Pharmacovigilance Bulletin

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Dolutegravir induced hypertension; Case report of one of the reports received at the National Pharmacovigilance Centre.

Editorial team

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Foreword:

The final quarter of 2023/2024 was filled with exciting activities that added energy to the end of the financial year. This issue highlights local safety trends and previews the inaugural International Society for Pharmacovigilance (ISoP) Africa Chapter in-person conference, scheduled for July 22-24, 2024, at Speke Resort Munyonyo. Additionally, we provide a brief overview of the stakeholder engagement held with Qualified Persons for Pharmacovigilance (QPPV) from various Marketing Authorization Holders (MAHs) and their Local Technical Representatives (LTRs). This issue includes a case report on dolutegravir-mediated hypertension and dysphonia, a newly reported reaction. We also present the quarterly ICSR summary, offering readers a clear picture of the safety issues observed across the country in the last part of the financial year, where reactions related to contraception methods accounted for the majority of ICSRs this quarter.

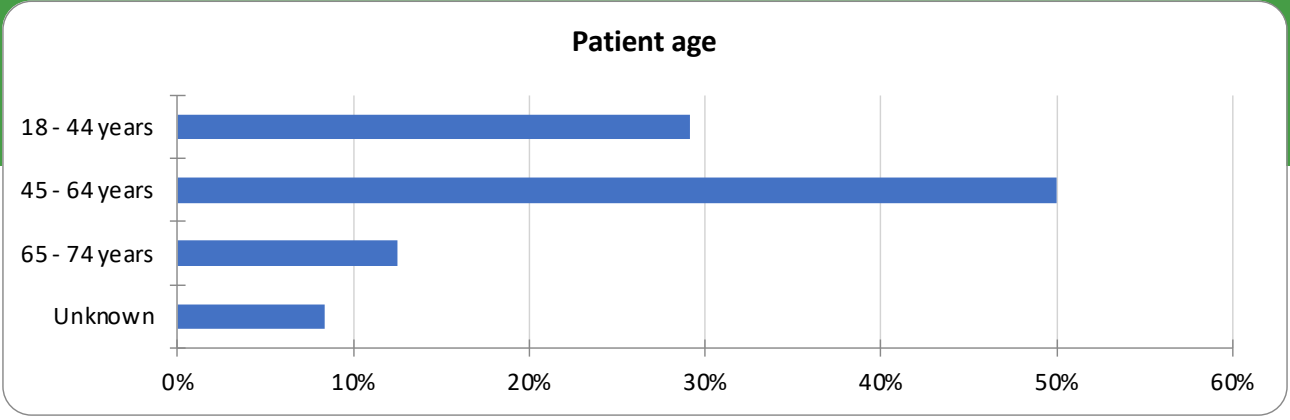
1. Dolutegravir induced hypertension; Case report of one of the reports received at the National Pharmacovigilance Centre.

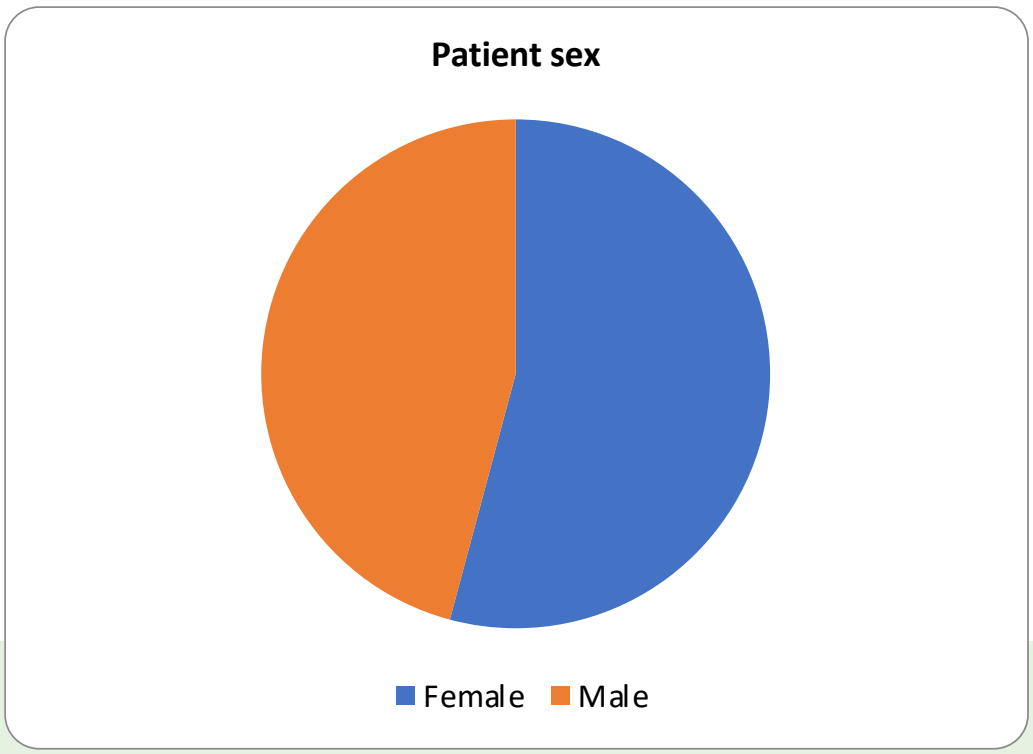
Case: NF, a female of unknown age was reported with elevated blood pressure. She complained of headache even when hydrating regularly and the caregiver suspected this could be DTG induced. The BP on 2 occasions was 162/102 and 162/100.

Missing information: This report is missing crucial information that's needed for proper causality assessment such as, base line BP, age of the patient or at least the date of birth, this would enable us rule out age related hypertension, dates and intervals when the blood pressure was taken, time to onset of the hypertension relative to the start date of administration of TLD and cconcomitant drugs if there were any involved

We have received a total of 24 reports to this date at the National Drug Authority, characterized as follows;

Majority (50%) of the cases fell between 45-64 years with more females taking up (54.2%). Half of the reports were reported as serious with the main seriousness criteria being life threatening at 37.5%





Mechanism:

HIV infection and treatment with antiretroviral therapy (ART) are known risk factors for developing hypertension, which is more prevalent among people living with HIV compared to the general population (Musekwa et al., 2021).

Our causality assessment revealed a possible association between dolutegravir-based regimens and the development of hypertension in all cases. While the exact mechanism behind the increase in blood pressure is unclear, a study conducted by Boston University's School of Public Health confirmed that dolutegravir is associated with weight gain, as observed in other clinical studies. The study found that patients who switched from efavirenz (EFV) to dolutegravir (DTG) gained an average of 1.78 kg over 12 months, whereas those who remained on EFV did not experience such weight gain. Additionally, the results indicated that patients on DTG had a 14-percentage point increase in their risk of developing hypertension compared to those who remained on EFV (HIV Drug May Be Linked to Increased Risk of Hypertension | SPH, n.d.).

Reference:

HIV Drug May Be Linked to Increased Risk of Hypertension | SPH. (n.d.). Retrieved July 31, 2024, from https://www.bu.edu/sph/news/articles/2023/hiv-drug-may-be-linked-to-increased-risk-of-hypertension/

Musekwa, R., Hamooya, B. M., Koethe, J. R., Nzala, S., & Masenga, S. K. (2021). Prevalence and correlates of hypertension in hiv-positive adults from the livingstone central hospital, Zambia. Pan African Medical Journal, 39. https://doi.org/10.11604/pamj.2021.39.237.29718

2. ISoP Africa, Kampala meeting

The National Drug Authority secured the honour of hosting the inaugural International Society of Pharmacovigilance (ISoP) - Africa Chapter in-person meeting in Kampala, Uganda.

ISoP, as an international non-profit scientific organization, is committed to advancing Pharmacovigilance both scientifically and educationally, with the goal of ensuring the safe and appropriate use of medicines worldwide. Through regional chapters, ISoP facilitates addressing region-specific challenges in Pharmacovigilance. The World Health Organization, and the Africa Union Agency (AUDA-NEPAD) are among its several collaborators.

The primary objective of this gathering will be to exchange knowledge on current pharmacovigilance issues within the continent, focusing on the theme "**Advancing Pharmacovigilance Practice in Africa: Moving from Data Collection to Data-Driven Decision Making**." The event will span three days, commencing on 22nd and concluding on 24th July 2024, hosted at Speke Resort Munyonyo, Uganda

We take this opportunity to invite you to attend this conference.

For further details, please visit our website at www.isopafrica.com. For any inquiries or clarifications, feel free to reach out to the ISoP Africa Chapter President at hndagije.isopafrica@gmail.com or the Local Organizing Committee at isopmeeting@nda.or.ug

It will be our utmost honour to welcome you to this momentous gathering of pharmacovigilance leaders across Africa. Your participation will enrich the discussions and contribute to advancing Pharmacovigilance practices across the African continent.

3. We met the QPPVs this quarter.

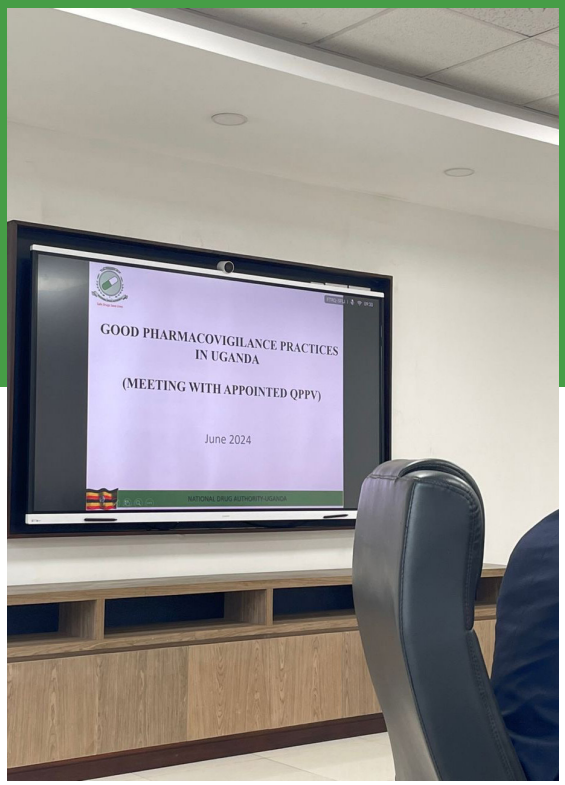
Market Authorization holders are required by law to establish pharmacovigilance systems to effectively monitor the safety of the products they market. This is aimed at ensuring timely interaction and litigation of use for their products.

Part of these systems are the qualified persons for pharmacovigilance (QPPVs) who are the technical persons responsible for implementing the safety measures by the MAHs. Given that these requirements and their implementation is relatively new in Uganda, the capacity of QPPVs and the local MAHs is still low and their implementation is lacking. Therefore, part of NDA's initiatives to build capacity, a meeting was held the appointed QPPVs and the objective were;

1. to clarify on their legal obligations and for them to communicate their expectations regarding these requirements.
2. Communicate and discuss common observations and deficiencies observed from the pilot Good Vigilance Practices inspection (GVP) inspections.
3. Receive and discuss the expectations

During the meeting the QPPVs were informed of an up coming training from experts from Europe and were encouraged to attend.

The meeting came up with a way forward starting by forming a WhatsApp group for all the QPPVs where communication will be shared easily and for continued follow up. They were encouraged to do more training where Intuvigilance was identified to offer these trainings and were invited to apply for them. NDA was requested to continue organizing such trainings bi annually or at least annually as a way of continuous capacity building of the MAHs.



4. Dysphonia and dolutegravir

Dysphonia is defined as a disorder affecting the voice. This is a newly reported adverse drug reaction suspected to be caused by dolutegravir. No other cases of dysphonia have been reported in Uganda, and only five cases have been reported globally. It is not a labeled reaction, and the causality analysis of the report suggests an unlikely association with dolutegravir.

We recommend that health workers be vigilant for any cases of dysphonia related to dolutegravir and its regimens and report them to the National Pharmacovigilance Centre at the NDA.

5. Foreign safety trends of interest

Cefazolin sodium hydrate and cefazolin sodium Risk of acute coronary syndrome accompanying allergic reaction- Japan.

The Ministry of Health, Labour and Welfare (MHLW) and the Pharmaceuticals and Medical Devices Agency (PMDA) have announced that the product information for cefazolin sodium hydrate and cefazolin sodium will be updated to include the risk of acute coronary syndrome accompanying allergic reaction. Cefazolin sodium hydrate and cefazolin sodium are indicated for sepsis, infective endocarditis, superficial skin infections, deep-seated skin infections, lymphangitis /lymphadenitis, chronic pyoderma, secondary infections following trauma, thermal burn, etc. The MHLW and the PMDA assessed 7 cases involving acute coronary syndrome accompanying allergic reaction in Japan, and concluded that a causal relationship between cefazolin and acute coronary syndrome accompanying allergic reaction was reasonably possible. Reference: Safety Information, MHLW/PMDA, 29 August 2023 (link to the source within www.pmda.go.jp/english/)

Clomiphene citrate Risk of serious visual disturbance (blindness)- France.

The National Agency for the Safety of Medicines and Health Products (ANSM) is reminding health-care professionals by issuing a Direct Health-care Professional Communication (DHPC) that there are new visual adverse reactions have been reported with the use of clomiphene citrate (Clomid®). This includes optic neuritis, optic ischemic neuropathy, central retinal vein occlusion, retinal detachment and vitreous detachment. These adverse reactions have in some cases resulted in reversible or irreversible visual impairment, partial or total (blindness), including after discontinuation of clomiphene citrate, especially when increasing the dosage or duration of treatment. Clomiphene citrate is a medication used to treat infertility in women who do not ovulate, including those with polycystic ovary syndrome. The ANSM reminded health-care professionals that at the start of treatment, patients should be warned of the risk of serious visual disturbances, including blindness. If unusual visual disturbances occur, patients should immediately discontinue their clomiphene citrate treatment and notify their doctor. In cases of visual disturbances, a comprehensive ophthalmological examination is necessary. If no cause of visual disturbance other than clomiphene citrate is identified, treatment with clomiphene citrate should be permanently discontinued. Reference: Security information, ANSM, 27 June 2023 (link to the source within ansm.sante.fr)

6. Quarterly ADR analysis

Females made up the majority of the reports (n= 859, 73%). Nearly 1000 of the reports were from the adult age categories of age categories 19-44 years and 45-64 years (n= 908, 78.07%).

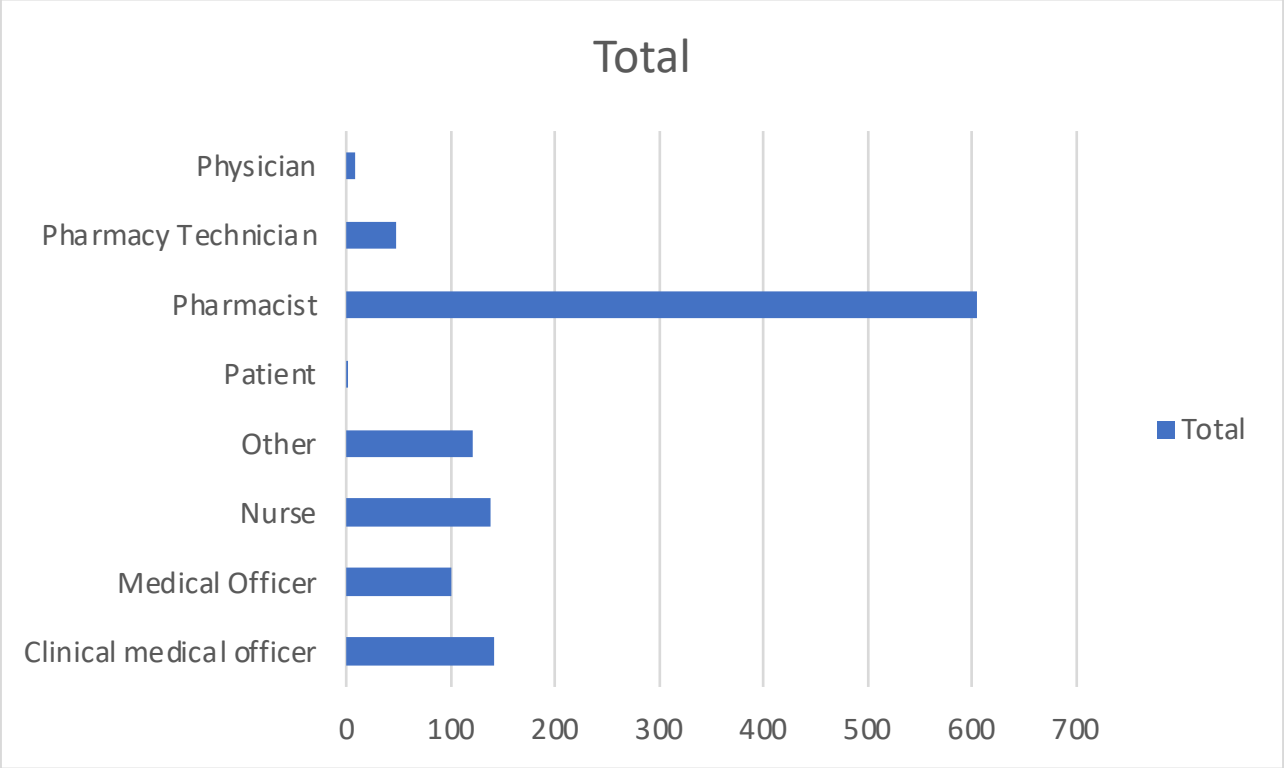
42.9% of the reports were graded serious based on the number of reactions reported (184 reports) with life threatening in nature as the most common reason for seriousness

Gender

	Count of Gender
FEMALE	859
MALE	287
UNKNOWN	17
Grand Total	**1163**
Age	
0-18 years	82
19- 44 years	556
45-64 years	352
65-74 years	79
Above 75	35
Unknown	59
Grand Total	1163
Nature of Reaction	
Row Labels	**Count of Nature of reaction**
Not serious	664
Serious	499
Grand Total	**1163**
Reason for seriousness	
Row Label	**Count of Seriousness of the reaction**
Involved Disability	85
Life Threatening	261
NIL	2
Other Medically Important condition	110
Patient Died	14
Prolonged Impatient Hospitalisation	96
TREASURE	1
(blank)	
Grand Total	**569**
Top reporting facilities	**Count of Health facility**
LUWEERO GENERAL HOSPITAL	301
ENTEBBE RRH	160
MUGABI MEDICAL CENTER	100
MBARARA RRH	74

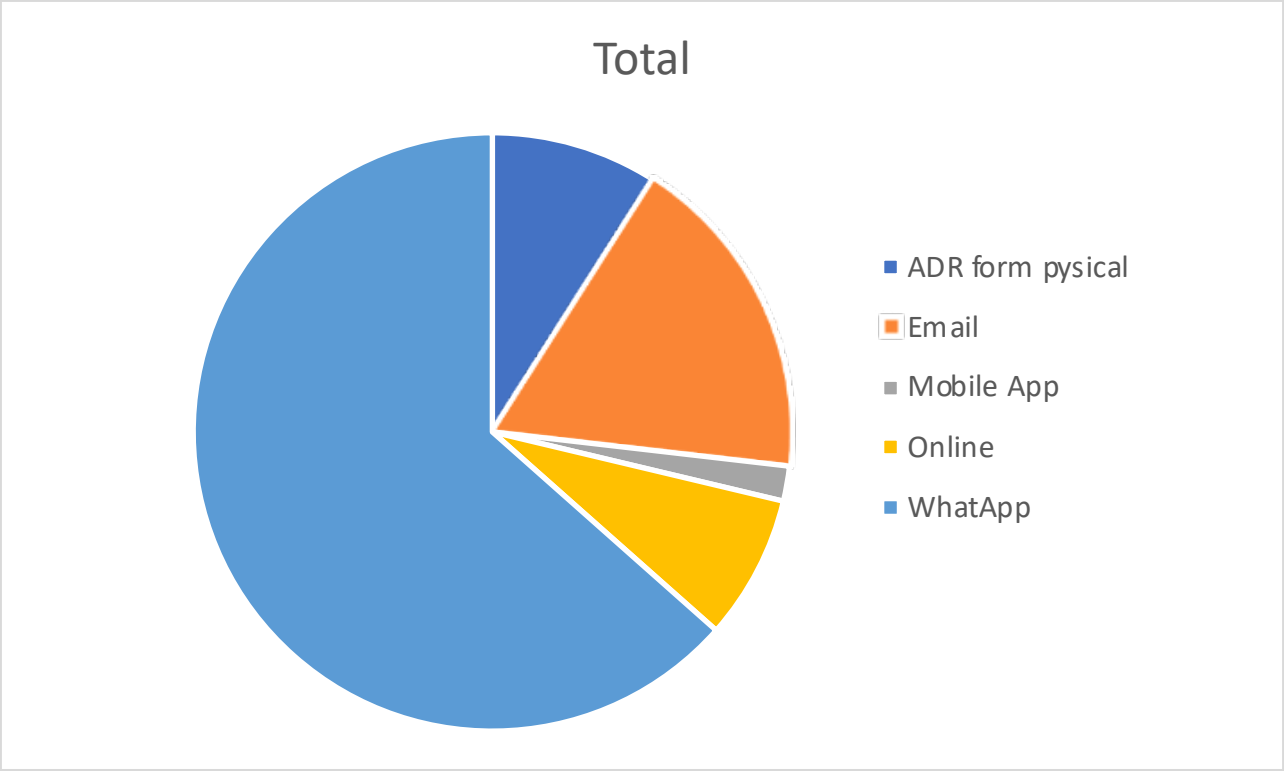
GULU RRH	51
MJAP MULAGO	46
ARUA RRH	37
SOROTI RRH	32
TASO MASAKA	31
BUSOLWE GENERAL HOSPITAL	26
YUMBE RRH	26
IDI MULAGO	25
UGANDA HEART INSTITUTE	25
BUTABIKA NR HOSPITAL	17
KAYUNGA RRH	16
MUBENDE RRH	12
LIRA RRH	11

Reporter Category



Pharmacists submitted the highest number of reports (n= 605, 52%) closely followed by nurses with (n=138, 11%).

Top reporting health facility was Luwero General Hospital with 301 reports, followed by Entebbe RRH with 160 reports, followed by Mugabi Medical Centre with 100 reports.



Reporter category

Row Labels	Count of Mode of reporting
ADR form Physical	105
Email	207
Mobile App	22
Online	91
WhatApp	738
Grand Total	**1163**

Reporter category

Reporters are shifting away from the usual traditional reporting ways preferring to use WhatsApp more (n=738, 63.4%) followed by Email at (n=207, 17.9%). The Online link and the Mobile app were the least preferred porting channels.

ADRs reporters in Q4

Name	Facility	Name	Facility
Oscar Ogwang Oteng	Lira RRH	Angie Treasure	Entebbe RRH
Harriet Musene	Namwenda HC IV	Muhammad Mubiru	Kiruddu RRH
Johnpaul Kizza	Lyantonde Hospital	Isaac Jorum Matovu	Kiruddu RRH
Charles Okopiro	Jinja RRH	Ali Kizza	Kiruddu RRH
Liverson Wakabi	Gulu RRH	Frank Kisaaliita	Kiruddu RRH
Shadia Nalwoga	Mulagi ISS Clinic	Rachel Alinaitwe	Kiruddu RRH
Pamela Lyavala	Buwenge GH	Phiona Namara	Lubaga Hospital
David Lubanga	Adjumani GH	Daniel Akol	Atutur GH
Agape PM		Jovial Nalukwago	Luwero GH

Bessie Ikiror	Mbale	Treasure Nassolo Hilary	IDI mulago
Louis Ssemigadde	Mubende RRH	Safia Ibiara	Amuria GH
Stephen Ongom	Angal St Luke Hosp	George Arachan	Entebbe RRH
Samuel Aligowa	Mityana	Sylvia Nalugya	IDI Mulago
Sandra Balungi	Hoima RRH	Ariane Rutu Nabisere	IDI Mulago
Emmanuel Akampurira	Mulago ISS Clinic	Allen Kitiore	
Rittah Atugonza	Nyaradot HC II	Yasin Nambohe	
Javan Kafuko	Entebbe RRH	Emma Situma	Yumbe RRH
Joan Lufafa	Entebbe RRH	Innocent Okot	Gulu RRH
Saul Kolyo	Kayunga RRH	Ivan Nuwamanya	Mbarara RRH
Muyomba Eria	Moroto RRH	Edwin Agaba	Bwera GH
Anita Birungi	IDI Mulago	Conrad Sserunjogi	Mildmay Uganda
Patrick Collins Emopus	Jinja RRH	Caleb Mwesigwa	Mbarara RRH
Fredrick Bukenya	Mubende RRH	Silagi Kigenyi	Walukuba HC IV
Jolly Apio	Koboko Hospital	Christopher Cox	Mulago RRH
Ben Babingo		Pius Adoa	Soroti RRH
Jane Aido	Tororo Prison HC III	John Lukoma	Mildmay Uganda
Berna Naggirinya	Masaka RRH	Ivan Katende	Soroti RRH
Sauda Naggayi	St Bal Ug Cares	Robert Alinde	Yerya HCIII
Naume Ainembambazi		David Bagonza	Yerya HC III
Rehema Nabukeera	Butabika NRH	Agnes Oumo	Musuku HC IV
Norman Kamugura	UHI	Irene Lydia Asiimwe	Gulu RRH
Banuli Balibuza	Bugiri GH	Silus Ojuka	UHI
Ruth Nagawa	Luwero GH	Andrew Nyanzi	Masaka RRH
Felistus Nyaketcho	Busolwe GH		

Safety label variation as of June 2024

Product Name	Licence Holder	Summary of Approved Changes	Date of NDA Approval
Sodium Valproate Controlled Release (Valcontin®)	Modi Mundipharma Pvt. Ltd	Addition of the following indications: In Mania/Bipolar; Prophylaxis of Migraine	25th June 2024
Nebivolol hydrochloride + Hydrochlorothiazide (Nebilet®)	Menarini International Operations Luxembourg S.A	Update to Sections 4.4 and 4.8 of the SmPC and section 2 of the PIL; Warnings and precautions to include; Non-melanoma skin cancer and choroidal effusion, acute myopia and secondary anfle-closure glaucoma.	25th June 2024
Amlodipine	Novartis Pharma Services Inc	Update to section 4.9 of the SmPC to include a write up on overdose that manifests as non-cardiogenic pulmonary oedema.	25th June 2024

Artemether + Lumefantrine (Coartem®)	Novartis Pharma Services Inc	Route of administration added on primary packaging	25th June 2024
Amoxicillin+ Clavulanic Acid (Augmentin®, Clavulin®)	Glaxosmithkline Pharmaceutical Kenya Limited	Addition of drug induced enterocolitis to the section of warnings and precautions and adverse reactions. Addition of linear IgA disease to adverse reactions section. Addition of information of the interaction of penicillins and methotrexate under the section of interactions.	14th June 2024
Human Albumin (Albunorm®)	Octapharma Ag.	Update of SmPC and PIL to include a warning on sodium in Albunorm 20%	14th June 2024
Bedaquiline Fumarate (Sirturo®)	Janssen-Cilag International Nv	Update of section 4.6 of the SmPC in order to update information on breast-feeding based on new literature.	29th May 2024
Polio virus; (Mahoney) type 1-inactive+(MEF-1) type 2-inactive + (saukett) tyoe 3 inactive	Sanofi Aventis South Africa Pty Ltd	SmPC update: Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to the needle injection. Procedures should be put in place to prevent any injury due to fainting and to manage syncopal reactions. PIL Update: Fainting can occur following, or even before any needle injection. Also, talk to your doctor or nurse if you or your child has fainted during a previous injection.	14th June 2024
Empaglifozin+Metformin hydrochloride (Flozicard XR 10 mg/100mg®)	Cipla Ltd	Change of product name from Empaglifozin and Metformin hydrochloride extended-release tablets 10 mg/1000 mg to Flozicard XR 10 mg/1000 mg	14th June 2024
Cabotegravir (Apretude®)	Glaxosmithkline Pharmaceutical Kenya Limited	Addition of hypersensitivity to adverse reactions, warnings and precautions.	7th June 2024
Human Insulin (Humulin Mixture®)	Lily France SA	Addition of cutaneous amyloidosis and lipodystrophy information. Addition of hyperglycaemia and hypoglycaemia information related to site of injections.	5th June 2024

Betamethasone disodium phosphate + Betamethasone dipropionate (Diprofos®)	MSD (Pty) Ltd	Update: Studies have shown an increased risk of neonatal hypoglycaemia following antenatal administration of a short course of betamethasone to women at risk for late preterm delivery. Update: Phaeochromocytoma crisis, which can be fatal, has been reported after administration of systemic corticosteroids. Corticosteroids should only be administered to patients with suspected or identified phaeochromocytom after an appropriate risk/benefit evaluation.	24th May 2024
Darunavir (Prezista®)	Janssen Ortho LLC	Crystal neuropathy added to adverse reactions.	21st May 2024
Oxytocin Acetate (Oxytocin 10 IU®)	Minapharm Pharmaceutical& Chemical Industries	Removal of subcutaneous as a route of administration.	13th May 2024
Ebola Zaire vaccine (Ervebo®)	MSD (Pty) Ltd	Extension to the existing indication of ervebo vaccine to include vaccination of infants aged 1 year and older.	30th April 2024
Desloratadine (Aeriallerg®)	Pharma International Co. Ltd	Weight increase and increased appetite added to list of possible side effects.	16th April 2024

Reporting Channels for ADRs and AEFIs

0740 002 070
0800 101 999
druginfo@nda.or.ug

QR Code: