PHARMACOVIGILANCE NEWSLETTER

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Safety monitoring of new medical products used in public health programs, Dolutegravir & Bedaquiline

Content

Health professionals and patients are encouraged to **report adverse events** or **quality problems** experienced with the use of **vaccines and medicines** to the nearest NAFDAC office or via pharmacovigilance@nafdac.gov.ng or via eReporting platform available on the NAFDAC website www.nafdac.gov.ng or via Med Safety Application available for download on Android and IOS stores.

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EDITOR'S NOTE...

We wish to thank our numerous stakeholders who have been working tirelessly with the National Pharmacovigilance Centre (NPC) to ensure the safe use of medicines in Nigeria. The NPC is committed to sending out the quarterly newsletter to its stakeholders. The objectives of the Newsletter are to disseminate information on Pharmacovigilance activities nationally and globally, to educate stakeholders on medicine safety issues, to promote rational use of drugs and to promote reporting of Adverse Drugs Reactions (ADRs) and AEFIs. This edition of the newsletter focuses on: **Safety monitoring of new medical products used in public health programs, Dolutegravir & Bedaquiline**

We encourage Health care Professionals and other stakeholders to continue to report all adverse drug reactions and AEFIs. Your valued comments and acknowledgement of receipt of this issue through our email addresses (pharmacovigilance@nafdac.gov.ng, fdic@nafdac.gov.ng) would be most appreciated.

Thank you for your relentless efforts in strengthening Pharmacovigilance System in Nigeria.

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Introduction

The core functions of a public health program are to assess and monitor the health of populations at risk so as to identify health problems and priorities; to formulate public policies designed to solve identified health problems and priorities; to ensure that all populations have access to appropriate and cost-effective care, which includes health promotion and disease prevention services.

In Nigeria, dedicated National public health Programmes such as those for tuberculosis, leprosy, malaria, HIV/AIDS, as well as immunization coverage programme are responsible for the control of endemic diseases and the prevention of communicable diseases through the use of medicines and vaccines. Diseases of public health significance affect large sections of the population, consequently, a large number of people are exposed to medicines used in their treatment or management. This together with the high toxicities of some of the medicines (such as those for HIV and TB/Leprosy) and issues of comorbidities (e.g., HIV/TB) or drug interactions make Safety monitoring of such medicines critical to sustaining a favourable benefit-risk ratio for their use among populations.

The National Pharmacovigilance Centre (NPC) situated in NAFDAC and the various public health programmes are continually engaged in the safety monitoring of medicines used in their respective programs. This is evidenced in the number of spontaneous reports of suspected Adverse Drug Reactions (ADRs) submitted to the NPC from 2005 till date. For example, antiretrovirals are the therapeutic class of drug with the highest number of reports submitted to the NPC with majority of the reports sent in by the HIV/AIDS program and supporting partners.

In recent times, new medicines, medicine regimens and medicines with new indications have been added for use in some diseases of public health concern. Some of these drugs have been included on the WHO Essential drug List for indications such as Dolutegravir: for HIV and Bedaquiline: for MDRTB.

Safety Monitoring of New Medicines

For a new drug to be approved by a National Drug Regulatory Authority, there must be sufficient evidence to show that the new drug is of good quality, safe and effective for the purpose for which it is proposed. The quality and efficacy criteria must be met before any consideration can be given to approval.

A medicinal product is authorised on the basis that in the specified indication(s), at the time of authorisation, the benefit-risk ratio is judged to be positive for the target population. A typical medicinal product may have multiple risks associated with it and individual risks will vary in terms of severity, effect on individual patients and public health impact. However, not all actual or potential risks will have been identified at the time when an initial authorisation is sought and many of the risks associated with the use of a medicinal product will only be discovered and characterised post

authorisation (NAFDAC Good Pharmacovigilance Practice Guidelines 2021). Pharmacovigilance (PV), a critical discipline in the healthcare system is aimed at promoting the safe and rational use of medicines through the prevention, identification, analysis, management, and documentation of adverse events and other drug-related problems including medication errors, therapeutic failure & drug misuse. Effective pharmacovigilance helps in the early identification of unexpected adverse reactions and their risk factors, thereby ensuring medicines are used with minimal harm. Robust PV systems are critical to ensure delivery of safe and effective medicines to patients worldwide. However, setting up and maintaining a PV system can be a challenge, especially in countries in the process of building their expertise or when resources are scarce (Peters et al, 2021).

Medical products (medicines, vaccines, and other essential health technologies) are among the main therapeutic tools used by health professionals for the prevention, detection, and treatment of diseases, including rehabilitation and palliative care. Although indispensable for improving health outcomes, the administration and use of medicines and vaccines can produce adverse effects, requiring continuous vigilance to ensure that the benefits outweigh the risks. Safety monitoring (pharmacovigilance) should therefore become much more explicit in efforts to strengthen health systems and prepare for pandemics because the world is determined to build back better after the COVID-19 pandemic (Wang et al, 2023).

Medicines are generally safe if they are used as prescribed or as directed on the label, however, there are risks in taking any medicine, in spite of all their benefits. The adverse events that occur after the administration of a drug are common, yet often mild and preventable, however, in some cases they cause disability and even death. Besides the intrinsic dangers associated with the drugs themselves, individual patients may exhibit particular and unpredictable sensitivities (idiosyncrasies) to certain medicines, and, if more than one medicine is prescribed, there is always a risk of negative interactions.

Bedaquiline and delamanid became the first two new drugs approved by regulatory authorities for the treatment of TB – currently recommended for use in the treatment of Rifampicin Resistant (RR-)/multidrug resistant TB (RR-/MDR-TB). The introduction brought hope to patients worldwide suffering from drug resistant TB (DR-TB), including its most complicated variant, Extensively drug-resistant TB (XDRTB), that have limited treatment options (Challenge TB, 2019)

In 2017, it was estimated that there were approximately 558,000 people suffering from Rifampicin Resistant (RR-)/Multidrug resistant TB (MDR-TB). MDR-TB is a public health crisis as it is more difficult to diagnose, its treatment is more expensive and longer (up to 24 months), and the drugs can have severe side effects, some of them permanent. Worldwide, only 55 percent of MDR-TB patients were treated successfully and in 2017, there were about 230,000 deaths from MDR/RR-TB.1

The Challenge TB (CTB) Project focused on increasing the treatment coverage of RR-/MDR-TB and improving the quality of DR-TB management, and actively helping countries to plan, implement, and introduce the new TB drugs and regimens, with the aim of improving the treatment outcomes of patients and reducing the treatment gap, thus ensuring that every patient has access to the treatment they need and that no MDRTB patient goes untreated. Tackling the above-mentioned issues not only aims to help patients but also

to reduce the risks that MDR-TB spread and further development of resistance poses to public health (Challenge TB, 2019).

Differences among side effects, adverse drug effects/adverse drug reactions

Although, side effects and adverse effects are similar terms often used in medicine, they are distinctly different. A side effect is an effect of a drug, chemical, or other medicine that is in addition to the intended effect, while an adverse effect is a harmful, undesirable effect that results from a medication or other intervention such as surgery. A side effect may be either harmful or beneficial; an adverse effect is typically harmful and undesirable. In addition, adverse effects tend to be more severe and life-threatening than side effects (Wang et al, 2023).

Reports of suspected ADRs associated with the use of New Program Medicines, Dolutegravir and Bedaquiline.

Within the study period of 1st January 2020 to 31st December 2024, the vigiflow showed a total of 2,400 individual case safety reports associated with Dolutegravir and 183 individual case safety reports associated with Bedaquilline (Table 1 below).

Further analysis of the individual case safety reports on table 1 produced table 2 and table 3. Table 2 elaborates on the most common reported adverse events associated with dolutegravir according to their System Organ Classification. From the top three System Organ Classes involved (out of 1596 reports) on dolutegravir: 560 (35%) events were Nervous System disorders; 529 (33%) events were Skin & subcutaneous tissue disorders and 507 (32%) were Gastrointestinal disorders.

Table 3 elaborates on the most common reported adverse events associated with bedaquiline according to their System Organ Classification. From the top three System Organ Classes involved (out of 158 reports) on bedaquiline: 76 (48%) events were Gastrointestinal disorders, 42 (27%) events were metabolic & nutrition disorders and 40 (25%) events were General disorders and administration site conditions.

Table

Table 1- Number of Suspected Adverse Events received from 2020 to 2024

Active ingredient/No of AEs report	2020	2021	2022	2023	2024
Dolutegravir	94	323	714	516	753
Bedaquiline	50	3	46	51	33

Table 2. Most Common Suspected Adverse Events associated with Dolutegravir Use, received from 2020 to 2024

S/N for SOC	SOC	Reaction / event reported to NPC	Frequency of Reaction / event
1.	Nervous System Disorders	Burning foot	1 (0.06%)
		Burning sensation	2 (0.12%)
		Central nervous system disorder	1 (0.06%)
		Chronic headaches	1 (0.06%)
		Cluster headaches	2 (0.12%)
		Convulsion	1 (0.06%)
		Dizziness	231 (14.47%)
		Dizziness aggravated	1 (0.06%)

		Drowsiness	9 (0.56%)
		Drowsy on awakening	1 (0.06%)
		Dysarthria	2 (0.12%)
		Epileptic seizure	1 (0.06%)
		Excessive daytime sleepiness	1 (0.06%)
		Fainting	6 (0.37%)
		Feeling of residual sleepiness	4 (0.25%)
		Forgetfulness	1 (0.06%)
		Freezing phenomenon	1 (0.06%)
		Frontal headache	1 (0.06%)
		Giddiness	1 (0.06%)
		Head pressure	1 (0.06%)
		Headache	223 (13.97%)
		Headache (excl migraine) aggravated	1 (0.06%)
		Dull headache	1 (0.06%)
		Heaviness of head	1 (0.06%)
		Hepatic encephalopathy	1 (0.06%)

		Hyperactivity	16 (1.00%)
		Hypersomnia	1 (0.06%)
		Incoherent	1 (0.06%)
		Intermittent headache	1 (0.06%)
		Jacksonian seizures	1 (0.06%)
		Lack of coordination	1 (0.06%)
		Loss of consciousness	1 (0.06%)
		Memory impaired	1 (0.06%)
		Movement disorder	1 (0.06%)
		Muscle contractions involuntary	1 (0.06%)
		Neurological disorder NOS	1 (0.06%)
		Neuropathic pain	1 (0.06%)
		Numbness	10 (0.62%)
		Numbness of hands	3 (0.18%)
		Numbness in leg	2 (0.12%)
		Numbness of	2

		extremities	(0.12%)
		Paraplegia	1 (0.06%)
		Peripheral neuropathy	2 (0.12%)
		Persistent headache	2 (0.12%)
		Shaking	2 (0.12%)
		Taste bitter	3 (0.18%)
		Tension headache	1 (0.06%)
		Tingling sensation	7 (0.43%)
		Tremor muscle	2 (0.12%)
		Nervous System Disorders total	**560**
2.	Skin and Subcutaneous Tissue Disorders	Alopecia	1 (0.06%)
		Angioedema	1 (0.06%)
		Black pigmentation of hair roots	1 (0.06%)
		Blisters	8 (0.50%)
		Blistery rash	2 (0.12%)

		Bullous eruption	1 (0.06%)
		Dark reddish macule	3 (0.18%)
		Darkened skin	2 (0.12%)
		Dermatitis	1 (0.06%)
		Eczema	1 (0.06%)
		Eruption facial	1 (0.06%)
		Excess sweating	2 (0.06%)
		Itchy sensation of the extremities	1 (0.06%)
		General pruritus	142 (8.89%)
		Generalised rash	13 (0.81%)
		Groin rash	1 (0.06%)
		Hair loss	1 (0.06%)
		Hand rash	1 (0.06%)
		Hives	1 (0.06%)
		Hyperhidrosis	1 (0.06%)
		Hyperpigmentation	10

		skin	(0.62%)
		Itching both hands	1 (0.06%)
		Itching papule	1 (0.06%)
		Itchy rash	15 (0.93%)
		Macular rash	1 (0.06%)
		Night sweat	2 (0.12%)
		Nocturnal pruritus	2 (0.12%)
		Painful rash	1 (0.06%)
		Papular rash	2 (0.12%)
		Patchy rash	2 (0.12%)
		Photosensitivity	1 (0.06%)
		Pruritic rash	4 (0.25%)
		Generalised rash	265 (16.60%)
		Rash on face	2 (0.12%)
		Rash on leg	1 (0.06%)
		Red rash	3 (0.18%)

		Redness	2 (0.12%)
		Scalp rash	1 (0.06%)
		Skin breakout	1 (0.06%)
		Skin burning sensation	1 (0.06%)
		Skin discoloration	3 (0.18%)
		Skin dry	1 (0.06%)
		Skin inflammation	1 (0.06%)
		Skin peeling	2 (0.12%)
		Skin reaction	5 (0.31%)
		Skin ulceration	1 (0.06%)
		Spot-like rash	1 (0.06%)
		Stevens Johnson reaction	1 (0.06%)
		Sweating	7 (0.43%)
		Urticaria	5 (0.31%)
		Skin and Subcutaneous Tissue Disorders Total	**529**

3.	Gastrointestinal disorders	Abdominal bloating	1 (0.06%)
		Abdominal crampy pains	1 (0.06%)
		Abdominal discomfort	10 (0.62%)
		Abdominal noises	1 (0.06%)
		Abdominal Pain	47 (2.94%)
		Abdominal pain NOS	1 (0.06%)
		Acute abdomen	1 (0.06%)
		Acute diarrhea	2 (0.12%)
		Belching	1 (0.06%)
		Blistering of mouth	3 (0.18%)
		Bloating	2 (0.12%)
		Bloody stool	2 (0.12%)
		Burning sensation in abdomen	1 (0.06%)
		Constipation	11 (0.68%)
		Constipation (excl fecal impaction)	1 (0.06%)
		Diarrhea	101

			(6.32%)
		Discoloration tooth	1 (0.06%)
		Dry mouth	4 (0.25%)
		Dyspepsia	3 (0.18%)
		Dysphagia	1 (0.06%)
		Epigastric pain	5 (0.31%)
		Flatulence	2 (0.12%)
		Gastrointestinal disturbance	6 (0.37%)
		Halitosis	1 (0.06%)
		Heartburn	4 (0.25%)
		Frequent Bowel Movement	3 (0.18%)
		Inflammation stomach	1 (0.06%)
		Lip sore	1 (0.06%)
		Loose stools	8 (0.50%)
		Lower abdominal pain	0.06
		Mouth dry	1 (0.06%)

		Mouth ulcer	1 (0.06%)
		Mucous stools	1 (0.06%)
		Nausea	105 (6.57%)
		Persistent vomiting	1 (0.06%)
		Stomach ache	40 (2.50%)
		Saliva secretion excessive	1 (0.06%)
		Sores mouth	2 (0.12%)
		Stomach burning sensation	1 (0.06%)
		Stomach cramps	3 (0.18%)
		Stomach discomfort	6 (0.37%)
		Stomach upset	12 (0.75%)
		Swollen abdomen	1 (0.06%)
		Swollen lips	4 (0.25%)
		Unable to swallow	1 (0.06%)
		Vomiting	95 (5.95%)
		Vomiting	1

		aggravated	(0.06%)
		Watery diarrhea	2 (0.12%)
		Gastrointestinal disorders Total	**507**

Table 3. Most Common Suspected

Adverse Events associated with Bedaquiline Use, 2020 to 2024

S/N for SOC	SOC	Reaction / event reported to NPC	Frequency of Reaction / event
1	**Gastrointestinal disorders**	Vomiting	54 (34.7%)
		Nausea	5 (3.16%)
		Diarrhea	2 (1.26%)
		Sores mouth	2 (1.26%)
		Gastritis	2 (1.26%)
		Vomiting aggravated	2 (1.26%)
		Gastrointestinal pain	1 (0.6%)
		Nausea aggravated	1 (0.6%)
		Fecal incontinence	1 (0.6%)
		Loose stools	1 (0.6%)
		Gastrointestinal upset	1 (0.6%)

		Abdominal pain	1 (0.6%)
		Large hematemesis	1 (0.6%)
		Abdominal disorder	1 (0.6%)
		Vomited	1 (0.6%)
		Total	**76**
2	**Metabolism and nutrition disorders**	Hypokalemia	30 (18.98%)
		Appetite lost	5 (3.16%)
		Hypokalaemia	4 (2.5%)
		Hypocalcemia	3 (1.89%)
		Total	**42** (%)
3	**General disorders and administration site conditions**	Weakness	18 (11.89%)
		General body pain	4 (2.5%)
		Fatigue	3 (1.89%)

		Chest pain	3 (1.89%)
		Tiredness	3 (1.89%)
		Adverse event	2 (1.26%)
		Swelling	2 (1.26%)
		Chest tightness	1 (0.6%)
		Walking difficulty	1 (0.6%)
		Pain	1 (0.6%)
		Fever	1 (0.6%)
		Weakness generalized	1 (0.6%)
		Total	**40**

Conclusion

Careful Safety monitoring of medicines and related products is critical but not limited to new commodities; it has an important role to play both in the introduction of generic medicines, and in review of the safety profile of older medicines already available, where new safety issues may arise.

The reported suspected adverse events for dolutegravir and Bedaquiline on the NPC database (vigiflow) are in agreement with the related SmPCs' reported safety data.

Monitoring drug safety serves as an early warning system that helps identify adverse events that occur after vaccination or the administration of other medicines, providing valuable information to assess possible safety concerns. These systems are especially useful for detecting unusual or unexpected patterns of adverse events that might indicate a possible safety problem with a vaccine or a medicine (Wang et al, 2023).

Spontaneous reporting of suspected adverse drug reactions remains a critical aspect of safety monitoring of medicines/related products and all adverse events that occur in association with the use of medicines should be reported to the National Pharmacovigilance Centre.

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