. Ltd. Pakistan (vet)
32. Shilpa Medicare Limited India
33. SPAL Pvt. Ltd. India
34. Stanford Laboratories Pvt. Ltd. India
35. Steril-gene Life Sciences P. Ltd. India
36. Sun Pharma Laboratories Ltd., district Kamrup Assam 781128, India
37. Unijules Lifesciences Limited India
38. VHB Medi Sciences Limited, India
39. Wellex Laboratories Private Limited (Ayurvedic)

B. ACTIVITES OF NATIONAL MEDICINES LABORATORY of FY 075/76

National Medicines Laboratory (NML) is the national regulatory laboratory as per the Drugs Act, 1978. It is responsible for the analysis of medicine samples submitted from DDA (inspection, market surveillance etc.), other government organizations and domestic/ foreign industries.

1. Analysis of medicine samples during FY 2075/76

Medicine samples were analyzed as per the pharmacopoeias recognized by the Drug standard regulation, 2043 for parameters like assay, dissolution, content uniformity, physical etc. The total samples received during this fiscal year were 1072. The analyzed samples were 1018 including samples from the previous fiscal year.

Sample Source	No. of samples tested	Compliance	Non-compliance
Samples from DDA	408	907	111
Samples from other sources	381		
Samples from market sample	229		
Total	1018	907	111

2. **Laboratory audited during FY 2075/76**

Quality control laboratories of Nepalese Pharmaceutical Industries and Private Analytical Laboratories were audited to assess the compliance for Good Laboratory Practice (GLP) with respect to different facilities like instrument, equipment, premises, personnel, chemicals/reagents environmental control, stability, documentation, self-audit and other activities. These sorts of activities were being carried out to encourage the laboratories for self-auditing and improvement as per the norms of GLP towards attaining the ultimate goal of quality system. 30 laboratories were audited, majority of them were in the process of upgrading as per the requirement of GLP.

3. **Participation in proficiency testing during FY 2075/76**

During this fiscal year NML had participated in two proficiency testing/ ILC program organized first one by EDQM with the support of WHO and second ILC organized by United States Pharmacopeia to assess performance of analytical capability.

4. **Conduction of training**

NML conducted following training in FY 075/76

- Training on Good Laboratory Practice Audit
- Training on Measurement Uncertainty.
- Training on Internal Calibration of Mass, Temperature and Volume
- Interaction on Revision of Quality Manual of NML

5. **Participation in external training/workshop**

Senior Quality Controller Ms Shiwani Khadgi and Pharmacy Officer Ms Samjhana Suwal participated in training program on Bioequivalence and Bioavailability Study in Drugs in Mangalore, India.

Pharmacy Officer Ms Binala Joshi participated in WHO training workshop on Good Distribution Practice (GDP), regulatory inspection using the risk-based approach in Bangkok, Thailand.

IMPORTANT INFORMATION

Codeine, dihydrocodeine, tramadol
Contraindication in children: Risk of serious respiratory depression
Japan's Ministry of Health, Labor and Welfare (MHLW) and the Pharmaceutical and Medical Device Agency (PMDA) have announced that the package inserts for products containing codeine, dihydrocodeine or tramadol should be revised to include contraindications in children under 12 years of age (for all uses), and patients under 18 years of age when used for pain relief after tonsillectomy or adenoidectomy, due to the risk of serious respiratory depression. Codeine, dihydrocodeine and tramadol are indicated to relieve coughs and pains. Following the announcement of the US Food and Drug Administration (FDA) in 2017 of the contraindication of products containing codeine, dihydrocodeine or tramadol in children under 12 years, MHLW and PMDA have reviewed available safety information and concluded that the revision of package inserts is necessary. In Japan there are four reports of morphine like toxic symptoms such as respiratory depression in patients using codeine, dihydrocodeine or tramadol. Mortality has not been reported.

Source: WHO Pharmaceuticals Newsletter No.4, 2019
In Nepal: Health care professionals are warned of the risk of serious respiratory depression in children with the use of Codeine, dihydrocodeine, tramadol.

Dulaglutide (genetical recombination)
Risk of severe diarrhoea and vomiting
MHLW and PMDA have announced that the package inserts for dulaglutide (Trulicity Subcutaneous Injection®) should be revised to include severe diarrhoea and vomiting as adverse drug reactions. Dulaglutide is indicated for treatment of type-2 diabetes mellitus. A total of seven cases involving severe gastrointestinal disorders have been reported in Japan during the previous three fiscal years. Of the seven cases, a causal relationship to the product could not be excluded in three cases.

Source: WHO Pharmaceuticals Newsletter No.3, 2019
In Nepal: Health care professionals are warned of the risk of severe diarrohoea and vomiting with the use of Dulaglutide.

Febuxostat, topiroxostat
Potential risk of cardiovascular death
The MHLW and the PMDA have announced that the package inserts for febuxostat (Feburic®) and topiroxostat (Uriadec®) should be revised to warn about the potential risk of cardiovascular death in patients with cardiovascular disease. Febuxostat and topiroxostat are indicated for gout or hyperuricemia. The PMDA investigated studies conducted overseas. In the US, the CARES study showed a higher risk of cardiovascular death in the study group treated with febuxostat

compared to the control group treated with allopurinol. The FDA restricted the use of febuxostat and revised the package insert in February 2019 to provide an alert on cardiovascular deaths. The European Medicines Agency (EMA) required the marketing authorization holder of febuxostat to conduct a clinical study (FAST study) to assess the cardiovascular risks of febuxostat in patients with gout who had a cardiac disease The FAST study is ongoing. In Japan, clinical trials do not show evidence of a higher incidence of cardiovascular events in the febuxostat study group compared to the control groups (placebo group or allopurinol group). However, considering the evidence from studies conducted overseas and available evidence in the literature, PMDA has concluded that it is appropriate to add the CARES study results concerning cardiovascular death to package insert. Although no concerns were expressed about cardiovascular risks in a similar drug with a xanthine oxidase inhibitory effect, topiroxostat, it is considered appropriate to add the same precautions to the package insert of topiroxostat.

Source: WHO Pharmaceuticals Newsletter No.4, 2019

In Nepal: Health care professionals are warned of the potential risk of cardiovascular death with the use of febuxostat, topiroxostat.

Finasteride

Potential risk of suicidal ideation

Health Canada has requested that manufacturers update the product information for finasteride (Proscar® and Propecia®) to include the potential risk of suicidal thoughts and/or behaviour (suicidal ideation). Finasteride is used to treat prostate gland enlargement (Proscar®), and male pattern hair loss (Propecia®). A re-assessment of initial reviews in 2012 and 2014 found that the Canadian reporting rate for finasteride and suicide/self-injury-related events increased by 2.5 times between 2012 and 2016. To date, Health Canada has received 26 reports of suicide and/or self-injury-related events reported in patients treated with finasteride. A search in the WHO global database of Individual Case Safety Reports, Vigibase (up to September 16, 2018), found 368 international reports. Health Canada has concluded that there may be a link between finasteride use and the risk of suicidal ideation.

Source: WHO Pharmaceuticals Newsletter No.2, 2019

In Nepal: Health care professionals and patients are warned of potential risk of suicidal ideation with the use of Finasteride.

Fluoroquinolone antibiotics

Risk of musculoskeletal and nervous systems damage

The MHRA has announced that new restrictions for the indication of fluoroquinolones are being introduced to reduce the risk of disabling, long-lasting or potentially irreversible adverse reactions affecting the musculoskeletal and nervous systems. Fluoroquinolone antibiotics are indicated for serious, life threatening bacterial infections. The restrictions follow an EU wide safety review.

Fluoroquinolones can very rarely cause long-lasting, disabling, and potentially irreversible adverse effects, sometimes affecting multiple systems, organ classes, and senses. The first signs of these adverse reactions include: tendinitis or tendon rupture, muscle pain, muscle weakness, joint pain, joint swelling, peripheral neuropathy and central nervous system effects. Health-care professionals should not prescribe fluoroquinolones for nonsevere or self-limiting infections, or non-bacterial conditions. Health-care professionals should prescribe with special caution for people older than 60 years and for those with renal impairment or solid-organ transplants, because they are at a higher risk of tendon injury. Also, use of corticosteroids with a fluoroquinolone should be avoided, since coadministration could exacerbate fluoroquinoloneinduced tendinitis and tendon rupture.

Source: WHO Pharmaceuticals Newsletter No.3, 2019
In Nepal: Health care professionals are warned of the risk of musculoskeletal and nervous system damage.

Gentian violet
Risk of cancer
Health Canada has announced that there is potential evidence of a link between the use of gentian violet and cancer. Gentian violet is a nonprescription medicine used to treat cutaneous and mucocutaneous infections. Following a review of the scientific literature and risk assessment on violet containing human therapeutic products, Health Canada concluded that the evidence from animal studies in the scientific literature suggests a potential link between gentian violet and cancer. The assessments were triggered by a recommendation from the WHO's Codex Alimentarius Commission which advised regulatory authorities to prevent exposure to gentian violet in food due to a potential cause of cancer. Health Canada notified the manufacturer of gentian violet of the assessment results. The manufacturer agreed to voluntarily discontinue marketing of their product in Canada and the health product drug licence for gentian violet has been cancelled.

Source: WHO Pharmaceuticals Newsletter No.4, 2019
In Nepal: Health care professionals are warned of the potential risk of cancer with the use of Gentian violet.

Influenza HA vaccine
Risk of acute generalized exanthematous pustulosis
MHLW and PMDA have announced that the package inserts for influenza HA vaccines (Influenza HA Vaccine KMB® and other preparations) should be revised to include acute generalized exanthematous pustulosis as an adverse drug reaction. Influenza HA vaccine is indicated for prophylaxis of influenza. One case associated with acute generalized exanthematous pustulosis has been reported in Japan during the previous three fiscal years. A causal relationship with the product could not be excluded for this case.

Source: WHO Pharmaceuticals Newsletter No.3, 2019

In Nepal: Health care professionals are warned of the potential risk of acute generalized exanthematous pustulosis with the use of Influenza HA vaccine.

Rivaroxaban and other direct-acting oral anticoagulants (DOACs)

Increased risk of recurrent thrombotic events

The MHRA has announced that a clinical trial has shown that there is an increased risk of recurrent thrombotic events associated with rivaroxaban (Xarelto®) use compared to warfarin, in patients with antiphospholipid syndrome and a history of thrombosis. Direct-acting oral anticoagulants (DOACs) are indicated for the treatment and prevention of venous thromboembolism, and prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation with one or more risk factors. DOACs available are rivaroxaban, apixaban (Eliquis®), edoxaban (Lixiana®) and dabigatran (Pradaxa®). A clinical trial compared rivaroxaban to warfarin in 120 patients and showed that use of rivaroxaban in patients with antiphospholipid syndrome could be associated with increased rates of recurrent thrombotic events compared to therapy with warfarin. There have been no completed clinical trials for use of other DOACs such as apixaban, edoxaban and dabigatran in patients with antiphospholipid syndrome, therefore available data for these medicines are limited. However, available data suggest that other DOACs may also be associated with a similarly increased risk of recurrent thrombotic events as with use of rivaroxaban. Health-care professionals are advised to review whether continued treatment with a DOAC is appropriate for patients diagnosed with antiphospholipid syndrome and consider switching to a vitamin K antagonist such as warfarin.

Source: WHO Pharmaceuticals Newsletter No.4, 2019

In Nepal: Health care professionals are warned of the increased risk of recurrent thrombotic events with the use of Rivaroxaban and other direct acting anticoagulants (DOACs).

Tofacitinib

Risk of pulmonary embolism

The EMA's PRAC has recommended, as a temporary measure, that doctors must not prescribe the 10 mg twice-daily dose of tofacitinib (Xeljanz®) in patients who are at high risk of blood clots in the lungs (e.g. patients who have heart failure, cancer, inherited blood clotting disorders or a history of blood clots) due to the risk of pulmonary embolism and overall mortality. Tofacitinib is an oral, immunomodulatory diseasemodifying anti-rheumatic medicine, indicated for the treatment of rheumatoid arthritis, psoriatic arthritis and severe ulcerative colitis. The PRAC's recommendation follows results from an ongoing study, which showed an increased risk of blood clots in the lungs and death with 19 cases of pulmonary embolism when the 10 mg twice daily dose was used. This is double the recommended dose for rheumatoid arthritis. Once the review is concluded, updated guidance will be provided to patients and health-care professionals.

Patients are advised not to stop or change their dose of tofacitinib without talking to their doctor. Patients receiving tofacitinib, irrespective of the indication, should be monitored for the signs and symptoms of pulmonary embolism.

Source: WHO Pharmaceuticals Newsletter No.4, 2019
In Nepal: Health care professionals are warned of the potential risk of pulmonary embolism with the use of tofacitinib.

Trastuzumab (genetical recombination)
Risk of lysis syndrome
The MHLW and the PMDA have announced that the package inserts for trastuzumab products (Herceptin® and Trastuzumab BS®) should be revised to include lysis syndrome as an adverse drug reaction. Trastuzumab is indicated for certain types of breast and gastric cancers. Patients should be carefully monitored by checking serum electrolyte levels and renal function. If any abnormalities are observed, administration of trastuzumab should be discontinued and appropriate measures such as management of hyperuricaemia should be taken. A total of three cases involving lysis syndrome have been reported in patients treated with trastuzumab in Japan during the previous three fiscal years. For two of the three cases, a causal relationship with the product could not be excluded. Out of the three cases, one case of patient mortality has been reported, although a causal relationship with the product could not be established. MHLW and PMDA concluded that the revision of the package insert was necessary based on the results of the investigation of the currently available evidence.

Source: WHO Pharmaceuticals Newsletter No.1, 2019
In Nepal: Health care professionals are warned of the risk of lysis syndrome with the use of Trastuzumab.

Quetiapine
Risk of serious skin diseases
MHLW and PMDA have announced that the package insert for quetiapine (Seroquel® and Bipresso®) should be revised to include toxic epidermal necrolysis (TEN), oculomucocutaneous syndrome (Stevens-Johnson syndrome) and erythema multiforme as adverse drug reactions. Quetiapine is indicated for schizophrenia and improvement of depressive symptoms in patients with bipolar disorder. One case of TEN, one case of oculomucocutaneous syndrome, and one case of erythema multiforme have been reported in Japan during the previous three fiscal years, respectively. Of these three cases no patient mortalities have been reported.

Source: WHO Pharmaceuticals Newsletter No.3, 2019
In Nepal: Health care professionals are warned of the risk of serious skin diseases with the use of Quetiapine.

SIGNAL

Desloratadine and the risk of experiencing dry eyes

Sarah Watson, Uppsala Monitoring Centre and Dr. Eugène van Puijenbroek, the Netherlands Pharmacovigilance Centre Lareb

Summary
Reports of the antihistamine desloratadine causing dry eyes in several patients worldwide have been shared in VigiBase, the WHO global database of individual case safety reports. Anticholinergic effects of antihistamines as a group are known, but this specific adverse drug reaction is not labelled, and the drug might be overlooked as a potential cause of the reaction.

Introduction
Desloratadine is a long-acting, non-sedating histamine antagonist with selective peripheral H_1- receptor antagonist activity. It is indicated in adults and children aged one year and above for allergic rhinitis (among which hay fever is one type) and urticaria. In patients with allergic rhinitis, desloratadine is effective in relieving symptoms such as sneezing, nasal discharge and itching, as well as ocular itching, tearing and redness, and itching of palate.[1] Dry eye occurs when the surface of the eye is inadequately lubricated due to a decreased quantity and/or quality of tears. Symptoms include itching, stinging or burning, excess tears following periods of dryness, pain, and redness in the eye. People with dry eyes may also experience blurred vision.[2]

Reports in VigiBase
There were 13 reports (after removal of a likely duplicate) of the MedDRA preferred term dry eye for desloratadine in VigiBase, the WHO global database of individual case safety reports, as of May 2018. The reports originated from Canada, Finland, Norway, Portugal, Sweden, Switzerland and the USA. Of the 13 reports, nine had desloratadine as the only suspected drug for the reaction. The time to onset was recorded in eight cases; the same day in three reports, "within a few days" in one, "since start of treatment" in one, and 14 days, one month and six months, respectively in the three other reports. The age distribution ranged from two to 75 years, and ten of the reports concerned female patients. Based on the overall reporting of adverse reactions for desloratadine and on the adverse reaction dry eye on its own in VigiBase, 5.2 reports were statistically expected for the drug–adverse drug reaction (ADR) combination based on the disproportionality

measure (IC). As there are more reports of desloratadine as well as for dry eyes in general for females, the relatively high number for females in this case series was not unexpected. In six of the reports there was a documented effect upon withdrawal of the drug; the reaction abated in all cases (one when the dose was decreased) and in the two cases where the drug was reintroduced, the reaction reoccurred. In four cases dry mouth/oral dryness was co-reported and other co-reported terms included dry skin, dry nose, chapped lips and vaginal dryness, all of which could indicate that those patients had multiple anticholinergic adverse reactions to the drug. In one of the reports where the reaction occurred on the same day as the drug was introduced, the reaction was experienced within 2- 3 hours and the patient experienced dry eyes, blurred vision and partial visual loss resulting in problems focussing on digital screens and driving their car.

Literature and Labelling

No adverse drug reactions for eyes are listed in the product label for desloratadine, but dry mouth which could indicate anticholinergic properties of the drug, is listed as a common ADR.[3,4] Adverse anticholinergic effects include among other reactions: dry mouth, constipation, urinary retention, bowel obstruction, dilated pupils, blurred vision, increased heart rate and decreased sweating.[5] The relative anticholinergic effect of different antihistamines has been shown by Orzechowski et al. in guinea pigs where desloratadine showed anticholinergic properties and to a larger extent than both diphenhydramine and loratadine both in vitro and in vivo.[6] Additionally, the ability of antihistamines such as desloratadine to interact with human muscarinic receptors was investigated in a study by Wolff et al. where they used in vitro cells stably expressing one of the five human muscarinic receptors (M1-M5). It was shown that desloratadine was a full antagonist at all five receptors, and the study concluded that several marketed antihistamines, of which desloratadine was one, possessed marked anticholinergic activity "with the potential to cause adverse ocular side effects such as dryness".[7]

Discussion and Conclusion

It is known that hay fever, which is one of the most common indications of desloratadine, may cause inflammation of the conjunctiva and is an alternative cause to eye discomfort experienced during the pollen season.[8] However, the reports with a rapid time to onset after drug administration point to a causal relationship with the drug. The small number of reports in VigiBase might be because it is not a serious reaction and that not all patients would report such complaints. However, dry eyes could be perceived as both painful and incapacitating, affecting both the ability to focus on

digital screens and to drive, as has been described in one of the reports in VigiBase. Based on the anticholinergic properties of desloratadine and strengthened by the reports with a short time to onset and both de- and rechallenges in VigiBase, this is likely to be an overlooked anticholinergic adverse drug reaction that should be considered for inclusion in the product labels and patient leaflets.

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Source: WHO Pharmaceuticals Newsletter No.3, 2019

REGULATORY NOTICES

नेपाल सरकार
स्वास्थ्य तथा जनसंख्या मन्त्रालय
औषधि व्यवस्था बिभागको

औषधि फिर्ता (RECALL) गर्ने सम्बन्धि अत्यन्त जरुरी सूचना

प्रकाशिन मिति २०७५/०१/१८

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

तपसिल

सि.न.	औषधिको नाम	ब्याच. न	Mfg/ Expiry date	कारण	उत्पादकको नाम र ठेगाना
१.	Sitopaladi Powder 100 gm	002	Jul 2018/ two yrs from mfg date	Non-compliance w.r.t. microbial test	Ashtanga Pharmaceuticals Pvt. Ltd.
२.	Ashwagandha powder 100 gm	002	Jun 2018/ two yrs from mfg date		
३.	Avipattikar Churna 100 gm	1400	Jan 2019/ two yrs from mfg date		Gorkha Ayurved co. (P) Ltd
४.	Sitopaladi Churna, 100 gm MS-177	301	Oct 2018/ two yrs from mfg date		
५.	Avipattikar Powder, 100 gm	130	Dec 2018/ Nov 2020		Gorakhnath Herbaceuticals Pvt. Ltd.
६.	Lawanbhaskar Powder, 100 gm	31	Mar 2018/ Feb 2020		

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प्रकाशिन मिति २०७६/०१/२०

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

तपसिल

सि.न.	औषधिको नाम	ब्याच. न	Mfg/ Expiry date	कारण	उत्पादकको नाम र ठेगाना
१.	Avipattikar Churna, 60 gm	AL0222	Feb 2018/ Jan 2020	Non-compliance w.r.t. microbial test	Dabur India Ltd, Rajasthan, India

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प्रकाशिन मिति २०७५/१२/०६

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

तपसिल

सि.न.	औषधिको नाम	ब्याच. न	Mfg/ Expiry date	कारण	उत्पादकको नाम र ठेगाना
१.	Ardoxime-50	ADD45001	Oct 2017/ Mar 2019	Non-compliance to USP 2018 w.r.t. assay	Arya Pharma Lab Pvt. Ltd.
२.	Wormex	WML-45002	Dec 2017/ Nov 2019		

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प्रकाशिन मिति २०७५/०२/३१

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तपसिल

सि.न.	औषधिको नाम	ब्याच. न	Mfg/ Expiry date	कारण	उत्पादकको नाम र ठेगाना
१.	Panloc	PLHT-901	Feb 2018/ Jan 2021	Non-compliance w.r.t. dissolution test in buffer stage	Alliance Pharmaceuticals Pvt. Ltd.

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औषधि फिर्ता (RECALL) गर्ने सम्बन्धि अत्यन्त जरुरी सूचना

प्रकाशिन मिति २०७६/०३/२१ गोरखापत्र

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

तपसिल

सि.न.	औषधिको नाम	ब्याच. न	Mfg/ Expiry date	कारण	उत्पादकको नाम र ठेगाना
१.	Formin-G1 Forte	LPN-74165	Jan 2018/ Dec 2019	Non-compliance w.r.t. physical appearance	Nepal Pharmaceuticals Laboratory Pvt. Ltd., Birgunj.
२.	Pantona	PT1T-1702	Aug 2017/ Jul 2019	Non-compliance w.r.t. acid stage dissolution test	G.D. Pharmaceuticals Pvt. Ltd.
३.	Almox-500	8282346	Mar 2018/ Feb 2020	Non-compliance w.r.t. dissolution test	Alkem Laboratories Ltd, Mumbai, India
४.	Amoxyn-500	Ex-0141018	Oct 2018/ Sep 2020	Non-compliance w.r.t. dissolution test	Saga Laboratories, Ahmedabad, India
५.	Avipattikar Churna	1351	Jul 2018/ 2 years from mfg date	Non-compliance w.r.t microbial test	Gorkha Ayurved co Pvt
६.	Pet Safa	05	Sep 2018/ 2 yrs from mfg date		Gorkha Ayurved co Pvt
७.	Arogya Balbel Churna	0169	Jul 2018/ 2 yrs from mfg date		Arogya Bhawan Works Pvt. Ltd.
८.	Pushyanug Churna	014	Jan 2019/ Dec 2020		Sagarmatha Ayurvedic Aushadhi Udhyog

नेपाल सरकार

स्वास्थ्य तथा जनसंख्या मन्त्रालय

औषधि व्यवस्था विभागको

औषधिको आम उपभोक्तालाई जानकारी

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

स्वस्थ्यकर्मी, औषधि सिफारिसकर्ता, औषधि उत्पादक, पैठारि कर्ता तथा व्यबशायीलाई जानकारी

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

औषधि प्रयोग गर्दा ध्यान दिनुपर्ने कुराहरू:

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

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

औषधि सम्बन्धि थप जानकारीका लागि तल उल्लेखित ठेगानामा सम्पर्क राख्नुहोला ।

औषधि व्यवस्था विभाग

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औषधि व्यवस्था विभागका शाखा कार्यालय

	कञ्चनवारी, विराटनगर	आदर्शनगर, नेपालगंज	मुरली बगैंचा, विरगंज
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E-mail:	biratnagar@dda.gov.np	nepalgunj@dda.gov.np	birgunj@dda.gov.np

For further infomation, please contact:

Government of Nepal

Ministry of Health and Population

Department of Drug Administration (DDA)

Madan Bhandari Path-4, Bijulibazar, New Baneshwor, Kathmandu

Phone:01-4780432,4780227, Fax:01-4780572

E-mail:info@dda.gov.np

dg@dda.gov.np

Website: www.dda.gov.np

National Medicines Laboratory (NML)

Madan Bhandari Path-4, Bijulibazar

New Baneshwor, Kathmandu

Phone:01-4781269, Fax:01-4780664

E-mail:nml@dda.gov.np

DDA Branch Offices

Kanchanbari, Biratnagar

Koshi Zone

Tel/Fax: 021-420849

E-mail: biratnagar@dda.gov.np

Adarshnagar, Surkhet Road

Nepalgunj, Bheri Zone

Tel/Fax: 081-522074

E-mail: nepalgunj@dda.gov.np

Murali Bagaicha, Birgunj, Parsa

Narayani Zone

Tel/Fax: 051-527753

E-mail:birgunj@dda.gov.np

For: Further information, Please visit www.dda.gov.np

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